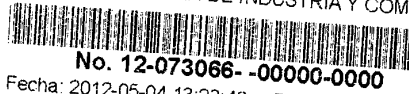




SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 12-073066- -00000-0000

Fecha: 2012-05-04 13:23:46
Tra. 11 PATENTEIYII
Act. 411 PRESENTACION

Dep. 2020 DIR.NUEVASCR
Eve: 378 FASENACIONALI
Folios: 159

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE
INVENCION

TITULO: DERIVADOS DE SULFONAMIDA HETEROCÍCLICOS ÚTILES COMO
INHIBIDORES DE MEK.

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH- 4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 04 de Mayo de 2012

P2012/000042



No. 12-073066-00000-0000

Fecha: 2012-05-04 13:23:46 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 159

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD

PATENTE PCT

ENTRADA EN FASE NACIONAL

P2012/000042

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE
(71)

Nombre: **NOVARTIS AG**

Dirección: Lichtstrasse 35, CH-4056 Basel

Nacionalidad o Domicilio: Suiza

Lugar de Constitución: Suiza

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 D.C.

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olartemoure.com

IDENTIFICACIÓN

C.C. ☒ 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/EP2010/066659

Fecha Noviembre 02, 2010

Publicación Internacional No. WO 2011/054828

Fecha Mayo 12, 2011

6

Título (54) **DERIVADOS DE SULFONAMIDA HETEROCÍCLICOS ÚTILES COMO INHIBIDORES DE MEK.**

Clasificación Internacional (51) C07D 471/04; C07D 498/04; C07D 513/04; A61K 31/4355; A61K 31/4365; A61K 31/437; A61P 29/00; A61P 35/00.

Prioridad

SI ☒ NO ☐

(33) País de Origen

IN

(32) Fecha

Noviembre 04, 2009

(31) Número de Solicitud

2678/CHE/2009

9

Comprobante de pago No. 12-0040906

Fecha Abril 26, 2012



ANEXOS



Comprobante de pago de la tasa de presentación de la solicitud.



Dóculoento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.



Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 08-102.832.



Documento de cesión del inventor al solicitante o a su causante.



Declaraciones.



Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).



Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).



Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).



Traducción del examen preliminar internacional efectuado por la IPEA.



De ser el caso, copia del contrato de acceso.



De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.



De ser el caso, certificado de depósito del material biológico.



Arte final 12 x 12.



De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.



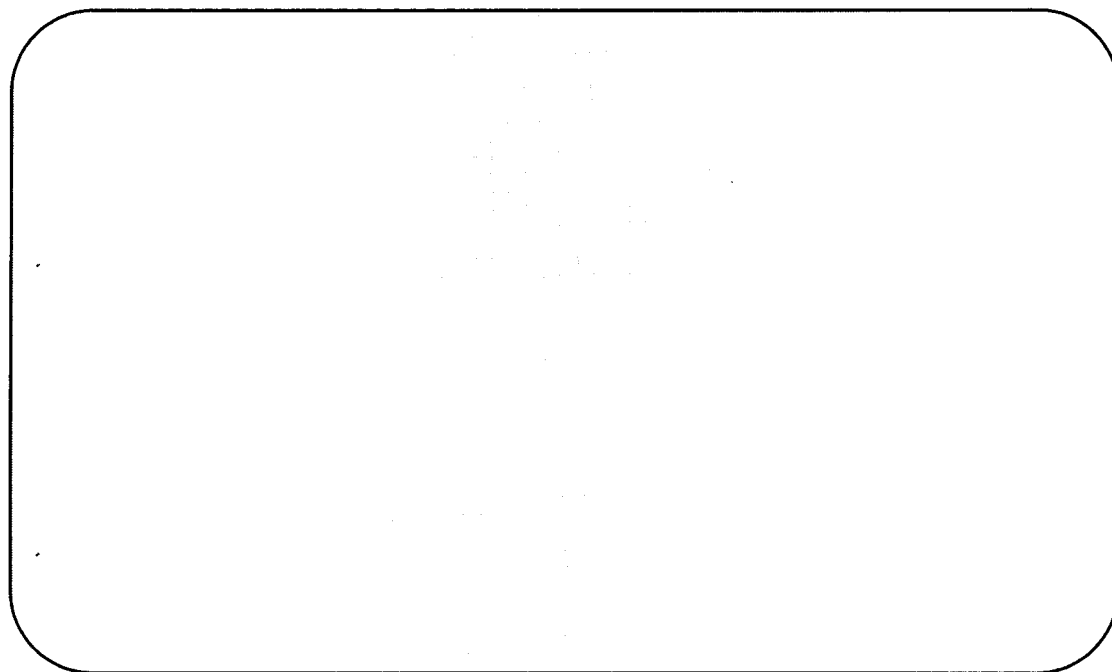
De ser el caso, modificaciones efectuadas a la solicitud internacional.



Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

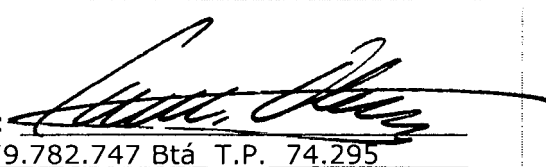


12

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/EP2010/066659

BOCK, Mark G.

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Citizen: United States of America

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Switzerland
Citizen: Germany

PANDIT, Chetan

Aurigene Discovery Technologies Limited
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Electronic City Phase II, Hosur Road, Bangalore,
Karnataka 560 100, India
Citizen: Canada

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

Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 12 - 0040906
		Bogotá D.C., Abril 26 de 2012 - 10:45:22

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	455539792	25/04/2012	5.900.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	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. 12-073066- -00000-0000

Fecha: 2012-05-04 13:23:46 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 159

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

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

Abril 26 de 2012 - 10:45:23

5

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.



Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.



Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 8346



Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
Jacqueline Chaparro
José Luis Loudoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahin
Graciela Melo

Power of Attorney

The undersigned,

domiciled in

NOVARTIS AG

El suscrito,

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Date/Fecha: June 27, 2006

City, Country/Ciudad, País: Basel, Switzerland

Arthur Canonica

Pascal Traub

7

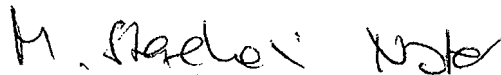
Attestation

- 1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.
- 2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.
- 3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.
- 4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)



Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven),
2009 (two thousand and nine).

Leg.Prot.Nr. 975 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)

This official document

2. is signed by *A. Stalder*

3. in his/her function as *off. not.*

4. and certified by the seal of the *Gemeinde*

Certified *24. Aug. 2003*

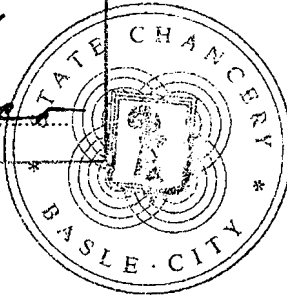
5. in Basel (Bâle) 6. on

7. by the State Chancery of the Canton of Basel-Stadt

8. no. *2099/18584*

9. Seal/stamp: 10. Signature: *Fischer*

Heidi Fischer



Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to the international application PCT/EP2010/066659,

Novartis AG, is entitled to apply for and be granted a patent by virtue of the following:

an assignment from:

Dinesh CHIKKANNA, citizen of India, Aurigene Discovery Technologies Limited, 39-40, KIADB Industrial Area, Electronic City Phase II, Hosur Road, Bangalore 560 100, Karnataka, IN, dated October 18, 2010

Chetan PANDIT, citizen of Canada, Aurigene Discovery Technologies Limited, 39-40, KIADB Industrial Area, Electronic City Phase II, Hosur Road, Bangalore 560 100, Karnataka, IN, dated October 18, 2010

to Aurigene Discovery Technologies Limited.

an assignment from:

Mark G. BOCK, citizen of United States of America, Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, MA 02139, US, dated October 14, 2010

Clive MCCARTHY, citizen of United Kingdom, Novartis Pharma AG, Werk Klybeck, Postfach, 4002 Basel, CH, dated October 15, 2010

Henrik MOEBITZ, citizen of Germany, Novartis Pharma AG, Werk Klybeck, Postfach, 4002 Basel, CH, dated October 13, 2010

Aurigene Discovery Technologies Limited, #39-P, 40-P, KIADB Industrial Layout, Electronics City Phase-2, Hosur Road, Bangalore-560100, Karnataka, IN, dated October 18, 2010

to Novartis AG.

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 May 2011 (12.05.2011)



(10) International Publication Number
WO 2011/054828 A1

(51) International Patent Classification:

C07D 471/04 (2006.01) A61K 31/4365 (2006.01)
C07D 498/04 (2006.01) A61K 31/437 (2006.01)
C07D 513/04 (2006.01) A61P 29/00 (2006.01)
A61K 31/4355 (2006.01) A61P 35/00 (2006.01)

(21) International Application Number:

PCT/EP2010/066659

(22) International Filing Date:

2 November 2010 (02.11.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2678/CH/2009 4 November 2009 (04.11.2009) IN

(71) Applicant (for all designated States except US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BOCK, Mark G.** [US/US]; Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **CHIKKANNA, Dinesh** [IN/IN]; Aurigene Discovery Technologies Limited, 39-40, KIADB Industrial Area, Electronic City Phase II, Hosur Road, Bangalore, Karnataka 560 100 (IN). **MC-CARTHY, Clive** [GB/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel (CH). **MOEBITZ, Henrik** [DE/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel (CH). **PANDIT, Chetan** [CA/IN]; Aurigene Discovery Technologies Limited,

39-40, KIADB Industrial Area, Electronic City Phase II, Hosur Road, Bangalore, Karnataka 560 100 (IN).

(74) Agent: **STRANG, Andrea**; NOVARTIS PHARMA AG, Patent Department, CH-4002 Basel (CH).

(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).

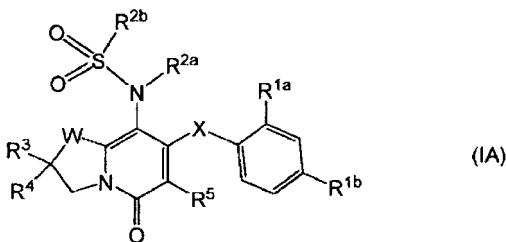
Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

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

(54) Title: HETEROCYCLIC SULFONAMIDE DERIVATIVES USEFUL AS MEK INHIBITORS



(57) Abstract: The present invention relates to compounds of Formula (IA) Where R^{1a}, R^{1b}, X, R^{2a}, R^{2b}, W, R³, R⁴, and R⁵ are as defined herein as well as pharmaceutically acceptable salts thereof. The compounds have been shown to act as MEK inhibitors which may be useful in the treatment of hyperproliferative diseases, like cancer and inflammation.

WO 2011/054828 A1

HETEROCYCLIC SULFONAMIDE DERIVATIVES USEFUL AS MEK INHIBITORS

FIELD OF THE INVENTION

The invention relates to heterocyclic sulfonamide compounds and
5 pharmaceutical compositions thereof, in particular heterocyclic sulfonamide
compounds that are specific inhibitors of kinase activity of MEK. The invention
also relates to the use of the compounds and compositions thereof in the
management of hyperproliferative diseases like cancer and inflammation.

BACKGROUND

10 Hyperproliferative diseases like cancer and inflammation are receiving a
lot of attention from the scientific community and there is a strong desire to
discover compounds that provide therapeutic benefits with regard to treating
hyperproliferative diseases. In this regard efforts have been made to identify and
target specific mechanisms which play a role in proliferating the diseases.

15 One target of interest is the over-activation of mitogen-activated protein
(MAP) kinase cascade which is known to play an important role in cell
proliferation and differentiation. This pathway can be activated when a growth
factor binds to its receptor tyrosine kinase. This interaction promotes RAS
association with RAF and initiates a phosphorylation cascade through MEK
20 (MAP kinase) to ERK. Inhibition of this pathway is known to be beneficial in
treating hyperproliferative diseases. MEK is an attractive therapeutic target
because the only known substrates for MEK phosphorylation are the MAP
kinases, ERK1 and ERK2. Constitutive activation of MEK/ERK was been found
in pancreatic, colon, lung, kidney and ovarian primary tumor samples.

25 Phosphorylation of MEK appears to increase its affinity and its catalytic
activity toward ERK as well as its affinity for ATP. This invention describes
compounds that inhibit MEK activity by modulation of ATP binding, association of
MEK with ERK by mechanisms that are competitive, and/or allosteric and/or
uncompetitive.

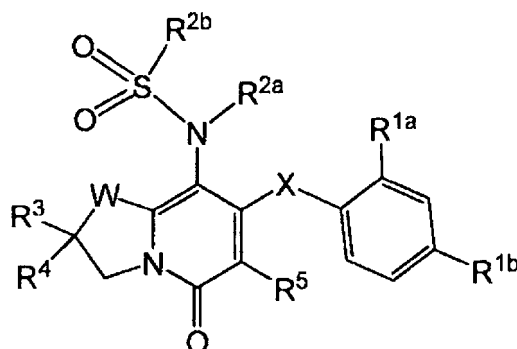
30 Activation of MEK has been demonstrated in many disease models thus
suggesting that inhibition of MEK could have potential therapeutic benefit in

various diseases such as Pain (see, e.g., Evidence of efficacy in pain models described in J. Neurosci. 22:478, 2002; Acta Pharmacol Sin. 26:789 2005; Expert Opin Ther Targets. 9:699, 2005; and Mol. Pain. 2:2, 2006); Stroke (see, e.g., Evidence of efficacy in stroke models significant neuroprotection against ischemic brain injury by inhibition of the MEK described in J. Pharmacol. Exp. Ther. 304:172, 2003; and Brain Res. 996:55, 2004); Diabetes (see, e.g., Evidence in diabetic complications described in Am. J. Physiol. Renal. 286, F120 2004); Inflammation (see e.g., Evidence of efficacy in inflammation models described in Biochem Biophys. Res. Com. 268:647, 2000); and Arthritis (see, e.g., Evidence of efficacy in experimental osteoarthritis and arthritis as described in J. Clin. Invest. 116:163, 2006).

Although inhibition of MEK has been shown to have potential therapeutic benefit in several studies, there still remains a need to find compounds having commercial application.

SUMMARY

The invention provides a sulfonamide compound of Formula (IA) is provided



(IA)

wherein

X is -N(R⁶)-, where R⁶ is H or (C₁-C₆)alkyl;

R^{1a} and R^{1b} are each independently selected from hydroxyl, cyano, nitro, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₂-C₆)alkenyloxy, (C₂-C₆)alkynyloxy, halogen, (C₁-C₆)alkyl-C(O)-, -C(O)OH, -C(O)-O(C₁-C₆)alkyl, amino, (C₁-C₆)alkylNH-, di((C₁-C₆)alkyl)N-, (C₁-C₆)alkylNH-C(O)-, di((C₁-C₆)alkyl)N-C(O)-

, (C₁-C₆)alkyl-C(O)-NH-, (C₁-C₆)alkyl-C(O)-N((C₁-C₆)alkyl)-, (C₁-C₆)alkyl-SO₂-NH-, (C₁-C₆)alkyl-SO₂-N((C₁-C₆)alkyl)-, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-S(O)-, (C₁-C₆)alkyl-SO₂-, NH₂-SO₂-, (C₁-C₆)alkylNH-SO₂- and di((C₁-C₆)alkyl)N-SO₂-, where each of said (C₁-C₆)alkyl, (C₂-C₆)alkenyl, and (C₂-C₆)alkynyl moieties are optionally substituted by one or more substituents each independently selected from halogen, hydroxyl, (C₁-C₆)alkoxy, amino, (C₁-C₆)alkyl-NH-, di((C₁-C₆)alkyl)N- or cyano;

R^{2a} is H or C₁₋₆alkyl;

R^{2b} is a chemical moiety selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, NR¹⁰R¹², cycloalkyl, aryl, heterocycloalkyl, or heteroaryl, wherein said chemical moiety is optionally substituted by one to three substituents each independently selected from halogen, cyano, hydroxyl, (C₁-C₆)alkoxy, (C₂-C₆)alkenyloxy, (C₂-C₆)alkynyloxy, (C₁-C₆)alkyl-S-, halo-substituted(C₁-C₆)alkyl, amino, (C₁-C₆)alkylNH-, di((C₁-C₆)alkyl)N-, HC(O)-NH-, (C₁-C₆)alkyl-C(O)-NH-, HC(O)-N(C₁-C₆)alkyl-, (C₁-C₆)alkyl-C(O)-N((C₁-C₆)alkyl)-, monocyclic cycloalkyl or monocyclic heterocycloalkyl, where said cycloalkyl and said heterocycloalkyl are optionally substituted by one or two substituents each independently selected from halogen, cyano, hydroxyl, (C₁-C₆)alkoxy, (C₂-C₆)alkenyloxy, (C₂-C₆)alkynyloxy, (C₁-C₆)alkyl-S-, C₁₋₆haloalkyl, amino, (C₁-C₆)alkylNH-, di((C₁-C₆)alkyl)N-, HC(O)-NH-, (C₁-C₆)alkyl-C(O)-NH-, HC(O)-N(C₁-C₆)alkyl-, or (C₁-C₆)alkyl-C(O)-N((C₁-C₆)alkyl)-;

W is NR²², O, or S;

R³ and R⁴ are each independently H, (C₁-C₆)alkyl, halo-substituted(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, or (C₁-C₆)alkoxy;

R⁵ is H, halogen, (C₁-C₃)alkyl, or halo-substituted(C₁-C₃)alkyl;

R¹⁰ and R¹² are each independently H, or a chemical moiety selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylC(O)-, (C₁-C₆)alkoxy, (C₃-C₁₄)cycloalkyl, (C₆-C₁₄)aryl, 4- to 14-membered cycloheteroalkyl, or 5- to 14-membered heteroaryl, wherein each of said chemical moieties are optionally substituted by one or more substituents each independently selected from

halogen, hydroxyl, (C₁-C₆)alkoxy, amino, (C₁-C₆)alkylamino, di-((C₁-C₆)alkyl)amino or cyano; and

R²² is H, or a chemical moiety selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, cycloalkyl, aryl, heterocycloalkyl, aryl-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-aryl-, or diaryl-(C₁-C₆)alkyl-, where each of said chemical moieties is optionally substituted by one or more substituents each independently selected from hydroxyl, cyano, nitro, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₂-C₆)alkenyloxy, (C₂-C₆)alkynyloxy, halogen, (C₁-C₆)alkyl-C(O)-, -C(O)OH, -C(O)-O(C₁-C₆)alkyl, amino, (C₁-C₆)alkylNH-, di((C₁-C₆)alkyl)N-, (C₁-C₆)alkylNH-C(O)-, di((C₁-C₆)alkyl)N-C(O)-, (C₁-C₆)alkyl-C(O)-NH-, (C₁-C₆)alkyl-C(O)-N((C₁-C₆)alkyl)-, (C₁-C₆)alkyl-SO₂-NH-, (C₁-C₆)alkyl-SO₂-N((C₁-C₆)alkyl)-, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-S(O)-, (C₁-C₆)alkyl-SO₂-, NH₂-SO₂-, (C₁-C₆)alkylNH-SO₂- and di((C₁-C₆)alkyl)N-SO₂-, where each of said (C₁-C₆)alkyl, (C₂-C₆)alkenyl, and (C₂-C₆)alkynyl moieties are optionally substituted by one or more substituents each independently selected from halogen, hydroxyl, (C₁-C₆)alkoxy, amino, (C₁-C₆)alkyl-NH-, di((C₁-C₆)alkyl)N-, or cyano; or a pharmaceutically acceptable salt thereof.

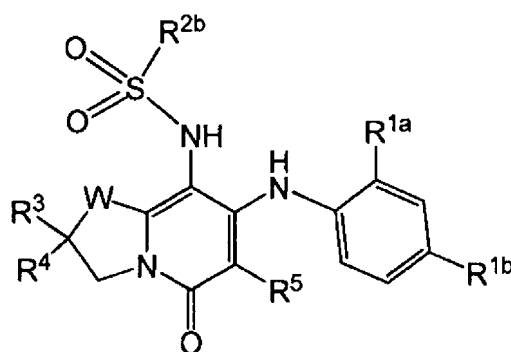
When W is NR²², then R²² is preferably H, (C₁-C₆)alkyl (e.g., methyl, ethyl, or propyl) (C₂-C₆)alkenyl (ethenyl), (C₂-C₆)alkynyl (e.g., ethynyl), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) aryl (e.g., phenyl), heterocycloalkyl (e.g., piperazinyl, piperidiny, tetrahydrofuranyl, or morpholinyl), aryl-(C₁-C₆)alkylene (e.g., phenyl-CH₂-, phenyl-CH₂-CH₂-, or phenyl-CH₂-CH₂-CH₂-), (C₁-C₆)alkyl-aryl-, (e.g., tolyl), diaryl-(C₁-C₆)alkylene (e.g., diphenyl-CH-); wherein said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycloalkylene, or aryl is optionally substituted by one or more groups each independently selected from List 1. More preferably, R²² is H, methyl, ethyl, propyl, cyclopropyl, cyclopentyl, phenyl, benzyl, or phenethyl, wherein said methyl, ethyl, propyl, cyclopropyl, cyclopentyl, phenyl, benzyl, or phenethyl is optionally substituted by one or more groups independently selected from List 1. Even more preferred, R²² is H, methyl, ethyl, phenyl, benzyl, or phenethyl, wherein said methyl, ethyl, phenyl, benzyl, or phenethyl is optionally substituted by one or more groups

independently selected from List 1. In one embodiment, R^{22} is H or benzyl. Most preferably, R^{22} is H.

Preferably, R^3 and R^4 are each independently H, methyl, or ethyl. More preferably, one of R^3 and R^4 is H, and the other is methyl. Most preferably, both R^3 and R^4 are H.

Preferably, R^5 is H, halogen (preferably, fluoro or chloro), (C_1-C_3) alkyl (preferably, methyl), or halo-substituted (C_1-C_3) alkyl (preferably, trifluoromethyl). More preferably, R^5 is fluoro, chloro, methyl, or trifluoromethyl. Most preferably, R^5 is methyl.

In another embodiment, a compound of Formula (IB) is provided



(IB)

wherein

R^{1a} and R^{1b} are each independently hydroxyl, cyano, nitro, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) alkoxy, halogen, amino, or (C_1-C_6) alkyl-NH-; R^{2b} is

(i) 3- to 6-membered cycloalkyl, where said cycloalkyl is optionally substituted with hydroxyl, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl, wherein said (C_1-C_6) alkyl, said (C_2-C_6) alkenyl, and said (C_2-C_6) alkynyl are optionally substituted with 1 to 3 hydroxyl,

(ii) (C_1-C_6) alkyl substituted by a monocyclic 3- to 6-membered cycloalkyl or a monocyclic 3- to 6-membered heterocycloalkyl containing 1 to 3 heteroatoms selected from O, S or N, where said substituted alkyl is optionally substituted with one to three substituents each independently selected from the group consisting of halogen, cyano, hydroxyl, $(C_1-$

C₆)alkoxy, (C₁-C₆)alkyl-S-, halo-substituted(C₁-C₆)alkyl, amino, (C₁-C₆)alkyl-NH-, di-((C₁-C₆)alkyl)-N-, and (C₁-C₆)alkylC(O)-NH-,

(iii) (C₂-C₆)alkenyl substituted by a monocyclic 3- to 6-membered cycloalkyl or a monocyclic 3- to 6-membered heterocycloalkyl containing 1 to 3 heteroatoms selected from O, S or N, where said substituted alkenyl is optionally substituted with one to three substituents each independently selected from the group consisting of halogen, cyano, hydroxyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-S-, halo-substituted(C₁-C₆)alkyl, amino, (C₁-C₆)alkyl-NH-, di-((C₁-C₆)alkyl)-N-, and (C₁-C₆)alkylC(O)-NH-,

(iv) (C₂-C₆)alkynyl substituted by a monocyclic 3- to 6-membered cycloalkyl or a monocyclic 3- to 6-membered heterocycloalkyl containing 1 to 3 heteroatoms selected from O, S or N, where said substituted alkynyl is optionally substituted with one to three substituents each independently selected from the group consisting of halogen, cyano, hydroxyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-S-, halo-substituted(C₁-C₆)alkyl, amino, (C₁-C₆)alkyl-NH-, di-((C₁-C₆)alkyl)-N-, and (C₁-C₆)alkylC(O)-NH-, or

(v) di((C₁-C₆)alkyl)amine;

R³ is H;

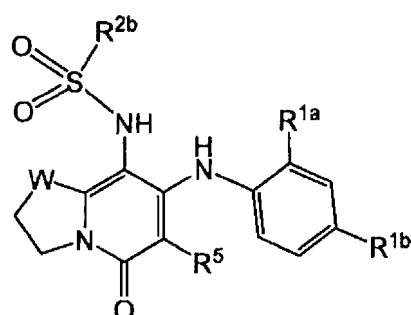
R⁴ is H or methyl;

W is NR²², O, or S, where R²² is H, methyl, ethyl, phenyl, benzyl, or phenethyl;

R⁵ is H, halogen, (C₁-C₃)alkyl, or halo-substituted(C₁-C₃)alkyl; or a pharmaceutically acceptable salt thereof.

