Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-113697- -00000-0000

Fecha: 2012-07-06 16:37:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 4

SOLICITUD DE PATE...

INVENCIÓN

TITULO: MÉTODO DE TRATAMIENTO

SOLICITANTE: GLAXO WELLCOME MANUFACTURING PTE LTD.

DIRECCIÓN: 1 Pioneer Sector 1 Jurong, 628413. Singapur.

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 06 de Julio de 2012

P2012/000088

OLARTEM
OLARTE MOURE & ASO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-113697- -00000-0000
Fecha: 2012-07-06 16:37:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 4

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2012/000088**

SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2)

SOLICITANTE (71)

Nombre: GLAXO WELLCOME MANUFACTURING PTE LTD.
Dirección: 1 Pioneer Sector 1 Jurong, 628413 Singapur
Nacionalidad o Domicilio: Singapur
Lugar de Constitución: Singapur

Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Carrera 5 No. 34-03, Bogotá
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA.
Dirección: VER PAGINA ADJUNTA.
Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2011/020231 Fecha Enero 05, 2011

Publicación Internacional No. WO 2011/085007 Fecha Julio 14, 2011

(6) **Título (54)** **MÉTODO DE TRATAMIENTO**

Clasificación Internacional (51) A61K 31/52.

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Enero 06, 2010	61/292,747

(9) **Comprobante de pago No.** 12- **Fecha** Junio 21 de 2012

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso. Adjunto copia simple ver expediente No.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/US2011/020231

Valeriu DAMIAN-IORDACHE
GlaxoSmithKline, Global Patents,
709 Swedeland Road
King of Prussia, PA 19406
Estados Unidos de America
Nacionalidad: Rumana

Andrew KING
GlaxoSmithKline, Global Patents
1250 South Collegeville Road
PO Box 5089
Collegeville, PA 19426
Estados Unidos de America
Nacionalidad: Estadounidense

Megan M. MCLAUGHLIN
GlaxoSmithKline, Global Patents
1250 South Collegeville Road
PO Box 5089
Collegeville, PA 19426
Estado Unidos de America
Nacionalidad: Estadounidense

Albert B. SUTTLE
GlaxoSmithKline, Global Patents
Five Moore Drive, C.2111.2F
PO Box 13398,
Research Triangle Park, NC 27709
Estados Unidos de America
Nacionalidad: Estadounidense

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0062855

Bogotá D.C., Junio 21 de 2012 - 13:09:59

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	455532556	20/06/2012	8.022.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr UNDITARIO	Vr CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	590.000.00	590.000.00
				$590.000.00

SON: **QUINIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-113697- -00000-0000

Fecha: 2012-07-06 16:37:24 Dep. 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 4

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha:	Recorrido:

Tipo de Radicación: Entrada: Salida: Traslado: Convenio:

Radicador:	Planilla:

ID	No. Radicación	Cons	Item
1	1.		
2			
3			
4			
5	12-113697-0		
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			

Item	Unidad de Conservación
1	CD
2	Disquetes
3	DVD
4	Fotos
5	Libro
6	Muestra Física
7	Otros
8	Planos
9	Periódico
10	Publicación Periódica
11	Sobre blanco tamaño carta
12	Sobre blanco tamaño oficio
13	Sobre de manila

Observaciones
Anexan CD
1

Assignment

WHEREAS, I/we Valeriu DAMIAN-IORDACHE a citizen of Romania, Andrew KING and Megan M. MCLAUGHLIN both citizen and the United States of America and all residing at Philadelphia, PA, and Albert B SUTTLE a citizen of the United States of America and residing at Research Triangle Park, North Carolina has/have invented or discovered certain improvements in **TREATMENT METHOD** hereinafter referred to as said invention and improvements for which a priority application 61/292,747 was filed on 6 January 2010 in the United States Patent and Trademark Office and for which a PCT international application PCT/US2011/020231 filed 5 January 2011 designating the United States of America and naming assignor as inventor, and in the United States only applicant/inventor.

WHEREAS, **GLAXO WELLCOME MANUFACTURING PTE LTD**, a corporation organized and existing under and by virtue of the laws of Singapore and having its principal place of business at 1 Pioneer Sector 1, Jurong 628413 Singapore, is desirous of acquiring the whole right, title and interest in and to said invention and improvements and said application, and in and to any Letters Patent to be obtained therefor, in the United States, its territories and possessions, and in and to any applications for said invention and improvements and any Letters Patent to be obtained therefor, in all countries other than the United States, its territories and possessions;

NOW, THEREFORE, to all whom it may concern, be it known that I/we Valeriu DAMIAN-IORDACHE, Andrew KING, Megan M. MCLAUGHLIN, Albert B SUTTLE for good and valuable consideration unto me/us moving, the receipt whereof is hereby acknowledged, have sold, assigned and transferred, and by these presents do sell, assign and transfer my/our whole right, title and interest in and to said invention and improvements to said **GLAXO WELLCOME MANUFACTURING PTE LTD**, throughout the United States of America, its territories and possessions, and in and to said application and any extensions, reissues, continuations, continuations-in-part, and any divisions thereof, and in and to any and all Letters Patent of the United States of America;

AND, my/our whole right, title and interest in and to said invention and improvements to **GLAXO WELLCOME MANUFACTURING PTE LTD**, in all other countries throughout the world, and in and to any applications in said other countries, and continuations-in-part, patents of addition, revalidation patents, patents of importation, registrations, and any renewals, extensions and divisions thereof, and in and to any and all

Letters Patent of said all other countries which may be granted on said invention and improvements including any priority rights under the International Convention.

AND, I/we do hereby authorize and request the issue of any Letters Patent in the respective areas referred to, to said **GLAXO WELLCOME MANUFACTURING PTE LTD**, as assignee of my/our whole right, title and interest in and to the same for the sole use and behalf of the said assignees, their successors and assigns as their interests appear herein;

AND, I/we warrant that I/we have not knowingly conveyed to others any right in said invention, improvements, applications or patents or any license to use the same or to make, use or sell anything embodying or utilizing said invention and improvements and that I/we have good right to assign the same to **GLAXO WELLCOME MANUFACTURING PTE LTD,**

AND, I/we the Valeriu DAMIAN-IORDACHE, Andrew KING, Megan M. MCLAUGHLIN, Albert B SUTTLE for the consideration aforesaid, do hereby agree that I/we or my/our executors or legal representatives, will provide information and make, execute and deliver any and all other instruments in writing, and any and all further acts, application papers, affidavits, assignments and other documents which may be necessary or desirable to more effectually secure to and vest in said **GLAXO WELLCOME MANUFACTURING PTE LTD**, their successors and assigns, the whole right, title and interest in and to the said invention and improvements, applications, Letters Patent, rights, title and interest hereby sold, assigned and conveyed, or intended so to be. *This assignment should be deemed effective as of 6 January 2010.*

IN WITNESS WHEREOF, I/we have hereunto set my/our hand(s) and affixed my/our seal(s) on the date(s) indicated below.

Inventor: **Valeriu DAMIAN-IORDACHE** MARCH 24, 2011 Date

Inventor: **Andrew KING** Date

Inventor: **Megan M. MCLAUGHLIN** Date

Inventor: **Albert B SUTTLE** Date

Assignment

WHEREAS, I/we Valeriu DAMIAN-IORDACHE a citizen of Romania, Andrew KING and Megan M. MCLAUGHLIN both citizen and the United States of America and all residing at Philadelphia, PA, and Albert B SUTTLE a citizen of the United States of America and residing at Research Triangle Park, North Carolina has/have invented or discovered certain improvements in **TREATMENT METHOD** hereinafter referred to as said invention and improvements for which a priority application 61/292,747 was filed on 6 January 2010 in the United States Patent and Trademark Office and for which a PCT international application PCT/US2011/020231 filed 5 January 2011 designating the United States of America and naming assignor as inventor, and in the United States only applicant/inventor.

WHEREAS, **GLAXO WELLCOME MANUFACTURING PTE LTD**, a corporation organized and existing under and by virtue of the laws of Singapore and having its principal place of business at 1 Pioneer Sector 1, Jurong 628413 Singapore, is desirous of acquiring the whole right, title and interest in and to said invention and improvements and said application, and in and to any Letters Patent to be obtained therefor, in the United States, its territories and possessions, and in and to any applications for said invention and improvements and any Letters Patent to be obtained therefor, in all countries other than the United States, its territories and possessions;

NOW, THEREFORE, to all whom it may concern, be it known that I/we Valeriu DAMIAN-IORDACHE, Andrew KING, Megan M. MCLAUGHLIN, Albert B SUTTLE for good and valuable consideration unto me/us moving, the receipt whereof is hereby acknowledged, have sold, assigned and transferred, and by these presents do sell, assign and transfer my/our whole right, title and interest in and to said invention and improvements to said **GLAXO WELLCOME MANUFACTURING PTE LTD**, throughout the United States of America, its territories and possessions, and in and to said application and any extensions, reissues, continuations, continuations-in-part, and any divisions thereof, and in and to any and all Letters Patent of the United States of America;

AND, my/our whole right, title and interest in and to said invention and improvements to **GLAXO WELLCOME MANUFACTURING PTE LTD**, in all other countries throughout the world, and in and to any applications in said other countries, and continuations-in-part, patents of addition, revalidation patents, patents of importation, registrations, and any renewals, extensions and divisions thereof, and in and to any and all

Letters Patent of said all other countries which may be granted on said invention and improvements including any priority rights under the International Convention.

AND, I/we do hereby authorize and request the issue of any Letters Patent in the respective areas referred to, to said **GLAXO WELLCOME MANUFACTURING PTE LTD**, as assignee of my/our whole right, title and interest in and to the same for the sole use and behalf of the said assignees, their successors and assigns as their interests appear herein;

AND, I/we warrant that I/we have not knowingly conveyed to others any right in said invention, improvements, applications or patents or any license to use the same or to make, use or sell anything embodying or utilizing said invention and improvements and that I/we have good right to assign the same to **GLAXO WELLCOME MANUFACTURING PTE LTD,**

AND, I/we the Valeriu DAMIAN-IORDACHE, Andrew KING, Megan M. MCLAUGHLIN, Albert B SUTTLE for the consideration aforesaid, do hereby agree that I/we or my/our executors or legal representatives, will provide information and make, execute and deliver any and all other instruments in writing, and any and all further acts, application papers, affidavits, assignments and other documents which may be necessary or desirable to more effectually secure to and vest in said **GLAXO WELLCOME MANUFACTURING PTE LTD**, their successors and assigns, the whole right, title and interest in and to the said invention and improvements, applications, Letters Patent, rights, title and interest hereby sold, assigned and conveyed, or intended so to be. *This assignment should be deemed effective as of 6 January 2010.*

IN WITNESS WHEREOF, I/we have hereunto set my/our hand(s) and affixed my/our seal(s) on the date(s) indicated below.

Inventor: **Valeriu DAMIAN-IORDACHE** Date

22-MAR-2011

Inventor: **Andrew KING** Date

Inventor: **Megan M. MCLAUGHLIN** Date

Inventor: **Albert B SUTTLE** Date

Assignment

WHEREAS, I/we Valeriu DAMIAN-IORDACHE a citizen of Romania, Andrew KING and Megan M. MCLAUGHLIN both citizen and the United States of America and all residing at Philadelphia, PA, and Albert B SUTTLE a citizen of the United States of America and residing at Research Triangle Park, North Carolina has/have invented or discovered certain improvements in **TREATMENT METHOD** hereinafter referred to as said invention and improvements for which a priority application 61/292,747 was filed on 6 January 2010 in the United States Patent and Trademark Office and for which a PCT international application PCT/US2011/020231 filed 5 January 2011 designating the United States of America and naming assignor as inventor, and in the United States only applicant/inventor.

WHEREAS, **GLAXO WELLCOME MANUFACTURING PTE LTD**, a corporation organized and existing under and by virtue of the laws of Singapore and having its principal place of business at 1 Pioneer Sector 1, Jurong 628413 Singapore, is desirous of acquiring the whole right, title and interest in and to said invention and improvements and said application, and in and to any Letters Patent to be obtained therefor, in the United States, its territories and possessions, and in and to any applications for said invention and improvements and any Letters Patent to be obtained therefor, in all countries other than the United States, its territories and possessions;

NOW, THEREFORE, to all whom it may concern, be it known that I/we Valeriu DAMIAN-IORDACHE, Andrew KING, Megan M. MCLAUGHLIN, Albert B SUTTLE for good and valuable consideration unto me/us moving, the receipt whereof is hereby acknowledged, have sold, assigned and transferred, and by these presents do sell, assign and transfer my/our whole right, title and interest in and to said invention and improvements to said **GLAXO WELLCOME MANUFACTURING PTE LTD**, throughout the United States of America, its territories and possessions, and in and to said application and any extensions, reissues, continuations, continuations-in-part, and any divisions thereof, and in and to any and all Letters Patent of the United States of America;

AND, my/our whole right, title and interest in and to said invention and improvements to **GLAXO WELLCOME MANUFACTURING PTE LTD**, in all other countries throughout the world, and in and to any applications in said other countries, and continuations-in-part, patents of addition, revalidation patents, patents of importation, registrations, and any renewals, extensions and divisions thereof, and in and to any and all

Letters Patent of said all other countries which may be granted on said invention and improvements including any priority rights under the International Convention.

AND, I/we do hereby authorize and request the issue of any Letters Patent in the respective areas referred to, to said **GLAXO WELLCOME MANUFACTURING PTE LTD,** as assignee of my/our whole right, title and interest in and to the same for the sole use and behalf of the said assignees, their successors and assigns as their interests appear herein;

AND, I/we warrant that I/we have not knowingly conveyed to others any right in said invention, improvements, applications or patents or any license to use the same or to make, use or sell anything embodying or utilizing said invention and improvements and that I/we have good right to assign the same to **GLAXO WELLCOME MANUFACTURING PTE LTD,**

AND, I/we the Valeriu DAMIAN-IORDACHE, Andrew KING, Megan M. MCLAUGHLIN, Albert B SUTTLE for the consideration aforesaid, do hereby agree that I/we or my/our executors or legal representatives, will provide information and make, execute and deliver any and all other instruments in writing, and any and all further acts, application papers, affidavits, assignments and other documents which may be necessary or desirable to more effectually secure to and vest in said **GLAXO WELLCOME MANUFACTURING PTE LTD**, their successors and assigns, the whole right, title and interest in and to the said invention and improvements, applications, Letters Patent, rights, title and interest hereby sold, assigned and conveyed, or intended so to be. *This assignment should be deemed effective as of 6 January 2010.*

IN WITNESS WHEREOF, I/we have hereunto set my/our hand(s) and affixed my/our seal(s) on the date(s) indicated below.

Inventor: **Valeriu DAMIAN-IORDACHE** Date

Inventor: **Andrew KING** Date

30 MAR 2011

Inventor: **Megan M. MCLAUGHLIN** Date

Inventor: **Albert B SUTTLE** Date

Assignment

WHEREAS, I/we Valeriu DAMIAN-IORDACHE a citizen of Romania, Andrew KING and Megan M. MCLAUGHLIN both citizen and the United States of America and all residing at Philadelphia, PA, and Albert B SUTTLE a citizen of the United States of America and residing at Research Triangle Park, North Carolina has/have invented or discovered certain improvements in **TREATMENT METHOD** hereinafter referred to as said invention and improvements for which a priority application 61/292,747 was filed on 6 January 2010 in the United States Patent and Trademark Office and for which a PCT international application PCT/US2011/020231 filed 5 January 2011 designating the United States of America and naming assignor as inventor, and in the United States only applicant/inventor.

WHEREAS, **GLAXO WELLCOME MANUFACTURING PTE LTD**, a corporation organized and existing under and by virtue of the laws of Singapore and having its principal place of business at 1 Pioneer Sector 1, Jurong 628413 Singapore, is desirous of acquiring the whole right, title and interest in and to said invention and improvements and said application, and in and to any Letters Patent to be obtained therefor, in the United States, its territories and possessions, and in and to any applications for said invention and improvements and any Letters Patent to be obtained therefor, in all countries other than the United States, its territories and possessions;

NOW, THEREFORE, to all whom it may concern, be it known that I/we Valeriu DAMIAN-IORDACHE, Andrew KING, Megan M. MCLAUGHLIN, Albert B SUTTLE for good and valuable consideration unto me/us moving, the receipt whereof is hereby acknowledged, have sold, assigned and transferred, and by these presents do sell, assign and transfer my/our whole right, title and interest in and to said invention and improvements to said **GLAXO WELLCOME MANUFACTURING PTE LTD**, throughout the United States of America, its territories and possessions, and in and to said application and any extensions, reissues, continuations, continuations-in-part, and any divisions thereof, and in and to any and all Letters Patent of the United States of America;

AND, my/our whole right, title and interest in and to said invention and improvements to **GLAXO WELLCOME MANUFACTURING PTE LTD**, in all other countries throughout the world, and in and to any applications in said other countries, and continuations-in-part, patents of addition, revalidation patents, patents of importation, registrations, and any renewals, extensions and divisions thereof, and in and to any and all

Letters Patent of said all other countries which may be granted on said invention and improvements including any priority rights under the International Convention.

AND, I/we do hereby authorize and request the issue of any Letters Patent in the respective areas referred to, to said **GLAXO WELLCOME MANUFACTURING PTE LTD**, as assignee of my/our whole right, title and interest in and to the same for the sole use and behalf of the said assignees, their successors and assigns as their interests appear herein;

AND, I/we warrant that I/we have not knowingly conveyed to others any right in said invention, improvements, applications or patents or any license to use the same or to make, use or sell anything embodying or utilizing said invention and improvements and that I/we have good right to assign the same to **GLAXO WELLCOME MANUFACTURING PTE LTD,**

AND, I/we the Valeriu DAMIAN-IORDACHE, Andrew KING, Megan M. MCLAUGHLIN, Albert B SUTTLE for the consideration aforesaid, do hereby agree that I/we or my/our executors or legal representatives, will provide information and make, execute and deliver any and all other instruments in writing, and any and all further acts, application papers, affidavits, assignments and other documents which may be necessary or desirable to more effectually secure to and vest in said **GLAXO WELLCOME MANUFACTURING PTE LTD**, their successors and assigns, the whole right, title and interest in and to the said invention and improvements, applications, Letters Patent, rights, title and interest hereby sold, assigned and conveyed, or intended so to be. *This assignment should be deemed effective as of 6 January 2010.*

IN WITNESS WHEREOF, I/we have hereunto set my/our hand(s) and affixed my/our seal(s) on the date(s) indicated below.

Inventor: **Valeriu DAMIAN-IORDACHE** Date

Inventor: **Andrew KING** Date

Inventor: **Megan M. MCLAUGHLIN** Date

A Ben Suttle III 22 Mar 2011

Inventor: **Albert B SUTTLE** Date

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 July 2011 (14.07.2011)

PCT

(10) International Publication Number
WO 2011/085007 A1

(51) International Patent Classification:
A61K 31/52 (2006.01)

(21) International Application Number:
PCT/US2011/020231

(22) International Filing Date:
5 January 2011 (05.01.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/292,747 6 January 2010 (06.01.2010) US

(71) Applicant *(for all designated States except US)*: **GLAXO WELLCOME MANUFACTURING PTE LTD** [SG/SG]; 1 Pioneer, Sector 1, Jurong 628413 (SG).

