

Clarke, Modet & Cº

COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 14-186994-00002-0000

Fecha: 2015-04-21 15:21:43 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eva: 378 FASENACIONALI
Act. 608 MODIFICASOLICIT Folios: 8

P-4415

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. 14-186.994

Solicitud de patente a nombre de **GILEAD SCIENCES, INC.**

Yo, SILVANA MARIA LÓPEZ DÍAZ identificada como aparece al pie de mi firma, domiciliada en la Cra. 11 No. 86-53 Piso 6, obrando como apoderada de la sociedad **GILEAD SCIENCES, INC.**, domiciliada en California, Estados Unidos, solicitante de la patente de la referencia, me permito informar lo siguiente:

Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial un nuevo capítulo reivindicatorio que comprende un total de 2 reivindicaciones, las cuales corresponden a aquellas de la patente estadounidense No. US 8,742,126 (B6), la cual se adjunta a este memorial, para su beneficio.

De esta manera, se asegura que este nuevo capítulo reivindicatorio está debidamente soportado en el capítulo descriptivo de la presente solicitud, por tanto no se incurre en ningún instante en ampliación de materia, razón por la cual se informa, que estas nuevas reivindicaciones remplazan por completo a las originalmente presentadas ante este Despacho y en consecuencia, se solicita amablemente, realizar el examen de fondo sobre este nuevo acápite reivindicatorio, en el momento que sea indicado. Por último, se adjunta el recibo de pago correspondiente a la tasa por modificación voluntaria.

Señor Superintendente,

SILVANA MARIA LÓPEZ DÍAZ

C.C. 22.468.787 de Barranquilla

T.P 147463 del CSJ

notificaciones@clarkemodet.com.co

Λ

Clarke, Modet & Cº

COLOMBIA

ANEXOS

- Nuevo capítulo reivindicatorio compuesto por 2 reivindicaciones.
- Copia de la patente estadounidense US 8,742,126
- Copia de recibo de pago por concepto de modificación voluntaria, por un valor de \$ 132.000.

2

**DIRECCIÓN DE NUEVAS CREACIONES
MODIFICACIONES Y/O CORRECCIONES**

1. Identificación del Trámite

☐ Error material

☒ **Modificación a una Solicitud en trámite**

☒ **Patente de Invención**

☐ Patente de Modelo de Utilidad

☐ Registro de Diseño Industrial

☐ Esquema de Trazado de Circuitos Integrados

2. Datos del solicitante

Persona Natural ☐

Persona Jurídica ☒

GILEAD SCIENCES, INC.

Nombre o denominación / Nombre o razón social completa

Nombre representante legal

Tipo de empresa

Micro ☐

Pequeña ☐

Mediana ☐

Otra ☐

Documento de identificación:

☐ C.C.

☐ C.E.

☐ NIT

☐ Otro Número

Nacionalidad/País de constitución
ESTADOS UNIDOS

Dirección y domicilio del titular
333 Lakeside Drive Foster City

Ciudad
California 94404

Dirección electrónica

No. Fax

Número telefónico

☐

Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del apoderado:

SILVANA MARIA LÓPEZ DÍAZ

C.C. 22.468.787

147463 CSI

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

Dirección y domicilio		Ciudad
Carrera 11 No. 86-53, Piso 6, Bogotá D.C., Colombia		Bogotá D.C.
Dirección electrónica	No. Fax	Número telefónico
<u>notificaciones@clarkemodet.com.co</u>	6350824	6181088

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general

4. Datos del trámite

Corrección:

Expediente No. 14-186.994

Aparece _____

Debe ser _____

Modificación:

Presentación Solicitud Divisional.

Modificación al capítulo descriptivo.

☐

☒ Modificación al capítulo Reivindicatorio

Presento junto con este memorial un nuevo pliego reivindicatorio que comprende un total de 2 reivindicaciones.

Modificación al resumen.