Preferably, R^{1a} and R^{1b} are each independently halogen.

In yet another embodiment, a compound of Formula (IC) is provided



(IC)

wherein

R^{1a} is F;

5 R^{1b} is Br or I;

R^{2b} is

(i) 3- to 6-membered cycloalkyl, where said cycloalkyl is optionally substituted with hydroxyl, or (C₁-C₆)alkyl, wherein said (C₁-C₆)alkyl is optionally substituted with 1 to 3 hydroxyl,

10 (ii) (C₁-C₆)alkyl, where said (C₁-C₆)alkyl is optionally substituted with oxetanyl or 1 to 3 hydroxyl, or

(iii) -N(CH₃)₂;

W is O, S or N(R²²), where R²² is H or benzyl; and

R⁵ is H, F, Cl, CH₃ or CF₃;

15 or a pharmaceutically acceptable salt thereof.

In one aspect of this embodiment, W is O. In another aspect of this embodiment, W is S. In yet another aspect of this embodiment, W is N(R²²), preferably R²² is H.

20 Suitable representative compounds where W is O include:

Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

2-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

25 1-(2-Hydroxy-ethyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

1-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

5 1-(3-Hydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

10 Cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

3-(1,3-dihydroxypropan-2-yl)-N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)cyclobutane-1-sulfonamide;

N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-1-(3-methyloxetan-3-yl)methanesulfonamide;

15 N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-2-(oxetan-3-yl)ethanesulfonamide; and

N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-4-hydroxy-3-(hydroxymethyl)butane-1-sulfonamide;

or a pharmaceutically acceptable salt thereof.

20

Suitable representative compounds where W is S include:

Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

25 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

2-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

1-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

30 N-[7-(2-Fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-dimethylaminosulfonamide;

Cyclopentanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

5 Cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide; and

Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

or a pharmaceutically acceptable salt thereof.

10

Suitable representative compounds where W is NH include:

Cyclopropanesulfonic acid [7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide;

15 Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide;

1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide;

20 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide; and

3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide;

or a pharmaceutically acceptable salt thereof.

25

Definitions

As used herein, the term "alkyl" refers to a hydrocarbon moiety of the general formula C_nH_{2n+1} . The alkane group may be straight or branched. For example, the term "(C₁-C₆)alkyl" refers to a monovalent, straight, or branched
30 aliphatic group containing 1 to 6 carbon atoms (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, hexyl, 2-methylpentyl, and the like).

Similarly, the alkyl portion (i.e., alkyl moiety) of an alkoxy, alkylamino, dialkylamino, acyl (i.e., alkyl-C(O)-), alkylamido (i.e., alkyl-C(O)-NH-, alkyl-C(O)-N(alkyl)(H)-), alkylthio (i.e., alkyl-S-), alkylsulfinyl (i.e., alkyl-S(O)-), alkylsulfonyl (i.e., alkyl-S(O)₂-), alkylsulfamyl (alkyl-NH-SO₂-), alkylsulfonamido

5 (alkyl-SO₂-NH-), etc. have the same definition as above. When indicated as being "optionally substituted", the alkane radical or alkyl moiety may be unsubstituted or substituted with one or more substituents (generally, one to three substituents except in the case of halogen substituents such as perchloro or perfluoroalkyls). "Halo-substituted alkyl" refers to an alkyl group having at
10 least one halogen substitution.

The term "alkenyl" refers to an alkyl moiety containing at least one unsaturation in the alkyl group. The alkenyl group may be straight or branched. For example, vinyl, prop-1-enyl, prop-2-enyl, 2-methylprop-2-enyl, 3-methylbut-2-enyl, and the like.

15 The term "alkylene" refers to an alkyl moiety where the moiety contains two binding sites. The alkylene group may be straight (e.g., -(CH₂)-, -(CH₂)₂-, -(CH₂)₃-, or branched (e.g., -CH(CH₃)-, -C(CH₃)₂-, -CH₂CH(CH₃)-, -CH(CH₃)-CH₂-, -C(CH₃)₂-CH₂-, etc.). Suitable alkylene moieties are the same as those described above for alkyl except with two binding sites instead of just one.

20 The term "alkenylene" refers to an alkenyl moiety containing two binding sites. For example, -CH₂-CH=CH-CH₂-. Suitable alkenylene moieties are the same as those described above for alkenyl except with two binding sites instead of just one.

The term "aryl" refers to aromatic moieties having a single (e.g., phenyl) or
25 a fused ring system (e.g., naphthalene, anthracene, phenanthrene, etc.). A typical aryl group is a 6- to 14-membered aromatic carbocyclic ring(s). A fused aromatic ring system may also include a phenyl fused to a partially or fully saturated cycloalkyl. For example, 2,3-dihydroindenyl, 1,2,3,4-tetrahydronaphthalenyl, 1,2-dihydronaphthalenyl, 2,3-dihydronaphthalenyl, 9,10-
30 dihydroanthracenyl, fluorenyl, and the like. A preferred aryl is phenyl.

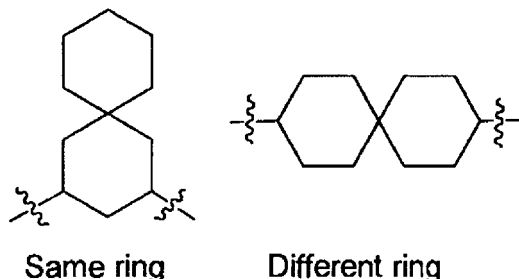
The term "arylene" refers to a carbocyclic aromatic moiety having two binding sites. Suitable arylens include those groups described above for an aryl moiety except with two binding sites rather than one. For example, 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,3-naphthylene, 1,4-naphthylene, 1,5-naphthylene, 1,6-naphthylene, 1,7-naphthylene, 2,3-naphthylene, 2,4-naphthylene, 2,5-naphthylene, 2,6-naphthylene, 2,7-naphthylene, 3,4-naphthylene, 3,5-naphthylene, 3,6-naphthylene, 3,7-naphthylene, etc. The two binding sites on the fused arylene system may be on the same ring or different rings. A preferred arylene is phenylene.

10 The term "cycloalkyl" or "partially or fully saturated cycloalkyl" refers to a carbocyclic ring which is fully hydrogenated (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.) or partially hydrogenated (e.g., cyclopropenyl, cyclobutenyl, cyclopentyl, cyclopenta-1,3-dienyl, cyclohexenyl, cyclohexa-1,3-dienyl, cyclohexa-1,4-dienyl, etc.). Unless specified
15 otherwise, the carbocyclic ring may be a single ring (as described above), a bicyclic ring (e.g., octahydropentalenyl, bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, bicyclo[2.1.1]hex-2-enyl, bicyclo[2.2.1]hept-2-enyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[2.2.2]oct-2-enyl, bicyclo[2.2.2]octa-2,5-dienyl, etc.) or a spiral ring (e.g., spiro[2.2]pentanyl, etc.),
20 and the like.

The term "cycloalkylene" or "partially or fully saturated cycloalkylene" refers to a carbocyclic ring having either no unsaturation in the ring (fully hydrogenated) or at least one unsaturation (partially hydrogenated) without being aromatic and contains two binding sites. Suitable ring systems include those
25 described above for a partially or fully saturated cycloalkyl except having two bind sites instead of one. For example, 1,2-cyclopropyl, 1,2-cycloprop-1-enyl, 1,2-cyclobutyl, 1,3-cyclobutyl, 1,2-cyclobut-1-enyl, 3,4-cyclobut-1-enyl, 3,5-cyclopent-1-enyl, 1,4-cyclopenta-1,3-dienyl, 1,5-cyclopenta-1,3-dienyl, 1,2-cyclopenta-1,3-dienyl, 1,3-cyclopenta-1,3-dienyl, etc. Unless specified
30 otherwise, the carbocyclic ring may be a single ring, a bicyclic ring, or a spiral

15

ring where the two binding sites on the bicyclic ring and spiral ring may be on the same ring or different rings. See, e.g., the illustration below.



5 The term "heterocycle" or "partially or fully saturated heterocycle" refers to a nonaromatic ring that is either partially or fully hydrogenated and may exist as a single ring, bicyclic ring (including fused rings) or a spiral ring. Unless specified otherwise, the heterocyclic ring is generally a 3- to 12-membered ring containing 1 to 3 heteroatoms (preferably 1 or 2 heteroatoms) independently selected from sulfur, oxygen and/or nitrogen. Partially saturated or fully saturated heterocyclic rings include groups such as epoxy, aziridinyl, azetidiny, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, pyrrolidinyl, imidazolidinyl, imidazoliny, 1H-dihydroimidazolyl, hexahydropyrimidinyl, piperidinyl, piperazinyl, pyrazolidinyl, 2H-pyranyl, 4H-pyranyl, 2H-chromenyl, oxazinyl, morpholino, thiomorpholino, 15 tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, oxazolidinyl, thiazolidinyl, octahydropyrrolo[3,2-b]pyrrolyl, and the like. A partially saturated heterocyclic ring also includes groups wherein the heterocyclic ring is fused to an aryl or heteroaryl ring (e.g., 2,3-dihydrobenzofuranyl, indoliny (or 2,3-dihydroindolyl), 2,3-dihydrobenzothiophenyl, 2,3-dihydrobenzothiazolyl, 1,2,3,4-tetrahydroquinoliny, 1,2,3,4-tetrahydroisoquinoliny, 5,6,7,8-tetrahydropyrido[3,4-b]pyrazinyl, and the like). Examples of spiral rings include 2,6-diazaspiro[3.3]heptanyl, 3-azaspiro[5.5]undecanyl, 3,9-diazaspiro[5.5]undecanyl, and the like.

25 The term "heteroaryl" refers to aromatic moieties containing at least one heteroatom (e.g., oxygen, sulfur, nitrogen or combinations thereof) within a 5- to 10-membered aromatic ring system (e.g., pyrrolyl, pyridyl, pyrazolyl, indolyl, indazolyl, thienyl, furanyl, benzofuranyl, oxazolyl, imidazolyl, tetrazolyl, triazinyl, pyrimidyl, pyrazinyl, thiazolyl, purinyl, benzimidazolyl, quinoliny, isoquinoliny,

benzothiophenyl, benzoxazolyl, 1H-benzo[d][1,2,3]triazolyl, and the like.). The heteroaromatic moiety may consist of a single or fused ring system. A typical single heteroaryl ring is a 5- to 6-membered ring containing one to three heteroatoms independently selected from oxygen, sulfur and nitrogen and a
5 typical fused heteroaryl ring system is a 9- to 10-membered ring system containing one to four heteroatoms independently selected from oxygen, sulfur and nitrogen. The fused heteroaryl ring system may consist of two heteroaryl rings fused together or a heteroaryl fused to an aryl (generally, phenyl).

The term "heteroarylene" refers to a heteroaryl having two binding sites
10 instead of one. Suitable heteroarylene groups include those described above for heteroaryl having two binding sites instead of one.

Unless specified otherwise, the term "compounds of the present invention" refers to compounds of Formula (IA), (IB) or (IC), and salts thereof, as well as all stereoisomers (including diastereoisomers and enantiomers), tautomers, and
15 isotopically labeled compounds (including deuterium substitutions), as well as inherently formed moieties (e.g., polymorphs, solvates and/or hydrates).

DETAILED DESCRIPTION

The present invention provides compounds and pharmaceutical
20 compositions thereof that are useful in the treatment of diseases, conditions and/or disorders modulated by the inhibition of kinase activity of MEK.

Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials
25 are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl.
30 ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)).

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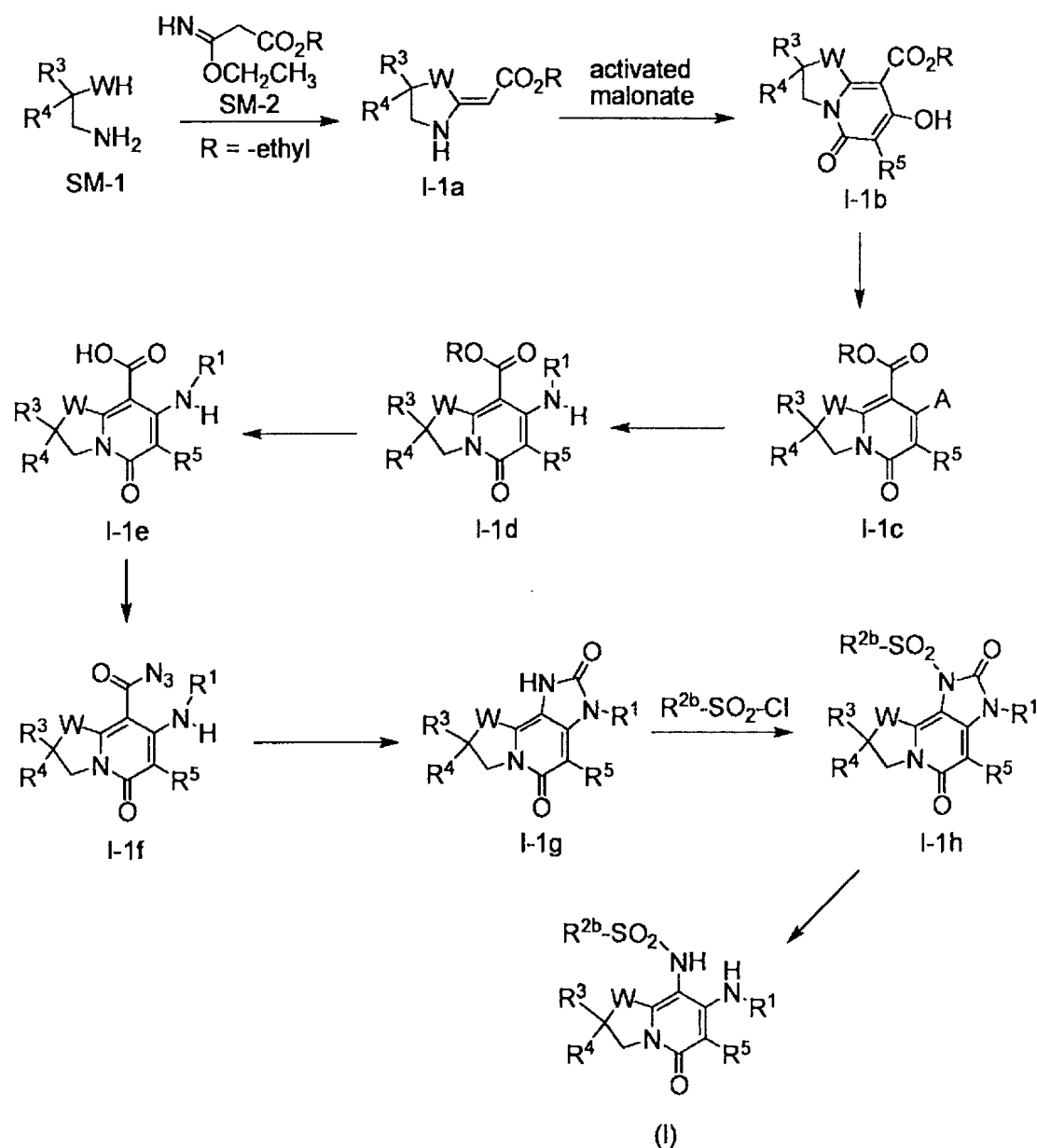
The invention provides, in another aspect, a process for preparing a compound of Formula (IA), (IB) and (IC). For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed

5 description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of

10 derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

Scheme 1 below illustrates how one could prepare compounds of the present invention ((1A), (1B), and (IC), where R¹ represents the disubstituted

15 phenyl).

**Scheme 1**

Intermediate (I-1a) can be prepared from the desired amine (SM-1) by refluxing with ethyl ethoxycarbonyl ethanimidate hydrochloride (SM-2, where R = ethyl) in a suitable protic solvent (e.g., ethanol). The resultant intermediate (I-1a) can then be converted to intermediate (I-1b) by refluxing with an activated malonate (e.g., malonic acid bis-(2,4,6-trichloro-phenyl) ester) in a non-protic solvent (e.g., xylene). The leaving group A is then introduced into intermediate (I-1b) to form intermediate (I-1c) by treating intermediate (I-1b) with a

halogenating agent (e.g., phosphorus oxybromide) either neat or in a suitable non-protic solvent (e.g., toluene) at temperatures ranging from about room temperature to about 140°C. Alternatively, intermediate (I-1b) may be reacted with nonafluorobutane sulphonyl fluoride in the presence of a suitable base (e.g., diisopropyl ethylamine) and a catalyst (e.g., N,N-dimethyl-4-aminopyridine) in a non-protic solvent (e.g., dichloromethane) at about room temperature, or with N-phenyltrifluoromethanesulfonylimide in the presence of a suitable base (e.g., diisopropylethyl amine) in a suitable solvent (e.g., 1,2-dimethoxyethane) at temperatures ranging from about room temperature to the refluxing temperature of the solvent. Alternatively, intermediate (I-1b) may be treated with trifluoromethanesulphonic acid anhydride in the presence of base (e.g., pyridine) in a non-protic solvent (dichloromethane) at temperatures ranging from about -20°C to ambient temperature.

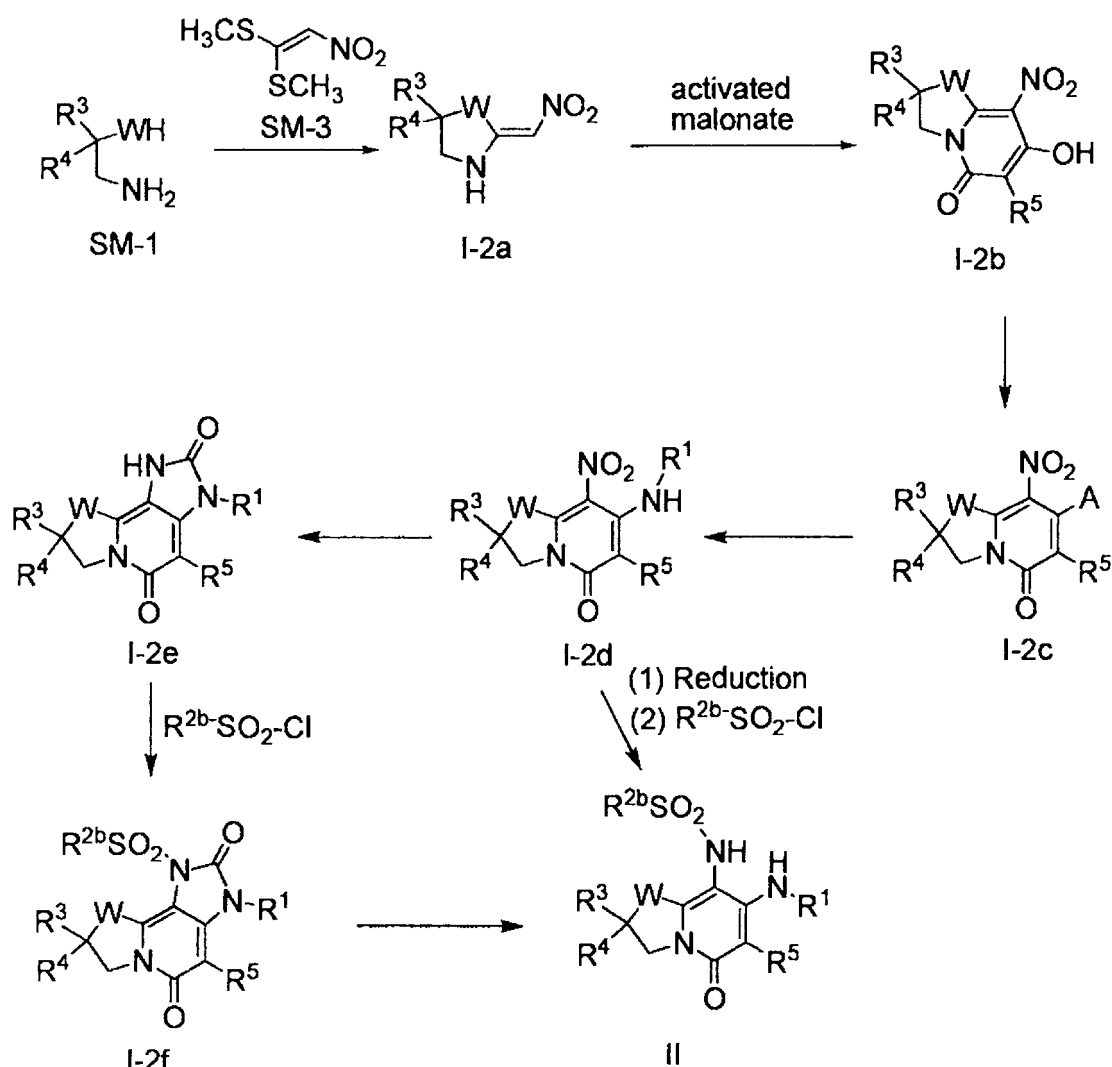
Intermediate (I-1d) may be prepared from intermediate (I-1c) by reacting with an appropriate aniline (R^{2b} -NH) using Buchwald-Hartwig C-N coupling conditions. The Buchwald-Hartwig reactions may be performed in presence of a catalyst (e.g., tris(dibenzylideneacetone)dipalladium (0) or palladium acetate), a base (e.g., potassium phosphate, sodium tert-butoxide, 1,8-diazobicyclo-[5.4.1]undec-7-ene or cesium carbonate), and a ligand (e.g., 9,9'-dimethyl-4,5-bis(diphenylphosphino)-xanthene, 2,2'-bis(diphenylphosphino)-1-1'-binaphthyl, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl, 2-dicyclohexylphosphino-2',6'-(dimethoxy)biphenyl or tributylphosphine) in a suitable solvent (e.g., toluene, 1,2-dimethoxyethane, tetrahydrofuran or dioxane) at a temperature ranging from about room temperature to the refluxing temperature of the solvent, or under microwave irradiation at a temperature ranging from about 70°C to about 150°C. Intermediate (I-1e) can then be prepared from intermediate (I-1d) by reacting with a strong base (e.g., sodium hydroxide) in a protic solvent (e.g., ethanol or methanol) at a temperature ranging from about room temperature to the refluxing temperature of the solvent.

Intermediate acyl azide (I-1f) can be prepared from Intermediate (I-1e) via the acid halide (e.g., treatment with an acid chloride using standard conditions)

followed by treatment with sodium azide or diphenylphosphoryl azide (DPPA) in the presence of an amine (e.g., triethylamine) in a non-protic solvent (e.g., DMF). Intermediate (I-1f) can then be transformed *via* the Curtius rearrangement to give intermediate (I-1g).

5 The R^{2b} -sulfonyl group can be introduced into intermediate (I-1g) to form intermediate (I-1h) by treating with the desired sulfonyl chloride (R^{2b} -SO₂-Cl) in suitable solvent (e.g., dichloromethane) in presence base (e.g., triethyl amine, diisopropyl ethylamine or pyridine). The final compound (I) is then prepared by hydrolyzing intermediate (I-1h). For example, intermediate (I-1h) is heated in the
10 presence of a strong base (e.g., sodium hydroxide) in an aqueous protic solvent (e.g., ethanol/water).

Scheme 2 below provides an alternative procedure for preparing compounds of the present invention ((1A), (1B), and (1C), where R^1 represents the disubstituted phenyl).