(72) Inventors; and

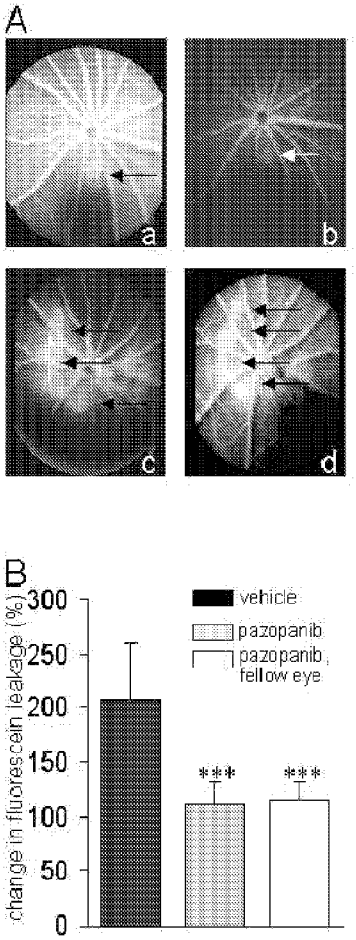
(75) Inventors/Applicants *(for US only)*: **DAMIAN-IORDACHE, Valeriu** [RO/US]; GlaxoSmithKline, c/o Global Patents, 709 Swedeland Road, King of Prussia, Pennsylvania 19406 (US). **KING, Andrew** [US/US]; GlaxoSmithKline, c/o Global Patents, 1250 South Collegeville Road, PO Box 5089, Collegeville, Pennsylvania 19426 (US). **MCLAUGHLIN, Megan M** [US/US]; GlaxoSmithKline, c/o Global Patents, 1250 South Collegeville Road, PO Box 5089, Collegeville, Pennsylvania 19426 (US). **SUTTLE, Albert B** [US/US]; GlaxoSmithKline, c/o Global Patents, 5 Moore Drive, C.2111.2F, PO Box 13398, RTP, North Carolina 27709 (US).

(74) Agent: **STRICKLAND, J. Michael**; GlaxoSmithKline, Global Patents, Five Moore Drive, C.2111.2F, PO Box

[Continued on next page]

(54) Title: TREATMENT METHOD

(57) Abstract: The present invention is directed to methods of treating disorders of ocular angiogenesis or vascular leakage in a patient by administration of suitable inhibitors, including pazopanib or pharmaceutically acceptable salts or hydrates thereof.



WO 2011/085007 A1

13398, Research Triangle Park, North Carolina 27709 (US).

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

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

Published:

— *with international search report (Art. 21(3))*

TREATMENT METHOD

FIELD OF THE INVENTION

The present invention relates to methods of treating disorders of ocular angiogenesis or vascular leakage in a mammal. The methods comprise administering pyrimidine derivatives, benzodiazepinyl derivatives, and pharmaceutical compositions containing the same.

BACKGROUND OF THE INVENTION

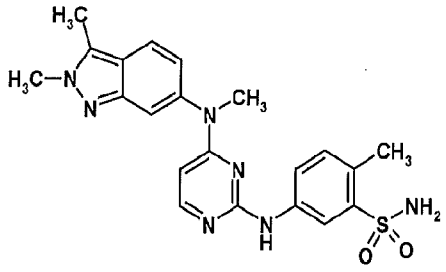
Neovascularization, also called angiogenesis, is the process of forming new blood vessels. Neovascularization occurs during normal development, and also plays an important role in wound healing following injury to a tissue. However, neovascularization has also been implicated as an important cause of a number of pathological states including, for example, cancer, rheumatoid arthritis, atherosclerosis, psoriasis, and diseases of the eye.

An eye disorder in which neovascularization plays a role is age-related macular degeneration (AMD), which is the major cause of severe visual loss in the elderly. The vision loss in AMD results from choroidal neovascularization (CNV). The neovascularization originates from choroidal blood vessels and grows through Bruch's membrane, usually at multiple sites, into the sub-retinal pigmented epithelial space and/or the retina (see, for example, Campochiaro *et al.* (1999) *Mol. Vis.* 5:34). Leakage and bleeding from these new blood vessels results in vision loss.

SUMMARY OF THE INVENTION

In an aspect of the present invention, a method of treating a disorder of ocular angiogenesis or vascular leakage in a patient suffering from such condition includes orally administering to the patient between 1 and 50 mg of a suitable inhibitor.

In another aspect of the present invention, a method of treating a disorder of ocular angiogenesis or vascular leakage in a patient suffering from such condition includes orally administering to the patient between 1 and 50 mg of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or hydrate thereof.

In still another aspect according to the present invention, the use of a suitable inhibitor in the manufacture of a medicament containing between 1 and 50 mg of the suitable inhibitor for the treatment of a disorder of ocular angiogenesis or vascular leakage in a patient in need thereof is provided.

In yet another aspect according to the present invention, there is provided between 1 and 50 mg of a suitable inhibitor for use in the treatment of a disorder of ocular angiogenesis or vascular leakage in a patient in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A illustrates representative fluorescein angiograms with a pazopanib-induced change of the CNV leakage in experimental CNV;

Figure 1B illustrates analysis of fluorescein leakage areas for treatment with vehicle and pazopanib. Changes were determined using digital image analysis (*** $p < .005$);

Figure 2A illustrates representative light micrographs of hematoxylin and eosin-stained areas comprising neovascular lesions (encircled) on post-laser day 14;

Figure 2B illustrates averaged lesion areas from eyes treated with the vehicle or pazopanib (*** $p < .005$; $n = 6$);

Figure 2C illustrates averaged lesion areas from eyes when the fellow eye was treated with the vehicle of pazopanib;

Figure 3A illustrates single dose plasma kinetics in Brown Norway rats (composite data from $n = 3$ rats per point); and

Figure 3B illustrates plasma and eye cup (sclera/ choroid/ retina) pazopanib content 5 hours after the third eye drop administered over 24 hours. OS – left treated eye, OD – fellow non-treated eye ($n = 3$ rats per point);

DETAILED DESCRIPTION OF THE INVENTION

The invention provides methods for treating a disorder of ocular angiogenesis or vascular leakage, such as age-related macular degeneration. As used herein, "treatment" means any manner in which one or more symptoms associated with the disorder are beneficially altered. Accordingly, the term includes healing or amelioration of a symptom or side effect of the disorder or a decrease in the rate of advancement of the disorder.

As used herein, the term "suitable inhibitor" means an inhibitor that inhibits one or more of the following receptors: VEGFR1, VEGFR2, VEGFR3, PDGFRalpha, PDGFRbeta, c-kit, and/or FGFR.

As used herein, the term "therapeutically effective amount" means the amount of a therapeutic agent that is sufficient to treat, prevent and/or ameliorate one or more symptoms of the disorder.

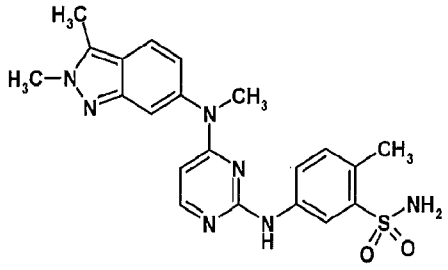
According to embodiments of the present invention, a method of treating a disorder of ocular angiogenesis or vascular leakage in a patient suffering from such condition includes orally administering to the patient between 1 and 50 mg of a suitable inhibitor.

The suitable inhibitor can be various inhibitors that inhibit one or more of the following receptors: VEGFR1, VEGFR2, VEGFR3, PDGFRalpha, PDGFRbeta, c-kit, and/or FGFR including, but not limited to: a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof, a compound of formula (I') or a hydrate thereof, a complex of formula (I''), a compound of formula (II) or a pharmaceutically acceptable salt thereof, apatinib, sunitinib, sorafenib, bivanib, midostaurin (PKC412) (an inhibitor of FLT3, c-KIT, VEGFR-2, PDGFR and multiple isoforms of the serine/threonine protein kinase C (PkC), under development by Novartis), E-7050 (a C-met and VEGFR tyrosine kinase inhibitor, under development by Eisai), XL-184 a spectrum-selective kinase inhibitor that inhibits Met, Ret and VEGFR2, under development by Exelixis), XL-647 (an orally-available tyrosine kinase inhibitor under development by Exelixis that inhibits EGFR, HER2, VEGFR and EphB4), cediranib, linifanib, motesanib, RAF-265 (formerly CHIR-265) a B-Raf and VEGFR kinase inhibitor, under development by Novartis), tivozanib, TAK-593 (a VEGFR/PDGFR tyrosine kinase inhibitor, under development by Millennium (Takeda)), ARQ-197 (an ATP-independent inhibitor of c-Met under development by ArQule (Cyclis Pharmaceuticals before the acquisition)), OSI-930 (a c-kit and VEGFR-2 tyrosine kinase inhibitor under development by OSI Pharmaceuticals), DCC-2036 (a Bcr-abl inhibitor inhibits that also inhibits the Src-like kinases LYN, HCK and

FGR, as well as the TIE2 and KDR kinases, under development by Deciphera Pharmaceuticals), MGCD-265 (an inhibitor of c-Met, VEGFR1, VEGFR2, VEGFR3, Tie-2 and Ron tyrosine receptor kinases, under development by MethylGene, in collaboration with ChemBridge Research Laboratories, CA, the US), PF-337210 (an inhibitor of VEGFR2, under development of Pfizer), BIBF-1120 (a VEGFR-2, PDGF and FGF kinase inhibitor, which also inhibits the src, lck and lyn tyrosine kinases, under development by Boehringer Ingelheim), ENMD-2076 (a kinase inhibitor that selectively targets aurora kinase A vs B, and also inhibits Flt3, c-kit, CSF1R and KDR (VEGFR2) as well as VEGFR3, PDGFR-alpha, FGFR1, FGFR2, EphA1 and src, under development by EntreMed), TG-100-801 (a VEGFR, Src, Yes, Lck, Lyn kinases and PDGFR-ß inhibitor, under development by TargeGen), BMS-690514 (an inhibitor of EGFR, HER2, ErbB4 and VEGFR1-3, under development by Bristol-Myers Squibb), SSR-106462 (a TIE-2 inhibitor and VEGFR-2 tyrosine kinase inhibitor, under development by Sanofi-Aventis), BAY-73-4506 (a VEGFR, KIT, RET, FGFR and PDGFR kinase inhibitor, under development by Bayer), plitidepsin, axitinib, vandetinib, and nilotinib. The suitable inhibitors may be in the form of pharmaceutically acceptable salts and, in some cases, in the form of pharmaceutically acceptable solvates to the extent that such suitable inhibitors have been described in the art as being in a solvated form.

In some embodiments, the suitable inhibitor is pazopanib or a pharmaceutically acceptable salt or solvate thereof, such as a compound of formulae (I) or a pharmaceutically acceptable solvate thereof, a compound of formula (I') or a solvate thereof, or a complex of formula (I''). In other embodiments, the suitable inhibitor is a compound of formula (II) or a pharmaceutically acceptable salt thereof. In still other embodiments, the suitable inhibitor is sorafenib or a pharmaceutically acceptable salt thereof, such as the tosylate salt. In still other embodiments, the suitable inhibitor is sunitinib or a pharmaceutically acceptable salt thereof, such as the malate salt.

According to embodiments of the present invention, a method of treating a disorder of ocular angiogenesis or vascular leakage in a patient suffering from such condition includes orally administering to the patient between 1 and 50 mg of a compound of formula (I):

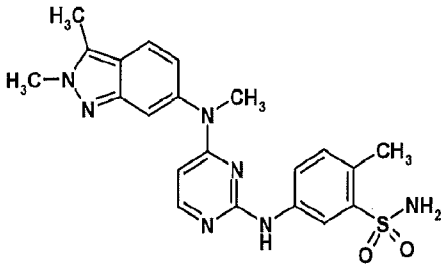


(I)

or a pharmaceutically acceptable salts or hydrates thereof.

The compound of formula (I) has the chemical name 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide and the generic name pazopanib.

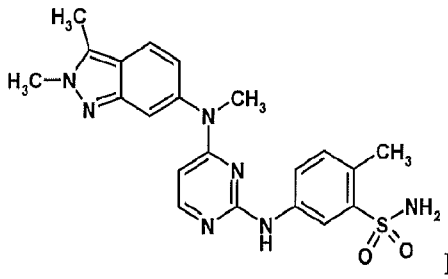
In certain embodiments, the salt of the compound of formula (I) is a hydrochloride salt. In a particular embodiment, the salt of the compound of formula (I) is a monohydrochloride salt as illustrated by formula (I'). The monohydrochloride salt of the compound of formula (I) has the chemical name 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride.



HCl

(I')

In other embodiments, the salt of the compound of formula (I) is a monohydrochloride monohydrate solvate of the compound of formula (I). The monohydrochloride monohydrate solvate of the compound of formula (I) has the chemical name 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methylbenzenesulfonamide monohydrochloride monohydrate, as illustrated in formula (I'').

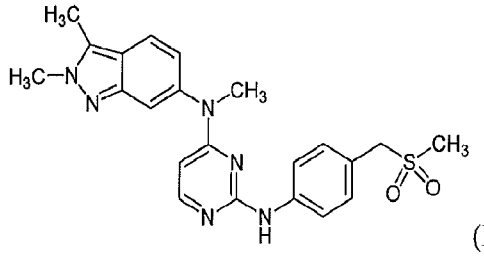


$HCl \cdot H_2O$

(I")

The free base, salts and hydrates of the compound of formula (I) may be prepared, for example, according to the procedures of International Patent Application No. PCT/US01/49367 filed December 19, 2001, and published as WO 02/059110 on August 1, 2002, and International Patent Application No. PCT/US03/19211 filed June 17, 2003, and published as WO 03/106416 on December 24, 2003.

According to embodiments of the present invention, a method of treating a disorder of ocular angiogenesis or vascular leakage in a patient suffering from such condition includes orally administering to the patient between 1 and 50 mg of a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof. The free base and salts of the compound of formula (II) may be prepared, for example, according to the procedures of International Patent Application No. PCT/US01/49367 filed December 19, 2001, and published as WO 02/059110 on August 1, 2002, and International Patent Application No. PCT/US03/19211 filed June 17, 2003, and published as WO 03/106416 on December 24, 2003.

As used herein, the term "pharmaceutically acceptable salts" may comprise acid addition salts derived from a nitrogen on a substituent in the compound of formula (I). Representative salts include the following salts: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate,

mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, trimethylammonium and valerate.

In embodiments of methods according to the invention, the disorder of ocular angiogenesis or vascular leakage can be edema or neovascularization for any occlusive or inflammatory retinal vascular disease, such as rubeosis irides, neovascular glaucoma, pterygium, vascularized glaucoma filtering blebs, conjunctival papilloma; choroidal neovascularization, such as neovascular age-related macular degeneration (AMD), myopia, prior uveitis, trauma, or idiopathic; macular edema, such as post surgical macular edema, macular edema secondary to uveitis including retinal and/or choroidal inflammation, macular edema secondary to diabetes, and macular edema secondary to retinovascular occlusive disease (i.e. branch and central retinal vein occlusion); retinal neovascularization due to diabetes, such as retinal vein occlusion, uveitis, ocular ischemic syndrome from carotid artery disease, ophthalmic or retinal artery occlusion, sickle cell retinopathy, other ischemic or occlusive neovascular retinopathies, retinopathy of prematurity, or Eale's Disease; and genetic disorders, such as VonHippel-Lindau syndrome.

In one embodiment, the neovascular age-related macular degeneration is wet age-related macular degeneration. In another embodiment, the neovascular age-related macular degeneration is dry age-related macular degeneration and the patient is characterized as being at increased risk of developing wet age-related macular degeneration.

While it is possible that the suitable inhibitor may be administered as the raw chemical, it is also possible to present the active ingredient as a pharmaceutical composition. Accordingly, embodiments of the invention further provide pharmaceutical compositions, which include therapeutically effective amounts of the suitable inhibitor, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The suitable inhibitor is as described above. In one embodiment, the suitable inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof. In another embodiment, the suitable inhibitor is a compound of formula (I') or a hydrate thereof. In still another embodiment, the suitable inhibitor is a complex of formula (I''). In yet another embodiment, the suitable inhibitor is a compound of formula (II) or a pharmaceutically acceptable salt thereof. In still other embodiments, the

suitable inhibitor is sorafenib or a pharmaceutically acceptable salt thereof, such as the tosylate salt. In still other embodiments, the suitable inhibitor is sunitinib or a pharmaceutically acceptable salt thereof, such as the malate salt. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing the suitable inhibitor with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. In certain embodiments, the unit dosage formulations are those containing a dose to be administered as frequently as daily or sub-dose or an appropriate fraction thereof of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for oral administration. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or

sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor

additives such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The suitable inhibitor can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The suitable inhibitor may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide–phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

According to the methods of the invention, a suitable inhibitor is administered or prescribed to a patient. The amount of administered or prescribed compound will depend upon a number of factors including, for example, the age and weight of the patient, the precise condition requiring treatment, the severity of the condition, and the nature of the formulation. Ultimately, the amount will be at the discretion of the attendant physician.

In some embodiments of the methods of the invention, the total amount of the suitable inhibitor administered or prescribed to be administered as frequently as daily can be from a lower limit of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg to an upper limit of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 mg. The suitable inhibitor

is as described above. In one embodiment, the suitable inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof. In another embodiment, the suitable inhibitor is a compound of formula (I') or a hydrate thereof. In still another embodiment, the suitable inhibitor is a complex of formula (I''). In yet another embodiment, the suitable inhibitor is a compound of formula (II) or a pharmaceutically acceptable salt thereof. In still other embodiments, the suitable inhibitor is sorafenib or a pharmaceutically acceptable salt thereof, such as the tosylate salt. In still other embodiments, the suitable inhibitor is sunitinib or a pharmaceutically acceptable salt thereof, such as the malate salt.

The methods of the present invention may also be employed in combination with other methods for the treatment of ocular neovascular disorders. In some embodiments, the methods of the invention encompass a combination therapy in which a suitable inhibitor is administered in conjunction with one or more additional therapeutic agents for the treatment of neovascular disorders, which therapeutic agents can, themselves be suitable inhibitors as described herein. In one embodiment, a suitable inhibitor used in the combination is a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof. In another embodiment, a suitable inhibitor used in the combination is a compound of formula (I') or a hydrate thereof. In still another embodiment, a suitable inhibitor used in the combination is a complex of formula (I''). In yet another embodiment, a suitable inhibitor used in the combination is a compound of formula (II) or a pharmaceutically acceptable salt thereof. In still another embodiment, a suitable inhibitor used in the combination is sorafenib or a pharmaceutically acceptable salt thereof, such as the tosylate salt. In still another embodiment, a suitable inhibitor used in the combination is sunitinib or a pharmaceutically acceptable salt thereof, such as the malate salt. Non-limiting examples of additional therapeutic agents that may be used in a combination therapy include pegaptanib, ranibizumab, bevacizumab, midostaurin, nepafenac, integrin receptor antagonists (including vitronectin receptor agonists), and any of the various suitable inhibitors described herein. See, for example, Takahashi *et al.* (2003) *Invest. Ophthalmol. Vis. Sci.* 44: 409-15, Campochiaro *et al.* (2004) *Invest. Ophthalmol. Vis. Sci.* 45:922-31, van Wijngaarden *et al.* (2005) *JAMA* 293:1509-13, U.S. Patent No. 6,825,188 to Callahan *et al.*, and U.S. Patent No. 6,881,736 to Manley *et al.*; each of which is herein incorporated by reference for their teachings regarding these compounds.