☐

Modificación a los dibujos.

☐

Modificación al solicitante.

5. Anexos

☒

Comprobante de pago de la tasa para la presentación de la corrección y/o modificación

☐

Poder, si fuere el caso.

☒

Documento que contiene las modificaciones o correcciones.

☐

Copia de la solicitud y sus anexos en formato magnético.

6. Firma


SILVANA MARIA LÓPEZ DÍAZ

C.C. 22.468.787 de Barranquilla

T.P 147463 del CSJ

notificaciones@clarkemodet.com.co

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -



RECIBO DE CAJA

No. 15 - 0037963

Bogotá D.C., Abril 08 de 2015 - 07:57:55

RECIBIDO DE : CLARKE MODET

NI 830.008.643

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	696971376	07/04/2015	5.658.000.00

*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1 50005-01-03 CAMBIO DE MODALIDAD Y MODIFICACIONES EN CREACION CORRECCION A SOLICITUD EN TRAMITE / MODIFICA		132.000.00	132.000.00
			\$132.000.00

SON: **CIENTO TREINTA Y DOS MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 14-186994- -00002-0000

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Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Abril 8 de 2015 - 07:58:10

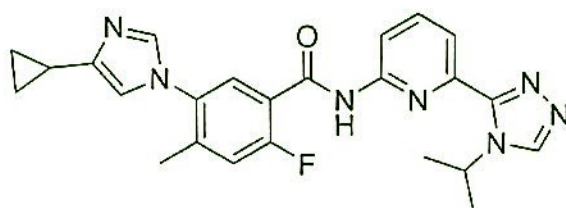
5

P-4415

P-4415
Reiv. Modificadas
21/04/2015

REIVINDICACIONES

1. Un compuesto de fórmula (I)



(I)

o una sal farmacéuticamente aceptable de la misma.

2. Una composición farmacéutica que comprende el compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo y un portador farmacéuticamente aceptable.



US008742126B2

(12) **United States Patent**
Notte

(10) **Patent No.:** **US 8,742,126 B2**
(45) **Date of Patent:** **Jun. 3, 2014**

(54) **APOPTOSIS SIGNAL-REGULATING KINASE INHIBITOR**

2010/0029619 A1 2/2010 Uchikawa et al.
2011/0009410 A1* 1/2011 Corkey et al. 546/256
2012/0004267 A1 1/2012 Corkey et al.

(71) Applicant: **Gilead Sciences, Inc., Foster City, CA (US)**

FOREIGN PATENT DOCUMENTS

(72) Inventor: **Gregory Notte, San Mateo, CA (US)**

EP 2058309 A1 5/2009
WO WO-2008042867 A2 4/2008
WO WO-2009011850 A2 1/2009
WO WO-2009027283 A1 3/2009

(73) Assignee: **Gilead Sciences, Inc., Foster City, CA (US)**

(Continued)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

OTHER PUBLICATIONS

Knittel J and Zavod R. Drug Design and Relationship of Functional Groups to Pharmacological Activity; Foye's Principles of Medicinal Chemistry, 5th Edition, Lippincott Williams & Wilkins; ed. David A Williams and Thomas L Lemke; 2002; 37-67.*

(21) Appl. No.: **13/748,901**

(Continued)

(22) Filed: **Jan. 24, 2013**

(65) **Prior Publication Data**
US 2013/0197037 A1 Aug. 1, 2013

Primary Examiner — Timothy Thomas

Assistant Examiner — Rayna B Rodriguez

(74) Attorney, Agent, or Firm — Gilead Sciences, Inc.; Yu-Ming Dammann

Related U.S. Application Data

(60) Provisional application No. 61/591,710, filed on Jan. 27, 2012.