Scheme 2

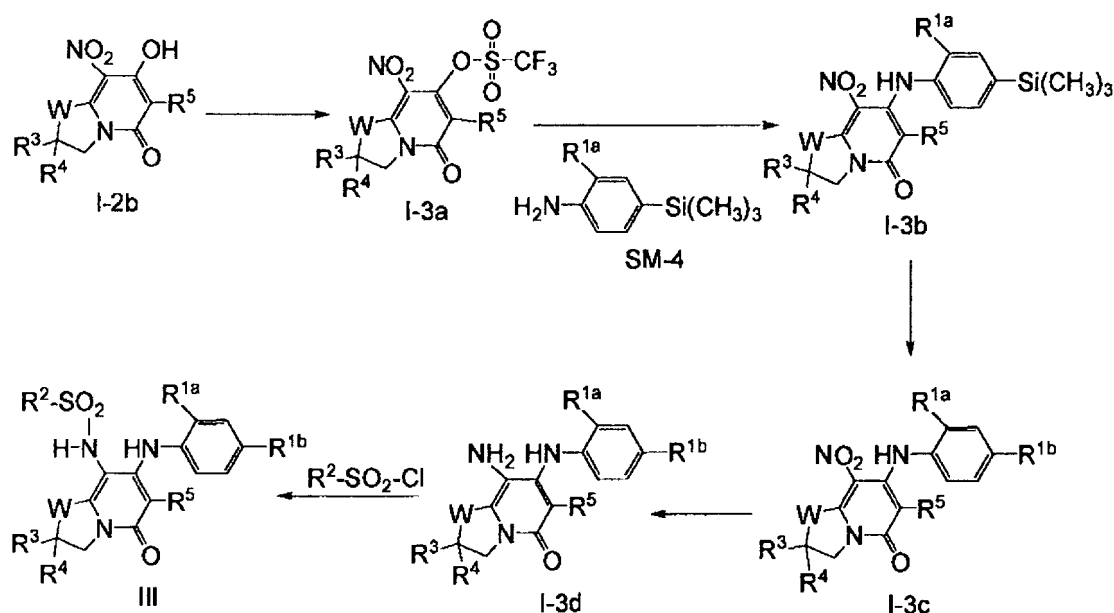
- Intermediate (I-2a) can be prepared from the desired amine (SM-1) by treating with equimolar amounts of 1,1-bis(alkylthio)-2-nitroethylene in a polar solvent (e.g., methanol, ethanol, acetonitrile, tetrahydrofuran, water or mixtures thereof) at temperatures up to the reflux temperature of the solvent. A proton acceptor (e.g., NaOH, sodium carbonate or triethylamine) can be used in the reaction. Intermediate (I-2b) can then be prepared using conditions analogous to those described in Scheme I above for the preparation of intermediate (I-1b). Similarly, intermediates (I-2c) and (I-2d) can be prepared using the conditions described above in Scheme I for the preparation of intermediates (I-1c) and (I-1d), respectively. Alternative, intermediate (I-2d) can also be prepared from

intermediate (I-2c) using the standard reduction conditions. For example, treatment with Fe/NH₄Cl in a solvent (e.g., THF) followed by reaction with triphosgene in non-protic solvent (e.g., DMF).

5 Intermediate (I-2d) can be converted directly into a compound of the present invention (II) by using standard reduction conditions, well known to those of skill in the art, followed by treating with the desired sulfonyl chloride (R^{2b}-SO₂-Cl) in a suitable solvent (e.g., dichloromethane) in the presence of a base (e.g., triethyl amine, diisopropyl ethylamine or pyridine).

10 Alternatively, the nitro group of intermediate (I-2d) can first be reduced to an amino group followed by treatment with N,N'-carbonyldiimidazole (CDI) or triphosgene in the presence of triethylamine (TEA) to produce the imidazolone intermediate (I-2e). Intermediate (I-2e) can then be reacted with the desired sulfonyl chloride (R^{2b}-SO₂-Cl) in a suitable solvent (e.g., pyridine or DMF) in the presence of a base (e.g., triethyl amine, diisopropyl ethylamine or pyridine) to
15 produce sulfonamide intermediate (I-2f). The final product (II) can then be produced using procedures analogous to those described above in Scheme I. For example, intermediate (I-2f) is heated in the presence of a strong base (e.g., sodium hydroxide) in an aqueous protic solvent (e.g., ethanol/water).

20 Scheme 3 below illustrates the preparation of compounds of Formula (IA), where X is -N(R⁶)-, wherein R⁶ is H (referred to in Scheme 3 as (III)). When R³ and R⁴ are both H, then Scheme 3 also illustrates how one could prepare compounds of Formula (IB) and (IC).



Scheme 3

The OH group of intermediate (I-2b) can be converted to a triflic ester by reacting with triflic anhydride in the presence of a base (e.g., triethyl amine). The resultant intermediate (I-3a) can then be reacted with a desired aryl amine (SM-4) using conditions well known to those of skill in the art (e.g., Buchwald-Hartwig conditions) to form intermediate (I-3b). Preferred conditions of the Buchwald-Hartwig reactions include reacting intermediate (I-3a) and the desired amine (SM-4) in the presence of a catalyst (e.g., Pd(OAc)₂), a base (e.g., cesium carbonate), and a ligand (e.g., 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)), in the presence of a suitable solvent (e.g., dioxane).

The trimethylsilyl group of Intermediate (I-3b) is then replaced with the desired substituent using procedures well-known to those of skill in the art. For example, the trimethylsilyl group may be substituted by iodide by reacting intermediate (I-3b) with iodine monochloride and silver tetrafluoroborate in dry DCM under an inert atmosphere at reduced temperatures (e.g., about -50°C.) Intermediate (I-3d) can then be prepared from intermediate (I-3c) reducing the nitro group using procedures well-known to those of skill in the art. For example, intermediate (I-3c) can be treated with a reducing agent (e.g., sodium dithionite or stannous chloride) in the presence of an acid (e.g.,

hydrochloric acid). The final compound (III) can then be prepared using procedures analogous to those described in Schemes 1 and 2. For example, intermediate (I-3d) is reacted with the desired sulfonyl chloride (R^2-SO_2-Cl) in a suitable solvent (e.g., pyridine or DMF) in the presence of a base (e.g., triethyl amine, diisopropyl ethylamine or pyridine).

The compounds and intermediates described in the schemes above can be isolated per se or as their corresponding salts. For example, many of the compounds represented by Formula (IA), (IB) and (IC) are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts.

Pharmaceutically acceptable acid addition salts of the compound of Formula (IA), (IB), or (IC) include those of inorganic acids, for example, hydrohalic acids such as hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids, for example aliphatic monocarboxylic acids such as formic acid, acetic acid, , propionic acid and butyric acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as maleic acid or succinic acid, aromatic carboxylic acids such as benzoic acid, p-chlorobenzoic acid, diphenylacetic acid or triphenylacetic acid, aromatic hydroxy acids such as o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of Formula (IA), (IB), or (IC) by known salt-forming procedures.

Compounds of Formula (IA), (IB), or (IC) which contain acidic, e.g. carboxyl, groups, are also capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art; suitable such salts include metal salts, particularly alkali metal or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines, benzylamines or pyridine. These salts may be prepared from compounds of Formula (IA), (IB), or (IC) by known salt-forming procedures.

It will be recognized by those skilled in the art that the compounds of the present invention may contain chiral centers and as such may exist in different isomeric forms. As used herein, the term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound.

"Enantiomers" are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate.

"Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-.

Unless specified otherwise, the compounds of the present invention are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a

disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

Compounds of the invention that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of the present invention by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of the present invention with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of the present invention.

The compounds of the present invention include isotopically-labeled compounds wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention comprises isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulphur, such as ^{35}S .

Substitution with heavier isotopes such as deuterium, *i.e.* ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Isotopically-labeled compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations Sections using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

21

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. For purposes of the present invention, solvates (including

5 hydrates) are considered pharmaceutical compositions, e.g., a compound of Formula (IA), (IB), or (IC) (or a pharmaceutically acceptable salt thereof) in combination with an excipient, wherein the excipient is a solvent.

The present invention is also in relation to a pharmaceutical composition comprising a compound of the present invention and pharmaceutically

10 acceptable excipients.

Suitable excipients generally include binders, anti-adherents, disintegrants, fillers, diluents, flavors, colorants, glidants, lubricants, preservatives, sorbents and sweeteners or combination(s) thereof.

A typical formulation is prepared by mixing a compound of the present

15 invention and a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water, and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for

20 which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol,

25 propylene glycol, polyethylene glycols (e.g., PEG400, PEG300), etc. and mixtures thereof. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and

30 other known additives to provide an elegant presentation of the drug (i.e., a

compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent)) is dissolved in a suitable solvent in the presence of one or more of the excipients. The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient an elegant and easily handleable product.

The composition is generally formulated into various dosage forms selected from a group comprising tablet, troches, lozenges, aqueous or oily suspensions, ointment, patch, gel, lotion, dentifrice, capsule, emulsion, creams, spray, drops, dispersible powders or granules, emulsion in hard or soft gel capsules, syrups and elixirs.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

The compounds of the present invention are useful as both prophylactic and therapeutic treatments for diseases or conditions related to the hyperactivity of MEK, as well as diseases or conditions modulated by the Raf/Ras/Mek pathway.

Thus, as a further aspect, the invention relates to a method for treating a disease or condition related to the hyperactivity of MEK, or a disease or condition

modulated by the MEK cascade, comprising administration of an effective therapeutic amount of a compound of Formula (IA), (IB) or (IC), or a pharmaceutically acceptable salt thereof.

As a further aspect, the invention relates to a method for treating
5 proliferative diseases, such as cancer, comprising administration of an effective amount of a compound of the present invention.

Examples of cancers include but are not limited to: angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, teratoma; bronchogenic carcinoma, squamous cell carcinoma,
10 undifferentiated small cell carcinoma, undifferentiated large cell carcinoma, alveolar (bronchiolar) carcinoma, bronchial adenoma, lymphoma, chondromatous hamartoma, mesothelioma, esophageal squamous cell carcinoma, leiomyosarcoma, leiomyoma, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, vipoma, stomach and small bowel carcinoid tumors,
15 adenocarcinoma, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma, tubular adenoma, villous adenoma, hamartoma, Wilm's tumor [nephroblastoma, leukemia, bladder and urethra squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma, seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, interstitial cell carcinoma,
20 fibroadenoma, adenomatoid tumors, hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, hepatocellular adenoma, hemangioma, osteogenic sarcoma (osteosarcoma), malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma,
25 osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors, osteoma, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma, gliomatosis, astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiforme,
30 oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, spinal cord neurofibroma, meningioma, glioma, endometrial carcinoma, cervical carcinoma,

pre-tumor cervical dysplasia, ovarian carcinoma, serous cystadenocarcinoma, mucinous cystadenocarcinoma, granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma, intraepithelial carcinoma, adenocarcinoma, melanoma), vaginal clear cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tube carcinoma, acute and chronic
5 myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, malignant lymphoma, malignant melanoma, basal cell carcinoma, moles, dysplastic nevi, angioma,
10 dermatofibroma, keloids, psoriasis, and neuroblastoma.

The compounds of the present invention may also be useful in the treatment of other diseases or conditions related to the hyperactivity of MEK. Thus, as a further aspect, the invention relates to a method of treatment of a disorder selected from: xenograft (cellos), skin, limb, organ or bone marrow
15 transplant) rejection; osteoarthritis; rheumatoid arthritis; cystic fibrosis; complications of diabetes (including diabetic retinopathy and diabetic nephropathy); hepatomegaly; cardiomegaly; stroke (such as acute focal ischemic stroke and global cerebral ischemia); heart failure; septic shock; asthma; chronic obstructive pulmonary disorder; Alzheimer's disease; and chronic or neuropathic
20 pain.

The term "chronic pain" for purposes of the present invention includes, but is not limited to, idiopathic pain, and pain associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism. Chronic pain is associated with numerous conditions including, but not limited to, inflammation, and post-
25 operative pain.

As used herein, the term "neuropathic pain" is associated with numerous conditions which include, but are not limited to, inflammation, postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma,
30 vasculitis, viral infection, crush injury, constriction injury, tissue injury, limb

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amputation, and nerve injury between the peripheral nervous system and the central nervous system.

Compounds of the invention may also be useful as antiviral agents for treating viral infections such as HIV, hepatitis (B) virus (HBV) human papilloma virus (HPV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV).

Compounds of the invention may also be useful in the treatment of restenosis, psoriasis, allergic contact dermatitis, autoimmune disease, atherosclerosis and inflammatory bowel diseases, e.g. Crohn's disease and ulcerative colitis.

10 In certain instances, it may be advantageous to administer the compound of the present invention in combination with at least one additional pharmaceutical (or therapeutic) agent (e.g., an anti-cancer agent or adjunct therapy typically used in chemotherapy). The compound of the present invention may be administered either simultaneously with, or before or after, one
15 or more other therapeutic agent(s). Alternatively, the compound of the present invention may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agent(s).

For example, a compound of the present invention may be administered
20 simultaneously, sequentially or separately in combination with one or more agents selected from chemotherapy agents, e.g. mitotic inhibitors such as a Docetaxel (sold under the tradename Taxotere® by Sanofi-Aventis), taxane, a vinca alkaloid, paclitaxel, vincristine, vinblastine, vinorelbine or vinflunine, and other anticancer agents, e.g. cisplatin, 5-fluorouracil or 5-fluoro-2-4(1 H,3H)-
25 pyrimidinedione (5FU), flutamide or gemcitabine.

Such combinations may offer significant advantages, including synergistic activity, in therapy.

A compound of the present invention may also be used to advantage in combination with other antiproliferative compounds. Such antiproliferative
30 compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active

compounds; alkylating compounds; histone deacetylase inhibitors, such as LBH589; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors, such as RAD001; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3, such as PKC412; Hsp90 inhibitors such as 17-AAG (17-allylamino-geldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics and AUY922; temozolomide (TEMODAL); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; PI3K inhibitors, such as BEZ235; RAF inhibitors, such as RAF265; EDG binders, antileukemia compounds, ribonucleotide reductase inhibitors, S-adenosylmethionine decarboxylase inhibitors, antiproliferative anti-bodies or other chemotherapeutic compounds. Further, alternatively or in addition they may be used in combination with other tumor treatment approaches, including surgery, ionizing radiation, photodynamic therapy, implants, e.g. with corticosteroids, hormones, or they may be used as radiosensitizers. Also, in anti-inflammatory and/or antiproliferative treatment, combination with anti-inflammatory drugs is included. Combination is also possible with antihistamine drug substances, bronchodilatory drugs, NSAID or antagonists of chemokine receptors.

The term "aromatase inhibitor" as used herein relates to a compound which inhibits the estrogen production, i.e. the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The

term includes, but is not limited to steroids, especially atame-stane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark AROMASIN. Formestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark LENTARON. Fadrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark AFEMA. Anastrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark ARIMIDEX. Letrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark FEMARA or FEMAR. Amino glutethimide can be administered, e.g., in the form as it is marketed, e.g. under the trademark, ORIMETEN. A combination of the invention comprising a chemo-therapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g., breast tumors.

The term "anti-estrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be administered, e.g., in the form as it is marketed, e.g. under the trademark NOLVADEX. Raloxifene hydrochloride can be administered, e.g., in the form as it is marketed, e.g. under the trademark EVISTA. Fulvestrant can be formulated as disclosed in US 4,659,516 or it can be administered, e.g., in the form as it is marketed, e.g. under the trademark FASLODEX. A combination of the invention comprising a chemotherapeutic agent which is an anti-estrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g. breast tumors.

The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, Nilutamide (sold under the tradenames Nilandron® and Anandron®), flutamide (sold under the tradename Fulexin™), bicalutamide (CASODEX), which can be formulated, e.g. as disclosed in US 4,636,505.

The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin is disclosed in US 4,100,274 and can be administered, e.g., in the form as it is marketed, e.g. under the trademark ZOLADEX. Abarelix can be formulated, e.g. as disclosed in US 5,843,901.

The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/ 17804). Irinotecan can be administered, e.g. in the form as it is marketed, e.g. under the trademark CAMPTOSAR. Topotecan can be administered, e.g., in the form as it is marketed, e.g. under the trademark HYCAMTIN.

The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the an-thracyclines such as doxorubicin (including liposomal formulation, e.g. CAELYX), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide. Etoposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark ETOPOPHOS. Teniposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark VM 26-BRISTOL. Doxorubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ADRIBLASTIN or ADRIAMYCIN. Epirubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark FARMORUBICIN. Idarubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZAVEDOS. Mitoxantrone can be administered, e.g. in the form as it is marketed, e.g. under the trademark NOVANTRON.

The term "microtubule active compound" relates to microtubule stabilizing, microtubule destabilizing compounds and microtubulin polymerization inhibitors including, but not limited to taxanes, e.g. paclitaxel and docetaxel, vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides, cochicine and epothilones

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CV

and derivatives thereof, e.g. epothilone B or D or derivatives thereof. Paclitaxel may be administered e.g. in the form as it is marketed, e.g. TAXOL. Docetaxel can be administered, e.g., in the form as it is marketed, e.g. under the trademark TAXOTERE. Vinblastine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark VINBLASTIN R.P. Vincristine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark FARMISTIN. Discodermolide can be obtained, e.g., as disclosed in US 5,010,099. Also included are Epothilone derivatives which are disclosed in WO 98/10121, US 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247. Especially preferred are Epothilone A and/or B.

The term "alkylating compound" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark CYCLOSTIN. Ifosfamide can be administered, e.g., in the form as it is marketed, e.g., under the trademark HOLOXAN.

The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes compounds such as sodium butyrate, LDH589 disclosed in WO 02/22577, especially N-hydroxy-3-[4-[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl] phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino] methyl]phenyl]-2E-2-propenamide and pharmaceutically acceptable salts thereof, especially the lactate salt. It further especially includes suberoylanilide hydroxamic acid (SAHA), MS275, FK228 (formerly FR901228), trichostatin A and compounds disclosed in US 6,552,065, in particular, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]-methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof.

The term "antineoplastic antimetabolite" includes, but is not limited to, 5-Fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine can be administered, e.g.,

in the form as it is marketed, e.g. under the trademark XELODA. Gemcitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark GEMZAR.

5 The term "platin compound" as used herein includes, but is not limited to, carboplatin, cis-platin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark CARBOPLAT. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark ELOXATIN.

10 The term "compounds targeting/decreasing a protein or lipid kinase activity"; or a "protein or lipid phosphatase activity"; or "further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g.,

a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which
15 target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib, SU101, SU6668 and GFB-111;

b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR);

20 c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, such as those compounds disclosed in WO 02/092599, or antibodies that target the extracellular domain of IGF-I receptor or its growth
25 factors;

d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors;

e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

30 f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase;

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g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, i.e C-kit receptor tyrosine kinases - (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, e.g. imatinib;

h) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825)

i) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in US 5,093,330, e.g. midostaurin; examples of further compounds include e.g. UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds such as those disclosed in WO 00/09495; FTIs; BEZ235 (a P13K inhibitor) or AT7519 (CDK inhibitor);

j) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC) or tyrphostin. A tyrphostin is preferably a low molecular weight (mw<1500) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzylidenemalonitrile class or the S-arylbenzenemalonitrile or bisubstrate quinoline class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-[[[2,5-

dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin);

k) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g. EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g. the compound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (e.g. compound known as CP 358774), WO 96/33980 (e.g. compound ZD 1839) and WO 95/03283 (e.g. compound ZM105180); e.g. trastuzumab (Herceptin), cetuximab (Erbix), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives which are disclosed in WO 03/013541; and

l) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF.

Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition e.g. thalidomide (THALOMID) and TNP-470.

Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are e.g., inhibitors of phosphatase 1, phosphatase 2A, or CDC25, e.g. okadaic acid or a derivative thereof.

Compounds which induce cell differentiation processes are e.g. retinoic acid, or tocopherol or tocotrienol.

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The term cyclooxygenase inhibitor as used herein includes, but is not limited to, e.g. Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g. 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

The term "bisphosphonates" as used herein includes, but is not limited to, etridronic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. "Etridronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark DIDRONEL. "Clodronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONEFOS. "Tiludronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark SKELID. "Pamidronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark AREDIA. "Alendronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark FOSAMAX. "Ibandronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONDRANAT. "Risedronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark ACTONEL. "Zoledronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZOMETA.

The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune), everolimus (Certican[®]), CCI-779 and ABT578.

The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88.

The term "biological response modifier" as used herein refers to a lymphokine or interferons, e.g. interferon.

The term "inhibitor of Ras oncogenic isoforms", e.g. H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the

oncogenic activity of Ras e.g. a "farnesyl transferase inhibitor" e.g. L-744832, DK8G557 or R115777 (Zarnestra).

The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, e.g. telomestatin.

The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are e.g. bengamide or a derivative thereof.

The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include e.g. Bortezomid (Velcade) and MLN 341.

The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors e.g. compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-b-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors e.g. compounds which target, decrease or inhibit anaplastic lymphoma kinase.

Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, e.g. PKC412, TKI258, midostaurin, a staurosporine derivative, SU11248 and MLN518.

The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteasome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90 e.g., 17-allylamino, 17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds, and radicicol.

The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (Herceptin), Trastuzumab-DM1, erbitux, bevacizumab (Avastin), rituximab (Rituxan), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant e.g. intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

For the treatment of acute myeloid leukemia (AML), compounds of formula (I) can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of formula (I) can be administered in combination with, e.g., farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

The term "antileukemic compounds" includes, for example, Ara-C, a pyrimidine analog, which is the 2-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate.

Somatostatin receptor antagonists as used herein refers to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230 (pasireotide).

Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and

gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in Principles and Practice of Oncology, Devita et al., Eds., 4th Edition, Vol. 1, pp. 248-275 (1993).

5 The term "EDG binders" as used herein refers a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720.

 The term "ribonucleotide reductase inhibitors" refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-
10 mercaptapurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1H-isoindole-1,3-dione derivatives, such as PL-1, PL-2, PL-3, PL-4, PL-5, PL-6, PL-7 or PL-8 mentioned in Nandy et al., Acta Oncologica, Vol. 33, No. 8, pp. 953-961 (1994).

15 The term "S-adenosylmethionine decarboxylase inhibitors" as used herein includes, but is not limited to the compounds disclosed in US 5,461,076.

 Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the
20 succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by Prewett et al, Cancer Res, Vol. 59, pp. 5209-5218 (1999); Yuan et al., Proc Natl Acad Sci U S A, Vol. 93, pp. 14765-14770 (1996); Zhu et al., Cancer Res, Vol. 58, pp. 3209-3214 (1998); and Mordenti et al., Toxicol Pathol, Vol. 27, No. 1, pp. 14-21 (1999); in WO
25 00/37502 and WO 94/10202; ANGIOSTATIN, described by O'Reilly et al., Cell, Vol. 79, pp. 315-328 (1994); ENDOSTATIN, described by O'Reilly et al., Cell, Vol. 88, pp. 277-285 (1997); anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor
30 antibodies, e.g. rhuMAb and RHUFab, VEGF aptamer e.g. Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgG1 antibody, Angiozyme (RPI 4610) and Bevacizumab (Avastin).

Photodynamic therapy as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy includes treatment with compounds, such as e.g. VISUDYNE and porfimer sodium.

5 Angiostatic steroids as used herein refers to compounds which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone, hydrocortisone, 11--epihydrocortisol, cortexolone, 17-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

10 Implants containing corticosteroids refers to compounds, such as e.g. fluocinolone, dexamethasone.

 "Other chemotherapeutic compounds" include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or
15 compounds with other or unknown mechanism of action.

 The structure of the active compounds identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

20 None of the quotations of references made within the present disclosure is to be understood as an admission that the references cited are prior art that would negatively affect the patentability of the present invention.

 The compounds of the invention may also be administered simultaneously, separately or sequentially in combination with one or more other
25 suitable active agents selected from the following classes of agents: Anti IL-1 agents, e.g: Anakinra; anti cytokine and anti-cytokine receptor agents, e.g. anti IL-6 R Ab, anti IL-15 Ab, anti IL-17 Ab, anti IL-12 Ab; B-cell and T-cell modulating drugs, e.g. anti CD20 Ab; CTL4-Ig, disease-modifying anti-rheumatic agents (DMARDs), e.g. methotrexate, leflunamide, sulfasalazine; gold salts,
30 penicillamine, hydroxychloroquine and chloroquine, azathioprine, glucocorticoids and non-steroidal anti-inflammatories (NSAIDs), e.g. cyclooxygenase inhibitors,

selective COX-2 inhibitors, agents which modulate migration of immune cells, e.g. chemokine receptor antagonists, modulators of adhesion molecules, e.g. inhibitors of LFA-1, VLA-4.

The pharmaceutical composition or combination of the present invention
5 can be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. In general, suitable daily dosages for oral administration are from about 0.1 to about 10 mg/kg. However, it will be understood by those of skill in the art that the therapeutically
10 effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients
15 necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, e.g., aqueous solutions,
20 and *in vivo* either enterally, parenterally, advantageously intravenously, e.g., as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, or between about 1-100 mg/kg.

25 In general, a therapeutically effective amount of a compound of the present invention is administered to a patient in need of treatment. The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an
30 enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc.

In yet another embodiment, a method for treating cancer in a mammal is provided which comprises administering to a mammal in need of such treatment an effective amount of a compound of the present invention.

As used herein, the term "subject" refers to an animal. Typically the
5 animal is a mammal. A subject also refers to for example, primates (e.g., humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. Preferably, the subject is a human.