Where a combination therapy is employed, the therapeutic agents may be administered together or separately. The same means for administration may be used for more than one

therapeutic agent of the combination therapy; alternatively, different therapeutic agents of the combination therapy may be administered by different means. When the therapeutic agents are administered separately, they may be administered simultaneously or sequentially in any order, both close and remote in time. The amounts of the suitable inhibitor and/or the other pharmaceutically active agent or agents and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way.

EXAMPLES

The free base, salts and hydrates of pazopanib used in these examples may be prepared, for example, according to the procedures of International Patent Application No. PCT/US01/49367 filed December 19, 2001, and published as WO 02/059110 on August 1, 2002, and International Patent Application No. PCT/US03/19211 filed June 17, 2003, and published as WO 03/106416 on December 24, 2003.

Biological Data:

Reagents

Topical eye drops were formulated in a buffered 7% cyclodextrin solution containing 5 mg/ ml pazopanib. Sodium fluorescein (10% w/v) was purchased from Alcon (Alcon Pharma, Freiburg, Germany). Endothelial cell basal medium (EBM) and endothelial cell growth medium (EGM) were obtained from Lonza, Verviers, Belgium. Hank`s balanced salt solution (HBSS) and Ham`s-F10 were from Invitrogen (Karlsruhe, Germany). All other chemicals were reagent-grade products obtained commercially from Sigma (Taufkirchen, Germany).

Animals and anaesthesia

Male Brown Norway rats (10-12 weeks of age, male and female weighing 170 to 360 g) were used throughout this study. The animals were treated according to ARVO Statement on the use of animals in ophthalmic and vision research, and all animal experiments were reviewed and approved by municipal and University Hospital animal care committees in Leipzig. The rats were anesthetized with intraperitoneal ketamine (100 mg/ kg; Ratiopharm, Ulm, Germany) and

xylazine (BayerVital, Leverkusen, Germany; 10 mg/ kg). Topical application of tropicamide (5 mg/ ml) and phenylephrine hydrochloride (Ankerpharm, Rudolstadt, Germany; 50 mg/ ml) were instilled for mydriasis during laser photocoagulation and fluorescein angiography. Fourteen days after laser injury, rats were humanely euthanized using overdoses of carbon dioxide.

Induction of CNV in rats and treatment with pazopanib

Animals were treated using laser photocoagulation-induced rupture of Bruch's membrane using a 545 nm dye laser (Coherent Argon Dye Laser #920, Coherent Medical Laser, Palo Alto, CA) attached to a slit lamp (Carl Zeiss, Oberkochen, Germany). A contact lens was used to retain corneal clarity through photocoagulation. The laser spots were placed separately using the following settings: 50-µm diameter, 0.1 second duration, and 180-mW intensity. To rupture Bruch's membrane, four to seven laser spots were applied between the major retinal vessels close to the optic disc. Pazopanib (approximately 30 µl of a 5 mg/ ml sterile-filtered solution) was administered twice daily. Animals of the control group received a vehicle only.

Fluorescence angiography in experimental CNV

Aiming to document treatment of CNV in its early stage, a treatment schedule was used as follows. Laser photocoagulation was carried out as described above, and pazopanib was applied twice a day topically from post laser day 6 until study end on post laser day 14. Coagulated lesions were first documented by angiography on day 7 post laser, and only rats with ocular CNV were included in the analysis. Sodium fluorescein was injected into tail vein of the anesthetized rats and fluorescein angiograms were obtained by means of a fundus camera (FD-31A, Topcon, Tokyo, Japan). On day 14, rats underwent a second angiography. Angiograms taken 100 to 140 seconds after injection were converted to digital images, and areas of fluorescein leakage with intensity as high as in major vessels were quantified in a masked fashion BY two of us (YY; XMY) using a computer software (NIH image, Research Service Branch, Bethesda, MD). Differences in fluorescence were calculated by the following formula: Area of fluorescein leakage on day 14 x 100% / area of fluorescein leakage on day 7.

Histology and immunohistochemistry

After the rats were euthanized on day 14, eyes were immediately dissected and fixed with 4% paraformaldehyde (dissolved in PBS). Five minutes later, the eyes were perforated at

the equator and left overnight at 4°C in the same solution. Subsequently, the eyes were divided into anterior and posterior segments with total removal of lens and vitreous body. Serial six-micrometer sections were prepared and either stained with hematoxylin and eosin (HE) or processed for immunohistochemistry. HE-stained sections were examined at 200 x magnification using a light microscope (Axioplan 2; Carl Zeiss Meditec, Jena, Germany) and a digital color camera (AxioCam MRc5; Carl Zeiss Meditec). The maximal area of CNV complexes was estimated indirectly, by measuring the difference between the thickness from the outer border of the pigmented choroidal layer to the top of the CNV complex and the thickness of the intact, pigmented choroids adjacent to the lesion. Three to five serial sections from each CNV membrane were measured, and the highest value (representing the top of a given CNV complex) was stored. Digitized images were analyzed and measured with the concomitant image-analysis software (Axiovision; Carl Zeiss). Each lesion was encircled manually, and their area (in μm^2) was calculated by the program.

Additionally, some sections were stained with a polyclonal goat anti-rat VEGF antibody (R&D Systems). Briefly, sections were washed using PBS-TD (PBS/ 1% dimethyl sulfoxide/ 0.3% Triton X-100) followed by quenching endogenous peroxidase activity in PBS/ 0.3% H_2O_2 for 5 min followed by washing in PBS. Subsequently, sections were blocked with PBS-TD/ 10% rabbit normal serum at 37°C for 1 h and incubated with anti-VEGF (5 µg/ ml in PBS/ 2% BSA) overnight. In negative control sections, the primary antibody was replaced by normal goat immunoglobulin (Ig) G. After washing three times with PBS-TD, the slices were incubated at room temperature with horseradish peroxidase-conjugated rabbit anti-goat IgG (Dianova, Hamburg, Germany; diluted 1:1000 in PBS/ 2% BSA) for 2 h. A buffered solution of 3,3'-diaminobenzidine (Vector Laboratories, Burlingame, CA) was used as a chromogen together with H_2O_2 in order to detect peroxidase activity. Sections were counterstained with Meyer's hematoxylin, washed in PBS and water and mounted. All slides were examined using a Zeiss Axioskop microscope equipped with a digital camera.

Ocular tissue drug concentration procedures

Female Norway Brown rats were used during these studies. Rats were purchased from Charles River (Portage, MI). In two independent studies, Norway Brown rats received 30 µl pazopanib eye drops (5 mg/ ml in buffered 7% cyclodextrin) for either 24 hours (3 total drops given every 8-12 hours), once daily for 5 days, or twice daily for 14 days.

Tissue collection procedures

Rats were euthanized by CO_2 inhalation before enucleation and collection of plasma samples. Samples were frozen immediately over dry ice after collection and then stored at -80°C. The ocular tissues were processed through a dissection-pulverization-drug extraction process. Frozen eye sectioning was performed by the following steps. The preparation of rat eye cups was done by removing the anterior portion of the eye with a razor blade followed by removal of the lens and frozen vitreous with forceps. A sagittal section was made in the eye cup before collection of the retina/choroid tissue by scraping the exposed sclera with the round end of a spatula until the pigmented tissue was completely removed from the scleral tissue. The collected tissues were pulverized under liquid nitrogen. Frozen tissue was carefully placed in a liquid nitrogen primed BioPulverizer (Biospec Products Inc, Bartlesville, OK). Following pulverization the tissue powder was removed from the pulverizer and transferred into a polypropylene tube. Extraction buffer (50% methanol/ 50% 0.5 M HCl) was added to tissue powder followed by two cycles of sonication, centrifugation, and supernatant collection. Tissue homogenate supernatant was pooled and frozen on dry ice then stored at -80°C until drug analysis. The extraction efficacy of this methodology was assumed to be 100% for calculation purposes.

Drug analysis

Plasma samples and eye tissue extracts were analyzed for pazopanib using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis. Using 50 µl aliquot of plasma and eye tissue extract, the lower limit of quantification of pazopanib was 1 ng/ ml for plasma and 10 ng/ ml for eye tissue extract. The higher limit of quantification was 500 ng/ ml for plasma and 5000 ng/ ml for eye tissue extracts. The computer systems that were used on these studies to acquire and quantify data included Analyst Version 1.4.1 and SMS2000 Version 1.6. Plasma sample concentrations were expressed as ng pazopanib/ ml. Tissue concentrations were determined by the following formula: Pazopanib ng/ g tissue = ([concentration in supernatant ng/ ml * extract volume ml]/ tissue weight g).

Statistical analysis

Results are expressed as means ± standard deviation (SD) if not indicated otherwise. Statistical comparisons were performed using ANOVA and significant differences were judged at $p < .05$ to reject the null hypothesis.

Results

Pazopanib suppresses development of CNV in a rat model of CNV

To determine whether pazopanib affects experimental CNV *in vivo* neovascularisation was induced in eyes of rats by subjecting the Bruch's membrane to a laser-induced rupture. This methodology has been commonly applied in experimental studies of neovascular AMD and allows predictions to be made on drug efficacy in humans. In particular, VEGF expression becomes upregulated and effects of VEGFR as well as PDGFR tyrosine kinase receptors can be well predicted since suchlike antagonists inhibit CNV. See, Yi X, Ogata N, Komada M, Yamamoto C, Takahashi K, Omori K, Uyama M. Vascular endothelial growth factor expression in choroidal neovascularization in rats. *Graefe's Arch Clin Exp Ophthalmol.* 1997;235:313-319; Shen WY, Yu MJ, Barry CJ, Constable IJ, Rakoczy PE. Expression of cell adhesion molecules and vascular endothelial growth factor in experimental choroidal neovascularisation in the rat. *Br J Ophthalmol.* 1998;82:1063-1071; Kwak N, Okamoto N, Wood JM, Campochiaro PA. VEGF is major stimulator in model of choroidal neovascularization. *Invest Ophthalmol Vis Sci.* 2000;41:3158-3164.

When areas of vessel leakage were followed up by fluorescence angiography from post laser days 7 to 14, topically administered pazopanib significantly reduced development of CNV lesions. In contrast, leakage of CNV lesions continued to progress in eyes of the control group treated with the vehicle (**Fig. 1A**; $p < .001$). In **Figure 1A**, panels a and c demonstrate leakage of fluorescein in the photocoagulated lesions seven days following laser injury. Topical application of pazopanib significantly reduced the progression of CNV leakage by postlaser day 14 (represented by panels b), compared to eyes of the vehicle control group (represented by panels d and c). Sites of laser injury are indicated with arrows.

Specifically, when the eyes were treated with the drug, the area of fluorescein leakage revealed non-significant changes to 111.41 ± 21.34% (mean ± SD, baseline lesion size normalized to 100% at day 7), whereas control eyes developed an increase up to 208.5 ± 51.51%

(Fig. 1B). These results indicated that a twice-daily topical administration of pazopanib inhibited further lesion development by > 89%. Remarkably, applying pazopanib topically to the fellow (contralateral) eye also significantly inhibited lesion size progression in these studies. Thus, in lesioned eyes whose fellow eye was pazopanib-treated, CNV demonstrated only a marginal increase to 115.24 ± 16.72% of baseline (**Fig. 1B**).

Additionally, histological retinal sections were analyzed on day 14 after laser treatment using staining with hematoxylin and eosin or immunohistochemistry. **Figures 2A and B** demonstrate that CNV lesions in vehicle-treated eyes (**Fig. 2A**, panels **b** and **c**) were larger than those treated topically with pazopanib. Figure 2A shows choroid/ retinal sections derived from eyes without laser treatment (a) and from the lasered eyes (b–d) which either were treated topically with pazopanib (b) or vehicle (d: control group). Note reduction of CNV lesions when the contralateral eye was treated (c). Assessing the extent of CNV by measuring the relative thickness of the CNV membrane in the lesions revealed a significant difference. While the lesion area in vehicle-treated eyes was 27,397.3 ± 7,386.4 μm^2 the area in eyes treated with pazopanib amounted to 7,760.3 ± 2,312.0 μm^2. Thus a significant 71.7% inhibition in lesion size compared to vehicle control ($p < .001$) (**Fig. 2B**) was noted. Neovascular areas were measured by quantitative digital image analysis. In another study, lasered eyes from rats treated topically with pazopanib in the fellow eye demonstrated a ~34% inhibition in lesion size (**Fig. 2C**). The histology data together with the data obtained by fluorescence angiography (see above) point to a systemic effect produced by the drug in the fellow eye, which implies that a low oral dose that is able to achieve a similar systemic effect should be effective in treating CNV and, thus, disorders of ocular angiogenesis or vascular leakage such as those described above.

Topical administration of pazopanib results in detectable drug in the plasma of Norway Brown rats. After administration of a single 30 µl eye drop, peak levels of pazopanib were measured 60 minutes later in the 300 ng/ ml range (**Fig. 3A**). Plasma levels declined to undetectable levels after 24 hours. Topical administration of single 30 µl drops to the left eye (OS) only, three times over a 24 hour period, resulted in a mean of 503 ng/ g pazopanib in the treated eye cup tissues (sclera, choroid, and retina). Interestingly, detectable levels were also observed in the fellow (OD) eye (mean = 159 ng/ g) although at a statistically lower amount (**Fig. 3B**).

Examination of Occular Tissue Distribution and Systemic Concentrations of Pazopanib

The ocular tissue distribution and systemic concentrations of radioactivity were assessed following topical ocular administration of pazopanib to Dutch belted (pigmented) rabbits. A single 60-μL at a target dose of 0.3 mg/dose (30 μCi/dose) was administered to the right eye. Blood and ocular tissues from both the dosed and non-dosed (left) eye were collected from one animal at each of eight sampling times up to 24 h, and analyzed for total radioactivity.

The levels of radioactivity were quantifiable in all blood and plasma samples from earliest sampling time (0.25 h) to the last sampling time (24 h) with the highest concentrations observed at 1 h in blood (11.3 ng eq/g) and at 2 h in plasma (12.8 ng eq/g).

Choroid levels reached (40.6 ng eq/g) at 2 h and peaked at (60.1 ng eq/g) at 8 h. Similarly retina levels reached (9.17 ng eq/g) at 2 h and peaked at (10.2 ng eq/g) at 4 h. This shows that more than half of the maximum levels in the CNV target tissues were reached within the first 2 hours after eye drop administration. Based on Stokes Einstein equation for the diffusion of a small molecule in water, it is estimated that in the best case scenario pazopanib would have diffused via local drug diffusion at most 0.4 cm in 2 hours which is much less than the size of the rabbit eye (approximately 1-2 cm). Without a systemic contribution, local drug diffusion could not explain the speed at which pazopanib reached the retina and the choroid.

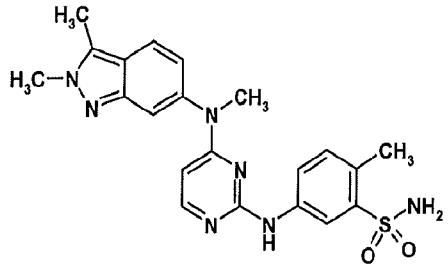
The results obtained in this study provide evidence that the systemic delivery route provides an important contribution to the retina and choroid tissue levels. In addition it shows that any efficacy seen in the untreated eye would come mainly from low level systemically delivered drug.

Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present invention and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.

CLAIMS

What is claimed is:

1. A method of treating a disorder of ocular angiogenesis or vascular leakage in a patient suffering from such condition comprising orally administering to the patient between 1 and 50 mg of a compound of formula (I):



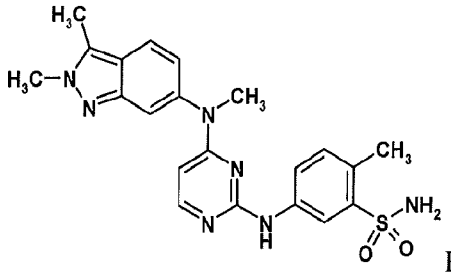
(I)

or a pharmaceutically acceptable salt or hydrate thereof.

2. The method according to claim 1, comprising administering between 1 and 20 mg of a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof.

3. The method according to claim 1, comprising administering between 5 and 15 mg of a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof.

4. The method according to any one of claims 1-3, wherein the compound is a compound of formula (I'):

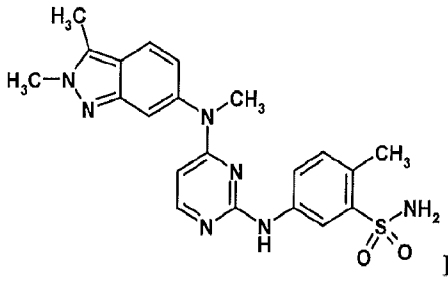


HCl

(I')

or a hydrate thereof.

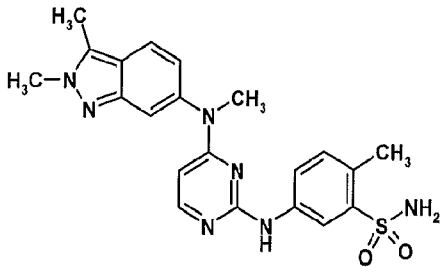
5. The method according to any one of claims 1-3, wherein the compound is a compound of formula (I''):



$HCl \cdot H_2O$

(I").

6. A method of treating neovascular age-related macular degeneration in a patient suffering from such condition comprising orally administering to the patient between 1 and 50 mg of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or hydrate thereof.

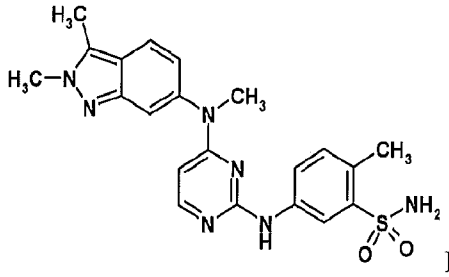
7. The method according to claim 6, comprising administering between 1 and 20 mg of a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof.

8. The method according to claim 6, comprising administering between 5 and 15 mg of a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof.

9. The method according to any one of claims 6-8, wherein the neovascular age-related macular degeneration is wet age-related macular degeneration.

10. The method according to any one of claims 6-8, wherein the neovascular age-related macular degeneration is dry age-related macular degeneration and the patient is characterized as being at increased risk of developing wet age-related macular degeneration.

11. The method according to any one of claims 6-10, wherein the compound is a compound of formula (I'):

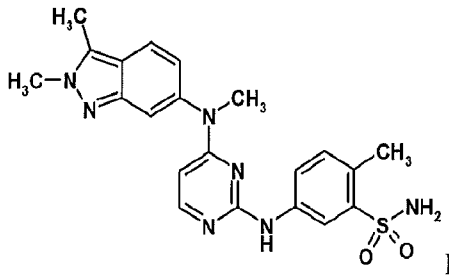


HCl

(I')

or a hydrate thereof.

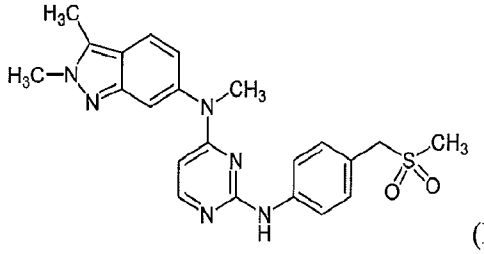
12. The method according to any one of claims 6-10, wherein the compound is a complex of formula (I''):



$HCl \cdot H_2O$

(I'').