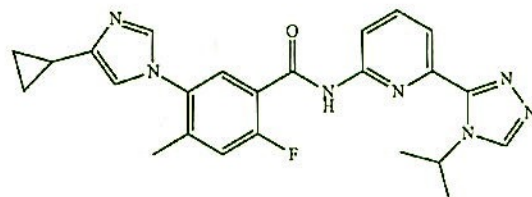
(57) **ABSTRACT**

The present invention relates to a compound of formula (I):

(51) Int. Cl. **C07D 213/56** (2006.01)

(52) U.S. Cl. **CPC** **C07D 213/56** (2013.01)
USPC **546/340**

(58) **Field of Classification Search**
CPC **C07D 401/14; C07D 213/56**
See application file for complete search history.



(I)

The compound has apoptosis signal-regulating kinase ("ASK1") inhibitory activity, and is thus useful in the treatment of diseases such as kidney disease, diabetic nephropathy and kidney fibrosis.

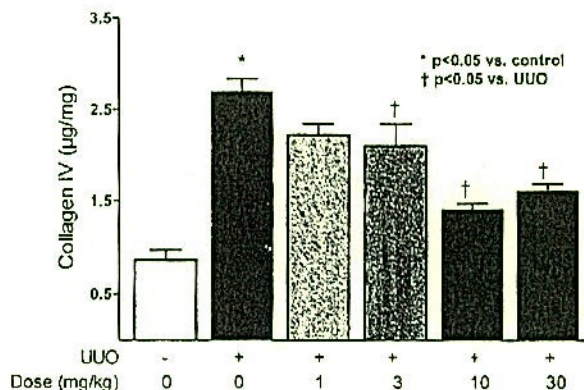
(56) **References Cited**

U.S. PATENT DOCUMENTS

8,263,595 B2 9/2012 Swinnen et al.
8,378,108 B2 2/2013 Corkey et al.
2006/0223996 A1 10/2006 Sun et al.
2009/0318425 A1 12/2009 Chang et al.

2 Claims, 2 Drawing Sheets

Kidney Collagen IV Protein



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General Study Design for the Rat Unilateral Ureter Obstruction (UUO) Model of Kidney Fibrosis.

Male Sprague-Dawley rats were fed normal chow, housed under standard conditions, and allowed to acclimate for at least 7 days before surgery. At the inception of study, rats were placed into weight-matched groups, and administered (2 ml/kg p.o. bid) via oral gavage vehicle, one of four dose levels of compounds (1, 3, 10, or 30 mg/kg). Rats were anesthetized with isoflurane anesthesia on a nosecone, and laparotomy was performed. Rats underwent complete obstruction of the right ureter (UUO) using heat sterilized instruments and aseptic surgical technique. Rats were administered 50 µl Penicillin G (i.m.) immediately post-operatively. Rats were allowed to recover in a clean, heated cage before being returned to normal vivarium conditions. Rats were administered compounds at the dose described above twice daily (at 12 hour intervals) for the subsequent 7 days. On day 7 following surgery, rats were anesthetized with isoflurane and serum, plasma, and urine collected. Animals were then euthanized, the kidneys harvested, and renal cortical biopsies collected for morphological, histological, and biochemical analysis. All tissues for biochemical analysis are flash-frozen in liquid nitrogen and stored at -80° C., tissues for histological analysis were fixed in 10% neutral buffered formalin.

Renal fibrosis was evaluated by measuring the amount of collagen IV in the kidney by an ELISA method and by examining the accumulation of alpha-smooth muscle actin positive myofibroblasts in the kidney by immunohistochemistry. For the former, a small piece of frozen kidney cortex was transferred homogenized in RIPA buffer then centrifuged at 14000xg for 10 minutes at 4° C. The supernatant was collected into pre-chilled tubes and the protein concentration was determined. Equivalent amount of total protein were subjected to a Col IV ELISA assay (Exocell) according to the manufacturers instructions.

Formalin fixed and paraffin embedded kidney tissue was stained with an alpha-smooth muscle actin as previously described (Stambe et al., The Role of p38 Mitogen-Activated Protein Kinase Activation in Renal Fibrosis *J Am Soc Nephrol* 15: 370-379, 2004).