As used herein, the term "inhibit", "inhibition" or "inhibiting" refers to the
10 reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term "treat", "treating" or "treatment" of any disease or disorder, refers (i) to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the
15 clinical symptoms thereof); (ii) to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient; or (iii) to preventing or delaying the onset or development or progression of the disease or disorder. In general, the term "treating" or "treatment" describes the management and care of a patient for the purpose of combating the disease,
20 condition, or disorder and includes the administration of a compound of the present invention to prevent the onset of the symptoms or complications, alleviating the symptoms or complications, or eliminating the disease, condition or disorder.

As used herein, a subject is "in need of" a treatment if such subject would
25 benefit biologically, medically or in quality of life from such treatment (preferably, a human).

Another aspect of the invention is a product comprising a compound of the present invention and at least one other therapeutic agent (or pharmaceutical agent) as a combined preparation for simultaneous, separate or sequential use in
30 therapy to enhance apoptosis.

In the combination therapies of the invention, the compound of the present invention and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the present invention and the other therapeutic (or pharmaceutical agent) may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (e.g. in the case of a kit comprising the compound of the invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, e.g. during sequential administration of the compound of the invention and the other therapeutic agent.

Accordingly, the invention provides the use of a compound of the present invention for treating a disease or condition by inhibiting the MAP kinase pathway, wherein the medicament is prepared for administration with another therapeutic agent. The invention also provides for the use of another therapeutic agent, wherein the medicament is administered as a combination of a compound of the present invention with the other therapeutic agent.

Embodiments of the present invention are illustrated by the following Examples. It is to be understood, however, that the embodiments of the invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

EXAMPLES

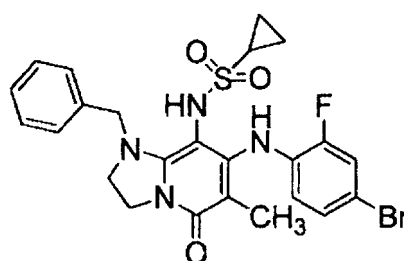
The following abbreviations used herein below have the corresponding meanings,:

- | | | |
|----|--------|--|
| 25 | BINAP: | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| | ByBOP: | benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate |
| | DCM: | dichloromethane |
| | DMF: | N,N-dimethylformamide |
| 30 | EDCI: | 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide |
| | HOBt: | N-hydroxybenzotriazole |

	KHMDS:	potassium bis(trimethylsilyl)amide
	LDA:	lithium diisopropylamide
	LiHMDS:	lithium bis(trimethylsilyl)amide
	NaHMDS:	sodium bis(trimethylsilyl)amide
5	NBS:	N-bromosuccinamide
	NCS:	N-chlorosuccinimide
	NIS:	N-iodosuccinimide
	TBTU:	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
10	TEA:	triethyl amine
	THF:	tetrahydrofuran
	TMS:	trimethylsilyl
	Xantphos:	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
15	HPLC:	high pressure liquid chromatography or high performance liquid chromatography
	LC-MS :	liquid chromatography-mass spectrometry
	NMR:	nuclear magnetic resonance
	TLC:	thin layer chromatography

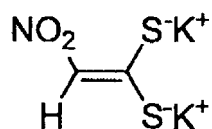
Example 1

20 Synthesis of Cyclopropanesulfonic acid [1-benzyl-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (1A):



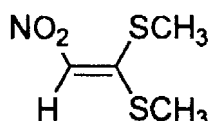
(1A)

25 Synthesis of Intermediate Potassium salt of 2-Nitro-ethene-1,1-dithiol (I-1a):



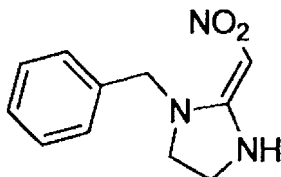
Ethanol KOH (148g, 2.64mol) was added to a solution of carbon disulphide (200g, 2.63mol) and nitromethane (161g, 2.63mol) at 0°C. The resulting mixture was stirred at 0°C for 1 hour and at room temperature for 1 hour. The reaction mixture was filtered, washed with ethanol (500mL) and dried under reduced pressure to afford 400g of the product (71.5% yield).

Synthesis of Intermediate 1, 1-Bis-methylsulfanyl-2-nitro-ethene (I-1b):



Methyl iodide (227g, 1.598mol) was added to a solution of potassium salt of 2-nitro-ethene-1,1-dithiol (150g, 0.704mol) in DMF (800mL) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature overnight. The reaction mixture was monitored by TLC (30% ethylacetate in hexane). The reaction mixture was quenched with ice water; the precipitate formed was collected and dried to afford 90g of the product (77.5% yield).

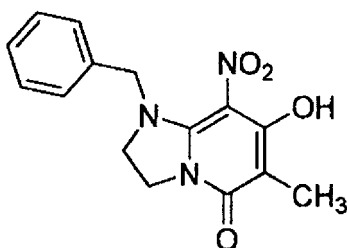
Synthesis of Intermediate 1-Benzyl-2-nitromethylene-imidazolidine (I-1c):



Ethanol (200mL) was added to a solution of 1,1-bis-methylsulfanyl-2-nitro-ethene (14.5g, 0.0878mol) and N1-benzyl-ethane-1,2-diamine (12g, 0.080mol). The resulting mixture was heated to reflux for 2 hours. The reaction mixture was monitored by TLC (10% MeOH in CHCl₃). The reaction mixture was concentrated and the concentrate was dissolved in ethylacetate. The precipitate formed was collected and washed with ethylacetate to afford 13g of the product (74.7% yield).

¹H NMR (DMSO-D₆, 300 MHz) δ: 8.9 (br s, 1H), 7.5-7.2 (m, 5H), 6.6 (s, 1H), 4.5 (s, 2H), 3.7-3.5 (m, 4H).

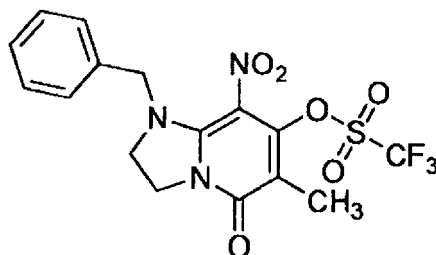
Synthesis of Intermediate 1-Benzyl-7-hydroxy-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (I-1d):



Xylene (15mL) was added to a solution of 1-benzyl-2-nitromethylene-dazolidine (1g, 0.005mol) and 2-methyl-malonic acid bis-(2,4,6-trichloro-phenyl) ester (2.39g, 0.005mol). The resulting mixture was heated to reflux for 2 hours. The reaction mixture was monitored by TLC (5% MeOH in CHCl₃). The reaction mixture was concentrated and the concentrate was dissolved in ethanol. The precipitate formed was collected and washed with ethanol to afford 900mg of the product (65.69% yield).

¹H NMR (CDCl₃, 300 MHz) δ: 11.5 (br s, 1H), 7.4-7.2 (m, 5H), 4.6 (s, 2H), 4.2-4.0 (m, 2H), 4.0-3.8 (m, 2H), 1.9 (s, 3H).

Synthesis of Intermediate Trifluoro-methanesulfonic acid 1-benzyl-6-methyl-8-nitro-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-7-yl ester (I-1e):



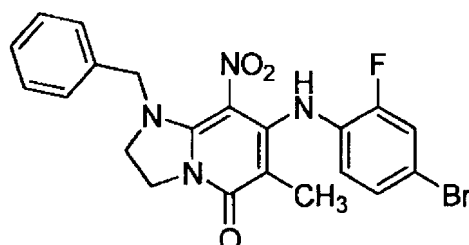
Triflic anhydride (2.8g, 0.010mol) was added to a stirred solution of 1-benzyl-7-hydroxy-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (2g, 0.007 mol) and TEA (1.34g, 0.013mol) in DCM (40mL) at -78°C. The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was monitored by TLC (100% ethyl acetate). The reaction mixture was partitioned between DCM and water. The organic layer was washed with NaHCO₃ solution, brine solution, dried over Na₂SO₄ and concentrated.

Purification by column chromatography on silica gel (30% ethylacetate in hexane) afforded 2.5 g of the product (89% yield).

^1H NMR (CDCl_3 , 300 MHz) δ : 7.4-7.32 (m, 3H), 7.27-7.2 (m, 2H), 4.6 (s, 2H), 4.23-4.13 (t, 2H), 3.91-3.8 (t, 2H), 2.1 (s, 3H)

5

Synthesis of Intermediate 1-Benzyl-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (I-1f):

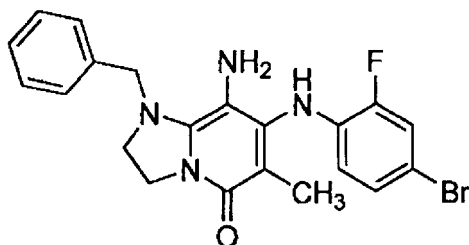


Palladium acetate (129mg, 0.001mol), BINAP (538mg, 0.001mol), cesium carbonate (2.8g, 0.009mol) were dissolved in toluene (20mL) and the resulting mixture was sparged for 30 mins with nitrogen. This was followed by addition of trifluoro-methanesulfonic acid 1-benzyl-6-methyl-8-nitro-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-7-yl ester (2.5g, 0.006 mol) and 4-bromo-2-fluoro-phenylamine (1.15 g, 0.006 mol) in toluene (20mL) and the reaction flask was again sparged for another 15 minutes. The reaction mixture was heated at 90°C for 1 hour. The reaction was monitored by TLC (80% ethylacetate in hexane). The reaction mixture was filtered through celite bed and concentrated. Purification by column chromatography on silica gel (40% ethylacetate in hexane) afforded 1.3 g of the product (48% yield).

^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ : 8.05 (br s, 1H), 7.5 (dd, 1H), 7.4-7.25 (m, 5H), 7.21-7.15 (d, 1H), 6.6 (t, 1H), 4.5 (s, 2H), 4.15 (t, 2H), 3.9 (t, 2H), 1.6 (s, 3H).

Synthesis of Intermediate 8-Amino-1-benzyl-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (I-1g):

25



Zinc (414 mg, 0.006 mol) was added to a stirred solution of 1-benzyl-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-

- 5 The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was monitored by TLC (100% ethylacetate). The reaction mixture was concentrated and partitioned between ethylacetate and water. The organic layer was washed with saturated NaHCO₃ solution and concentrated to afford 400mg of the crude product which was used in the next step without
- 10 further purification.

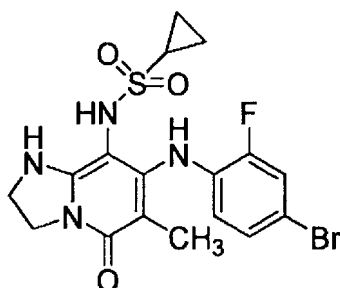
Synthesis of the title compound: Cyclopropanesulfonic acid [1-benzyl-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (1A):

- 15 Cyclopropanesulfonyl chloride (254 mg, 0.0002 mol) was added to a stirred solution of 8-amino-1-benzyl-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (400 mg, 0.001 mol) in pyridine (4 mL). The resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was monitored by TLC (100% ethylacetate). The reaction
- 20 mixture was concentrated and partitioned between ethylacetate and water. The organic layer was concentrated to afford the crude product. Purification by column chromatography on silica gel (80% ethylacetate in hexane), followed by preparative HPLC afforded 30 mg of the product (6% yield).

- ¹H NMR (DMSO-D₆, 300 MHz) δ: 8.4-8.35 (br s, 1H), 7.5 (dd, 1H), 7.4-7.25 (m, 5H), 7.2 (d, 1H), 6.5 (t, 1H), 5.0 (d, 1H), 4.8 (d, 1H), 4.1-4.0 (m, 1H), 3.9 (d, 1H), 3.6-3.5 (m, 1H), 2.3 (d, 1H), 1.6 (s, 3H), 1.3 (s, 1H), 0.9-0.7 (m, 4H), 0.5-0.4 (m, 1H). LCMS: 98.98%, m/z = 547(M+1) HPLC: 97.95%
- 25

Example 2

Synthesis of Cyclopropanesulfonic acid [7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (2A):



(2A)

5

Borontribromide (20mg, 0.0001 mol) was added to a stirred solution of cyclopropanesulfonic acid [1-benzyl-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (**1A**: 30 mg, 0.0001 mol) in DCM (3 mL) at 0°C. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was monitored by TLC (100%ethylacetate). The reaction mixture was quenched with methanol and concentrated. The concentrate was partitioned between ethyl acetate and water. The organic layer was concentrated to afford the crude product. Purification by column chromatography on silica gel (4% methanol in DCM) afforded 7 mg of the product (28% yield).

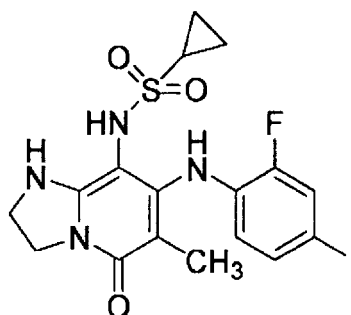
10

¹H NMR (DMSO-D₆, 300 MHz) δ: 7.2 (d, 1H), 7.1 (d, 1H), 6.5-6.4 (m, 2H), 5.9-5.8 (m, 1H), 5.7-5.6 (br s, 1H), 4.95 (d, 1H), 4.3 (t, 2H), 3.8 (t, 2H), 2.45-2.35 (m, 1H), 2.05-2.0 (d, 2H), 1.8 (s, 3H), 1.12 (d, 3H). LCMS: 74.36%, m/z = 457(M+1) HPLC: 97.7%

15

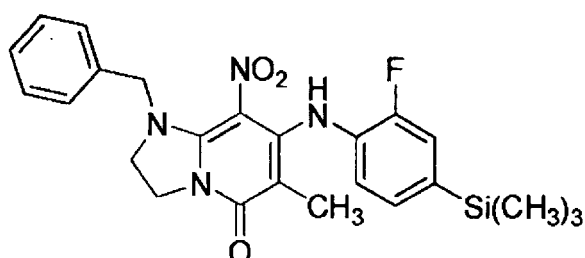
Example 3

Synthesis of Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (3A):



(3A)

Synthesis of Intermediate 1-Benzyl-7-(2-fluoro-4-trimethylsilylphenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (I-3a):



5

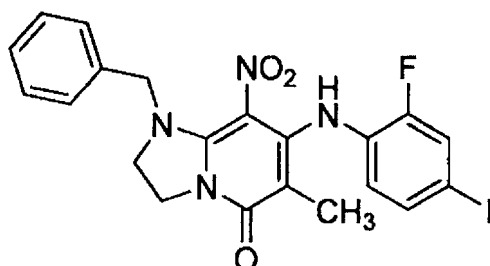
Trifluoro-methanesulfonic acid 1-benzyl-6-methyl-8-nitro-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-7-yl ester (I-1e: 500 mg, 0.001 mol) in toluene (15 mL) was reacted with 2-fluoro-4-trimethylsilylphenylamine (221 mg, 0.001 mol) in the presence of $\text{Pd}_2(\text{dba})_3$ (63.3mg, 0.0001 mol), xantphos (40 mg, 0.0001 mol) and K_3PO_4 (367mg, 0.002 mol) and the reaction mixture was heated to reflux for 1 hour. Reaction workup yields the crude product which was purified by column chromatography on silica gel (40% ethylacetate in hexane) to afford 400 mg of the product (74.48% yield).

10

^1H NMR (DMSO- D_6 , 300 MHz) δ : 8.0 (br s, 1H), 7.4 (d, 1H), 7.45-7.2 (m, 5H), 7.1 (d, 1H), 6.65 (t, 1H), 4.5 (s, 2H), 4.15 (t, 2H), 3.9 (t, 2H), 1.6 (s, 3H), 0.3 (s, 9H)

15

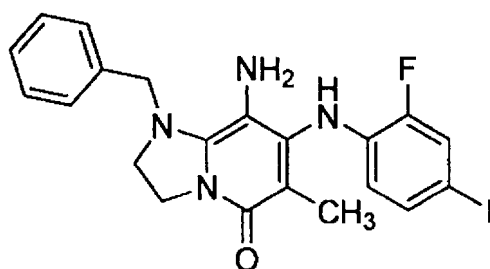
Synthesis of Intermediate 1-Benzyl-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (I-3b):



1-Benzyl-7-(2-fluoro-4-trimethylsilyl-phenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (400 mg, 0.001 mol) in DCM (10 mL) was added to AgBF₄ (500 mg) in DCM (10 mL) previously sparged with nitrogen for 10 minutes at -50°C. The resulting mixture was stirred at -50°C for 30 minutes under nitrogen atmosphere. This was followed by the addition of ICl (0.85mL) and the stirring was continued for a further 1 hour at -50°C under nitrogen atmosphere. The reaction mixture was monitored by TLC (65%ethylacetate in hexane). The reaction mixture was quenched with sodium thiosuphate and extracted with DCM. The organic layer was washed with ammonia solution and concentrated to get the crude product which was washed with diethyl ether to afford 250 mg of the product (56.1% yield).

¹H NMR (DMSO-D₆, 300 MHz) δ: 8.0 (br s, 1H), 7.5 (d, 1H), 7.4-7.2 (m, 6H), 6.5 (t, 1H), 4.5 (s, 2H), 4.2 (t, 2H), 4.0 (t, 2H), 1.6 (s, 3H). LCMS: 83.8%, m/z = 521(M+1)

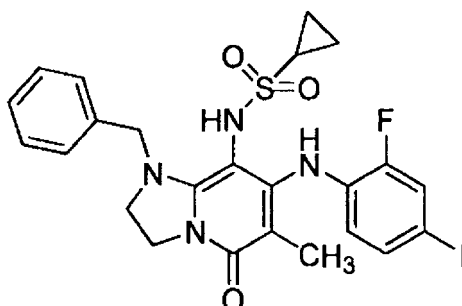
Synthesis of Intermediate 8-Amino-1-benzyl-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (I-3c):



Following the procedure set forth in Example 1 for the preparation of I-1g, 1-benzyl-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (280mg, 0.001 mol) in THF (30 mL) was reacted with

zinc (211 mg, 0.003 mol) and HCl (1 mL) to afford 250 mg of the crude product which was used in the next step without further purification.

Synthesis of Intermediate Cyclopropanesulfonic acid [1-benzyl-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (I-3d):



Following the procedure set forth for the preparation of Example 1A, 8-amino-1-benzyl-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (250 mg, 0.001 mol) in pyridine (4 mL) was reacted with cyclopropanesulfonyl chloride (144 mg, 0.001 mol) to afford the crude product. Purification by column chromatography on silica gel (80% ethylacetate in hexane) afforded 40 mg of the product (13.2% yield).
LCMS: 83.8%, m/z = 595.1(M+1)

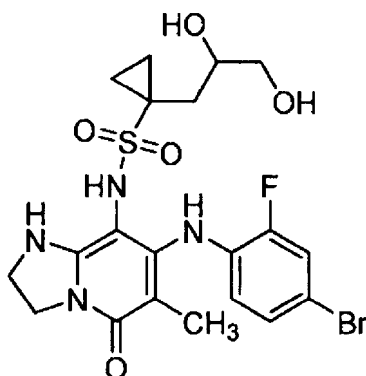
Synthesis of the title compound: Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide.(3A):

Following the procedure set forth for the preparation of Example 2A, cyclopropanesulfonic acid [1-benzyl-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (40 mg, 0.0001 mol) in DCM (3 mL) was reacted with borontribromide (0.025 g, 0.0001 mol) to afford the crude product. Purification by column chromatography on silica gel (4% methanol in CHCl₃) afforded 3 mg of the product (9.09% yield).

¹H NMR (DMSO-D₆, 300 MHz) δ: 8.4 (br s, 1H), 7.6 (d, 1H), 7.4 (d, 1H), 7.2 (br s, 1H), 7.0 (br s, 1H), 6.4 (t, 1H), 4.0 (t, 2H), 3.8 (t, 4H), 2.1 (s, 1H), 1.6 (s, 3H), 0.8 (s, 4H). LCMS: 94.3%, m/z = 504.8(M+1). HPLC: 87.6%

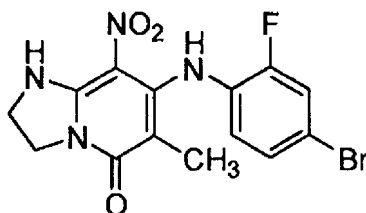
Example 4

Synthesis of 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (4A):



(4A)

Synthesis of Intermediate 7-(4-Bromo-2-fluoro-phenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (I-4a):

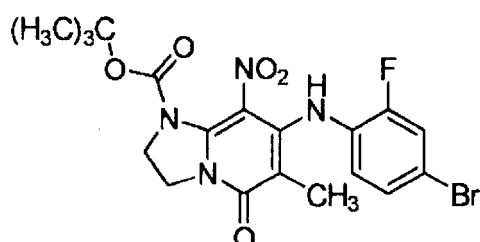


HBr in acetic acid (20 mL) was added to 1-benzyl-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (I-1f: 1.4 g) and the resulting mixture was stirred at room temperature for 2 hours. The reaction was monitored by TLC (100% ethylacetate). The reaction mixture was partitioned between ice water and ethyl acetate. The organic layer was concentrated to afford the crude product. Purification by column chromatography on silica gel (65% ethylacetate in hexane) afforded 600 mg of the product (54.5% yield).

¹H NMR (DMSO-D₆, 300 MHz) δ: 9.6 (br s, 1H), 9.0 (s, 1H), 7.6 (d, 1H), 7.4 (s, 1H), 6.8 (t, 1H), 4.1 (t, 2H), 3.9 (t, 2H), 1.6 (s, 3H)

36

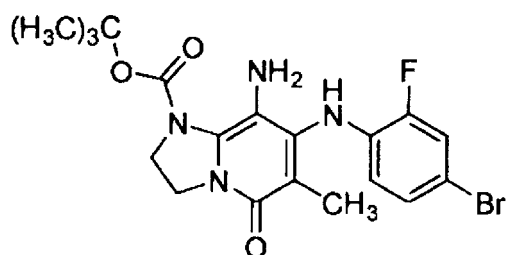
Synthesis of Intermediate 7-(4-Bromo-2-fluoro-phenylamino)-6-methyl-8-nitro-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (I-4b):



5 BOC anhydride (21 mg, 0.0001 mol) was added to a stirred solution of 7-(4-bromo-2-fluoro-phenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (35 mg, 0.0001 mol) and DMAP (2.4mg, 0.0001 mol) in acetonitrile (3 mL). The resulting mixture was stirred at room temperature for 2 hours. The reaction was monitored by TLC (100% ethylacetate). The reaction
10 mixture was concentrated and partitioned between ethylacetate and water. The organic layer was concentrated to afford the crude product. Purification by column chromatography on basic alumina (60% ethylacetate in hexane) afforded 30 mg of the product (68.18% yield).

¹H NMR (CDCl₃, 300 MHz) δ: 7.8 (s, 1H), 7.3 (d, 1H), 7.1 (d, 1H), 6.5 (t, 1H), 4.3-4.2 (m, 4H), 1.8 (s, 3H), 1.5 (s, 9H)

Synthesis of Intermediate 8-Amino-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (I-4c):

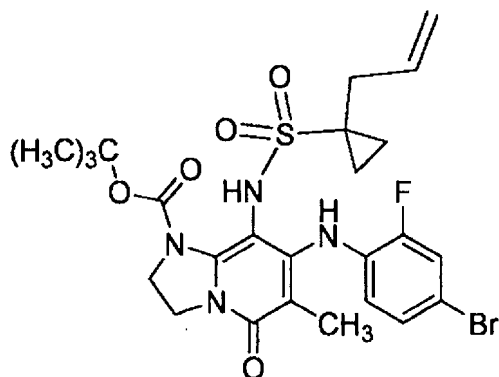


20

Zinc (284 mg, 0.004 mol) was added to a stirred solution of 7-(4-bromo-2-fluoro-phenylamino)-6-methyl-8-nitro-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (350 mg, 0.0007 mol) and NH₄Cl (310 mg, 0.006 mol) in water and THF (10mL). The resulting mixture was stirred at

room temperature for 40 minutes. The reaction was monitored by TLC (100% ethylacetate). The reaction mixture was concentrated and partitioned between ethylacetate and water. The organic layer was washed with saturated NaHCO₃ solution and concentrated to afford 150 mg of the crude product which was used in the next step without further purification.

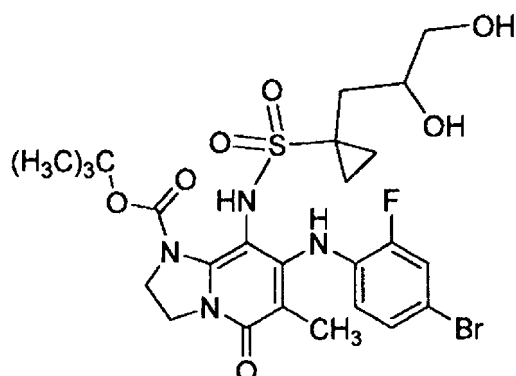
Synthesis of Intermediate 8-(1-Allyl-cyclopropanesulfonylamino)-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (I-4d):



1-Allyl-cyclopropanesulfonyl chloride (121 mg, 0.001 mol) was added to a stirred solution of 8-amino-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (150 mg, 0.0003 mol) in pyridine (3 mL). The resulting mixture was stirred at room temperature for 12 hours. The reaction was monitored by TLC (100% ethylacetate). The reaction mixture was concentrated and partitioned between ethylacetate and water. The organic layer concentrated to afford the crude product. Purification by column chromatography on silica gel (60% ethylacetate in hexane) afforded 120 mg of the product (60.6% yield).