13. A method of treating a disorder of ocular angiogenesis or vascular leakage in a patient suffering from such condition comprising orally administering to the patient between 1 and 50 mg of a compound of formula (II):



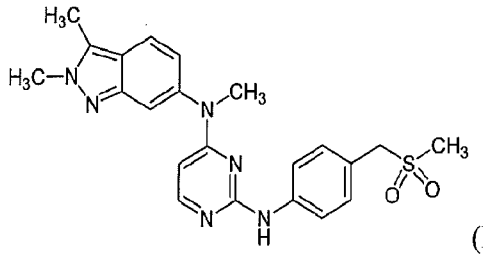
(II)

or a pharmaceutically acceptable salt thereof.

14. The method according to claim 13, comprising administering between 1 and 20 mg of a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof.

15. The method according to claim 13, comprising administering between 5 and 15 mg of a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof.

16. A method of treating neovascular age-related macular degeneration in a patient suffering from such condition comprising orally administering to the patient between 1 and 50 mg of a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

17. The method according to claim 16, comprising administering between 1 and 20 mg of a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof.

18. The method according to claim 16, comprising administering between 5 and 15 mg of a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof.

19. The method according to any one of claims 16-18, wherein the neovascular age-related macular degeneration is wet age-related macular degeneration.

20. The method according to any one of claims 16-18, wherein the neovascular age-related macular degeneration is dry age-related macular degeneration and the patient is characterized as being at increased risk of developing wet age-related macular degeneration.

21. A method of treating a disorder of ocular angiogenesis or vascular leakage in a patient suffering from such condition, said method comprising orally administering to the patient between 1 and 50 mg of a suitable inhibitor, or pharmaceutically acceptable salt thereof.

22. The method according to claim 21, wherein the suitable inhibitor is sorafenib tosylate.

23. The method according to claim 21, wherein the suitable inhibitor is sunitinib malate.

24. The method according to any one of claims 21-23, comprising administering between 1 and 20 mg of the suitable inhibitor or a pharmaceutically acceptable salt thereof.

25. The method according to any one of claims 21-23, comprising administering between 5 and 15 mg of the suitable inhibitor or a pharmaceutically acceptable salt thereof.

26. The method according to any one of claims 21-25, wherein the disorder of ocular angiogenesis or vascular leakage is neovascular age-related macular degeneration.

27. The method according to claim 26, where the neovascular age-related macular degeneration is wet age-related macular degeneration.

28. The method according to claim 26, wherein the neovascular age-related macular degeneration is dry age-related macular degeneration and the patient is characterized as being at increased risk of developing wet age-related macular degeneration.

FIGURE 1

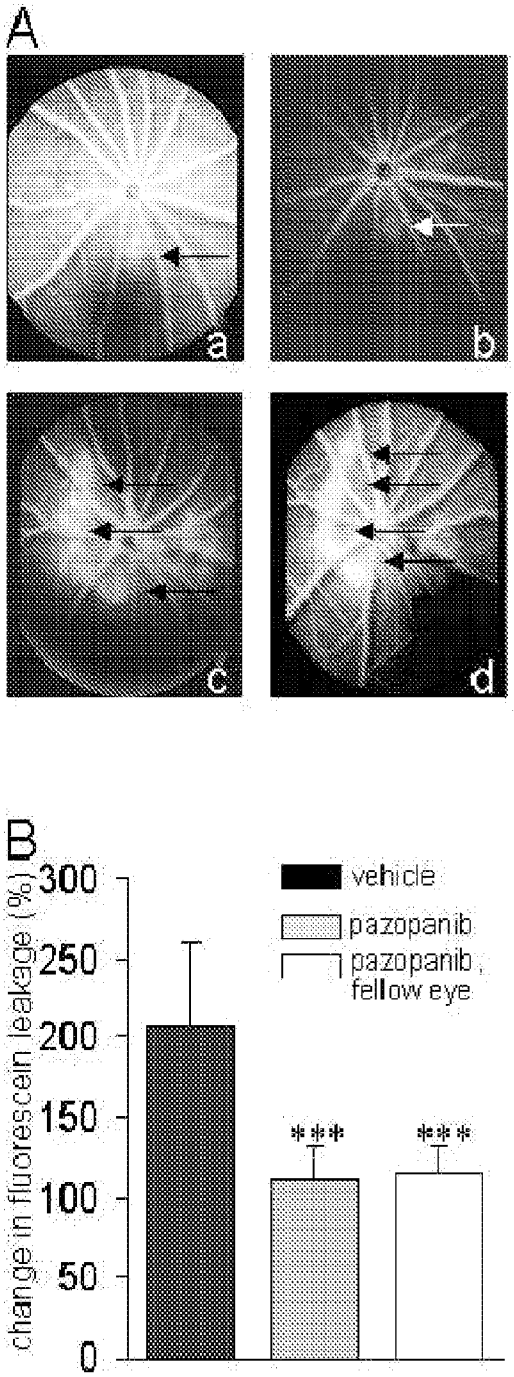

A
a
b
c
d
B
change in fluorescein leakage (%)
300
250
200
150
100
50
0
vehicle
pazopanib
pazopanib, fellow eye
***
***

FIGURE 2

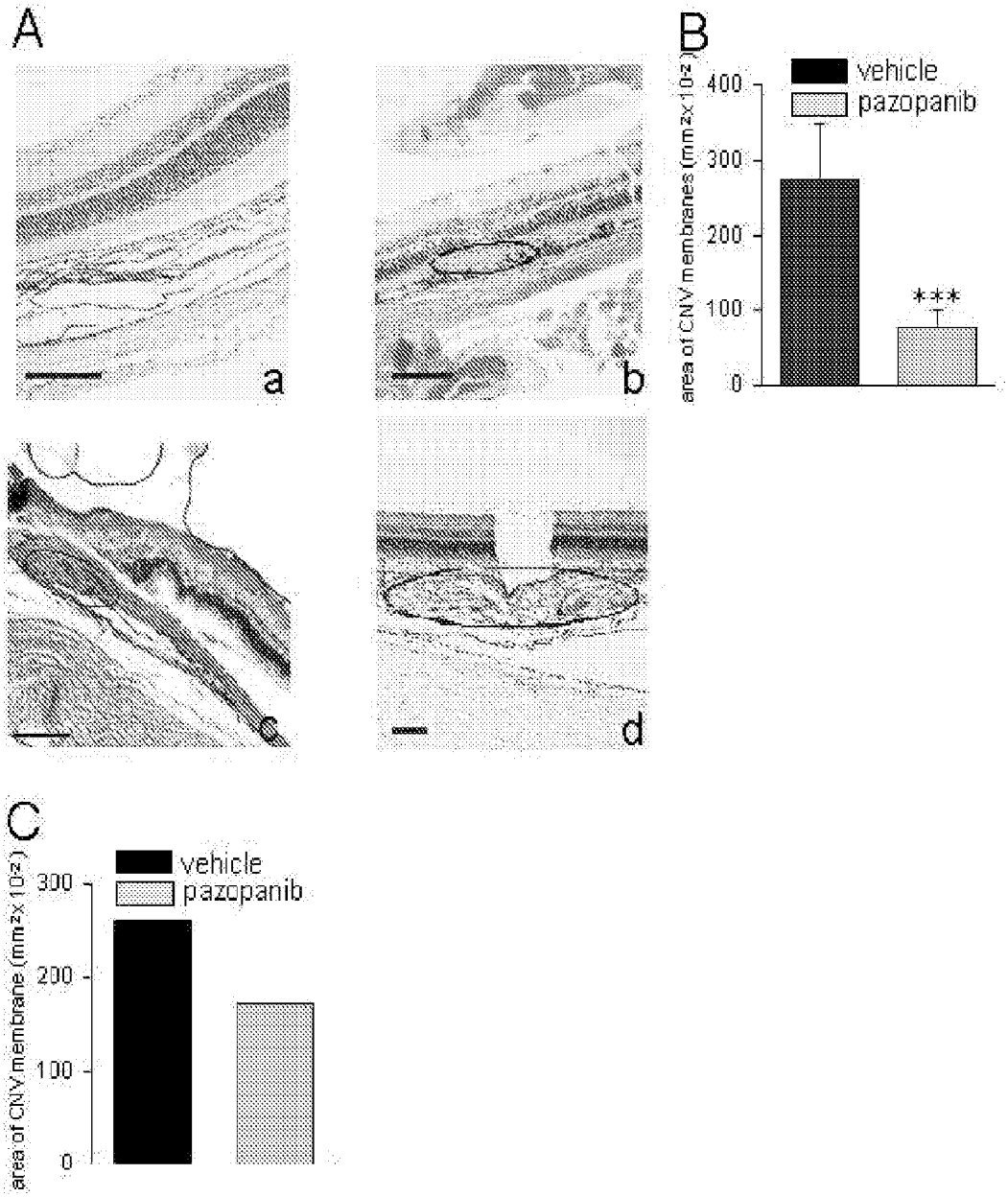
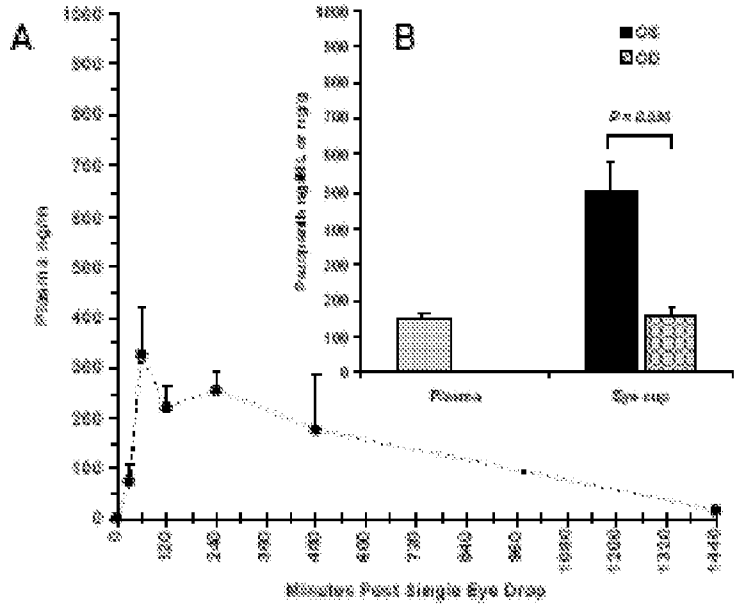

A
a
b
c
d
B
vehicle
pazopanib
area of CNV membranes (mm2x10-2)
400
300
200
100
0
***
C
vehicle
pazopanib
area of CNV membrane (mm2x10-2)
300
200
100
0

FIGURE 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/20231

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/52 (2011.01)
USPC - 514/263.22
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)
IPC(8)- A61K 31/52 (2011.01);
USPC- 514/263.22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/117, 600, 601, 210.14;
Patents and NPL

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (US Pat, PgPub, EPO, JPO: classification, keyword; search terms below), GoogleScholar;
search terms: pazopanib, votrient, benzene sulfonamide, angiogenesis, occular, vascular, leakage, macular, degeneration, sorafenib, sunitinib, tosylate, malate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2008/0293691 A1 (BRIGANDI et al.) 27 November 2008 (27.11.2008), para [0002], [0006], [0012]-[0018], [0023]-[0027], [0038], [0039], [0126], [0127], [0133]-[0137]	1-9, 13-19, 21, 24/(21), 25/(21) ---------- 10, 20, 22, 23, 24/(22,23), 25/(22, 23)
Y	US 2009/0246124 A1 (KODADEK et al.) 01 October 2009 (01.12.2009), para [0100], [0102], [0144], [0147]	10, 20
Y	US 2009/0004213 A1 (SINGH et al.) 01 January 2009 (01.01.2009), para [0056], [0059], [0063]-[0066]	22, 23, 24/(22,23), 25/(22, 23)
Y	US 2009/0325959 A1 (VITTITOW et al.) 31 December 2009 (31.12.2009), para [0030], [0274], Table A	1-10, 13-25
Y	CIULLA et al. "Anti-vascular endothelial growth factor therapy for neovascular ocular diseases other than age-related macular degeneration." Current Opinion in Ophthalmology [online], May 2009 [Retrieved on 2011-02-10], Vol. 20, Iss. 3, pp. 166-174, Retrieved from the Internet: <URL: http://journals.lww.com/>	1-10, 13-25
Y	US 2007/0270427 A1 (BOLOOR et al.) 22 November 2007 (22.11.2007), para [0109], [0189], [0303]	1-10, 13-25
Y	WO 02/059110 A1 (BOLOOR et al.) 01 August 2002 (01.08.2002), pg 25, ln 8-9, pg 42, ln 4-31	1-10, 13-25

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2011 (10.02.2011)	23 MAR 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/20231

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 11-12, 26-28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

MÉTODO DE TRATAMIENTO

CAMPO DE LA INVENCIÓN

La presente invención se refiere a métodos para el tratamiento de trastornos de angiogénesis ocular o filtración vascular en un mamífero. Los métodos comprenden administrar derivados de pirimidina, derivados de benzo-diazepinilo, y composiciones farmacéuticas que los contienen.

ANTECEDENTES DE LA INVENCIÓN

La neovascularización, también denominada como angiogénesis, es el proceso de formación de nuevos vasos sanguíneos. La neovascularización se presenta durante el desarrollo normal, y también tiene una función importante en el sanado de heridas en seguida de la lesión a un tejido. Sin embargo, la neovascularización también se ha implicado como una causa importante de un número de estados patológicos, incluyendo, por ejemplo, cáncer, artritis reumatoide, ateroesclerosis, soriasis, y enfermedades de los ojos.

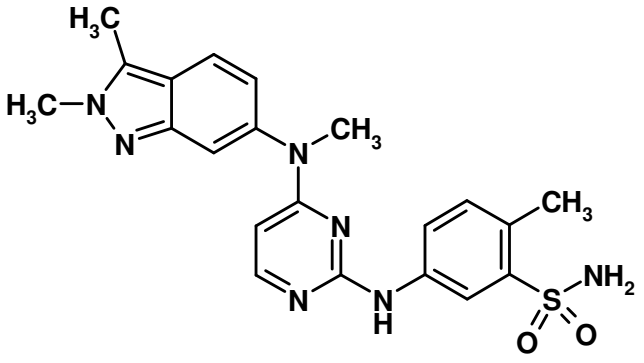
Un trastorno de los ojos en donde la neovascularización tiene una función es la degeneración macular relacionada con la edad (AMD), la cual es la principal causa de pérdida visual grave en los ancianos. La pérdida de visión en la degeneración macular relacionada con la edad (AMD) resulta a partir de la neovascularización coroidal (CNV). La neovascularización se origina a partir de los vasos sanguíneos coroidales y crece a través de la

membrana de Bruch, usualmente en múltiples sitios, hasta el espacio epitelial pigmentado sub-retinal y/o la retina (véase, por ejemplo, Campochiaro y colaboradores (1999) *Mol. Vis.* 5:34). La filtración y hemorragia a partir de estos nuevos vasos sanguíneos da como resultado pérdida de visión.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

En un aspecto de la presente invención, un método para el tratamiento de un trastorno de angiogénesis ocular o filtración vascular en un paciente que padezca esa condición, incluye administrar oralmente al paciente entre 1 y 50 miligramos de un inhibidor adecuado.

En otro aspecto de la presente invención, un método para el tratamiento de un trastorno de angiogénesis ocular o filtración vascular en un paciente que padezca esa condición, incluye administrar oralmente al paciente entre 1 y 50 miligramos de un compuesto de la fórmula (I):



(I)

o una sal farmacéuticamente aceptable o hidrato del mismo.

En todavía otro aspecto de acuerdo con la presente invención,

se proporciona el uso de un inhibidor adecuado en la elaboración de un medicamento que contiene entre 1 y 50 miligramos del inhibidor adecuado, para el tratamiento de un trastorno de angiogénesis ocular o filtración vascular en un paciente que lo necesite.

En todavía otro aspecto de acuerdo con la presente invención, se proporcionan entre 1 y 50 miligramos de un inhibidor adecuado para utilizarse en el tratamiento de un trastorno de angiogénesis ocular o filtración vascular, en un paciente que lo necesite.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

La Figura 1A ilustra los angiogramas de fluoresceína representativos con un cambio de la filtración de la neovascularización coroidal (CNV) inducido por pazopanib en la neovascularización coroidal (CNV) experimental.

La Figura 1B ilustra el análisis de las áreas de filtración de fluoresceína para el tratamiento con vehículo y pazopanib. Los cambios se determinaron utilizando análisis de imágenes digitales (*** $p < .005$).

La Figura 2A ilustra micrografías de luz representativas de las áreas teñidas con hematoxilina y con eosina, las cuales comprenden lesiones neovasculares (encerradas en círculos) en el día 14 después del láser.

La Figura 2B ilustra las áreas de lesión promediadas a partir de los ojos tratados con el vehículo o pazopanib (*** $p < .005$; $n = 6$).

La Figura 2C ilustra las áreas de lesión promediadas a partir de los ojos cuando el otro ojo se trató con el vehículo o pazopanib;

La Figura 3A ilustra la cinética en plasma de una sola dosis en ratas Brown Norway (datos combinados a partir de *n* = 3 ratas por punto).

La Figura 3B ilustra el contenido de pazopanib en plasma y en la copa ocular (esclerótica / coroides / retina), 5 horas después de la tercera gota para los ojos administrada en 24 horas. OS – ojo izquierdo tratado, OD – el otro ojo no tratado (*n* = 3 ratas por punto).

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La invención proporciona métodos para el tratamiento de un trastorno de angiogénesis ocular o filtración vascular, tal como la degeneración macular relacionada con la edad. Como se utiliza en la presente, "tratamiento" significa cualquier forma en la que se alteren benéficamente uno o más síntomas asociados con el trastorno. De conformidad con lo anterior, el término incluye sanar o mitigar un síntoma o efecto secundario del trastorno o una disminución en la velocidad de avance del trastorno.

Como se utiliza en la presente, el término “inhibidor adecuado” significa un inhibidor que inhibe uno o más de los siguientes receptores: VEGFR1, VEGFR2, VEGFR3, PDGFRalfa, PDGFRbeta, c-kit, y/o FGFR.

Como se utiliza en la presente, el término "cantidad terapéuticamente efectiva" significa la cantidad de un agente terapéutico que es suficiente para tratar, prevenir, y/o mitigar uno o más síntomas del trastorno.

De acuerdo con las modalidades de la presente invención, un

método para el tratamiento de un trastorno de angiogénesis ocular o filtración vascular, en un paciente que padezca esa condición, incluye administrar oralmente al paciente entre 1 y 50 miligramos de un inhibidor adecuado.