Results:

The compound of formula (I) was found to significantly reduce kidney Collagen IV induction (FIG. 1) and accumulation of alpha-smooth muscle positive myofibroblasts (FIG. 2) at doses of 3 to 30 mg/kg.

Comparative Data for Compound of Formula (I) and Reference Compounds

The following table provides comparative results for the compound of formula (I) and the reference compounds A and B disclosed in U.S. Patent publication No. 2011/00095410A1, published Jan. 13, 2011. Applicants note that experiments for which results are compared below were performed under similar conditions but not necessarily simultaneously.

TABLE

	Compound of formula (I)	Compound A	Compound B
IC ₅₀ (nM)	3	5	6.5
EC ₅₀ (nM)	2	3.4	18 (9X)
PBAdj EC ₅₀ (nM)	17	71 (4X)	563 (33X)
CACO (A/B, B/A)	27/35	3.1/18.5	0.26/4

TABLE-continued

	Compound of formula (I)	Compound A	Compound B
Efflux ratio (B/A)/(A/B)	1.3	6.0	15.4
fu	12	4.8	3.2
Cyp3A4 IC ₅₀ Testosterone (TST) (uM)	11	1.1 (10X)	4 (2.8X)
Cyp3A4 IC ₅₀ /PBAdj.EC ₅₀	647	15 (43X)	7 (92X)
Vss (L/Kg) in rats	0.55	0.17 (3.2X)	0.54
CL (L/hr/kg) in rats	0.11	0.30 (2.7X)	0.39 (3.6X)
% F in rats	75	11 (6.8X)	50 (1.5X)
t _{1/2} in rats (hr)	5.07	0.59 (8.6X)	1.3 (3.9X)

() values in parenthesis represent the number of times the compound of formula (I) shows an improvement over the indicated compound for the indicated parameter.

15 The following can be deduced from the above comparative data:

The compound of formula (I) has an EC₅₀ that is comparable to that of Compound A.

The compound of formula (I) has a functional IC₅₀ that is comparable to IC₅₀ for compounds A and B.

20 The compound of formula (I) has a protein binding adjusted EC₅₀ that is 4 times lower than that of compound A and 33 times lower than that of compound B.

The compound of formula (I) is a weaker Cyp3A4 inhibitor compared to compounds A and B.

25 The compound of Formula (I) has a CYP3A4 IC₅₀/PBAdj.EC₅₀ value that is 43 times higher than that for compound of formula A, and 92 times higher than for the compound of formula B.

30 The compound of formula (I) has a Rat CL value that is 2.7 times lower than that for compound of formula A, and 3.6 times lower than that for the compound of formula B.

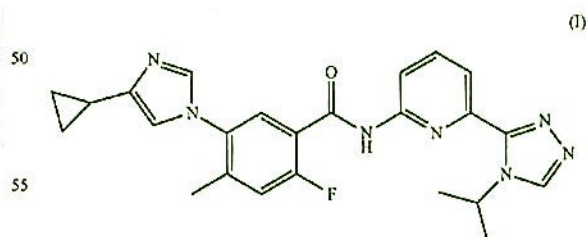
The compound of formula (I) has a percent bioavailability in rats that is 6.8 times higher than compound A and 1.5 times higher than compound B.

35 The compound of formula (I) has a half life in rats that is 8.6 times longer than that of compound A and 3.9 times longer than that of compound B.

The above data fairly suggest that the compound of formula (I) has unexpected and advantageous properties compared to compounds of formula A and B; and that the compound of formula (I) is likely a better candidate for further development for the treatment of chronic kidney disease, lung and/or kidney fibrosis, and/or cardio-renal diseases.

45 What is claimed is:

1. A compound of formula (I)



or a pharmaceutically acceptable salt thereof.

60 2. A pharmaceutically composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

* * * * *

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