Synthesis of Intermediate 7-(4-Bromo-2-fluoro-phenylamino)-8-[1-(2,3-dihydroxy-propyl)-cyclopropanesulfonylamino]-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (I-4e):

32



OsO₄ (0.1 mg, 0.00002 mol) was added to a stirred solution of 8-(1-allyl-cyclopropanesulfonylamino)-7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (120 mg, 0.0002 mol) and N-methylmorpholine-N-oxide (35 mg, 0.0003 mol) in water and THF (3 mL). The resulting mixture was stirred at room temperature for 12 hours. The reaction was monitored by TLC (10% MeOH in CHCl₃). The reaction mixture was partitioned between ethylacetate and water. The organic layer was concentrated to afford 75 mg of the crude product which was used in the next step without further purification.

Synthesis of the title compound: 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridin-8-yl]-amide (4A):

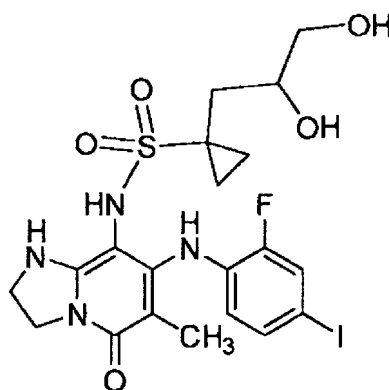
Concentrated HCl (3mL) was added to a stirred solution of 7-(4-bromo-2-fluoro-phenylamino)-8-[1-(2,3-dihydroxy-propyl)-cyclopropanesulfonylamino]-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (75mg) in THF (10mL). The resulting mixture was stirred at 45°C for 1 hour. The reaction was monitored by TLC (10% MeOH in CHCl₃). The reaction mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with saturated NaHCO₃ solution and concentrated to afford 25 mg of the product (39.58% yield).

¹H NMR (DMSO-D₆, 300 MHz) δ: 8.5-8.3 (br s, 1H), 7.5 (dd, 1H), 7.2 (d, 1H), 7.1 (s, 1H), 7.0-6.8 (t, 1H), 5.1-4.9 (s, 1H), 4.7 (t, 1H), 4.5 (t, 1H), 4.2-4.0 (q, 2H), 3.7-3.5 (m, 4H), 2.3 (d, 1H), 1.8-1.6 (q, 2H), 1.6 (s, 4H), 1.2-0.9 (m, 4H)

LCMS: 98.58%, m/z = 533.0(M+2) HPLC: 97.31%

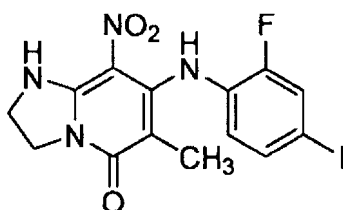
Example 5

5 Synthesis of 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (5A):



(5A)

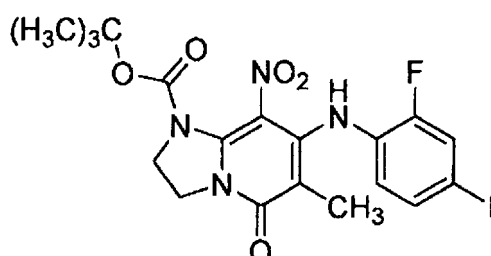
10 Synthesis of Intermediate 7-(2-Fluoro-4-iodo-phenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (I-5a):



HBr in acetic acid (30 mL) was added to 1-benzyl-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (I-3b: 2.5 g) and the resulting mixture was stirred at room temperature for 2 hours. The reaction was monitored by TLC (100% ethylacetate). The reaction mixture was basified with NaHCO₃ solution and partitioned between ice water and ethyl acetate. The organic layer was concentrated to afford the crude product. Purification by column chromatography on silica gel (60% ethylacetate in hexane) afforded 1.5 g of the product (75% yield).

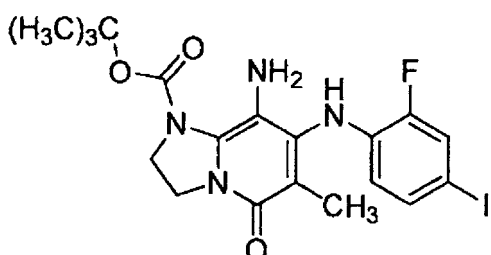
20

Synthesis of Intermediate 7-(2-Fluoro-4-iodo-phenylamino)-6-methyl-8-nitro-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (I-5b):



5 BOC anhydride (761 mg, 0.003 mol) was added to a stirred solution of 7-(2-fluoro-4-iodo-phenylamino)-6-methyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (1 g, 0.002 mol) and DMAP (530 mg, 0.003 mol) in acetonitrile (20 mL). The resulting mixture was stirred at room temperature for 2 hours. The reaction was monitored by TLC (100% ethylacetate). The reaction mixture was concentrated and partitioned between ethylacetate and water. The organic layer was concentrated to afford 900 mg of the crude product which was used in the next step without further purification.

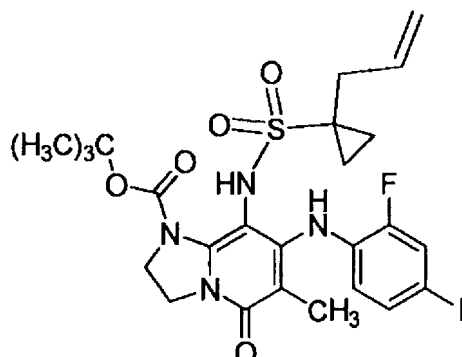
Synthesis of Intermediate 8-Amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (I-5c):



Zinc (296 mg, 0.005 mol) was added to a stirred solution of 7-(2-fluoro-4-iodo-phenylamino)-6-methyl-8-nitro-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (400 mg, 0.0008 mol) and NH₄Cl (322 mg, 0.006 mol) in water and THF (15 mL). The resulting mixture was stirred at room temperature for 30 minutes. The reaction was monitored by TLC (100% ethylacetate). The reaction mixture was concentrated and partitioned between

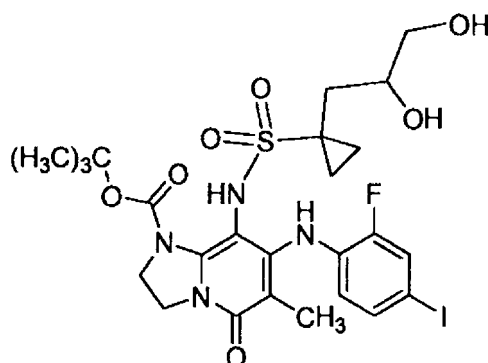
ethylacetate and water. The organic layer was washed with saturated NaHCO_3 solution and concentrated to afford 350 mg of the crude product which was used in the next step without further purification.

5 Synthesis of Intermediate 8-(1-Allyl-cyclopropanesulfonylamino)-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (I-5d):



10 1-Allyl-cyclopropanesulfonyl chloride (259 mg, 0.001 mol) was added to a stirred solution of 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (350 mg, 0.001 mol) in pyridine (3mL). The resulting mixture was stirred at room temperature for 12 hours. The reaction was monitored by TLC (100% ethylacetate). The reaction mixture was concentrated and partitioned between
15 ethylacetate and water. The organic layer concentrated to afford the crude product. Purification by column chromatography on silica gel (75% ethylacetate in hexane) afforded 125 mg of the product (27.7% yield).

20 Synthesis of Intermediate 8-[1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonylamino]-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (I-5e):



OsO₄ (0.004 g, 0.00002 mol) was added to a stirred solution of 8-(1-allyl-cyclopropanesulfonylamino)-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (125 mg, 0.0002 mol) and N-methylmorpholine-N-oxide (34 mg, 0.0003 mol) in water and THF (3 mL). The resulting mixture was stirred at room temperature for 3 hours. The reaction was monitored by TLC (10% MeOH in CHCl₃). The reaction mixture was partitioned between ethylacetate and water. The organic layer concentrated to afford 80 mg of the crude product which was used in the next step without further purification.

Synthesis of the title compound: 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (5A):

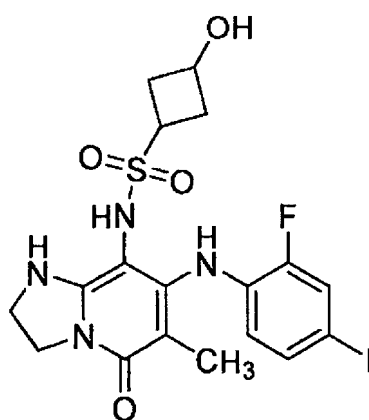
Concentrated HCl (3 mL) was added to a stirred solution of 8-[1-(2,3-dihydroxy-propyl)-cyclopropanesulfonylamino]-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (80 mg) in THF (5 mL). The resulting mixture was stirred at 40°C for 2 hours. The reaction was monitored by TLC (15% MeOH in CHCl₃). The reaction mixture was concentrated and partitioned between ethylacetate and water. The organic layer was washed with saturated NaHCO₃ solution and concentrated to afford the crude product. Purification by column chromatography on silica gel (5% methanol in CHCl₃), followed by preparative HPLC afforded 10mg of the product (14.7% yield)

^1H NMR (DMSO- D_6 , 300 MHz) δ : 8.4-8.3 (br s, 1H), 7.5 (d, 1H), 7.3 (d, 1H), 7.1 (s, 1H), 7.0-6.9 (br s, 1H), 6.3 (t, 1H), 5.1-4.9 (br s, 1H), 4.8-4.6 (br s, 1H), 3.7-3.5 (m, 3H), 1.6 (s, 3H), 1.3-1.2 (br s, 2H), 1.1-1.0 (m, 4H)
 LCMS: 98.58%, m/z = 578.9(M+1) HPLC: 97.67%

5

Example 6

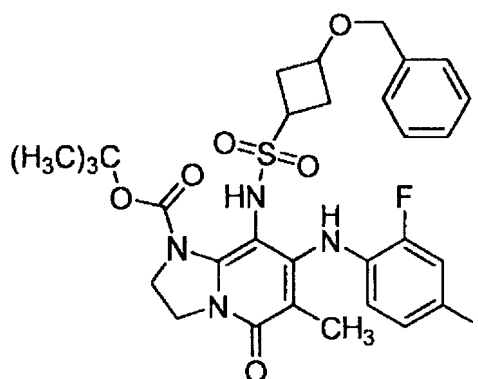
Synthesis of 3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (6A):



10

(6A)

Synthesis of Intermediate 8-(3-Benzyloxy-cyclobutanesulfonylamino)-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (I-6a):



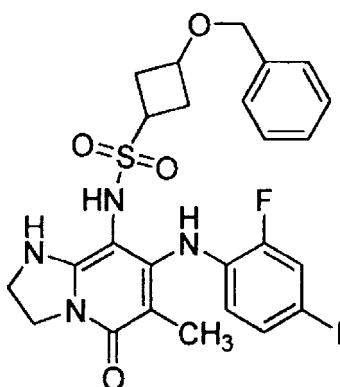
15

Using the same reaction conditions and workup as described for the preparation of Intermediate (I-5d), 8-Amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl

ester (**1-5c**: 350 mg, 0.7 mmol) in pyridine (3 mL) was reacted with 3-benzyloxy-cyclobutanesulfonyl chloride (273 mg, 1.05 mmol) to afford the crude product. Purification by column chromatography on silica gel (80% ethylacetate in hexane) afforded 250mg of the product (45.3% yield).

5 ^1H NMR (400MHz, DMSO- D_6): δ 7.68-7.64 (br s, 1H), 7.58 (d, 1H), 7.50 (s, 1H), 7.40-7.24 (m, 6H), 6.35 (t, 1H), 4.32 (s, 2H), 4.30-4.00 (m, 4H), 3.80 (t, 1H), 3.51-3.40 (m, 1H), 2.30-2.20 (br s, 2H), 2.10-1.90 (m, 2H), 1.70 (s, 3H), 1.50 (s, 9H)

10 Synthesis of Intermediate 3-Benzyloxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (**1-6b**):



Dioxane hydrochloride (3 mL) was added to 8-(3-benzyloxy-cyclobutanesulfonylamino)-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-imidazo[1,2-a]pyridine-1-carboxylic acid tert-butyl ester (250 mg) and the resulting mixture was stirred at room temperature for 12 hours. The reaction was monitored by TLC (5% MeOH in CHCl_3). The reaction mixture was concentrated; the concentrate was neutralized with NaHCO_3 solution and extracted with ethylacetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford 120 mg of the product (55.8% yield). LCMS: m/z = 624.8 ($\text{M}+1$)

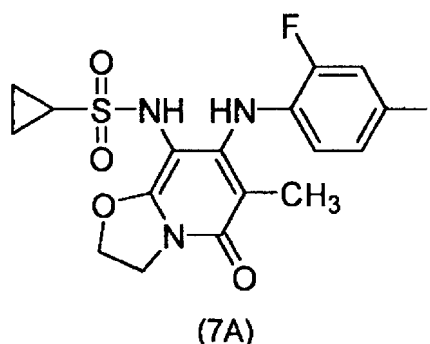
Synthesis of the title compound: 3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (6A):

3-Benzyloxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide (120 mg, 0.19 mmol) in DCM (3 mL) was reacted with 1M BCl₃ (67 mg, 0.57 mmol) at 0°C. The resulting mixture was stirred at room temperature for 6 hours. Purification by column chromatography on silica gel (5% MeOH in CHCl₃), followed by preparative HPLC afforded 30mg of the product (29.4% yield).

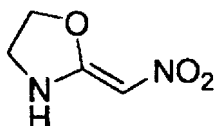
¹HNMR (400MHz, DMSO-D₆): δ 8.26-8.22 (br s, 1H), 7.6 (d, 1H), 7.33 (d, 1H), 7.32-7.28 (br s, 1H), 6.83-6.80 (br s, 1H), 6.3 (t, 1H), 4.1 (t, 2H), 3.75 (t, 1H), 3.6 (t, 2H), 3.4-3.3 (m, 2H), 2.4-2.3 (br s, 2H), 2.1-2.0 (m, 2H), 1.6 (s, 3H).
LCMS: 95.3%, m/z = 534.7 (M+1). HPLC: 97.2%

Example 7

Synthesis of Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide. (7A):



Synthesis of Intermediate 2-Nitromethylene-oxazolidine (I-7a):

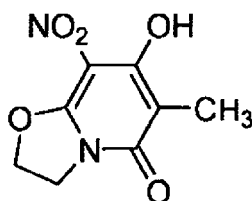


p-Toluene sulfonic acid (0.5g) was added to a boiling solution of 1,1-bis-methylsulfanyl-2-nitro-ethene (I-1b: 20 g, 12.13 mol) in ethanol (200 mL). This was followed by the addition of ethanolamine (7.4 g, 12.13 mmol) and the resulting mixture was heated to reflux for 12 hours. The reaction mixture was

monitored by TLC (100% ethylacetate). The reaction mixture was concentrated, 300 mL of water added and resultant filtered. The filtrate was further concentrated and was followed by the addition of acetone. The reaction mixture was refluxed for 1 hour, cooled to room temperature, and filtered. The acetone layer was concentrated to afford 4.1 g of the crude product which was used in the next step without further purification.

¹HNMR (300MHz, DMSO-D₆): δ 9.9 (s, 1H), 6.6 (s, 1H), 4.6 (t, 2H), 3.7 (t, 2H)

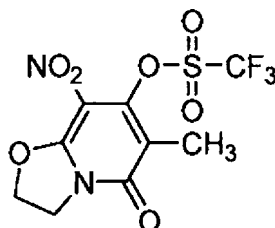
10 Synthesis of Intermediate 7-Hydroxy-6-methyl-8-nitro-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (I-7b):



2-Nitromethylene-oxazolidine (3 g, 23.0 mmol) was added portion wise to a stirred solution of 2-methyl-malonic acid bis-(2,4,6-trichloro-phenyl) ester (12 g, 25.15 mmol) in Xylene (50 mL) under nitrogen atmosphere over a period of 1 hour at 125°C. The resulting mixture was heated to 125°C for 5 hours. The reaction mixture was monitored by TLC (50% ethylacetate in hexane). The reaction mixture was concentrated and the concentrate was purified by column chromatography on silica gel (60% ethylacetate in hexane) to afford 1.5 g of the product (30% yield).

¹HNMR (300MHz, DMSO-D₆): δ 11.1 (s, 1H), 5.0 (t, 2H), 4.2 (t, 2H), 1.85 (s, 3H)

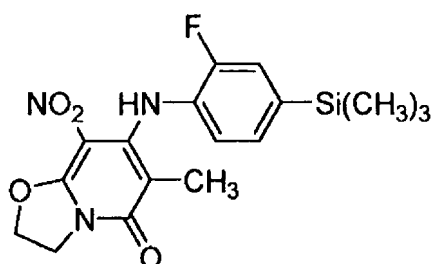
25 Synthesis of Intermediate Trifluoro-methanesulfonic acid 6-methyl-8-nitro-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-7-yl ester (I-7c):



Triflic anhydride (2.78 g, 9.9 mmol) was added dropwise to a stirred solution of 7-hydroxy-6-methyl-8-nitro-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (1.5 g, 7.0 mmol) and TEA (1.42 g, 14.060 mmol) in DCM (30 mL) at -78° C over
 5 a period of 1 hour. The resulting mixture was stirred at room temperature for 5 hours. The reaction mixture was monitored by TLC (50% ethylacetate in hexane). The reaction mixture was partitioned between DCM and water. The organic layer was washed with water, brine solution, dried over Na₂SO₄ and concentrated. Purification by column chromatography on silica gel (50%
 10 ethylacetate in hexane) afforded 0.5 g of the product (20.6% yield).

¹HNMR (300MHz, DMSO-D₆): δ 5.0 (t, 2H), 4.25 (t, 2H), 2.0 (s, 3H)

Synthesis of Intermediate 7-(2-Fluoro-4-trimethylsilanyl-phenylamino)-6-methyl-8-nitro-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (I-7d):



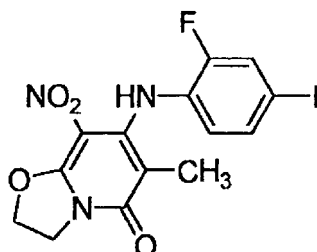
Pd(dba)₃ (0.1 g, 0.109 mmol), potassium phosphate tribasic (0.5 g, 2.35 mmol), xantphos (0.07 g, 0.120 mmol) were dissolved in dry toluene (30 mL) and the resulting mixture was sparged for 30 minutes with argon. This was followed by addition of trifluoro-methanesulfonic acid 6-methyl-8-nitro-5-oxo-2,3-dihydro-
 15 5H-oxazolo[3,2-a]pyridin-7-yl ester (0.5 g, 1.45 mmol) and 2-fluoro-4-trimethylsilanyl-phenylamine (0.3 g, 1.64 mmol) and the reaction flask was again sparged for another 15 minutes. The reaction mixture was heated at 100° C for 5 hours. The reaction was monitored by TLC (60% ethylacetate in hexane). The reaction mixture was filtered through celite bed and the filtrate was concentrated.

Purification by column chromatography on silica gel (60% ethylacetate in hexane) afforded 0.25 g of the product (45.8% yield).

¹HNMR (400MHz, DMSO-D₆): δ 8.25 (s, 1H), 7.1-7.3 (m, 2H), 6.7 (t, 1H), 4.95 (t, 2H), 4.25 (t, 2H), 1.7 (s, 3H), 0.25 (s, 9H)

5

Synthesis of Intermediate 7-(2-Fluoro-4-iodo-phenylamino)-6-methyl-8-nitro-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (I-7e):

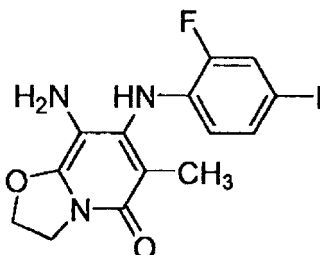


A stirred solution of 7-(2-fluoro-4-trimethylsilyl-phenylamino)-6-methyl-8-nitro-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (0.25 g, 0.66 mmol) in dry DCM (10 mL) and iodine monochloride (0.8 mL) were added to silver tetrafluoroborate (0.4 g, 2.05 mmol) in DCM (10 mL) previously degassed with nitrogen for 30 minutes at -50° C. The resulting mixture was stirred at -50°C for 1 hour. The reaction was monitored by TLC (50% ethylacetate in hexane). This was followed by the addition of 20 mL of sodium thiosulphate and filtered through celite. The filtrate was concentrated to afford 0.2 g of the product (70% yield).

15

¹HNMR (300MHz, CDCl₃): δ 8.6 (s, 1H), 7.2-7.6 (m, 2H), 6.45 (t, 1H), 5.0 (t, 2H), 4.45 (t, 2H), 1.65 (s, 3H)

20 Synthesis of Intermediate 8-Amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (I-7f):



Concentrated HCl (0.2 mL) and SnCl₂.H₂O (0.24 g, 1.06 mmol) were added to 7-(2-fluoro-4-iodo-phenylamino)-6-methyl-8-nitro-2,3-dihydro-

oxazolo[3,2-a]pyridin-5-one (0.15 g, 0.347 mmol) in ethanol (5 mL). The resulting mixture was heated to reflux for 2 hours. The reaction was monitored by TLC (100% ethylacetate). The reaction mixture was cooled to room temperature, diluted with ethylacetate, basified with saturated bicarbonate solution and filtered through celite. The organic layer was washed with brine solution, dried over Na₂SO₄ and concentrated to afford 0.08 g of the crude product which was used in the next step without further purification.

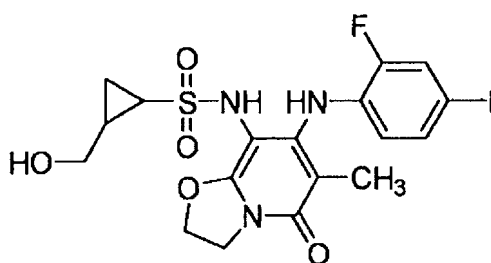
Synthesis of the title compound: Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (7A):

Cyclopropane sulfonyl chloride (50 mg, 0.35 mmol) was added to a solution of 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (1-7f: 80 mg, 0.199 mmol) in dry pyridine (1 mL) at 0°C. The resulting mixture was stirred at room temperature for 1 hour. The reaction was monitored by TLC (100% ethylacetate). The reaction mixture was partitioned between ethylacetate and water. The organic layer was washed with water, brine solution, dried over Na₂SO₄ and concentrated. Purification by column chromatography on silica gel (1.5% MeOH in DCM) afforded 3 mg of the product (3% yield).

¹HNMR (300MHz, CDCl₃): δ 7.3-7.4 (m, 1H), 6.85 (s, 1H), 6.35 (t, 1H), 5.7 (s, 1H), 4.8 (t, 2H), 4.35 (t, 2H), 1.75 (s, 3H), 0.9-1.1 (m, 4H)

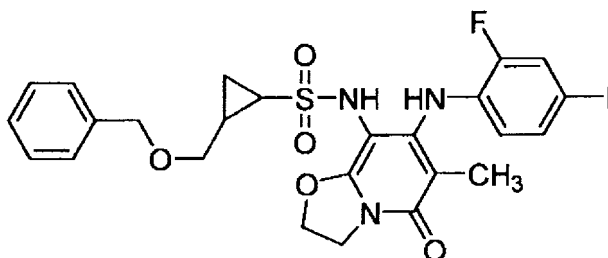
Example 8

Synthesis of 2-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (8A):



(8A)

Synthesis of Intermediate 2-Benzyloxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (I-8a):



Using the same reaction conditions and workup as described for the preparation of Example 7A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (I-7f: 0.08 g, 0.0002 mol) in dry pyridine (2 ml) was reacted with 2-benzyloxymethyl-cyclopropanesulfonyl chloride (57 mg, 0.0002 mol) to afford the crude product. Purification by column chromatography on silica gel (2% MeOH in DCM) afforded 51 mg of the product (21% yield). LCMS: 95.06%, m/z = 625.9 (M+1)

Synthesis of the title compound: 2-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (8A):

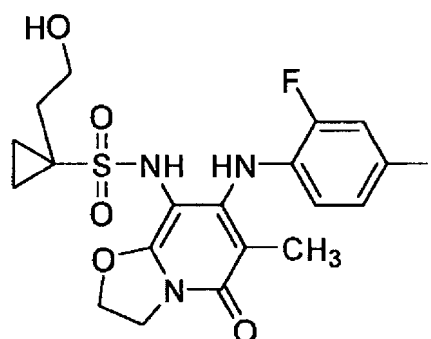
2-Benzyloxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (0.05 g, 0.0001 mol) was added to a stirred solution of $\text{BF}_3 \cdot \text{EtO}_2$ (0.34 g, 0.002 mol) in ethane thiol (0.05 g, 0.001 mol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC (100% ethylacetate). The reaction mixture was quenched with saturated NaHCO_3 solution and extracted with ethylacetate. The organic layer was washed with water, dried over Na_2SO_4 and concentrated. Purification by column chromatography on silica gel (2-3% MeOH in DCM) afforded 11 mg of the product (27% yield).