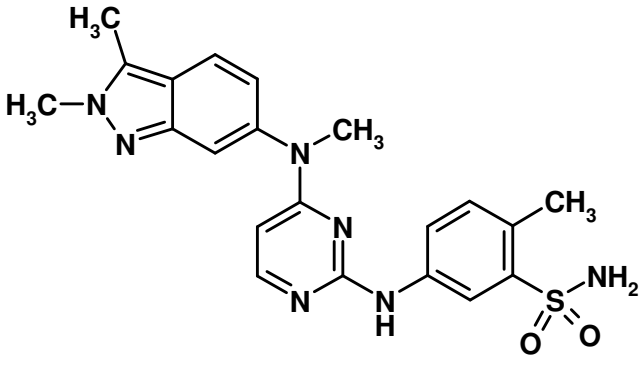
El inhibidor adecuado puede ser de diferentes inhibidores que inhiban uno o más de los siguientes receptores: VEGFR1, VEGFR2, VEGFR3, PDGFRalfa, PDGFRbeta, c-kit, y/o FGFR, incluyendo, pero no limitándose a: un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo, un compuesto de la fórmula (I') o un hidrato del mismo, un complejo de la fórmula (I''), un compuesto de la fórmula (II) o una sal farmacéuticamente aceptable del mismo, apatinib, sunitinib, sorafenib, bivanib, midostaurina (PKC412) (un inhibidor de FLT3, c-KIT, VEGFR-2, PDGFR, y múltiples isoformas de la cinasa C de proteína serina/treonina (PkC), en desarrollo en Novartis), E-7050 (una C-met y un inhibidor de la cinasa de tirosina VEGFR, en desarrollo en Eisai), XL-184, un inhibidor de cinasa de espectro selectivo que inhibe Met, Ret y VEGFR2, en desarrollo en Exelixis), XL-647 (un inhibidor de cinasa de tirosina disponible oralmente, en desarrollo en Exelixis que inhibe EGFR, HER2, VEGFR y EphB4), cediranib, linifanib, motesanib, RAF-265 (anteriormente CHIR-265) un inhibidor de cinasa B-Raf y VEGFR, en desarrollo en Novartis), tivozanib, TAK-593 (un inhibidor de cinasa de tirosina VEGFR/PDGFR, en desarrollo en Millennium (Takeda)), ARQ-197 (un inhibidor de c-Met independiente del ATP, en desarrollo en ArQule (Ciclis Pharmaceuticals antes de la

adquisición)), OSI-930 (un inhibidor de cinasa de tirosina c-kit y VEGFR-2, en desarrollo en OSI Pharmaceuticals), DCC-2036 (un inhibidor de Bcr-abl, que también inhibe las cinasas tipo Src: LYN, HCK y FGR, así como las cinasas TIE2 y KDR, en desarrollo en Deciphera Pharmaceuticals), MGCD-265 (un inhibidor de las cinasas de tirosina receptoras c-Met, VEGFR1, VEGFR2, VEGFR3, Tie-2 y Ron, en desarrollo en MethylGene, en colaboración con ChemBridge Research Laboratories, CA, US), PF-337210 (un inhibidor de VEGFR2, en desarrollo en Pfizer), BIBF-1120 (un inhibidor de cinasa VEGFR-2, PDGF, y FGF, el cual también inhibe las cinasas de tirosina src, lck y lyn, en desarrollo en Boehringer Ingelheim), ENMD-2076 (un inhibidor de cinasa que se dirige selectivamente hacia la cinasa Aurora A contra B, y también inhibe Flt3, c-kit, CSF1R y KDR (VEGFR2), así como VEGFR3, PDGFR-alfa, FGFR1, FGFR2, EphA1 y src, en desarrollo en EntreMed), TG-100-801 (un inhibidor de las cinasas VEGFR, Src, Yes, Lck, Lyn y PDGFR-ß, en desarrollo en TargeGen), BMS-690514 (un inhibidor de EGFR, HER2, ErbB4 y VEGFR1-3, en desarrollo en Bristol-Myers Squibb), SSR-106462 (un inhibidor de TIE-2, y un inhibidor de cinasa de tirosina VEGFR-2, en desarrollo en Sanofi-Aventis), BAY-73-4506 (un inhibidor de cinasa VEGFR, KIT, RET, FGFR y PDGFR, en desarrollo en Bayer), plitidepsina, axitinib, vandetinib, y nilotinib. Los inhibidores adecuados pueden estar en la forma de sales farmacéuticamente aceptables y, en algunos casos, en la forma de los solvatos farmacéuticamente aceptables hasta el grado en que estos

inhibidores adecuados se hayan descrito en la técnica como en una forma solvatada.

En algunas modalidades, el inhibidor adecuado es pazopanib o una sal farmacéuticamente aceptable o un solvato del mismo, tal como un compuesto de la fórmula (I) o un solvato farmacéuticamente aceptable del mismo, un compuesto de la fórmula (I') o un solvato del mismo, o un complejo de la fórmula (I''). En otras modalidades, el inhibidor adecuado es un compuesto de la fórmula (II) o una sal farmacéuticamente aceptable del mismo. En todavía otras modalidades, el inhibidor adecuado es sorafenib o una sal farmacéuticamente aceptable del mismo, tal como la sal de tosilato. En todavía otras modalidades, el inhibidor adecuado es sunitinib o una sal farmacéuticamente aceptable del mismo, tal como la sal de malato.

De acuerdo con las modalidades de la presente invención, un método para el tratamiento de un trastorno de angiogénesis ocular o filtración vascular, en un paciente que padezca esa condición, incluye administrar oralmente al paciente entre 1 y 50 miligramos de un compuesto de la fórmula (I):

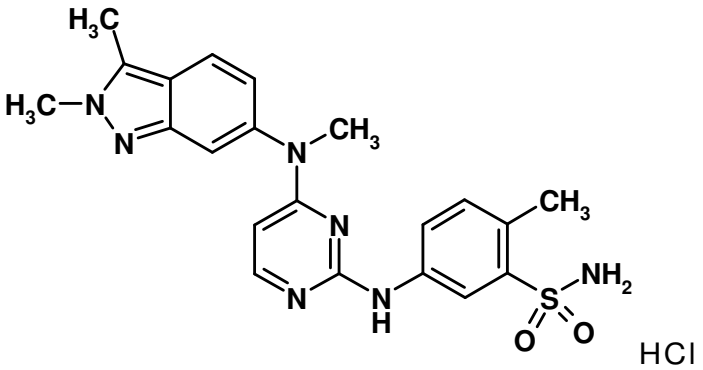


(I)

o sales farmacéuticamente aceptables o hidratos del mismo.

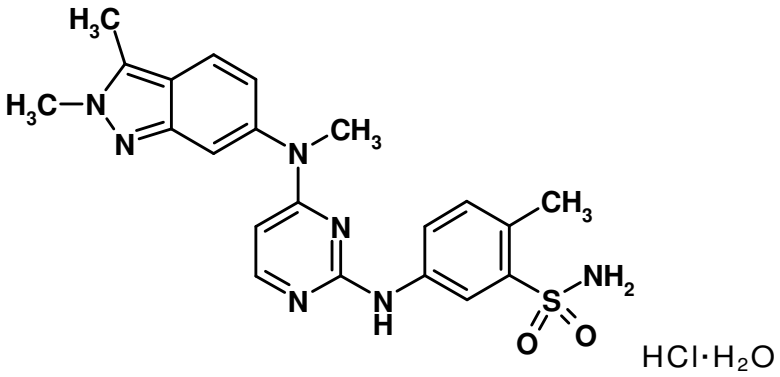
El compuesto de la fórmula (I) tiene el nombre químico de 5-[[4-[(2,3-dimetil-2H-indazol-6-il)-metil-amino]-2-pirimidinil]-amino]-2-metil-bencen-sulfonamida y el nombre genérico de pazopanib.

En ciertas modalidades, la sal del compuesto de la fórmula (I) es una sal de clorhidrato. En una modalidad, particular, la sal del compuesto de la fórmula (I) es una sal de monoclorhidrato como se ilustra mediante la fórmula (I'). La sal de monoclorhidrato del compuesto de la fórmula (I) tiene el nombre químico de monoclorhidrato de 5-[[4-[(2,3-dimetil-2H-indazol-6-il)-metil-amino]-2-pirimidinil]-amino]-2-metil-bencen-sulfonamida.



(I')

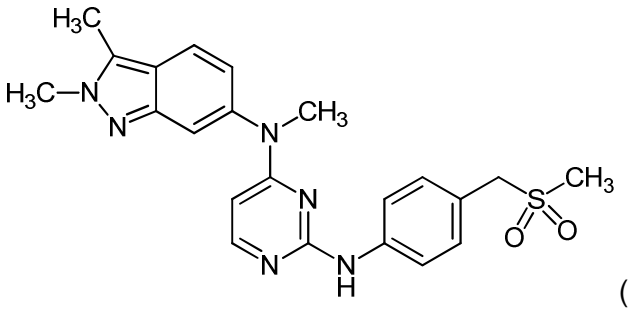
En otras modalidades, la sal del compuesto de la fórmula (I) es un solvato de monohidrato de monoclorhidrato del compuesto de la fórmula (I). El solvato de monohidrato de monoclorhidrato del compuesto de la fórmula (I) tiene el nombre químico de monohidrato de monoclorhidrato de 5-({4-[(2,3-dimetil-2H-indazol-6-il)-metil-amino]-2-pirimidinil}-amino)-2-metil-bencen-sulfonamida, como se ilustra en la fórmula (I''):



(I'')

La base libre, las sales e hidratos del compuesto de la fórmula (I) se pueden preparar, por ejemplo, de acuerdo con los procedimientos de la Solicitud Internacional de Patente Número PCT/US01/49367 presentada el 19 de Diciembre de 2001, y publicada como la WO 02/059110 el 1 de Agosto de 2002, y de la Solicitud Internacional de Patente Número PCT/US03/19211 presentada el 17 de Junio de 2003, y publicada como la WO 03/106416 el 24 de Diciembre de 2003.

De acuerdo con las modalidades de la presente invención, un método para el tratamiento de un trastorno de angiogénesis ocular o filtración vascular, en un paciente que padezca esa condición, incluye administrar oralmente al paciente entre 1 y 50 miligramos de un compuesto de la fórmula (II):



(II)

o una sal farmacéuticamente aceptable del mismo. La base libre y las sales del compuesto de la fórmula (II) se pueden preparar, por ejemplo, de acuerdo con los procedimientos de la Solicitud Internacional de Patente Número PCT/US01/49367 presentada el 19 de Diciembre de 2001, y publicada como la WO 02/059110 el 1 de Agosto de 2002, y de la Solicitud Internacional de Patente Número PCT/US03/19211 presentada el 17 de Junio de 2003, y publicada como la WO 03/106416 el 24 de Diciembre de 2003.

Como se utiliza en la presente, el término "sales farmacéuticamente aceptables" puede comprender las sales de adición de ácido derivadas a partir de un nitrógeno sobre un sustituyente en el compuesto de la fórmula (I). Las sales representativas incluyen las siguientes sales: acetato, bencen-sulfonato, benzoato, bicarbonato, bisulfato, bitartrato, borato, bromuro, edetato de calcio, camsilato, carbonato, cloruro, clavulanato, citrato, diclorhidrato, edetato, edisilato, estolato, esilato, fumarato, gluceptato, gluconato, glutamato, glicolil-arsanilato, hexil-resorcinato, hidrabamina, bromhidrato, clorhidrato, hidroxi-naftoato, yoduro, isetionato, lactato, lactobionato, laurato, malato, maleato, mandelato, mesilato, metil-bromuro, metil-nitrato, metil-sulfato, mono-maleato de potasio, mucato, napsilato, nitrato, N-metil-glucamina, oxalato, pamoato (embonato), palmitato, pantotenato, fosfato/ difosfato, poligalacturonato, potasio, salicilato, sodio, estearato, subacetato, succinato, tanato, tartrato, teoclato, tosilato, trietil-yoduro, trimetil-amonio, y valerato.

En las modalidades de los métodos de acuerdo con la invención, el trastorno de angiogénesis ocular o filtración vascular puede ser edema o neovascularización para cualquier enfermedad vascular retinal oclusiva o inflamatoria, tal como rubeosis iridis, glaucoma neovascular, pterigión, flictenas filtrantes de glaucoma vascularizado, papiloma conjuntival; neovascularización coroidal, tal como degeneración macular relacionada con la edad (AMD) neovascular, miopía, uveítis previa, por trauma, o idiopática; edema macular, tal como edema macular post-quirúrgico, edema macular secundario a uveítis, incluyendo inflamación retinal y/o coroidal, edema macular secundario a diabetes, y edema macular secundario a enfermedad oclusiva retinovascular (es decir, oclusión de vena retinal ramificada y central); neovascularización retinal debida a diabetes, tal como oclusión de vena retinal, uveítis, síndrome isquémico ocular a partir de enfermedad de arteria carótida, oclusión de arteria oftálmica o retinal, retinopatía drepanocítica, otras retinopatías neovasculares isquémicas u oclusivas, retinopatía de prematuridad, o enfermedad de Eale; y trastornos genéticos, tales como síndrome de VonHippel-Lindau.

En una modalidad, la degeneración macular relacionada con la edad (AMD) neovascular es la degeneración macular relacionada con la edad (AMD) húmeda. En otra modalidad, la degeneración macular relacionada con la edad (AMD) neovascular es la degeneración macular relacionada con la edad (AMD) seca, y el paciente se caracteriza por tener mayor riesgo de desarrollar la degeneración

macular relacionada con la edad (AMD) húmeda.

Aunque es posible que el inhibidor adecuado se administre como el producto químico en bruto, también es posible presentar el ingrediente activo como una composición farmacéutica. De conformidad con lo anterior, las modalidades de la invención proporcionan además composiciones farmacéuticas, las cuales incluyen cantidades terapéuticamente efectivas del inhibidor adecuado, y uno o más vehículos, diluyentes, o excipientes farmacéuticamente aceptables. El inhibidor adecuado es como se describe anteriormente. En una modalidad, el inhibidor adecuado es un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo. En otra modalidad, el inhibidor adecuado es un compuesto de la fórmula (I') o un hidrato del mismo. En todavía otra modalidad, el inhibidor adecuado es un complejo de la fórmula (I''). En todavía otra modalidad, el inhibidor adecuado es un compuesto de la fórmula (II) o una sal farmacéuticamente aceptable del mismo. En todavía otras modalidades, el inhibidor adecuado es sorafenib o una sal farmacéuticamente aceptable del mismo, tal como la sal de tosilato. En todavía otras modalidades, el inhibidor adecuado es sunitinib o una sal farmacéuticamente aceptable del mismo, tal como la sal de malato. Los vehículos, diluyentes, o excipientes deben ser aceptables en el sentido de ser compatibles con los otros ingredientes de la formulación y no perjudiciales para el receptor de los mismos. De acuerdo con otro aspecto de la invención, también se proporciona un proceso para la

preparación de una formulación farmacéutica, el cual incluye mezclar el inhibidor adecuado con uno o más vehículos, diluyentes o excipientes farmacéuticamente aceptables.

Las formulaciones farmacéuticas se pueden presentar en formas de dosis unitaria conteniendo una cantidad previamente determinada del ingrediente activo por unidad de dosis. En ciertas modalidades, las formulaciones de dosificación unitaria son aquéllas que contienen una dosis para administrarse con tanta frecuencia como diariamente, o una sub-dosis o una fracción apropiada de la misma, de un ingrediente activo. Adicionalmente, estas formulaciones farmacéuticas se pueden preparar mediante cualquiera de los métodos bien conocidos en la técnica de la farmacia.

Las formulaciones farmacéuticas se pueden adaptar para su administración oral. Estas formulaciones se pueden preparar mediante cualquier método conocido en la técnica de la farmacia, por ejemplo poniendo en asociación el ingrediente activo con los vehículos o excipientes.

Las formulaciones farmacéuticas adaptadas para su administración oral se pueden presentar como unidades separadas, tales como cápsulas o tabletas; polvos o gránulos; soluciones o suspensiones en líquidos acuosos o no acuosos; espumas o batidos comestibles; o emulsiones líquidas de aceite en agua, o emulsiones líquidas de agua en aceite.

Por ejemplo, para su administración oral en la forma de una tableta o cápsula, el componente de fármaco activo se puede

combinar con un vehículo inerte oral no tóxico farmacéuticamente aceptable, tal como etanol, glicerol, agua y similares. Los polvos se preparan mediante la trituración del compuesto hasta un tamaño fino adecuado, y se mezclan con un vehículo farmacéutico similarmente triturado, tal como un carbohidrato comestible como, por ejemplo, almidón o manitol. También puede haber saborizantes, conservadores, dispersantes, y colorantes presentes.

Las cápsulas se hacen mediante la preparación de una mezcla en polvo como se describe anteriormente, y se rellenan las cubiertas de gelatina formadas. Antes de la operación de llenado, a la mezcla en polvo se le pueden agregar derrapantes y lubricantes, tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio, o polietilenglicol sólido. También se puede agregar un agente desintegrante o solubilizante, tal como agar-agar, carbonato de calcio, o carbonato de sodio, para mejorar la disponibilidad del medicamento cuando se ingiera la cápsula.

Más aún, cuando se desee o sea necesario, también se pueden incorporar a la mezcla, los aglutinantes, lubricantes, agentes desintegrantes, y agentes colorantes adecuados. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales, tales como glucosa o beta-lactosa, edulcorantes de maíz, gomas naturales y sintéticas, tales como acacia, tragacanto, o alginato de sodio, carboxi-metil-celulosa, polietilenglicol, ceras, y similares. Los lubricantes utilizados en estas formas de dosificación incluyen oleato de sodio, estearato de sodio, estearato de magnesio, benzoato de

sodio, acetato de sodio, cloruro de sodio, y similares. Los desintegrantes incluyen, sin limitación, almidón, metil-celulosa, agar, bentonita, goma de xantano, y similares. Las tabletas se formulan, por ejemplo, mediante la preparación de una mezcla en polvo, se granula o se forman trozos, se agrega un lubricante y un desintegrante, y se comprimen las tabletas. Una mezcla en polvo se prepara mediante la mezcla del compuesto, adecuadamente triturado, con un diluyente o con una base como se describe anteriormente, y opcionalmente, con un aglutinante, tal como carboxi-metil-celulosa, un alginato, gelatina, o polivinil-pirrolidona, una solución retardante, tal como parafina, un acelerador de resorción, tal como una sal cuaternaria y/o un agente de absorción, tal como bentonita, caolín o difosfato de calcio. La mezcla de polvo se puede granular humedeciendo con un aglutinante, tal como jarabe, pasta de almidón, mucílago de acadia, o soluciones de materiales celulósicos o poliméricos, y forzando a través de un tamiz. Como una alternativa a la granulación, la mezcla de polvo se puede pasar a través de la máquina de tabletas, y el resultado es el de trozos imperfectamente formados que se rompen en gránulos. Los gránulos se pueden lubricar para evitar que se adhieran a los dados formadores de tabletas, por medio de la adición de ácido esteárico, una sal de estearato, talco, o aceite mineral. Entonces la mezcla lubricada se comprime en tabletas. Los compuestos de la presente invención también se pueden combinar con un vehículo inerte de flujo libre, y se comprimen en tabletas directamente sin ir a través de

los pasos de granulación o formación de trozos. Se puede proporcionar un recubrimiento protector transparente u opaco consistente en un recubrimiento sellador de shellac, un recubrimiento de azúcar o de un material polimérico, y un recubrimiento pulido de cera. Se pueden agregar materiales colorantes a estos recubrimientos para distinguir diferentes dosificaciones unitarias.

Los fluidos orales, tales como soluciones, jarabes, y elíxires se pueden preparar en una forma unitaria de dosificación, de tal manera que una cantidad dada contenga una cantidad previamente determinada del compuesto. Los jarabes se pueden preparar disolviendo el compuesto en una solución acuosa adecuadamente saborizada, mientras que los elíxires se preparan mediante el uso de un vehículo alcohólico no tóxico. Las suspensiones se pueden formular mediante la dispersión del compuesto en un vehículo no tóxico. También se pueden agregar solubilizantes y emulsionantes, tales como alcoholes isoestearílicos etoxilados y éteres de sorbitol de polioxietileno, conservadores, aditivos de sabor tales como aceite de menta, o edulcorantes naturales o sacarina u otros edulcorantes artificiales, y similares.