^1H NMR (300MHz, DMSO- D_6): δ 8.8 (s, 1H), 7.6-7.1 (m, 3H), 6.35 (t, 1H), 4.8-4.6 (m, 3H), 4.2 (t, 2H), 2.1 (s, 1H), 1.65 (s, 3H), 1.5-1.4 (m, 1H), 0.9-0.8 (m, 2H). LCMS: 94.35%, m/z = 536 ($\text{M}+1$) HPLC: 89%

5

Example 9

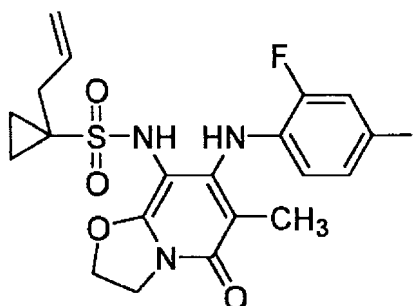
Synthesis of 1-(2-Hydroxy-ethyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (9A):



10

(9A)

Synthesis of Intermediate 1-Allyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (I-9a):



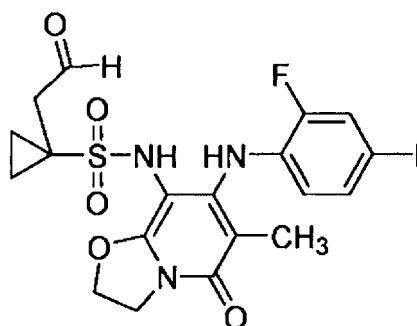
15

Using the same reaction conditions and workup as described for the preparation of Example 7A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (**I-7f**: 0.46 g, 0.001 mol) in dry pyridine (3 mL) was reacted with 1-allyl-cyclopropane sulfonyl chloride (0.25 g, 0.0014 mol) to afford the crude product. Purification by column chromatography on silica gel (2% MeOH in DCM) afforded 0.19 g of the product (30% yield).

20

¹HNMR (300MHz, CDCl₃): δ 7.3-7.4 (m, 1H), 6.85 (s, 1H), 6.35 (t, 1H), 5.6-5.8 (m, 2H), 5.2-5.3 (m, 2H), 4.85 (t, 2H), 3.85 (t, 2H), 2.8 (d, 2H), 1.75 (s, 3H), 1.25 (t, 2H), 0.8 (t, 2H).

5 Synthesis of Intermediate 1-(2-Oxo-ethyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (I-9b):



Osmium tetra oxide (8 mg, 0.035 mmol), 2,6-lutidine (0.08 g, 0.74 mmol)
 10 and sodium periodate (0.3 g, 0.001 mol) were added to a solution of 1-allyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (0.19 g, 0.35 mmol) in dioxane (7 mL) and water (2 mL). The resulting mixture was stirred at room temperature for 5 hours. The reaction was monitored by TLC (5% MeOH in DCM). The reaction
 15 mixture was partitioned between ethylacetate and water. The organic layer was washed with water, brine solution, dried over Na₂SO₄, filtered and the filtrate was concentrated. Purification by column chromatography on silica gel (2% MeOH in DCM) afforded 0.12 g of the product (63% yield). LCMS: m/z = 549 (M+1)

20 Synthesis of the title compound: 1-(2-Hydroxy-ethyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (9A):

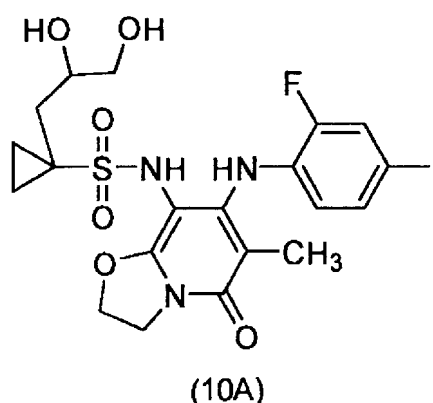
Sodium borohydride (0.1 g, 2.6 mmol) was added to a stirred solution of 1-(2-Oxo-ethyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (0.12 g, 0.21
 25 mmol) in THF (5 mL) and MeOH (2 mL) at room temperature. The resulting

mixture was stirred at room temperature for 1 hour. The reaction was monitored by TLC (10% MeOH in DCM). The reaction mixture was concentrated under reduced pressure and partitioned between ethylacetate and water. The organic layer was washed with water, brine solution, dried over Na₂SO₄, filtered and the filtrate was concentrated. Purification by column chromatography on silica gel (2-4% MeOH in DCM) afforded 70 mg of the product (58% yield).

¹HNMR (300MHz, DMSO-D₆): δ 8.75 (s, 1H), 7.2-7.4 (m, 3H), 6.25 (t, 1H), 4.75 (t, 2H), 4.45-4.6 (m, 1H), 4.25 (t, 2H), 3.5-3.6 (m, 2H), 2.1 (t, 2H), 1.6(s, 3H), 0.7-0.9 (m, 4H). HPLC: 90%

Example 10

Synthesis of 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (10A):



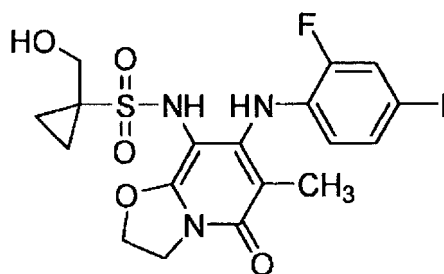
Osmium tetra oxide (8 mg, 0.003 mmol), N-methyl morpholine (8 mg, 0.068 mmol) and water (0.5 mL) were added to a stirred solution of 1-allyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (*1-9a*: 0.04 g, 0.073 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC (5% MeOH in DCM). The reaction mixture was partitioned between ethylacetate and water. The organic layer was washed with water, brine solution, dried over Na₂SO₄ and concentrated. Purification by thin layer chromatography on silica gel (5% MeOH in DCM) afforded 0.005 g of the product (11% yield).

¹HNMR (300MHz, CDCl₃): δ 7.4-7.25 (m, 3H), 6.9 (s, 1H), 6.32 (t, 1H), 5.3 (s, 1H), 4.8 (t, 2H), 4.35 (t, 2H), 4.1-3.9 (m, 1H), 3.6-3.4 (m, 3H), 2.25-2.30 (m, 1H), 1.75 (s, 3H), 0.8-0.7 (m, 5H). LCMS: 97.5%, m/z = 580.1 (M+1) HPLC: 97.67%

5

Example 11

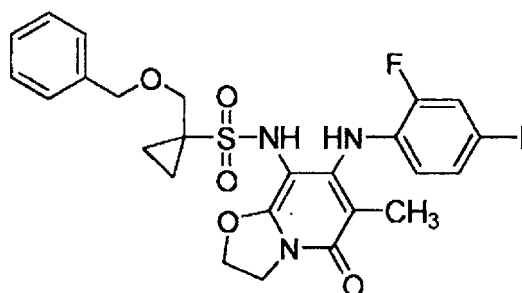
Synthesis of 1-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (11A):



(11A)

10

Synthesis of Intermediate 1-Benzyloxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (I-11a):



15

Using the same reaction conditions and workup as described for the preparation of Example 7A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (I-7f: 0.35 g, 0.873 mmol) in pyridine (3 mL) was reacted with 1-benzyloxymethyl-cyclopropanesulfonyl chloride (0.34 mg, 1.30 mmol) to afford the crude product. Purification by column chromatography on silica gel (2% MeOH in CHCl₃) afforded 0.27 g of the product (50% yield).

20

LCMS: 88.4%, m/z = 625.8 (M+1). HPLC: 80.3%

Synthesis of the title compound: 1-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (11A):

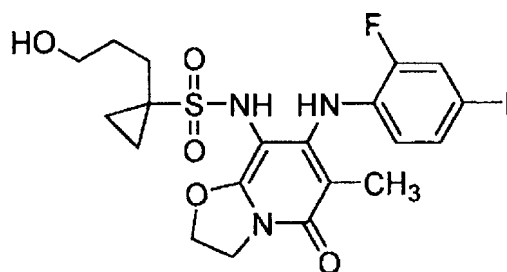
5 Using the same reaction conditions and workup as described for the
preparation of Example 7A, 1-benzyloxymethyl-cyclopropanesulfonic acid [7-(2-
fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-
8-yl]-amide (0.27 g, 0.515 mmol) was reacted with $\text{BF}_3 \cdot \text{OEt}_2$ (1.94 mL, 15.45
mmol) and ethane thiol (0.3 g, 5.15 mmol). The resulting mixture was stirred at
10 room temperature for 3 days. Purification by preparative HPLC afforded 60 mg
of the product (26% yield).

^1H NMR (400MHz, CD_3OD): δ 7.5-7.4 (d, 1H), 7.4-7.3 (d, 1H), 6.6-6.5 (t,
1H), 4.9-4.8 (t, 2H), 4.4-4.3 (t, 2H), 4.0-3.9 (s, 2H), 1.7 (s, 3H), 1.2 (t, 2H), 1.0-0.9
(t, 2H). LCMS: 98.7%, m/z = 535.7 (M+1). HPLC: 99.32%

15

Example 12

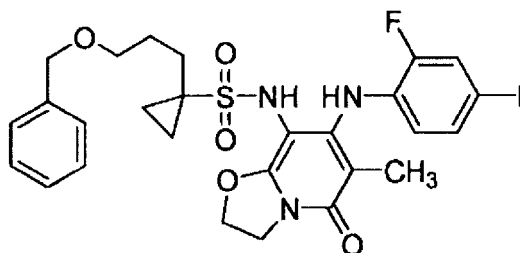
Synthesis of 1-(3-Hydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (12A):



(12A)

20

Synthesis of Intermediate 1-(3-Benzyloxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (I-12a):



Using the same reaction conditions and workup as described for the preparation of Example 7A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (**1-7f**: 0.5 g, 1.246 mmol) in pyridine (5 ml) was reacted with 1-(3-benzyloxy-propyl)-cyclopropanesulfonyl chloride (0.39 mg, 1.371 mmol) to afford the crude product. Purification by column chromatography on silica gel (2% MeOH in CHCl₃) afforded 0.23 g of the product (28% yield). LCMS: 93.01%, m/z = 654.0 (M+1). HPLC: 74.6%

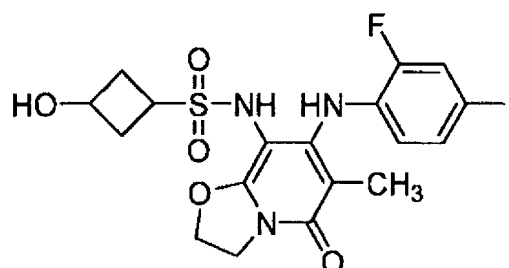
Synthesis of the title compound; 1-(3-Hydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (12A**):**

1-(3-Benzyloxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (0.23 g, 0.352 mmol) in DCM (10 mL) was reacted with 1M BCl₃ (0.12 g, 1.056 mmol) at 0°C. The resulting mixture was stirred at 0°C for 3 hours. Purification by column chromatography on silica gel (4% MeOH in CHCl₃) afforded 70 mg of the product (36% yield).

¹HNMR (400MHz, CD₃OD): δ 7.5-7.4 (d, 1H), 7.4-7.3 (d, 1H), 6.5-6.4 (t, 1H), 4.9-4.8 (t, 2H), 4.4-4.3 (t, 2H), 3.6-3.5 (t, 2H), 2.1-2.0 (m, 2H), 1.75 (s, 3H), 1.7-1.6 (m, 2H), 1.2-1.1 (m, 2H), 0.9-0.8 (t, 2H). LCMS: 96.73%, m/z = 563.9 (M+1). HPLC: 95.14%

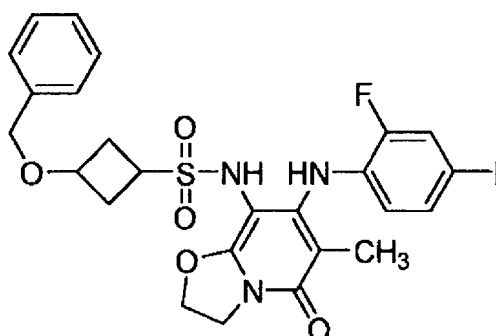
Example 13

Synthesis of 3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (13A**):**



(13A)

Synthesis of Intermediate 3-Benzyloxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (I-13a):



Using the same reaction conditions and workup as described for the preparation of Example 7A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (I-7f: 0.53 g, 1.0 mmol) in pyridine (4 mL) was reacted with 3-benzyloxy-cyclobutanesulfonyl chloride (0.179 mg, 1.2 mmol) to afford the crude product. Purification by column chromatography on silica gel (2% MeOH in DCM) afforded 195 mg of the product (23.8% yield).

Synthesis of the title compound; 3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (13A):

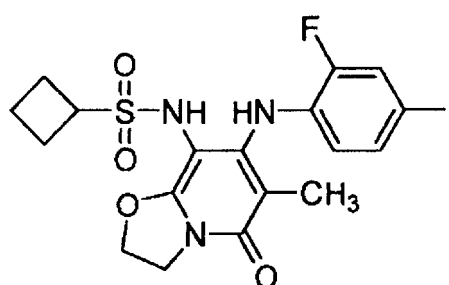
3-Benzyloxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (180 mg, 0.288 mmol) in DCM (10 mL) was reacted with 1M BCl₃ (0.86 mL, 0.864 mmol) at -78°C. The resulting mixture was stirred at room temperature for 1 hour. Purification by column chromatography on silica gel (4% MeOH in DCM), followed by preparative HPLC afforded 45 mg of the product (30% yield).

¹HNMR (300MHz, CD₃OD): δ 7.36 (t, 1H), 6.46-6.40 (m, 1H), 4.87 (t, 2H), 4.48 (dd, 1H), 4.38 (t, 2H), 4.17-4.08 (m, 1H), 3.57-3.48 (m, 1H), 2.63-2.55 (m, 2H), 2.35-2.24 (m, 2H), 1.73 (s, 3H). LCMS: 91.1%, m/z = 535.9 (M+1). HPLC: 96.2%

5

Example 14

Synthesis of Cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide (14A):



10

(14A)

Using the same reaction conditions and workup as described for the preparation of Example 7A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (1-7f: 400 mg, 0.99 mmol) in pyridine (4 ml) was reacted with cyclobutanesulfonyl chloride (274 mg, 1.7 mmol) to afford the crude product. Purification by preparative HPLC afforded 26 mg of the product (5% yield).

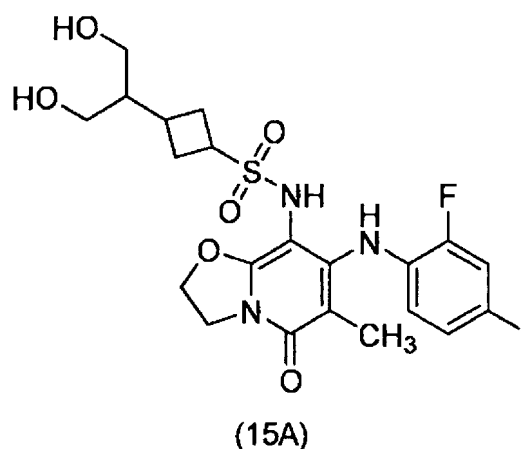
¹HNMR (300MHz, CD₃OD): δ 7.50-7.40 (d, 1H), 7.40-7.30 (d, 1H), 6.50-6.40 (t, 1H), 4.90-4.80 (t, 2H), 4.40-4.30 (t, 2H), 4.10-3.90 (m, 1H), 2.50-2.40 (m, 2H), 2.40-2.30 (m, 2H), 2.10-1.90 (m, 2H), 1.80-1.70 (s, 3H). LCMS: 96%, m/z = 519.9 (M+1). HPLC: 96.5%.

20

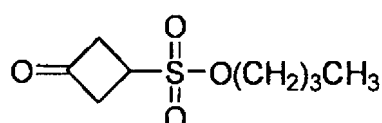
Example 15

Synthesis of 3-(1,3-dihydroxypropan-2-yl)-N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)cyclobutane-1-sulfonamide (15A):

25



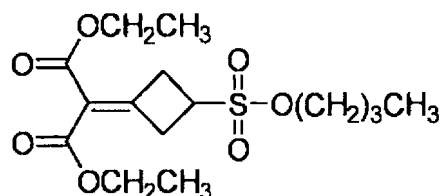
Synthesis of Intermediate butyl 3-oxocyclobutane-1-sulfonate (I-15a):



- 5 Pyridinium chloro chromate (10.3 g, 48.07 mmol) was added to a cooled solution of butyl 3-hydroxycyclobutane-1-sulfonate (5 g, 24.03 mmol) in dry DCM (50 mL) at 0°C. The resulting reaction mixture was stirred at room temperature overnight. The reaction was monitored by TLC (40% ethyl acetate in hexane). The reaction mixture was diluted with DCM, filtered and the filtrate was
- 10 concentrated to afford the crude product. Purification by column chromatography on silica gel (15% ethyl acetate in hexane) afforded 2.8g of the product (58% yield).

¹HNMR (CDCl₃, 300MHz): δ 4.4-4.3 (t, 3H), 4.0-3.9 (m, 1H), 3.7-3.6 (m, 2H), 3.5-3.4 (m, 2H), 1.8-1.7 (q, 2H), 1.5-1.4 (q, 2H), 1.0-0.9 (t, 3H).

- 15 Synthesis of Intermediate diethyl 2-(3-(butoxysulfonyl)cyclobutylidene)malonate (I-15b):

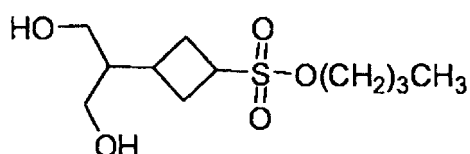


- 20 TiCl₄ (0.5 mL, 4.854 mmol) was added to a solution of THF (25 mL) and CCl₄ (5 mL) at 0°C. This was followed by the addition of butyl 3-oxocyclobutane-

1-sulfonate (0.5g, 2.42mmol) at 0°C and diethyl malonate (0.38 mL, 2.42 mmol). The resulting mixture was stirred at 0°C for 5 minutes. Then pyridine (0.78 mL, 9.68 mmol) in THF (10 mL) was added and stirred at room temperature for 96 hours. The reaction was monitored by TLC (30% ethyl acetate in hexane). The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with sodium bicarbonate solution, brine solution, dried over anhydrous Na₂SO₄ and concentrated. Purification by column chromatography on silica gel (13% ethyl acetate in hexane) afforded 200mg of the product (25% yield).

¹HNMR (CDCl₃, 300MHz): δ 4.3-4.2 (m, 6H), 4.0-3.9 (m, 1H), 3.7-3.5 (m, 4H), 1.8-1.7 (q, 2H), 1.5-1.4 (q, 2H), 1.3 (t, 6H), 1.0-0.9 (t, 3H).

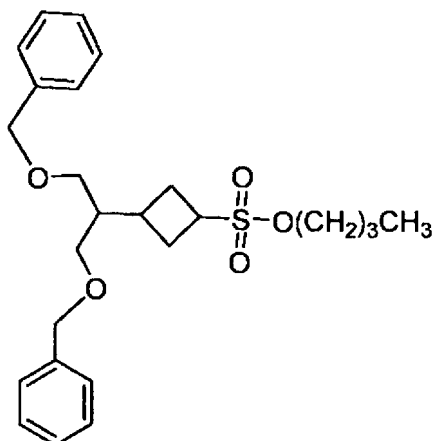
Synthesis of Intermediate butyl 3-(1,3-dihydroxypropan-2-yl)cyclobutane-1-sulfonate (I-15c):



Borane-DMS (0.2 mL, 2.3 mmol) was added to a solution of diethyl 2-(3-(butoxysulfonyl)cyclobutylidene)malonate (0.2 g, 0.575 mmol) in THF (5 mL) and the resulting reaction mass was stirred at room temperature overnight. The reaction was monitored by TLC (100% ethyl acetate). The reaction mixture was quenched with 1N HCl and extracted using ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous Na₂SO₄ and concentrated. Purification by column chromatography on silica gel (70% ethyl acetate in hexane) afforded 0.13g of the product (74% yield).

¹HNMR (CDCl₃, 300MHz): δ 4.2 (t, 2H), 3.9-3.6 (m, 4H), 2.5-2.4 (m, 2H), 2.4-2.3 (m, 2H), 2.1-1.9 (m, 3H), 1.7-1.6 (m, 2H), 1.5-1.4 (q, 2H), 1.0-0.9 (t, 3H).
LCMS: 99%, m/z = 266 (M+1)

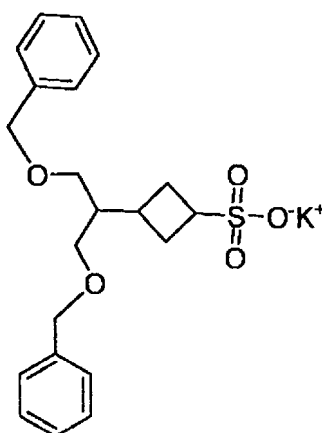
Synthesis of butyl 3-(1,3-bis(benzyloxy)propan-2-yl)cyclobutane-1-sulfonate (I-15d):



Using the same reaction conditions, procedure and work up as described Intermediate I-25a (below), butyl 3-(1,3-dihydroxypropan-2-yl)cyclobutane-1-sulfonate (0.13 g, 0.489 mmol) was reacted with benzyl bromide (0.13 mL, 1.075 mmol), 60% NaH (60 mg, 1.467 mmol) and THF (5 mL) to afford the crude product. Purification by column chromatography on silica gel (8% ethyl acetate in hexane) afforded 0.07 g of the product (78% yield).

¹HNMR (CDCl₃, 300MHz): δ 7.4-7.2 (m, 10H), 4.5-4.4 (d, 4H), 4.2-4.1 (t, 2H), 3.5-3.4 (d, 4H), 3.6-3.8 (m, 1H), 2.5-2.3 (m, 5H), 2.0-1.9 (m, 1H), 1.7-1.6 (m, 2H), 1.4-1.3 (m, 2H), 1.0-0.9 (t, 3H). LCMS: 87%, m/z = 446 (M+1)

Synthesis of Intermediate potassium 3-(1,3-bis(benzyloxy)propan-2-yl)cyclobutane-1-sulfonate (I-15d):



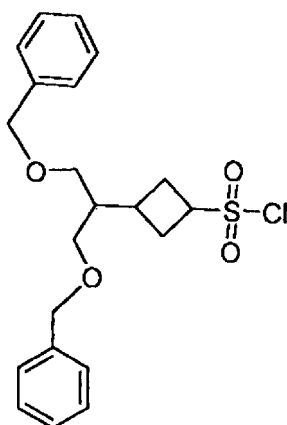
Using the same reaction conditions, procedure and work up as described Intermediate I-25b (below), butyl 3-(1,3-bis(benzyloxy)propan-2-yl)cyclobutane-1-

sulfonate (0.1 g, 0.22 mmol) was reacted with KSCN (24mg, 0.24mmol) and DME-water mixture (2 mL) to afford 0.07 g of the product (83% yield).

¹HNMR (DMSO-*d*₆, 300MHz): δ 7.4-7.2 (m, 10H), 4.4-4.3 (m, 4H), 3.4-3.3 (m, 4H), 3.0 (m, 1H), 2.1-1.9 (m, 2H), 1.9-1.6 (m, 4H)

5

Synthesis of Intermediate 3-(1,3-bis(benzyloxy)propan-2-yl)cyclobutane-1-sulfonyl chloride (I-15f):



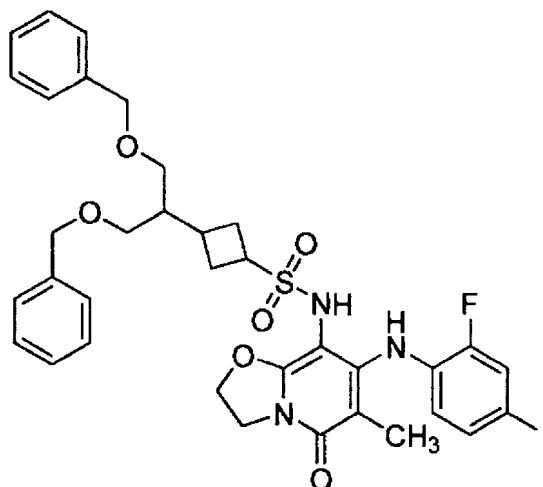
Using the same reaction conditions, procedure and work up as described for the preparation of Intermediate I-25c (below), potassium 3-(1,3-bis(benzyloxy)propan-2-yl)cyclobutane-1-sulfonate (0.5 g, 1.168 mmol) was reacted with POCl₃ (0.22 mL, 2.336 mmol), diisopropyl ethyl amine (0.4 mL, 2.336mmol) and DCM (20 mL) to afford the crude product. Purification by column chromatography on silica gel (8% ethyl acetate in hexane) afforded 0.32g of the product (68% yield).