Cuando sea apropiado, las formulaciones unitarias de dosificación para administración oral se pueden microencapsular. La formulación también se puede preparar para prolongar o sostener la liberación, como por ejemplo, mediante recubrimiento o empotramiento del material en partículas en polímeros, cera, o similares.

El inhibidor adecuado también se puede administrar en la forma de sistemas de suministro de liposomas, tales como vesículas unilamelares pequeñas, vesículas unilamelares grandes, y vesículas multilamelares. Los liposomas se pueden formar a partir de una variedad de fosfolípidos, tales como colesterol, estearil-amina, o fosfatidil-colinas.

El inhibidor adecuado también se puede suministrar mediante el uso de anticuerpos monoclonales como vehículos individuales a los que se acoplan las moléculas del compuesto. Los compuestos también se pueden acoplar con polímeros solubles como vehículos de fármaco dirigibles. Estos polímeros pueden incluir polivinil-pirrolidona, copolímero de pirano, poli-hidroxi-propil-metacrilamida-fenol, poli-hidroxi-etil-aspartamida-fenol, o poli-etilen-oxido-poli-lisina sustituida con residuos de palmitoílo. Adicionalmente, los compuestos se pueden acoplar con una clase de polímeros biodegradables útiles para lograr la liberación controlada de un fármaco, por ejemplo poli-ácido láctico, poli-épsilon-caprolactona, poli-ácido hidroxi-butírico, poli-ortoésteres, poliacetales, poli-dihidropiranos, poli-ciano-acrilatos, y copolímeros de bloques reticulados o anfipáticos de hidrogeles.

Se debe entender que, en adición a los ingredientes particularmente mencionados en lo anterior, las formulaciones pueden incluir otros agentes convencionales en la técnica, teniendo consideración del tipo de formulación en cuestión, por ejemplo, aquéllas adecuadas para administración oral pueden incluir agentes

saborizantes.

De acuerdo con los métodos de la invención, se administra o se prescribe un inhibidor adecuado a un paciente. La cantidad de compuesto administrado o prescrito dependerá de un número de factores, incluyendo, por ejemplo, la edad y el peso del paciente, la condición precisa que requiera tratamiento, la gravedad de la condición, y la naturaleza de la formulación. Por último, la cantidad quedará a discreción del médico que atienda.

En algunas modalidades de los métodos de la invención, la cantidad total del inhibidor adecuado administrada o prescrita para administrarse con tanta frecuencia como diariamente, puede ser desde un límite inferior de 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, ó 20 miligramos, hasta un límite superior de 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 ó 50 miligramos. El inhibidor adecuado es como se describe anteriormente. En una modalidad, el inhibidor adecuado es un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo. En otra modalidad, el inhibidor adecuado es un compuesto de la fórmula (I') o un hidrato del mismo. En todavía otra modalidad, el inhibidor adecuado es un complejo de la fórmula (I''). En todavía otra modalidad, el inhibidor adecuado es un compuesto de la fórmula (II) o una sal farmacéuticamente aceptable del mismo. En todavía otras modalidades, el inhibidor adecuado es sorafenib o una sal farmacéuticamente aceptable del

mismo, tal como la sal de tosilato. En todavía otras modalidades, el inhibidor adecuado es sunitinib o una sal farmacéuticamente aceptable del mismo, tal como la sal de malato.

Los métodos de la presente invención también se pueden emplear en combinación con otros métodos para el tratamiento de trastornos neovasculares oculares. En algunas modalidades, los métodos de la invención abarcan una terapia de combinación en donde un inhibidor adecuado se administra en conjunto con uno o más agentes terapéuticos adicionales para el tratamiento de trastornos neovasculares, cuyos agentes terapéuticos pueden ser por sí mismos inhibidores adecuados, como se describen en la presente. En una modalidad, un inhibidor adecuado utilizado en la combinación es un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo. En otra modalidad, un inhibidor adecuado utilizado en la combinación es un compuesto de la fórmula (I') o un hidrato del mismo. En todavía otra modalidad, un inhibidor adecuado utilizado en la combinación es un complejo de la fórmula (I''). En todavía otra modalidad, un inhibidor adecuado utilizado en la combinación es un compuesto de la fórmula (II) o una sal farmacéuticamente aceptable del mismo. En todavía otra modalidad, un inhibidor adecuado utilizado en la combinación es sorafenib o una sal farmacéuticamente aceptable del mismo, tal como la sal de tosilato. En todavía otra modalidad, un inhibidor adecuado utilizado en la combinación es sunitinib o una sal farmacéuticamente aceptable del mismo, tal como la sal de malato. Los ejemplos no

limitantes de los agentes terapéuticos adicionales que se pueden utilizar en una terapia de combinación incluyen pegaptanib, ranibizumab, bevacizumab, midostaurina, nepafenaco, antagonistas de los receptores de integrina (incluyendo los agonistas de los receptores de vitronectina), y cualquiera de los diferentes inhibidores adecuados descritos en la presente. Véase, por ejemplo, Takahashi y colaboradores (2003) *Invest. Ophtalmol. Vis. Sci.* 44: 409-15, Campochiaro y colaboradores (2004) *Invest. Ophtalmol. Vis. Sci.* 45: 922-31, van Wijngaarden y colaboradores (2005) *JAMA* 293: 1509-13, Patente de los Estados Unidos de Norteamérica Número 6,825,188 a Callahan y colaboradores, y Patente de los Estados Unidos de Norteamérica Número 6,881,736 a Manley y colaboradores; cada uno de los cuales se incorpora a la presente como referencia por sus enseñanzas con respecto a estos compuestos.

Cuando se emplea una terapia de combinación, los agentes terapéuticos se pueden administrar juntos o por separado. Se pueden utilizar los mismos medios para la administración de más de un agente terapéutico de la terapia de combinación; de una manera alternativa, los diferentes agentes terapéuticos de la terapia de combinación se pueden administrar por diferentes medios. Cuando los agentes terapéuticos se administran por separado, se pueden administrar de una manera simultánea o en secuencia en cualquier orden, tanto cercanos como remotos en el tiempo. Las cantidades del inhibidor adecuado y/o del otro agente u otros agentes

farmacéuticamente activos, y los tiempos de administración relativos, se seleccionarán con el fin de lograr el efecto terapéutico combinado deseado.

Los siguientes ejemplos se pretenden para ilustración solamente, y no pretenden limitar el alcance de la invención de ninguna manera.

EJEMPLOS

La base libre, las sales e hidratos de pazopanib utilizados en estos ejemplos, se pueden preparar, por ejemplo, de acuerdo con los procedimientos de la Solicitud Internacional de Patente Número PCT/US01/49367 presentada el 19 de Diciembre de 2001, y publicada como la WO 02/059110 el 1 de Agosto de 2002, y de la Solicitud Internacional de Patente Número PCT/US03/19211 presentada el 17 de Junio de 2003, y publicada como la WO 03/106416 el 24 de Diciembre de 2003.

Datos Biológicos:

Reactivos

Se formularon gotas tópicas para los ojos en una solución de ciclodextrina al 7 por ciento regulada conteniendo 5 miligramos/ mililitro de pazopanib. La fluoresceína de sodio (10 por ciento en peso/volumen) se adquirió en Alcon (Alcon Pharma, Freiburg, Alemania). El medio basal celular endotelial (EBM), y el medio de cultivo celular endotelial (EGM) se obtuvieron en Lonza, Verviers, Bélgica. La solución de sal balanceada de Hank (HBSS) y el F10 de Ham fueron de Invitrogen (Karlsruhe, Alemania). Todos los demás

productos químicos fueron productos de grado de reactivo obtenidos comercialmente en Sigma (Taufkirchen, Alemania).

Animales y Anestesia

Se utilizaron ratas Brown Norway machos (de 10 a 12 semanas de edad, machos y hembras con un peso de 170 a 360 gramos) a través de todo este estudio. Los animales se trataron de acuerdo con la Declaración ARVO sobre el uso de animales en investigación oftálmica y de la visión, y todos los experimentos con animales fueron revisados y aprobados por los comités para el cuidado animal municipales y del University Hospital de Leipzig. Las ratas se anestesiaron con quetamina intraperitoneal (100 miligramos/ kilogramo; Ratiopharm, Ulm, Alemania), y xilazina (BayerVital, Leverkusen, Alemania; 10 miligramos/kilogramo). Se instiló una aplicación tópica de tropicamida (5 miligramos/mililitro), y clorhidrato de fenilefrina (Ankerpharm, Rudolstadt, Alemania; 50 miligramos/ mililitro) para la midriasis durante la fotocoagulación con láser y la angiografía con fluoresceína. Catorce días después de la lesión con láser, las ratas se sacrificaron humanitariamente utilizando una sobre-dosis de dióxido de carbono.

Inducción de neovascularización coroidal (CNV) en ratas y tratamiento con pazopanib

Los animales se trataron utilizando ruptura de la membrana de Bruch inducida por fotocoagulación con láser utilizando un dispositivo de láser de tinte de 545 nanómetros (Coherent Argon Dye Laser #920, Coherent Medical Laser, Palo Alto, CA) conectado a un

foco ranurado (Carl Zeiss, Oberkochen, Alemania). Se utilizó un lente de contacto para conservar la claridad de la córnea a través de la fotocoagulación. Se colocaron puntos de láser por separado utilizando las siguientes posiciones: diámetro de 50 micras, duración de 0.1 segundo, e intensidad de 180 mW. Con el fin de romper la membrana de Bruch, se aplicaron de cuatro a siete puntos de láser entre los vasos retinales mayores cerca del disco óptico. Se administró pazopanib (aproximadamente 30 microlitros de una solución esterilizada por filtración a 5 miligramos/mililitro) dos veces al día. Los animales del grupo de control recibieron solamente el vehículo.

Angiografía de fluorescencia en la neovascularización coroidal (CNV) experimental

Con el objeto de documentar el tratamiento de la neovascularización coroidal (CNV) en su etapa temprana, se empleó el programa de tratamiento como sigue. Se llevó a cabo la fotocoagulación con láser como se describe anteriormente, y se aplicó pazopanib dos veces al día tópicamente desde el día 6 después del láser hasta el final del estudio el día 14 después del láser. Primero se documentaron las lesiones coaguladas mediante angiografía en el día 7 después del láser, y solamente se incluyeron en el análisis las ratas con neovascularización coroidal (CNV) ocular. Se inyectó fluoresceína de sodio en la vena de la cola de las ratas anestesiadas, y se obtuvieron los angiogramas de fluoresceína por medio de una cámara del fondo (FD-31A, Topcon, Tokio, Japón). En

el día 14, las ratas se sometieron a una segunda angiografía. Los angiogramas tomados de 100 a 140 segundos después de la inyección, se convirtieron a imágenes digitales, y las áreas de filtración de fluoresceína con una intensidad tan alta como en los vasos mayores fueron cuantificadas por dos de nosotros (YY; XMY) en una forma enmascarada, utilizando un software de computación (NIH Image, Research Service Branch, Bethesda, MD). Las diferencias en la fluorescencia se calcularon mediante la siguiente fórmula:

Área de filtración de fluoresceína en el día 14 x 100 por ciento / área de filtración de fluoresceína en el día 7

Histología e Inmunohistoquímica

Después de que las ratas se sacrificaron en el día 14, se disectaron inmediatamente los ojos y se fijaron con para-formaldehído al 4 por ciento (disuelto en suero regulado con fosfato (PBS)). Cinco minutos más tarde, los ojos se perforaron en el ecuador y se dejaron durante la noche a 4°C en la misma solución. Subsiguientemente, los ojos se dividieron en los segmentos anterior y posterior con la remoción total del lente y del cuerpo vítreo. Se prepararon secciones en serie de seis micras, y se tiñeron con hematoxilina y eosina (HE), o se procesaron para la inmunohistoquímica. Las secciones teñidas con hematoxilina y eosina (HE) se examinaron a una amplificación 200x utilizando un microscopio de luz (Axioplan 2; Carl Zeiss Meditec, Jena, Alemania), y una cámara digital a color (AxioCam MRc5; Carl Zeiss Meditec). La

máxima área de los complejos de neovascularización coroidal (CNV) se estimó indirectamente, mediante la medición de la diferencia entre el espesor desde el límite externo de la capa coroidal pigmentada hasta la parte superior del complejo de neovascularización coroidal (CNV), y el espesor de la coroides pigmentada intacta adyacente a la lesión. Se midieron de tres a cinco secciones en serie a partir de cada membrana de neovascularización coroidal (CNV), y se almacenó el valor más alto (que representaba la parte superior de un complejo dado de neovascularización coroidal (CNV). Las imágenes digitalizadas se analizaron y se midieron con el software de análisis de imágenes concomitante (Axiovision; Carl Zeiss). Cada lesión se encerró en un círculo manualmente, y el programa calculó su área (en micras cuadradas (μm^2)).

Adicionalmente, algunas secciones se tiñeron con un anticuerpo policlonal de cabra anti-VEGF de rata (R&D Systems). Dicho de una manera breve, las secciones se lavaron utilizando PBS-TD (suero regulado con fosfato / sulfóxido de dimetilo al 1 por ciento / Triton X-100 al 0.3 por ciento), seguido por apagado de la actividad de peroxidasa endógena en suero regulado con fosfato / H_2O_2 al 0.3 por ciento, durante 5 minutos, seguido por lavado en suero regulado con fosfato. Subsiguientemente, las secciones se bloquearon con PBS-TD / suero normal de conejo al 10 por ciento a 37°C durante 1 hora, y se incubaron con anti-VEGF (5 microgramos/mililitro en suero regulado con fosfato / albúmina de suero bovino (BSA) al 2 por ciento) durante la noche. En las secciones de control negativo, el

anticuerpo primario fue reemplazado por inmunoglobulina (Ig) G normal de cabra. Después de lavar tres veces con PBS-TD, los portaobjetos se incubaron a temperatura ambiente con IgG de conejo anti-cabra conjugada con peroxidasa de radícula roja (Dianova, Hamburgo, Alemania; diluida a 1:1000 en suero regulado con fosfato / albúmina de suero bovino (BSA) al 2 por ciento) durante 2 horas. Se utilizó una solución regulada de 3,3'-diamino-bencidina (Vector Laboratories, Burlingame, CA) como un cromógeno, junto con H_2O_2, con el objeto de detectar la actividad de peroxidasa. Las secciones se contra-tiñeron con hematoxilina de Meyer, se lavaron en suero regulado con fosfato y agua, y se montaron. Todos los portaobjetos se examinaron utilizando un microscopio Zeiss Axioskop equipado con una cámara digital.

Procedimientos de concentración del fármaco en el tejido ocular

Se utilizaron ratas Norway Brown hembras durante estos estudios. Las ratas se adquirieron en Charles River (Portage, MI). En dos estudios independientes, las ratas Norway Brown recibieron 30 microlitros de gotas para los ojos de pazopanib (5 miligramos/ mililitro en ciclodextrina al 7 por ciento regulada) ya sea durante 24 horas (3 gotas en total dadas cada 8 a 12 horas), una vez al día durante 5 días, o dos veces al día durante 14 días.

Procedimientos de recolección del tejido

Las ratas se sacrificaron mediante inhalación de CO_2 antes de la enucleación y recolección de las muestras de plasma. Las muestras se congelaron inmediatamente sobre hielo seco después de

la recolección, y entonces se almacenaron a -80°C. Los tejidos oculares se procesaron a través de un proceso de disección-pulverización-extracción de fármaco. El seccionamiento del ojo congelado se llevó a cabo mediante los siguientes pasos. La preparación de las copas oculares de rata se hizo mediante la remoción de la porción anterior de los ojos con una hoja de rasurar, seguida por la remoción del lente y el vítreo congelado con fórceps. Se hizo una sección sagital en la copa ocular antes de la recolección del tejido de la retina/coroides raspando la esclerótica expuesta con el extremo redondo de una espátula, hasta que se removió completamente el tejido pigmentado del tejido de la esclerótica. Los tejidos recolectados se pulverizaron bajo nitrógeno líquido. El tejido congelado se colocó cuidadosamente en un BioPulverizer preparado con nitrógeno líquido (Biospec Products Inc, Bartlesville, OK). En seguida de la pulverización, se removió el polvo de tejido del pulverizador, y se transfirió a un tubo de polipropileno. Se agregó regulador de extracción (50 por ciento de metanol / 50 por ciento de HCl 0.5 M) al polvo de tejido, seguido por dos ciclos de sonicación, centrifugación, y recolección del sobrenadante. El sobrenadante del homogenado te tejido se reservó y se congeló sobre hielo seco, y entonces se almacenó a -80°C hasta el análisis del fármaco. Se asumió que la eficacia de extracción de esta metodología fue del 100 por ciento para los propósitos de cálculo.

Análisis del Fármaco

Se analizaron las muestras de plasma y los extractos de tejido

ocular para determinar el pazopanib, empleando un método analítico validado basado en la precipitación de la proteína, seguida por análisis mediante HPLC/MS/MS. Utilizando una alícuota de 50 microlitros de plasma y extracto de tejido ocular, el límite de cuantificación del pazopanib fue de 1 nanogramo/mililitro para el plasma, y de 10 nanogramos/mililitro para el extracto de tejido ocular. El límite de cuantificación más alto fue de 500 nanogramos/ mililitro para el plasma, y de 5,000 nanogramos/mililitro para los extractos de tejido ocular. Los sistemas de computación que se utilizaron en estos estudios para adquirir y cuantificar los datos incluyeron el Analyst Versión 1.4.1 y el SMS2000 Versión 1.6. Las concentraciones en las muestras en plasma se expresaron como nanogramos de pazopanib/mililitro. Las concentraciones en tejido se determinaron mediante la siguiente fórmula:

nanogramos de pazopanib / gramos de tejido = ([concentración en nanogramos de sobrenadante / mililitro * volumen del extracto en mililitros] / gramos de peso del tejido).

Análisis Estadístico

Los resultados se expresan como el promedio ± desviación estándar (SD) si no se indica de otra manera. Las comparaciones estadísticas se llevaron a cabo utilizando ANOVA, y las diferencias significativas se juzgaron en $p < .05$ para rechazar la hipótesis nula.

Resultados

El pazopanib suprime el desarrollo de la neovascularización coroidal (CNV) en un modelo de neovascularización coroidal (CNV)

de rata.

Con el fin de determinar si el pazopanib afecta a la neovascularización coroidal (CNV) experimental *in vivo*, se indujo la neovascularización en los ojos de las ratas sometiendo a la membrana de Bruch a una ruptura inducida por láser. Esta metodología se ha aplicado comúnmente en los estudios experimentales de degeneración macular relacionada con la edad (AMD) neovascular, y permite que se hagan predicciones sobre la eficacia del fármaco en los seres humanos. En particular, la expresión de VEGF llega a sobre-regularse, y se pueden predecir bien los efectos del VEGFR así como de los receptores de cinasa de tirosina PDGFR, debido a que este tipo de antagonistas inhiben la neovascularización coroidal (CNV). Véase, Yi X, Ogata N, Komada M, Yamamoto C, Takahashi K, Omori K, Uyama M. Vascular endothelial growth factor expression in choroidal neovascularization in rats. *Graefe`s Arch Clin Exp Ophtalmol.* 1997; 235: 313-319; Shen WY, Yu MJ, Barry CJ, Constable IJ, Rakoczy PE. Expression of cell adhesion molecules and vascular endothelial growth factor in experimental choroidal neovascularization in the rat. *Br J Ophtalmol.* 1998; 82: 1063-1071; Kwak N, Okamoto N, Wood JM, Campochiaro PA. VEGF is major stimulator in model of choroidal neovascularization. *Invest Ophtalmol Vis Sci.* 2000; 41: 3158-3164.