15

¹HNMR (CDCl₃, 300MHz): δ 7.4-7.2 (m, 10H), 4.5-4.4 (m, 4H), 4.2 (m, 1H), 3.5-3.4 (m, 4H), 2.6-2.4 (m, 4H), 2.1-1.9 (m, 1H)

Synthesis of Intermediate 3-(1,3-bis(benzyloxy)propan-2-yl)-N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)cyclobutane-1-sulfonamide (I-15g):

20



Using the same reaction conditions and procedure as described for the preparation of Example 7A, 8-Amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (1-7f: 0.22g, 0.539mmol) was reacted with 3-(1,3-bis(benzyloxy)propan-2-yl)cyclobutane-1-sulfonyl chloride (0.21g, 0.539mmol) in dry pyridine (2 mL) to afford the crude product. Purification by column chromatography on silica gel (80% ethyl acetate in hexane) afforded 0.3g of the product (71% yield). LCMS: 80%, m/z = 773 (M+1)

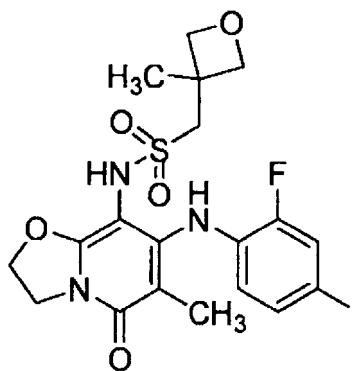
Synthesis of the title compound; 3-(1,3-dihydroxypropan-2-yl)-N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)cyclobutane-1-sulfonamide (15A):

3-(1,3-Bis(benzyloxy)propan-2-yl)-N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)cyclobutane-1-sulfonamide (0.3g, 0.388mmol) was reacted with 1M BCl_3 (1.1 mL, 1.164 mmol) and DCM (10 mL) at 0°C for 30 minutes to afford the crude product. Purification by column chromatography on silica gel (8% methanol in chloroform) afforded 60mg of the product (26% yield).

^1H NMR (300MHz, CD_3OD): δ 7.5 (d, 1H), 7.4 (d, 1H), 6.5 (t, 1H), 4.4-4.3 (t, 2H), 3.9 (m, 1H), 3.6-3.5 (m, 5H), 2.5-2.3 (m, 2H), 2.3-2.2 (m, 3H), 1.7 (s, 3H), 1.7-1.6 (m, 2H). LCMS: 90.98%, m/z = 593.9 (M+1). HPLC: 95.12%

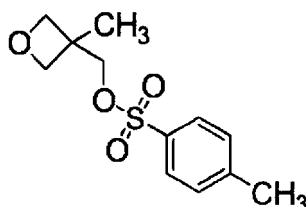
Example 16

Synthesis of N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-1-(3-methyloxetan-3-yl)methanesulfonamide (16A):



(16A)

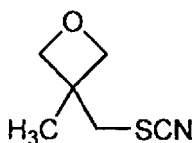
5 Synthesis of Intermediate (3-methyloxetan-3-yl)methyl 4-methylbenzenesulfonate (I-16a):



p-Toluene sulfonyl chloride (5.6 g, 29.41 mmol) was added to a cooled solution of (3-methyloxetan-3-yl)methanol (2 g, 19.60 mmol) in pyridine (25 mL) at 0°C and the resulting reaction mass was stirred at 0°C for 2 hours. The reaction was monitored by TLC (20% ethyl acetate in hexane). The reaction mass was poured into ice-water, stirred for 30 minutes, the solid formed was collected by filtration, washed with water and dried under reduced pressure to afford 2.5 g of the product (50% yield).

15 ¹HNMR (CDCl₃, 300MHz): δ 7.8 (d, 2H), 7.4 (d, 2H), 4.4 (m, 4H), 4.1 (s, 2H), 2.5 (s, 3H), 1.3 (s, 3H). LCMS: 99.13%, m/z = 256 (M+1)

Synthesis of Intermediate 3-methyl-3-(thiocyanatomethyl)oxetane (I-16b):

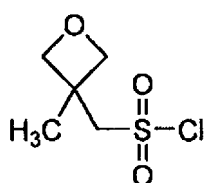


20 KSCN (0.75g, 7.81mmol) was added to a solution of (3-methyloxetan-3-yl)methyl 4-methylbenzenesulfonate (1 g, 3.90 mmol) in ethanol (25 mL) and the

resulting reaction mass was heated at 85°C overnight. The reaction was monitored by TLC (30% ethyl acetate in hexane). The reaction mass was concentrated under reduced pressure to afford 1.7 g of the crude product which was used for the next step without further purification.

5

Synthesis of Intermediate (3-methyloxetan-3-yl)methanesulfonyl chloride (I-16c):



Chlorine gas was purged through a cooled solution of 3-methyl-3-(thiocyanatomethyl)oxetane (1.7 g) in water (10 mL) at 0°C for 30 minutes. The reaction was monitored by TLC (30% ethyl acetate in hexane). The reaction mass was extracted using ether. The ether layer was washed with sodium bisulphate solution, sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 0.3 g of the crude product which was used for the next step without further purification.

¹HNMR (CDCl₃, 300MHz): δ 4.7 (d, 2H), 4.5-4.4 (d, 2H), 4.2 (s, 2H), 1.7 (s, 3H).

Synthesis of the title compound: N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-1-(3-methyloxetan-3-yl)methanesulfonamide (16A):

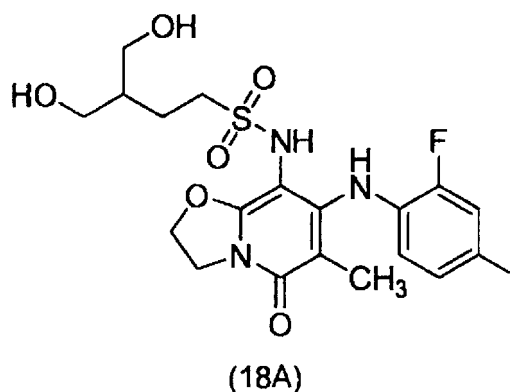
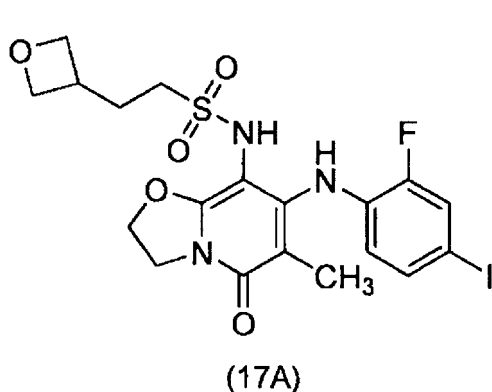
Using the same reaction conditions and procedure as described for the preparation of Example 7A, 8-Amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (I-7f: 0.2 g, 0.499 mmol) was reacted with (3-methyloxetan-3-yl)methanesulfonyl chloride (0.13 g, 0.748 mmol) in dry pyridine (3 mL) to afford the crude product. Purification by preparative HPLC afforded 25 mg of the product (9% yield).

¹HNMR (300MHz, CD₃OD): δ 7.5 (d, 1H), 7.4 (d, 1H), 6.5 (t, 1H), 4.9-4.8 (t, 2H), 4.7 (d, 2H), 4.40-4.35 (t, 2H), 4.3 (d, 2H), 3.6 (s, 2H), 1.8 (s, 3H), 1.6 (s, 3H). LCMS: 92.56%, m/z = 549.5 (M+1). HPLC: 92.40%

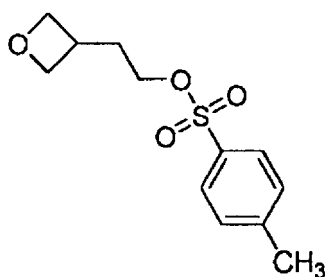
5

Examples 17 and 18

Synthesis of N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-2-(oxetan-3-yl)ethanesulfonamide (17A):



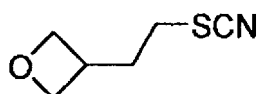
Synthesis of Intermediate 2-(oxetan-3-yl)ethyl 4-methylbenzenesulfonate (I-17a):



Using the same reaction conditions and procedure as described for the preparation of Intermediate (I-16a), 2-(oxetan-3-yl)ethanol (1g, 6.944mmol) was reacted with p-Toluene sulfonyl chloride (1.9g, 10.416mmol) in dry pyridine (10 mL) to afford the crude product. The reaction mass was poured into ice-water and extracted using ethyl acetate. The organic layer was washed with 1N HCl, brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product. Purification by column chromatography on silica gel (20% ethyl acetate in hexane) afforded 1g of the product (40% yield).

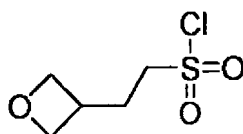
¹HNMR (CDCl₃, 300MHz): δ 7.8 (d, 2H), 7.4 (d, 2H), 4.7 (t, 2H), 4.4 (t, 2H), 4.0 (t, 2H), 3.1-3.0 (m, 1H), 2.5 (s, 3H), 2.1-2.0 (m, 2H)

Synthesis of Intermediate 3-(2-thiocyanatoethyl)oxetane (I-17b):



Using the same reaction conditions, procedure and work up as described for the preparation of Intermediate (I-16b), 2-(oxetan-3-yl)ethyl 4-methylbenzenesulfonate (1 g, 3.90 mmol) was reacted with KSCN (0.75 g, 7.81 mmol) in ethanol (20 mL) to afford 1.7 g of the crude product which was used for the next step without further purification.

Synthesis of Intermediate 2-(oxetan-3-yl)ethanesulfonyl chloride (I-17c):



Using the same reaction conditions, procedure and work up as described for the preparation of Intermediate (I-16c), 3-(2-thiocyanatoethyl)oxetane (1 g) in water (10 mL) was purged with chlorine gas for 30 minutes to afford 0.4 g of the product (56% yield) which was for next reaction with purification and characterization.

Synthesis of the title compound: N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-2-(oxetan-3-yl)ethanesulfonamide (17A):

Using the same reaction conditions and procedure as described for the preparation of Example 7A, 8-Amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-oxazolo[3,2-a]pyridin-5-one (I-7f: 0.2 g, 0.673 mmol) was reacted with 2-(oxetan-3-yl)ethanesulfonyl chloride (0.18 g, 1.009 mmol) in dry pyridine (3 mL) to afford the crude product. Purification by preparative HPLC, followed by flash column chromatography (3% methanol in chloroform) afforded 20 mg of the compound (17A) (9% yield) and 3 mg of the hydrolyzed by-product (compound (17B)).

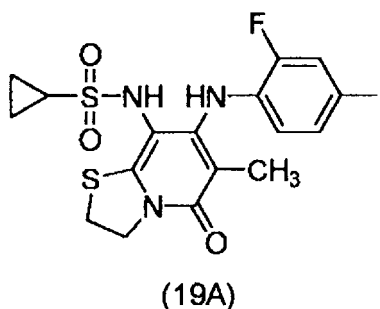
¹HNMR (300MHz, CD₃OD): δ 7.5 (d, 1H), 7.4 (d, 1H), 6.4 (t, 1H), 4.9-4.8 (m, 4H), 4.4 (m, 4H), 3.1 (m, 3H), 2.2 (m, 2H), 1.8 (s, 3H). LCMS: 100%, m/z = 549.8 (M+1). HPLC: 95.97%

By-Product of Example 17A: N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-4-hydroxy-3-(hydroxymethyl)butane-1-sulfonamide (18A):

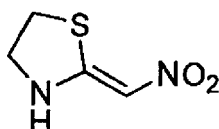
5 ^1H NMR (300MHz, CD_3OD): δ 7.5 (d, 1H), 7.4 (d, 1H), 6.5 (t, 1H), 4.8 (t, 2H), 4.4 (t, 2H), 3.6-3.4 (m, 4H), 3.2 (m, 2H), 1.9 (m, 2H), 1.8 (s, 3H), 1.75 (m, 1H). LCMS: 89%, m/z = 568 (M+1). HPLC: 90.96%

Example 19

10 Synthesis of Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (19A):



Synthesis of Intermediate 2-Nitromethylene-thiazolidine (I-19a):

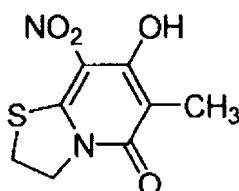


15 TEA (1.8 mL, 13.20 mmol) was added to a solution of 1,1-bis-methylsulfonyl-2-nitro-ethene (I-1b: 1.45 g, 8.802 mmol) and 2-amino-ethanethiol (1 g, 8.802 mmol) in ethanol (20 mL). The resulting mixture was heated to reflux for 3 hours. The reaction mixture was monitored by TLC (70% ethylacetate in hexane). The reaction mixture was concentrated to afford the crude product. Purification by column chromatography on silica gel (70% ethylacetate in hexane) afforded 0.6 g of the product (31% yield).

20 ^1H NMR (300MHz, $\text{DMSO}-d_6$): δ 9.2-9.1 (br s, 1H), 7.2-7.1 (br s, 1H), 4.0-3.6 (d, 2H), 3.5-3.1 (d, 2H). LCMS purity: 99.93%, m/z = 147 (M+1)

25

Synthesis of Intermediate 7-Hydroxy-6-methyl-8-nitro-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (I-19b):

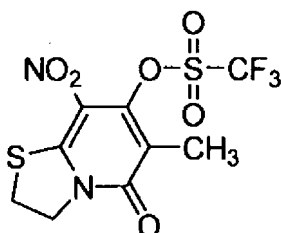


2-Nitromethylene-thiazolidine (7.3 g, 50 mmol) and 2-methyl-malonic acid
5 bis-(2,4,6-trichloro-phenyl) ester (23.8 g, 50 mmol) in xylene (80 mL) was taken
in a reaction flask and the flask was heated to reflux for 3 hours. The reaction
mixture was monitored by TLC (100% ethylacetate). The reaction mixture was
cooled, concentrated and partitioned between DCM and water. The organic
layer was washed with water, brine solution, dried over Na₂SO₄ and
10 concentrated. The crude product was kept at 0°C for overnight. The solid
formed was collected and washed with hexane and ether to afford 5.3 g of the
product (46% yield).

¹HNMR (300MHz, CDCl₃): δ 11.2 (s, 1H), 4.7-4.6 (t, 2H), 3.5-3.4 (t, 2H),
2.1-2.0 (s, 3H). LCMS: 100%, m/z = 229(M+1)

15

Synthesis of Intermediate Trifluoro-methanesulfonic acid 6-methyl-8-nitro-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-7-yl ester (I-19c):



Triflic anhydride (3.4 g, 12.06 mmol) was added to a stirred solution of 7-
20 hydroxy-6-methyl-8-nitro-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (2.5 g, 10.96
mmol) and TEA (2.3 mL, 16.44 mmol) in DCM (20 mL) at -70°C. The resulting
mixture was stirred at -70° C to -50°C for 2 hours. The reaction mixture was
monitored by TLC (50% ethylacetate in hexane). The reaction mixture was
diluted DCM and quenched with bicarbonate solution. The organic layer was
25 washed with brine solution, dried over Na₂SO₄ and concentrated. Purification by

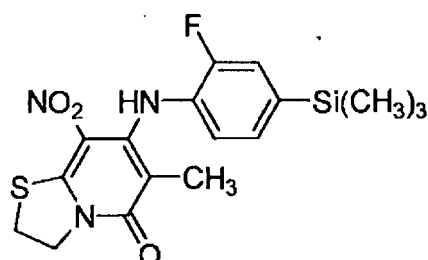
column chromatography on silica gel (30% ethylacetate in hexane) afforded 0.9 g of the product (38% yield).

^1H NMR (300MHz, CDCl_3): δ 4.7-4.6 (t, 2H), 3.5-3.4 (t, 2H), 2.1-2.0 (s, 3H)

LCMS: 100%, m/z = 361(M+1)

5

Synthesis of Intermediate 7-(2-Fluoro-4-trimethylsilyl-phenylamino)-6-methyl-8-nitro-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (I-19d):



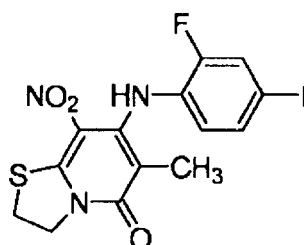
Trifluoro-methanesulfonic acid 6-methyl-8-nitro-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-7-yl ester (0.9 g, 2.5 mmol) was reacted with 2-fluoro-4-trimethylsilyl-phenylamine (0.5 g, 2.75 mmol), $\text{Pd}(\text{dba})_3$ (138 mg, 0.15 mmol), potassium phosphate (0.7 g, 3.75 mmol) and xantphos (87 mg, 0.15 mmol) in toluene (30 mL) at 110°C for 3 hours to afford the crude product. Purification by column chromatography on silica gel (30% ethylacetate in hexane) afforded 0.75 g of the product (76% yield).

15

^1H NMR (300MHz, CDCl_3): δ 9.0-8.9 (br s, 1H), 7.3-7.1 (m, 2H), 6.8-6.6 (t, 1H), 4.7-4.5 (t, 2H), 3.4-3.3 (t, 2H), 1.8-1.7 (s, 3H), 0.3-0.2 (s, 9H)

LCMS: 97.55%, m/z = 393.9 (M+1)

20 Synthesis of Intermediate 7-(2-Fluoro-4-iodo-phenylamino)-6-methyl-8-nitro-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (I-19e):



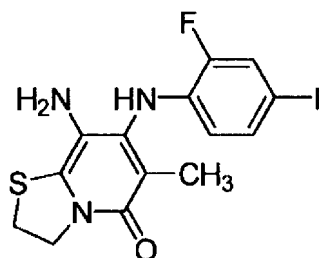
7-(2-Fluoro-4-trimethylsilyl-phenylamino)-6-methyl-8-nitro-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (0.5 g, 1.27 mmol) in DCM (10 mL) was added to

silver tetrafluoroborate (0.74 g, 3.81 mmol) in DCM (10 mL) previously degassed with nitrogen at -60°C and the resulting mixture was stirred at -60°C for 30 minutes. This was followed by the addition of iodine monochloride (1.3 mL, 1.399 mmol) and continued stirring for a further 30 minutes at -60°C to -50°C.

- 5 The reaction was monitored by TLC (50% ethylacetate in hexane). The reaction mixture was diluted with DCM, quenched with sodium thiosulphate solution, filtered through celite and the filtrate was extracted with DCM. The organic layer was washed with NH₃ solution, brine solution, dried over Na₂SO₄ and concentrated. Purification by column chromatography on silica gel (40% ethylacetate in hexane) afforded 0.45 g of the product (80% yield).

¹HNMR (300MHz, CDCl₃): δ 8.9 (s, 1H), 7.5-7.4 (d, 1H), 7.4-7.3 (d, 1H), 6.5 (t, 1H), 4.8-4.6 (t, 2H), 3.5-3.3 (t, 2H), 1.8-1.7 (s, 3H)
LCMS: 98.6%, m/z = 445.9 (M-1)

- 15 Synthesis of Intermediate 8-Amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (I-19f):



- Concentrated HCl (0.3 mL) and SnCl₂·H₂O (0.15 g, 0.671 mmol) were added to 7-(2-fluoro-4-iodo-phenylamino)-6-methyl-8-nitro-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (0.1 g, 0.22 mmol) in ethanol (3 mL). The resulting mixture was heated to reflux for 2 hours. The reaction was monitored by TLC (100% ethylacetate). The reaction mixture was cooled to room temperature, diluted with DCM, basified with saturated bicarbonate solution and filtered through celite. The filtrate was extracted with DCM. The organic layer was washed with brine solution, dried over Na₂SO₄ and concentrated to afford 0.09 g of the product (90% yield).
- 20
25

¹HNMR (300MHz, CDCl₃): δ 7.4-7.3 (d, 1H), 7.2-7.1 (d, 1H), 6.3-6.2 (t, 1H), 5.8 (s, 1H), 4.5 (t, 2H), 3.4-3.3 (t, 2H), 2.8-2.6 (br s, 2H), 1.8-1.7 (s, 3H).
LCMS: 89.9%, m/z = 417.9 (M+1)

5 Synthesis of the title compound; Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (19A):

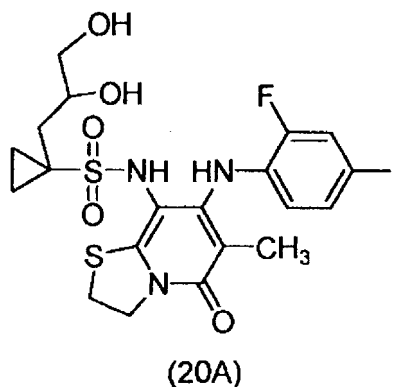
Cyclopropane sulfonyl chloride (34 mg, 0.23 mmol) was added to a solution of 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (0.09 g, 0.21 mmol) in pyridine (1 mL) at 0°C. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by TLC (5% MeOH in CHCl₃). The reaction mixture was partitioned between ethylacetate and water. The organic layer was washed with 2N HCl, brine solution, dried over Na₂SO₄ and concentrated. Purification by column chromatography on silica gel (1% MeOH in CHCl₃), followed by preparative HPLC afforded 25 mg of the product (22% yield).

¹HNMR (300MHz, CD₃OD): δ 7.5-7.4 (d, 1H), 7.4-7.3 (d, 1H), 6.4-6.2 (t, 1H), 4.6-4.5 (t, 2H), 3.6-3.5 (t, 2H), 2.7-2.6 (m, 1H), 1.8-1.7 (s, 3H), 1.1-1.0 (m, 4H). LCMS: 100%, m/z = 522 (M+1) HPLC: 98.8%

20

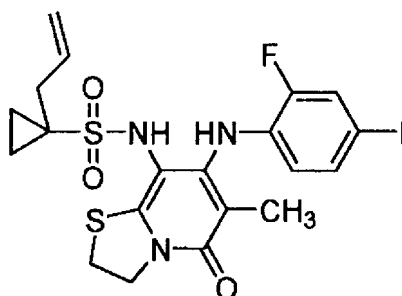
Example 20

Synthesis of 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (20A):



25

Synthesis of Intermediate 1-Allyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (I-20a):



5 8-Amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (I-19f: 0.3 g, 0.719 mmol) in pyridine (3 mL) was reacted with 1-allyl-cyclopropane sulfonyl chloride (0.15 g, 0.863 mmol) to afford the crude product. Purification by column chromatography on silica gel (40% ethylacetate in hexane) afforded 0.21 g of the product (52% yield).

10 ¹HNMR (300MHz, CDCl₃): δ 7.4-7.3 (d, 1H), 7.3-7.2 (d, 1H), 6.8 (br s, 1H), 6.3-6.2 (t, 1H), 5.85-5.7 (m, 1H), 5.65 (s, 1H), 5.2-5.15 (d, 1H), 5.15 (s, 1H), 4.6-4.5 (t, 2H), 3.5-3.4 (t, 2H), 2.8-2.7 (d, 2H), 1.8-1.7 (t, 3H), 0.9-0.8 (m, 4H).
LCMS: 100%, m/z = 562 (M+1)

15 Synthesis of the title compound: 1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (20A):

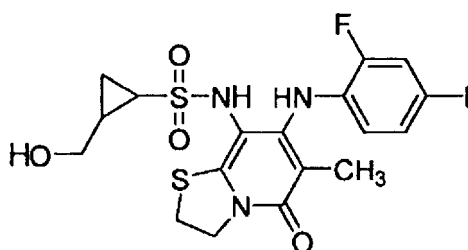
 Using the same reaction conditions and workup as described for the preparation of Intermediate (I-4d) in Example 4, 1-allyl-cyclopropanesulfonic acid
20 [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (0.05 g, 0.089 mmol) in THF (2 mL) was reacted with N-methoxy morpholin-N-oxide (10.5 mg, 0.089 mmol) and osmium tetra oxide (2.2 mg, 0.0089 mmol) to afford the crude product. Purification by column chromatography on silica gel (2% MeOH in CHCl₃), followed by preparative
25 HPLC afforded 12 mg of the product (22% yield).