Cuando las áreas de filtración de los vasos fueron seguidas mediante angiografía de fluorescencia desde los días 7 a 14 después del láser, el pazopanib tópicamente administrado redujo de una

manera significativa el desarrollo de las lesiones de la neovascularización coroidal (CNV). En contraste, la filtración de las lesiones de la neovascularización coroidal (CNV) continuó progresando en los ojos del grupo de control tratado con el vehículo (Figura 1A; $p < .001$). En la Figura 1A, los paneles a y c demuestran filtración de fluoresceína en las lesiones fotocoaguladas siete días después de la lesión con láser. La aplicación tópica de pazopanib redujo de una manera significativa el progreso de la filtración de la neovascularización coroidal (CNV) a partir del día 14 después del láser (representado por los paneles b), comparándose con los ojos del grupo de control con vehículo (representado por los paneles d y c). Los sitios de lesión con láser se indican con flechas.

De una manera específica, cuando los ojos se trataron con el fármaco, el área de filtración de fluoresceína reveló cambios no significativos de hasta el 111.41 ± 21.34 por ciento (promedio ± SD, tamaño de la lesión de la línea base normalizada hasta el 100 por ciento en el día 7), mientras que los ojos de control desarrollaron un aumento de hasta el 208.5 ± 51.51 por ciento (Figura 1B). Estos resultados indicaron que la administración tópica dos veces al día de pazopanib inhibió el desarrollo de lesión adicional por > 89 por ciento. Notoriamente, la aplicación de pazopanib tópicamente al otro ojo (contralateral) también inhibió de una manera significativa el progreso del tamaño de la lesión en estos estudios. Por consiguiente, en los ojos lesionados cuyo otro ojo fue tratado con pazopanib, la neovascularización coroidal (CNV) demostró solamente

un aumento marginal hasta el 115.24 ± 16.72 por ciento de la línea base (Figura 1B).

Adicionalmente, las secciones retinales histológicas se analizaron en el día 14 después del tratamiento con láser utilizando teñido con hematoxilina y eosina o inmunohistoquímica. Las Figuras 2A y B demuestran que las lesiones de la neovascularización coroidal (CNV) en los ojos tratados con vehículo (Figura 2A, paneles **b** y **c**) fueron más grandes que aquéllas tratadas tópicamente con pazopanib. La Figura 2A muestra las secciones de coroides/retina derivadas a partir de los ojos sin tratamiento con láser (a), y a partir de los ojos tratados con láser (**b** a **d**) que se trataron ya sea tópicamente con pazopanib (**b**) o bien con vehículo (**d**: grupo de control). Observe la reducción de las lesiones de la neovascularización coroidal (CNV) cuando se trató el ojo contralateral (c). La evaluación del grado de neovascularización coroidal (CNV) mediante la medición del espesor relativo de la membrana de neovascularización coroidal (CNV) en las lesiones, reveló una diferencia significativa. Aunque el área de la lesión en los ojos tratados con vehículo fue de 27,397.3 ± 7,386.4 micras cuadradas (μm^2) el área de los ojos tratada con pazopanib sumó hasta 7,760.3 ± 2,312.0 micras cuadradas (μm^2). Por consiguiente, se observó una inhibición significativa del 71.7 por ciento en el tamaño de la lesión, comparándose con el control de vehículo ($p <$ .001) (Fig. 2B). as áreas neovasculares se midieron mediante el análisis cuantitativo de imágenes digitales. En otro estudio, los ojos

tratados con láser de las ratas tratadas tópicamente con pazopanib en el otro ojo, demostraron una inhibición del tamaño de la lesión de aproximadamente el 34 por ciento (Figura 2C). Los datos de histología, junto con los datos obtenidos mediante angiografía de fluorescencia (véase anteriormente), señalan hacia un efecto sistémico producido por el fármaco en el otro ojo, lo cual implica que una dosis oral baja que sea capaz de lograr un efecto sistémico similar, debe ser efectiva en el tratamiento de la neovascularización coroidal (CNV) y, por consiguiente, de los trastornos de angiogénesis ocular o filtración vascular, tales como aquéllos descritos anteriormente.

La administración tópica de pazopanib da como resultado el fármaco detectable en el plasma de las ratas Norway Brown. Después de la administración de una sola gota para los ojos de 30 microlitros, se midieron niveles pico de pazopanib 60 minutos después en el rango de 300 nanogramos / mililitro (Figura 3A). Los niveles e plasma declinaron hasta niveles indetectables después de 24 horas. La administración tópica de gotas individuales de 30 microlitros al ojo izquierdo (OS) solamente, tres veces durante un período de 24 horas, dio como resultado un promedio de 503 nanogramos / gramo de pazopanib en los tejidos de la copa ocular tratada (esclerótica, coroides, y retina). Es interesante que también se observaron niveles detectables en el otro ojo (OD) (promedio = 159 nanogramos / gramo), aunque en una cantidad estadísticamente más baja (Figura 3B).

Examen de Distribución en el Tejido Ocular y Concentraciones Sistémicas del Pazopanib

La distribución en el tejido ocular y las concentraciones sistémicas de radioactividad se evaluaron en seguida de la administración ocular tópica de pazopanib a los conejos alemanes cintados (pigmentados). Se administró una sola dosis objetivo de 60 microlitros de 0.3 miligramos / dosis (30 µCi/dosis) al ojo derecho. Se recolectaron sangre y tejidos oculares a partir de tanto el ojo dosificado como no dosificado (izquierdo), de un animal en cada una de ocho veces de muestreo hasta 24 horas, y se analizaron para determinar la radioactividad total.

Los niveles de radioactividad fueron cuantificables en todas las muestras de sangre y de plasma desde el tiempo más temprano del muestreo (0.25 horas) hasta el último tiempo del muestreo (24 horas), observándose las concentraciones más altas a la 1 hora en sangre (11.3 equivalentes de nanogramos / gramo), y a las 2 horas en plasma (12. equivalentes de nanogramos / gramo).

Los niveles coroidales alcanzaron 40.6 equivalentes de nanogramos / gramo a las 2 horas, y llegaron a su pico en 60.1 equivalentes de nanogramos / gramo a las 8 horas. De una manera similar, los niveles de retina alcanzaron 9.17 equivalentes de nanogramos / gramo a las 2 horas, y llegaron a su pico en 10.2 equivalentes de nanogramos / gramo a las 4 horas. Esto muestra que se alcanzó más de la mitad de los niveles máximos en los tejidos objetivo de la neovascularización coroidal (CNV) dentro de las

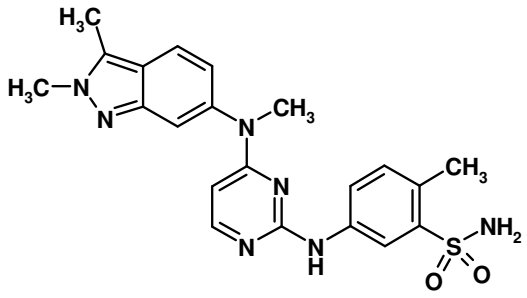
primeras 2 horas después de la administración de las gotas para los ojos. Basándose en la ecuación de Stokes Einstein para la difusión de una molécula pequeña en agua, se estima que, en el escenario del mejor caso, el pazopanib se habría difundido por medio de la difusión local del fármaco cuando mucho en 0.4 centímetros en 2 horas, el cual es un tamaño mucho menor del ojo del conejo (de aproximadamente 1 a 2 centímetros). Sin una contribución sistémica, la difusión local del fármaco no podría explicar la velocidad a la cual el pazopanib llegó a la retina y al coroides.

Los resultados obtenidos en este estudio proporcionan la evidencia de que la vía de suministro sistémico proporciona una contribución importante a los niveles en tejido de retina y coroides. En adición, muestran que cualquier eficacia que se vea en el ojo no tratado vendría principalmente a partir del fármaco sistémicamente suministrado en bajo nivel.

Aunque en la presente se ilustran y se describen con detalle las modalidades específicas de la presente invención, la invención no está limitada a las mismas. Las descripciones detalladas anteriores se proporcionan como ejemplos de la presente invención, y no deben interpretarse para constituir limitación alguna de la invención. Las modificaciones serán obvias para los expertos en la materia, y se pretende que todas las modificaciones que no se aparten del espíritu de la invención se incluyan dentro del alcance de las reivindicaciones adjuntas.

REIVINDICACIONES

1. Un método para el tratamiento de un trastorno de angiogénesis ocular o filtración vascular, en un paciente que padezca esa condición, el cual comprende administrar oralmente al paciente entre 1 y 50 miligramos de un compuesto de la fórmula (I):



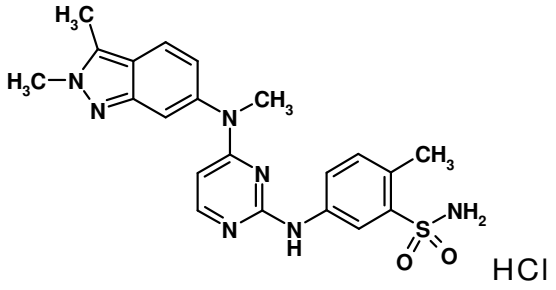
(I)

o una sal farmacéuticamente aceptable o hidrato del mismo.

2. El método de acuerdo con la reivindicación 1, el cual comprende administrar entre 1 y 20 miligramos de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo.

3. El método de acuerdo con la reivindicación 1, el cual comprende administrar entre 5 y 15 miligramos de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo.

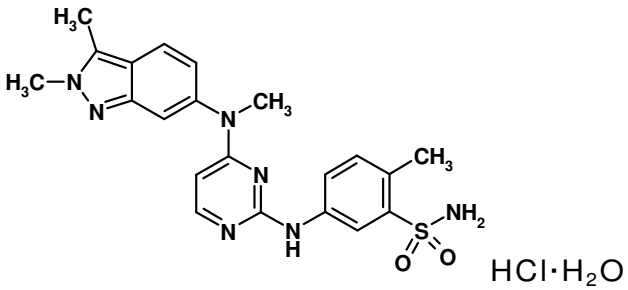
4. El método de acuerdo con cualquiera de las reivindicaciones 1 a 3, en donde el compuesto es un compuesto de la fórmula (I'):



(I')

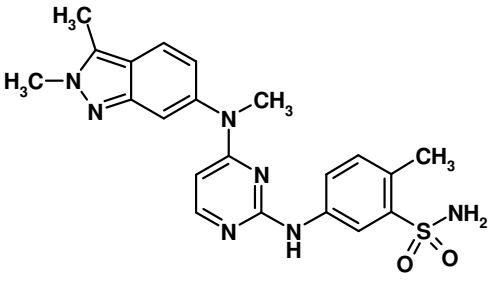
o un hidrato del mismo.

5. El método de acuerdo con cualquiera de las reivindicaciones 1 a 3, en donde el compuesto es un compuesto de la fórmula (I''):



(I'')

6. Un método para el tratamiento de la degeneración macular relacionada con la edad neovascular en un paciente que padezca esa condición, el cual comprende administrar oralmente al paciente entre 1 y 50 miligramos de un compuesto de la fórmula (I):



(I)

o una sal farmacéuticamente aceptable o hidrato del mismo.

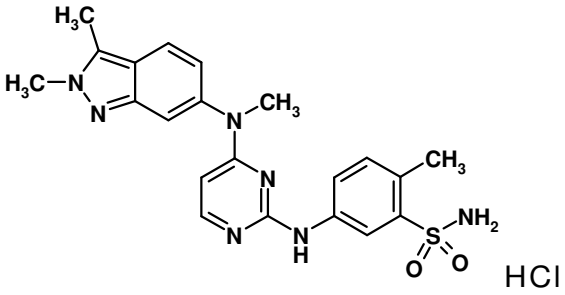
7. El método de acuerdo con la reivindicación 6, el cual comprende administrar entre 1 y 20 miligramos de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo.

8. El método de acuerdo con la reivindicación 6, el cual comprende administrar entre 5 y 15 miligramos de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo.

9. El método de acuerdo con cualquiera de las reivindicaciones 6 a 8, en donde la degeneración macular relacionada con la edad (AMD) neovascular es la degeneración macular relacionada con la edad (AMD) húmeda.

10. El método de acuerdo con cualquiera de las reivindicaciones 6 a 8, en donde la degeneración macular relacionada con la edad (AMD) neovascular es la degeneración macular relacionada con la edad (AMD) seca, y el paciente se caracteriza por tener mayor riesgo de desarrollar la degeneración macular relacionada con la edad (AMD) húmeda.

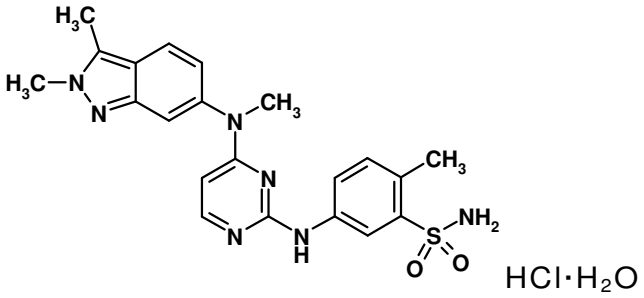
11. El método de acuerdo con cualquiera de las reivindicaciones 6 a 10, en donde el compuesto es un compuesto de la fórmula (I'):



(I')

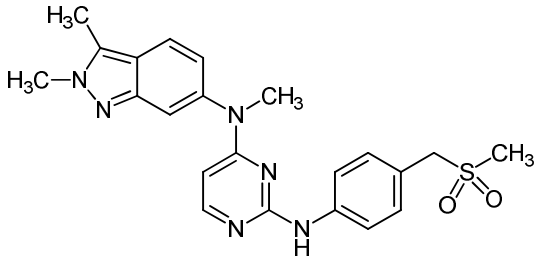
o un hidrato del mismo.

12. El método de acuerdo con cualquiera de las reivindicaciones 6 a 10, en donde el compuesto es un complejo de la fórmula (I''):



(I'')

13. Un método para el tratamiento de un trastorno de angiogénesis ocular o filtración vascular, en un paciente que padezca esa condición, el cual comprende administrar oralmente al paciente, entre 1 y 50 miligramos de un compuesto de la fórmula (II):



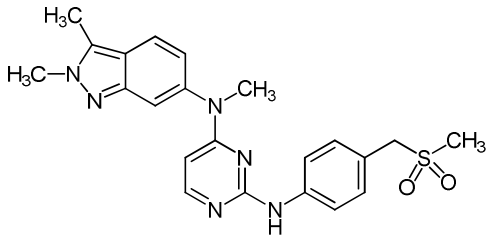
(II)

o una sal farmacéuticamente aceptable del mismo.

14. El método de acuerdo con la reivindicación 13, el cual comprende administrar entre 1 y 20 miligramos de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo.

15. El método de acuerdo con la reivindicación 13, el cual comprende administrar entre 5 y 15 miligramos de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo.

16. Un método para el tratamiento de la degeneración macular relacionada con la edad neovascular en un paciente que padezca esa condición, el cual comprende administrar oralmente al paciente, entre 1 y 50 miligramos de un compuesto de la fórmula (II):



(II)

o una sal farmacéuticamente aceptable del mismo.

17. El método de acuerdo con la reivindicación 16, el cual comprende administrar entre 1 y 20 miligramos de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo.

18. El método de acuerdo con la reivindicación 16, el cual comprende administrar entre 5 y 15 miligramos de un compuesto de

la fórmula (I) o una sal farmacéuticamente aceptable o hidrato del mismo.

19. El método de acuerdo con cualquiera de las reivindicaciones 16 a 18, en donde la degeneración macular relacionada con la edad (AMD) neovascular es la degeneración macular relacionada con la edad (AMD) húmeda.

20. El método de acuerdo con cualquiera de las reivindicaciones 16 a 18, en donde la degeneración macular relacionada con la edad (AMD) neovascular es la degeneración macular relacionada con la edad (AMD) seca, y el paciente se caracteriza por tener mayor riesgo de desarrollar la degeneración macular relacionada con la edad (AMD) húmeda.

21. Un método para el tratamiento de un trastorno de angiogénesis ocular o filtración vascular, en un paciente que padezca esa condición, comprendiendo este método administrar oralmente al paciente, entre 1 y 50 miligramos de un inhibidor adecuado, o una sal farmacéuticamente aceptable del mismo.

22. El método de acuerdo con la reivindicación 21, en donde el inhibidor adecuado es tosilato de sorafenib.

23. El método de acuerdo con la reivindicación 21, en donde el inhibidor adecuado es malato de sunitinib.

24. El método de acuerdo con cualquiera de las reivindicaciones 21 a 23, el cual comprende administrar entre 1 y 20 miligramos del inhibidor adecuado o una sal farmacéuticamente aceptable del mismo.

25. El método de acuerdo con cualquiera de las reivindicaciones 21 a 23, el cual comprende administrar entre 5 y 15 miligramos del inhibidor adecuado o una sal farmacéuticamente aceptable del mismo.

26. El método de acuerdo con cualquiera de las reivindicaciones 21 a 25, en donde el trastorno de angiogénesis ocular o filtración vascular es la degeneración macular relacionada con la edad neovascular.

27. El método de acuerdo con la reivindicación 26, en donde la degeneración macular relacionada con la edad (AMD) neovascular es la degeneración macular relacionada con la edad (AMD) húmeda.

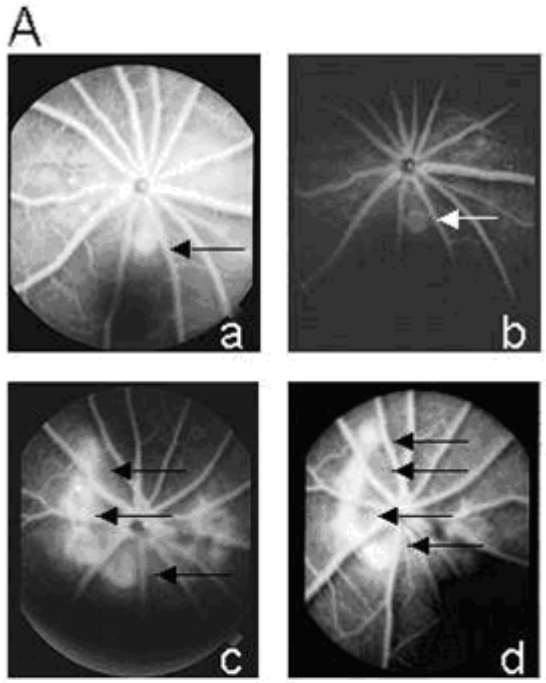
28. El método de acuerdo con la reivindicación 26, en donde la degeneración macular relacionada con la edad (AMD) neovascular es la degeneración macular relacionada con la edad (AMD) seca, y el paciente se caracteriza por tener mayor riesgo de desarrollar la degeneración macular relacionada con la edad (AMD) húmeda.

RESUMEN

La presente invención se refiere a métodos para el tratamiento de trastornos de angiogénesis ocular o filtración vascular en un paciente, mediante la administración de inhibidores adecuados, incluyendo pazopanib o sales farmacéuticamente aceptables o hidratos del mismo.

* * * * *

FIG. 1


A
a
b
c
d

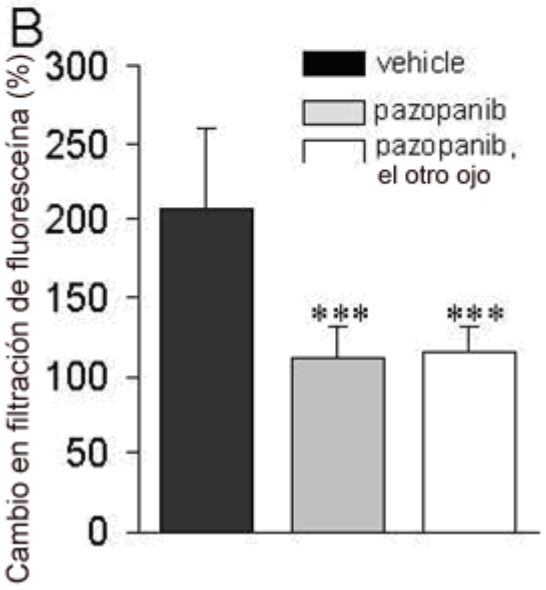

B
Cambio en filtración de fluoresceína (%)
300
250
200
150
100
50
0
vehicle
pazopanib
pazopanib, el otro ojo
***
***

FIG. 2

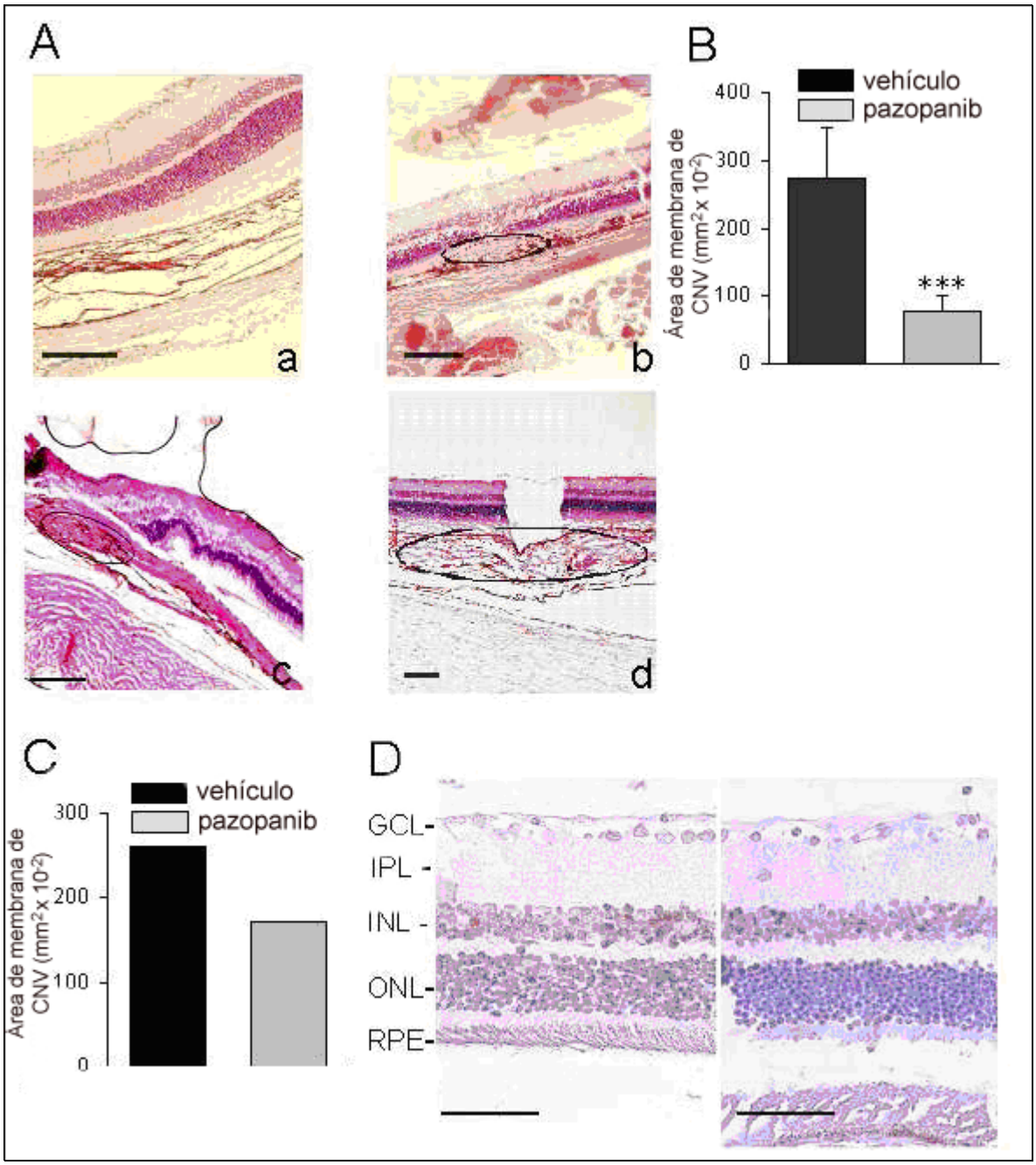
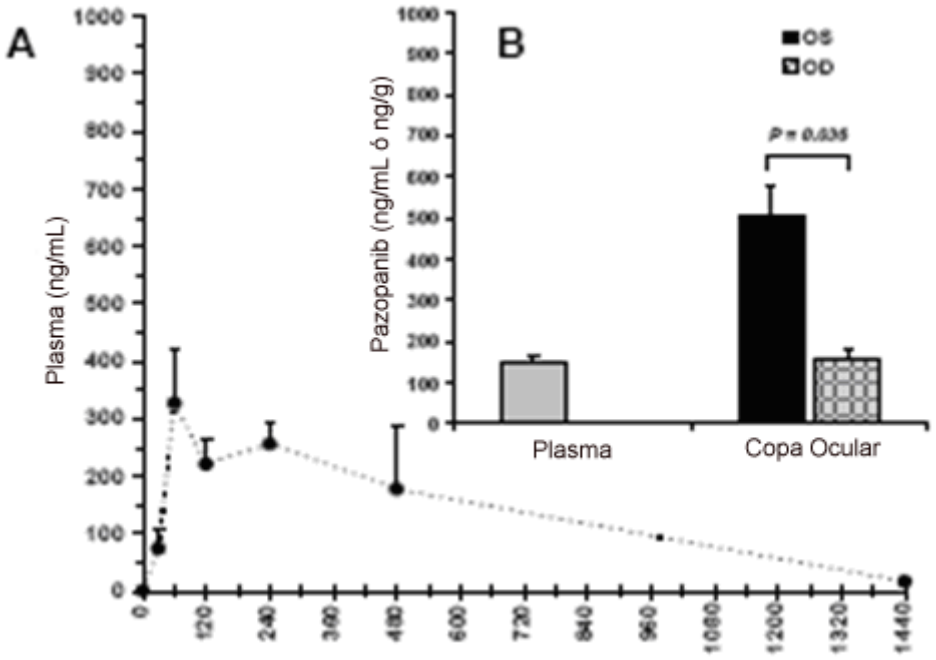

A
a
b
c
d
B
vehículo
pazopanib
Área de membrana de CNV (mm²x 10⁻²)
400
300
200
100
0
***
C
vehículo
pazopanib
Área de membrana de CNV (mm²x 10⁻²)
300
200
100
0
D
GCL
IPL
INL
ONL
RPE

FIG. 3


A
Plasma (ng/mL)
1000
900
800
700
600
500
400
300
200
100
0
0
120
240
360
480
600
720
840
960
1080
1200
1320
1440
B
Pazopanib (ng/mL ó ng/g)
OS
OD
P = 0.035
Plasma
Copa Ocular

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: J. MICHAEL STRICKLAND
GLAXOSMITHKLINE
GLOBAL PATENTS
FIVE MOORE DRIVE, C.2111.2F,
PO BOX 13398
RESEARCH TRIANGLE PARK, NC 27709

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	23 MAR 2011

Applicant's or agent's file reference	FOR FURTHER ACTION
PR64070WO	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 11/20231	05 January 2011 (05.01.2011)	06 January 2010 (06.01.2010)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/52 (2011.01)
USPC - 514/263.22

Applicant GLAXO WELLCOME MANUFACTURING PTE LTD

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 43*bis*.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 be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that 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 66.1*bis*(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 3 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/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	10 February 2011 (10.02.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/20231

Box No. I Basis of this 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.

   ☐ 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)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing 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.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/20231

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. 11-12, 26-28

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 11-12, 26-28 are so unclear that no meaningful opinion could be formed *(specify)*:

said claims are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 11-12, 26-28

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/20231

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)	Claims	10, 20, 22, 23, 24/(22,23), 25/(22, 23)	YES
	Claims	1-9, 13-19, 21, 24/(21), 25/(21)	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-10, 13-25	NO
Industrial applicability (IA)	Claims	1-10, 13-25	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-9, 13-19, 21, 24/(21), and 25/(21) lack novelty under PCT Article 33(2) as anticipated by US 2008/0293691 A1 to Brigandi, et al. (hereinafter 'Brigandi').

Regarding Claim 1, Brigandi discloses a method of treating a disorder of ocular angiogenesis (para [0002] and [0006]) or vascular leakage (para [0024]) in a patient suffering from such condition comprising orally administering (para [0039]) to the patient between 1 and 50 mg (para [0038]) of a compound of formula (I) (para [0012]-[0018]); or a pharmaceutically acceptable salt or hydrate thereof (para [0014]).

Regarding Claim 2, Brigandi further discloses administering between 1 and 20 mg (para [0038]) of a compound of formula (I) (para [0012]-[0018]) or a pharmaceutically acceptable salt or hydrate thereof (para [0014]).

Regarding Claim 3, Brigandi further discloses administering between 5 and 15 mg (para [0038]) of a compound of formula (I) (para [0012]-[0018]) or a pharmaceutically acceptable salt or hydrate thereof (para [0014]).

Regarding Claim 4, Brigandi further discloses that the compound is a compound of formula (I') (para [0012]-[0018], [0127], and [0135]).

Regarding Claim 5, Brigandi further discloses that the compound is a compound of formula (I'') (para [0133]).

Regarding Claim 6, Brigandi discloses a method of treating neovascular age-related macular degeneration (para [0023]) in a patient suffering from such condition comprising orally administering (para [0039]) to the patient between 1 and 50 mg (para [0038]) of a compound of formula (I) (para [0012]-[0018]) or a pharmaceutically acceptable salt or hydrate thereof (para [0014]).

Regarding Claim 7, Brigandi further discloses administering between 1 and 20 mg (para [0038]) of a compound of formula (I) (para [0012]-[0018]) or a pharmaceutically acceptable salt or hydrate thereof (para [0014]).

Regarding Claim 8, Brigandi further discloses administering between 5 and 15 mg (para [0038]) of a compound of formula (I) (para [0012]-[0018]) or a pharmaceutically acceptable salt or hydrate thereof (para [0014]).

Regarding Claim 9, Brigandi further discloses that the neovascular age-related macular degeneration is wet age-related macular degeneration (para [0027], See the exudative AMD, which is synonymous with wet AMD.).

Regarding Claim 13, Brigandi discloses a method of treating a disorder of ocular angiogenesis (para [0002] and [0006]) or vascular leakage (para [0024]) in a patient suffering from such condition comprising orally administering (para [0039]) to the patient between 1 and 50 mg (para [0038]) of a compound of formula (II) (para [0018] and [0137]) or a pharmaceutically acceptable salt thereof (para [0018]).

Regarding Claim 14, Brigandi further discloses administering between 1 and 20 mg (para [0038]) of a compound of formula (II) (para [0018] and [0137]) or a pharmaceutically acceptable salt or hydrate thereof (para [0136]).

Regarding Claim 15, Brigandi further discloses administering between 5 and 15 mg (para [0038]) of a compound of formula (II) (para [0018] and [0137]) or a pharmaceutically acceptable salt or hydrate thereof (para [0136]).

Regarding Claim 16, Brigandi discloses a method of treating neovascular age-related macular degeneration (para [0023]) in a patient suffering from such condition comprising orally administering (para [0039]) to the patient between 1 and 50 mg (para [0038]) of a compound of formula (II) (para [0018] and [0137]) or a pharmaceutically acceptable salt or hydrate thereof (para [0018]).

Regarding Claim 17, Brigandi further discloses administering between 1 and 20 mg (para [0038]) of a compound of formula (II) (para [0018] and [0137]) or a pharmaceutically acceptable salt or hydrate thereof (para [0014]).

continued on Supplemental Box

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/20231

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claims 14 and 15 lack proper antecedent basis for Formula (I) because said claims are dependent upon Claim 13, which recites a Formula (II). For the purposes of this opinion, Claims 14 and 15 are considered have antecedent basis to Formula (II), as recited in Claim 13.

Likewise, Claims 17 and 18 lack proper antecedent basis for Formula (I) because said claims are dependent upon Claim 16, which recites a Formula (II). For the purposes of this opinion, Claims 17 and 18 are considered have antecedent basis to Formula (II) as recited in Claim 16.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/20231

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V.2., Citations and explanations:

Regarding Claim 18, Brigandi further discloses administering between 5 and 15 mg (para [0038]) of a compound of formula (II) (para [0018] and [0137]) or a pharmaceutically acceptable salt or hydrate thereof (para [0014]).

Regarding Claim 19, Brigandi further discloses that the neovascular age-related macular degeneration is wet age-related macular degeneration (para [0027], See the exudative AMD, which is synonymous with wet AMD.).

Regarding Claim 21, Brigandi discloses a method of treating a disorder of ocular angiogenesis or vascular leakage in a patient suffering from such condition, said method comprising orally administering to the patient between 1 and 50 mg of a suitable inhibitor (para [0012] and [0126] and [0127], See the VEGF inhibitor as disclosed in Example 1, which corresponds with Formula (I) of the instant invention.), or pharmaceutically acceptable salt thereof.

Regarding Claim 24/(21), Brigandi further discloses administering between 1 and 20 mg of the suitable inhibitor or a pharmaceutically acceptable salt thereof (para [0038]).

Regarding Claim 25/(21), Brigandi further discloses administering between 5 and 15 mg of the suitable inhibitor or a pharmaceutically acceptable salt thereof (para [0038]).

Claims 10 and 20 lack an inventive step under PCT Article 33(3) as obvious over Brigandi, in view of US 2009/0246124 A1 to Kodadek et al. (hereinafter 'Kodadek').

Regarding Claims 10 and 20, Brigandi further discloses that the neovascular age-related macular degeneration is wet age-related macular degeneration (para [0027], See the exudative AMD, which is synonymous with wet AMD.); but does not specifically disclose that the neovascular age-related macular degeneration is dry age-related macular degeneration and the patient is characterized as being at increased risk of developing wet age-related macular degeneration.
However, Kodadek teaches that dry forms of advanced AMD currently have no treatment other than vitamin supplements (para [0144]) and that anti-VEGF agents can be used to treat wet AMD (para [0147]).
To a person of ordinary skill in the art, it would have been obvious to try treating dry AMD as taught by Kodadek using the method of treating age-related macular degeneration as in Brigandi in order to identify new treatments of AMD related disease progression (Kodadek: para [0144]), because Brigandi and Kodadek are directed towards VEGF therapies comprising Pazopanib (the generic name for the instant Formula (I)) in treating angiogenesis (Kodadek: para [0100] and [0102]).

Claims 22, 23, 24/(22,23), and 25/(22, 23) lack an inventive step under PCT Article 33(3) as obvious over Brigandi, in view of US 2009/0004213 A1 to Singh, et al. (hereinafter 'Singh')

Regarding Claims 22 and 23, Brigandi further discloses salts of the inhibitor as in Claim 21 comprising tosylate and malate (para [0036]); but does not specifically disclose that the suitable inhibitor is sorafenib tosylate (as in Claim 22) or the suitable inhibitor is sunitinib malate (as in Claim 23).
However, Singh teaches a pharmaceutical composition comprising VEGFR inhibitors (para [0059]) and pazopanib (para [0056]) for treatment of angiogenesis (para [0064]) comprising sorafenib tosylate (para [0063]-[0066]) or sunitinib malate (para [0063]-[0066]).
To a person of ordinary skill in the art, it would have been obvious to substitute the inhibiting agents as taught by Singh for the tosylate or malate salt compounds in the method of treating a disorder of ocular angiogenesis or vascular leakage as in Brigandi in order to enhance the kinase inhibitory function of the method of treating (Singh: para [0063]), because Brigandi and Singh are directed towards applications of pazopanib (the generic name for the instant Formula (I)) in treating angiogenesis.

Regarding Claim 24/(22, 23), Brigandi further discloses administering between 1 and 20 mg of the suitable inhibitor or a pharmaceutically acceptable salt thereof (para [0038]).

Regarding Claim 25/(22, 23), Brigandi further discloses administering between 5 and 15 mg of the suitable inhibitor or a pharmaceutically acceptable salt thereof (para [0038]).

Claims 1-10 and 13-25 have industrial applicability as defined by PCT Article 33(4) because the subject matter could be made or used in industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PR64070WO	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 11/20231	International filing date *(day/month/year)* 05 January 2011 (05.01.2011)	(Earliest) Priority Date *(day/month/year)* 06 January 2010 (06.01.2010)
Applicant GLAXO WELLCOME MANUFACTURING PTE LTD		

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 3 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. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ 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, 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. 1

☒ 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.
PCT/US 11/20231

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 11-12, 26-28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/20231

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/52 (2011.01)
USPC - 514/263.22
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)
IPC(8)- A61K 31/52 (2011.01);
USPC- 514/263.22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/117, 600, 601, 210.14;
Patents and NPL

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (US Pat, PgPub, EPO, JPO: classification, keyword; search terms below), GoogleScholar;
search terms: pazopanib, votrient, benzene sulfonamide, angiogenesis, occular, vascular, leakage, macular, degeneration, sorafenib, sunitinib, tosylate, malate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2008/0293691 A1 (BRIGANDI et al.) 27 November 2008 (27.11.2008), para [0002], [0006], [0012]-[0018], [0023]-[0027], [0038], [0039], [0126], [0127], [0133]-[0137]	1-9, 13-19, 21, 24/(21), 25/(21) ---------- 10, 20, 22, 23, 24/(22,23), 25/(22, 23)
Y	US 2009/0246124 A1 (KODADEK et al.) 01 October 2009 (01.12.2009), para [0100], [0102], [0144], [0147]	10, 20
Y	US 2009/0004213 A1 (SINGH et al.) 01 January 2009 (01.01.2009), para [0056], [0059], [0063]-[0066]	22, 23, 24/(22,23), 25/(22, 23)
Y	US 2009/0325959 A1 (VITTITOW et al.) 31 December 2009 (31.12.2009), para [0030], [0274], Table A	1-10, 13-25
Y	CIULLA et al. "Anti-vascular endothelial growth factor therapy for neovascular ocular diseases other than age-related macular degeneration." Current Opinion in Ophthalmology [online], May 2009 [Retrieved on 2011-02-10], Vol. 20, Iss. 3, pp. 166-174, Retrieved from the Internet: <URL: http://journals.lww.com/>	1-10, 13-25
Y	US 2007/0270427 A1 (BOLOOR et al.) 22 November 2007 (22.11.2007), para [0109], [0189], [0303]	1-10, 13-25
Y	WO 02/059110 A1 (BOLOOR et al.) 01 August 2002 (01.08.2002), pg 25, ln 8-9, pg 42, ln 4-31	1-10, 13-25

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2011 (10.02.2011)	23 MAR 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)