¹HNMR (300MHz, DMSO-D₆): δ 8.9-8.8 (s, 1H), 7.6-7.5 (d, 1H), 7.4-7.3 (d, 1H), 7.3-7.2 (s, 1H), 6.4-6.3 (t, 1H), 4.5-4.3 (t, 2H), 3.7-3.6 (m, 1H), 3.5-3.2 (m, 6H), 2.3-2.2 (d, 1H), 1.8-1.6 (m, 1H), 1.6 (s, 3H), 1.2-1.0 (m, 4H).
LCMS: 91.7%, m/z = 595.9 (M+1). HPLC: 90.8%

5

Example 21

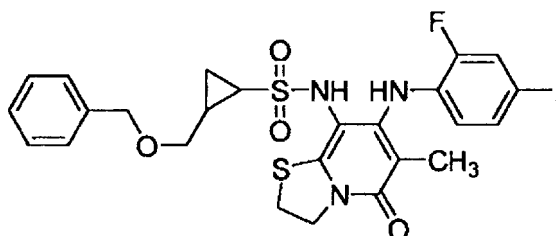
Synthesis of 2-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (21A):



10

(21A)

Synthesis of Intermediate 2-Benzyloxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (I-21a):



15

Using the same reaction conditions and workup as described for the preparation of Example 19A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (**I-19f**: 0.2 g, 0.048 mmol) in pyridine (2 mL) was reacted with 2-benzyloxymethyl-cyclopropanesulfonyl chloride (0.13 g, 0.52 mmol) to afford the crude product. Purification by column chromatography on silica gel (60% ethylacetate in hexane) afforded 0.26 g of the product (86% yield).

20

¹HNMR (300MHz, CDCl₃): δ 7.4-7.2 (m, 7H), 7.0-6.9 (s, 1H), 6.3-6.2 (t, 1H), 5.9 (s, 1H), 4.6-4.4 (m, 4H), 3.6-3.3 (m, 2H), 2.6-2.5 (m, 1H), 1.9-1.8 (m, 1H), 1.7 (s, 3H), 1.4-1.2 (m, 1H), 1.2-1.1 (m, 2H), 0.9-0.8 (m, 1H).
LCMS: 100 %, m/z = 642 (M+1); HPLC: 92.8%

5

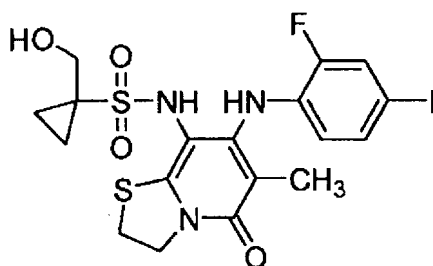
Synthesis of the title compound: 2-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (21A):

2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (0.1 g, 0.156 mmol) was added to a stirred solution of BF₃·OEt₂ (0.39 mL, 3.12 mmol) in ethane thiol (0.1 mL, 1.56 mmol) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 hours, followed by heating for 4 hours at 40°C. The reaction was monitored by TLC (10% MeOH in DCM). The reaction mixture was quenched in saturated NaHCO₃ solution and extracted with DCM. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. Purification by column chromatography on silica gel (4% MeOH in DCM) afforded 25 mg of the product (31% yield).

¹HNMR (300MHz, CD₃OD): δ 7.5-7.45 (d, 1H), 7.4-6.3 (d, 1H), 6.4-6.3 (t, 1H), 4.6-4.5 (t, 2H), 3.6-3.5 (m, 4H), 2.6-2.5 (m, 1H), 1.8-1.7 (s, 3H), 1.7-1.6 (m, 1H), 1.3-1.2 (m, 1H), 1.1-1.0 (m, 1H). LCMS: 96.2%, m/z = 551.9 (M+1).
HPLC: 97.19%

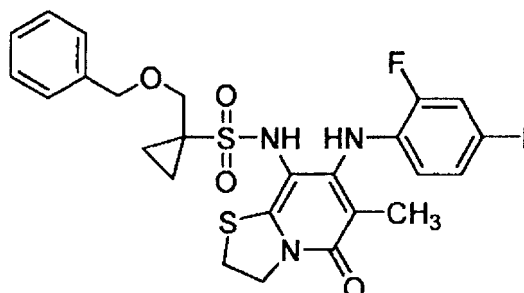
Example 22

Synthesis of 1-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (22A):



(22A)

Synthesis of Intermediate 1-Benzylloxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (I-22a):



5

Using the same reaction conditions and workup as described for the preparation of Example 19A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (I-19f: 0.2 g, 0.048 mmol) in pyridine (2 mL) was reacted with 1-benzylloxymethyl-cyclopropanesulfonyl chloride (137mg, 0.52mmol) to afford the crude product. Purification by column chromatography on silica gel (50% ethylacetate in hexane) afforded 0.21g of the product (70% yield).

10

¹HNMR (300MHz, CDCl₃): δ 7.4-7.3 (d, 1H), 7.25-7.1 (d, 7H), 6.3-6.2 (t, 1H), 6.1 (s, 1H), 4.6-4.5 (t, 4H), 3.9-3.8 (s, 2H), 3.4-3.3 (t, 2H), 1.7 (s, 3H), 1.5-1.4 (t, 1H), 1.3-1.2 (t, 2H), 1.0-0.9 (t, 1H). LCMS: 100%, m/z = 642 (M+1).

15

HPLC: 90.5%

Synthesis of the title compound: 1-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (22A):

20

Using the same reaction conditions and workup as described for the preparation of Example 21A, 1-benzylloxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (0.2 g, 0.321 mmol) was reacted with BF₃·OEt₂ (0.79 mL, 6.24 mmol) and ethane thiol (0.2 mL, 3.21 mmol). The resulting mixture was stirred at 40°C for 6 hours. Purification by column chromatography on silica gel (2% MeOH in CHCl₃) afforded 100 mg of the product (55% yield).

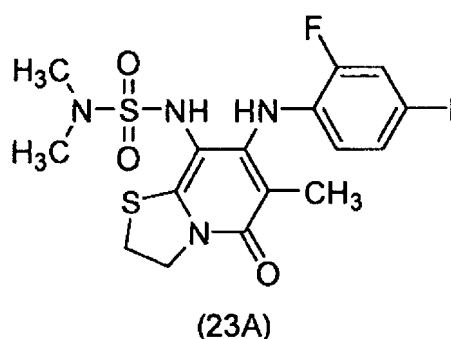
25

¹HNMR (300MHz, CD₃OD): δ 7.6-7.3 (dd, 2H), 6.6-6.5 (t, 1H), 4.6-4.5 (t, 2H), 4.0-3.8 (s, 2H), 3.5-3.4 (t, 2H), 1.65 (s, 3H), 1.4-1.2 (m, 2H), 0.9-0.8 (t, 2H). LCMS: 100%, m/z = 551.7 (M+1). HPLC: 94.13%

5

Example 23

Synthesis of N-[7-(2-Fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-dimethylaminosulfonamide (23A):



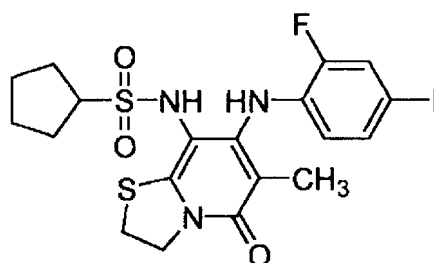
10 Using the same reaction conditions and workup as described for the preparation of Example 19A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (**1-19f**; 0.2 g, 0.048 mmol) in pyridine (2 mL) was reacted with dimethyl aminosulfonyl chloride (76 mg, 0.528 mmol) to afford the crude product. Purification by column chromatography on silica gel
15 (2% MeOH in CHCl₃) afforded 0.08 g of the product (32% yield).

¹HNMR (300MHz, DMSO-D₆): δ 8.8 (s, 1H), 7.6-7.5 (d, 1H), 7.4-7.3 (d, 1H), 7.3-7.2 (s, 1H), 6.4-6.2 (t, 1H), 4.5-4.3 (t, 2H), 3.5-3.4 (t, 2H), 2.9-2.6 (s, 6H), 1.65-1.55 (s, 3H). LCMS: 98.4%, m/z = 524.9 (M+1). HPLC: 92.8%

20

Example 24

Synthesis of Cyclopentanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (24A):



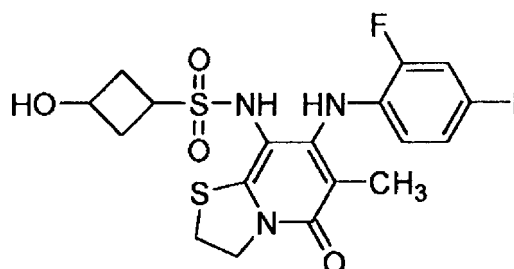
(24A)

Using the same reaction conditions and workup as described for the preparation of Example 19A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (I-19f: 0.2 g, 0.048 mmol) in pyridine (2 mL) was reacted with cyclopentanesulfonyl chloride (106 mg, 0.528 mmol) to afford the crude product. Purification by preparative HPLC afforded 0.03 g of the product (11% yield).

¹HNMR (300MHz, CD₃OD): δ 7.5-7.4 (d, 1H), 7.4-7.3 (d, 1H), 6.4-6.3 (t, 1H), 4.6-4.5 (t, 2H), 3.7-3.6 (t, 1H), 3.6-3.5 (t, 2H), 2.2-2 (s, 4H), 1.8-1.55 (m, 7H). LCMS: 100%, m/z = 549.8 (M+1). HPLC: 92.41%

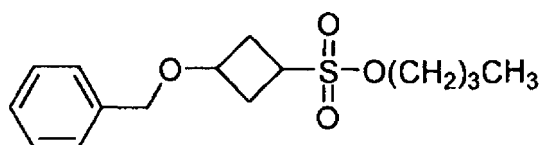
Example 25

Synthesis of 3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (25A):



(25A)

Synthesis of Intermediate butyl 3-(benzyloxy)cyclobutane-1-sulfonate (I-25a):

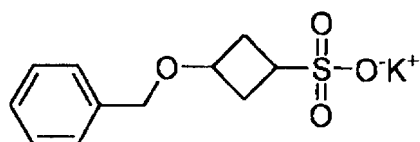


60% NaH (0.95 g, 2.52 (CH₂)₂CH₃ mmol) was added to a cooled solution of butyl 3-hydroxycyclobutane-1-sulfonate (0.35 g, 1.68 mmol) in dry THF (20 mL) at 0°C and the resulting reaction mass was stirred at room temperature for 30 minutes. This was followed by the addition of benzyl bromide (0.43 g, 2.52 mmol) and stirred the resulting mixture at room temperature for 2 hours. The reaction was monitored by TLC (20% ethyl acetate in hexane). The reaction

mixture was quenched with ice-water and extracted using ethyl acetate. The organic layer was washed with brine solution, dried over Na₂SO₄ and concentrated. Purification by column chromatography on silica gel (4% ethyl acetate in hexane) afforded 0.2 g of the product (50% yield).

5 ¹HNMR (CDCl₃, 300MHz): δ 7.6-7.4 (m, 5H), 4.5 (s, 2H), 4.3 (t, 3H), 4.2-4.1 (m, 1H), 3.6-3.4 (m, 1H), 2.8-2.5 (m, 4H), 1.8-1.7 (q, 2H), 1.5-1.4 (q, 2H), 1.1-1.0 (t, 3H). LCMS: 91.3%, m/z = 298 (M+1).

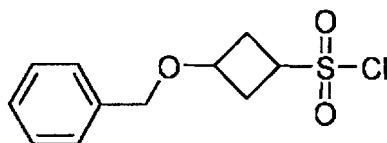
10 Synthesis of Intermediate potassium 3-(benzyloxy)cyclobutane-1-sulfonate (I-25b):



KSCN (68mg, 0.66mmol) and butyl 3-(benzyloxy)cyclobutane-1-sulfonate (0.18 g, 0.604 mmol) in DME-water mixture (1:1 ratio, 4 mL) were heated at 85°C overnight. The reaction was monitored by TLC (50% ethyl acetate in hexane). The reaction mass was concentrated under reduced pressure and the crude residue obtained was washed with ether to afford 0.11 g of the product (70% yield).

15 ¹HNMR (DMSO-*d*₆, 300MHz): δ 7.4-7.2 (bs, 5H), 4.4-4.3 (s, 2H), 3.9-3.7 (m, 1H), 2.9-2.7 (m, 1H), 2.4-2.2 (m, 2H), 2.1-1.9 (m, 2H). LCMS: 99.03%, m/z = 280 (M+1)

20 Synthesis of Intermediate 3-(benzyloxy)cyclobutane-1-sulfonyl chloride (I-25c):

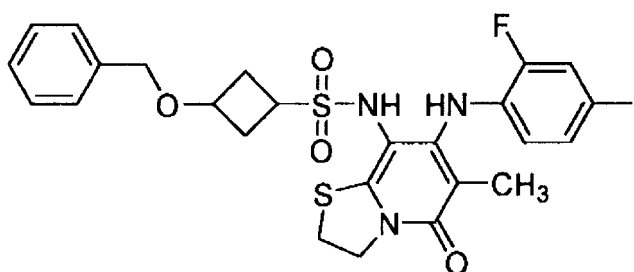


POCl₃ (0.34 mL, 3.558 mmol) was added to a cooled solution of potassium 3-(benzyloxy)cyclobutane-1-sulfonate (0.5 g, 1.779 mmol) in dry DCM (10 mL) at 0°C. This was followed by the slow addition of diisopropyl ethyl amine (0.65 mL, 3.558 mmol) and stirred the resulting reaction mixture at 0°C for 2 hours. The reaction was monitored by TLC (20% ethyl acetate in hexane). The

reaction mixture was extracted with DCM. The organic layer was washed with water, brine solution, dried over Na₂SO₄ and concentrated. Purification by column chromatography on silica gel (8% ethyl acetate in hexane) afforded 0.15 g of the product (38% yield).

5 ¹HNMR (CDCl₃, 300MHz): δ 7.4-7.1 (m, 5H), 4.5 (s, 2H), 4.1-3.9 (m, 2H), 2.9-2.6 (m, 4H)

10 Synthesis of Intermediate 3-Benzoyloxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (I-25d):



Using the same reaction conditions and workup as described for the preparation of Example 19A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (I-19f: 0.15 g, 0.35 mmol) in pyridine (2 mL) was reacted with 3-benzoyloxy-cyclobutanesulfonyl chloride (0.1 g, 0.39 mmol) to afford the crude product. Purification by column chromatography on silica gel (50% ethylacetate in hexane) afforded 0.1 g of the product (43% yield).

15 ¹HNMR (300MHz, CDCl₃): δ 7.4-7.2 (m, 7H), 6.9-6.8 (s, 1H), 6.3-6.2 (t, 1H), 4.6-4.5 (t, 2H), 4.45 (s, 2H), 4.0-3.5 (t, 1H), 3.5-3.4 (m, 4H), 2.7-2.5 (m, 4H), 1.8 (s, 3H). LCMS: 85%, m/z = 641.9 (M+1)

20 Synthesis of the title compound: 3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (25A):

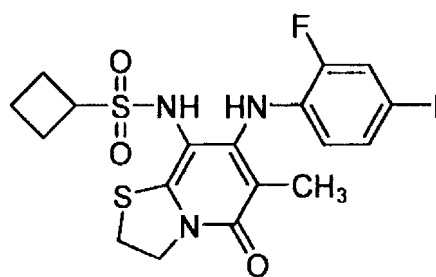
25 1M BCl₃ (0.46 mL, 0.468 mmol) was added to a solution of 3-benzoyloxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (0.1 g, 0.156 mmol) in dry DCM (3

mL) at -78°C. The resulting mixture was stirred at -78°C for 3 hours. The reaction was monitored by TLC (10% MeOH in CHCl₃). The reaction mixture was quenched with methanol, basified with saturated NaHCO₃ solution and extracted with DCM. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. Purification by column chromatography on silica gel (4% MeOH in CHCl₃), followed by preparative HPLC afforded 0.015 g of the product (18% yield).

¹HNMR (300MHz, CD₃OD): δ 7.5-7.4 (d, 1H), 7.4-7.3 (d, 1H), 6.4-6.3 (t, 1H), 4.6-4.5 (t, 2H), 4.2-4.0 (m, 1H), 3.6-3.5 (m, 3H), 2.7-2.6 (m, 2H), 2.4-2.2 (m, 2H), 1.8 (s, 3H). LCMS: 91.4%, m/z = 551.9 (M+1). HPLC: 94.6%

Example 26

Synthesis of Cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (26A):



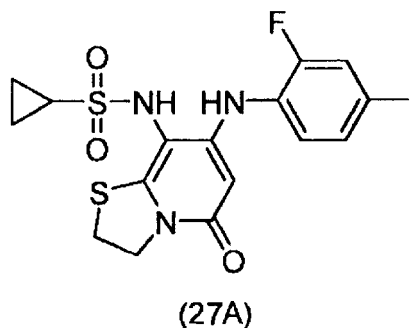
(26A)

Using the same reaction conditions and workup as described for the preparation of Example 19A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-6-methyl-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (1-19f: 0.1 g, 0.23 mmol) in pyridine (2 mL) was reacted with cyclobutanesulfonyl chloride (0.04 g, 0.20 mmol) to afford the crude product. Purification by preparative HPLC afforded 15 mg of the product (12% yield).

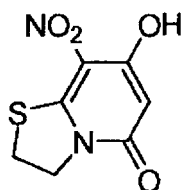
¹HNMR (300MHz, CD₃OD): δ 7.5-7.4 (d, 1H), 7.4-7.3 (d, 1H), 6.4-6.3 (t, 1H), 4.6-4.5 (t, 2H), 4.0-3.9 (m, 1H), 3.6-3.5 (m, 2H), 2.5-2.3 (m, 4H), 2.1-1.9 (m, 2H), 1.8 (s, 3H). LCMS: 95.5%, m/z = 535.9 (M+1). HPLC: 90.9%

Example 27

Synthesis of Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (27A):



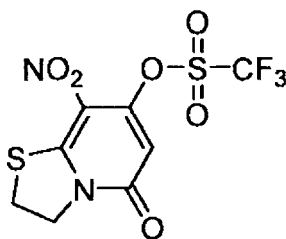
5 Synthesis of Intermediate 7-Hydroxy-8-nitro-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (I-27a):



Using the same reaction conditions and workup as described for the preparation of Intermediate (I-19b), 2-nitromethylene-thiazolidine (0.65 g, 4.45 mmol) was reacted with malonic acid bis-(2,4,6-trichloro-phenyl) ester (1.5 g, 4.45 mmol) in Xylene (10 mL) to afford the crude product. Purification by column chromatography on silica gel (100% ethylacetate) afforded 0.3 g of the product (33% yield).

¹HNMR (300MHz, DMSO-D₆): δ 11.6 (br s, 1H), 5.6-5.5 (s, 1H), 4.5-4.5 (t, 2H), 3.5-3.3 (t, 2H). LCMS: 100%, m/z = 214.9 (M+1)

Synthesis of Intermediate Trifluoro-methanesulfonic acid 8-nitro-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-7-yl ester (I-27b):

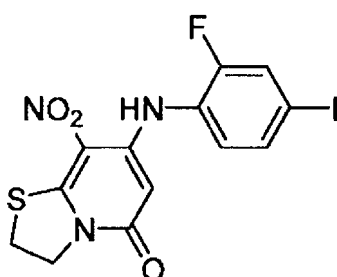


7-Hydroxy-8-nitro-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (0.3 g, 1.40 mmol) in DCM (10 mL) was reacted with triflic anhydride (0.26 mL, 1.54 mmol) and TEA (0.29 mL, 2.10 mmol) at -78°C. The resulting mixture was stirred at -78°C for 2 hours. Purification by column chromatography on silica gel (30% ethylacetate in hexane) afforded 0.27 g of the product (56% yield).

¹HNMR (300MHz, DMSO-D₆): δ 6.5 (s, 1H), 4.6-4.4 (t, 2H), 3.6-3.5 (t, 2H).

LCMS: 100%, m/z = 346.8 (M+1)

Synthesis of Intermediate 7-(2-Fluoro-4-iodo-phenylamino)-8-nitro-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (I-27c):

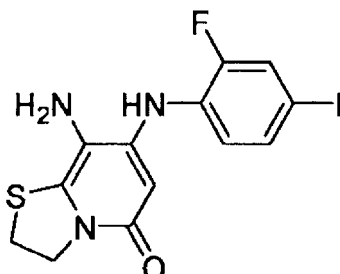


Trifluoro-methanesulfonic acid 8-nitro-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-7-yl ester (0.6 g, 1.7 mmol) was reacted with 2-fluoro-4-iodo-phenylamine (0.45 g, 1.9 mmol), Pd(OAc)₂ (38 mg, 0.17 mmol), BINAP (0.1 g, 0.17 mmol) and cesium carbonate (0.84 g, 2.6 mmol) in toluene (20 mL) at reflux for 3 hours to afford the crude product. Purification by column chromatography on silica gel (30% ethylacetate in hexane) afforded 90 mg of the product (12% yield).

¹HNMR (300MHz, CDCl₃): δ 9.4 (s, 1H), 7.6-7.5 (t, 2H), 7.2-7.1 (t, 1H),

5.5-5.4 (s, 1H), 4.7-4.5 (t, 2H), 3.5-3.3 (t, 2H). LCMS: 94.84%, m/z = 433.7 (M+1)

Synthesis of Intermediate 8-Amino-7-(2-fluoro-4-iodo-phenylamino)-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (I-27d):



Using the same reaction conditions and workup as described for the preparation of Intermediate (I-19f), 7-(2-fluoro-4-iodo-phenylamino)-8-nitro-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (0.08 g, 0.181 mmol) in ethanol (2 mL) was
 5 reacted with $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ (0.12 g, 0.541 mmol) and concentrated HCl (0.5 mL) to afford 0.08 g of crude product which was used in the next step without further purification. LCMS: 59%, $m/z = 403.9$ ($M+1$).

Synthesis of the title compound: Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide (27A):

Using the same reaction conditions and workup as described for the preparation of Example 19A, 8-amino-7-(2-fluoro-4-iodo-phenylamino)-2,3-dihydro-thiazolo[3,2-a]pyridin-5-one (0.08 g, 0.199 mmol) in pyridine (1 mL) was
 15 reacted with cyclopropylsulfonyl chloride (33 mg, 0.238 mmol) to afford the crude product. Purification by preparative HPLC afforded 20 mg of the product (20% yield).

^1H NMR (300MHz, $\text{DMSO}-d_6$): δ 9.0 (s, 1H), 7.8-7.7 (d, 1H), 7.6-7.5 (d, 2H), 7.2-7.1 (t, 1H), 5.1 (s, 1H), 4.4-4.2 (t, 2H), 3.5-3.3 (t, 2H), 2.9-2.7 (m, 1H), 1.0-0.8 (m, 4H). LCMS: 97.87%, $m/z = 507.9$ ($M+1$). HPLC: 99.35%

PHARMACOLOGICAL DATA

The utility of the compounds of the present invention may be demonstrated using any one of the following test procedures:

A BRAF-MEK-ERK cascade assay is used to evaluate the effects of the compounds as inhibitors of the MAP kinase pathway. An enzymatic cascade
 25 assay is set up using recombinant human activated BRAF (V599E) kinase (Cat No. 14-557), human full length inactive MEK1 kinase (Cat No. 14-706) and

human full length inactive MAP Kinase 2/ERK2 (Cat No. 14-536) enzymes procured from Upstate. TR-FRET (Time resolved fluorescence resonance energy transfer) detection technology is used for the read out. The assay buffer solution contains 50 mM Tris pH 7.5, 10 mM MgCl₂, 1 mM DTT, 0.01 % Tween 20, 0.1 nM activated BRAF, 2 nM inactive MEK1, 10 nM inactive ERK2, 100 μM ATP and 500 nM long chain biotin-peptide substrate (LCB- FFKNIVTPRTPPP) in a 384 well format. The kinase reaction is stopped after 90 minutes with 10 mM EDTA and Lance detection mix (2 nM Eu-labeled phospho-serine/threonine antibody (Cat. No. AD0176-Perkin Elmer), 20 nM SA-APC (Cat No. CR130-100-Perkin Elmer) is added. The TR-FRET signal (Excitation at 340 nm, Emission at 615 nm and 665 nm) is read with 50 μs delay time on a Victor3 V fluorimeter. The data is calculated using the ratio of readings at 665nm to 615 nm. The final concentration of DMSO is 2.5 % in the assay. Compounds are screened at 10 μM concentration with pre-incubation of the enzymes in the presence of test compound for 45 minutes.

Each individual IC₅₀ is determined using a 10 point dose response curve generated by GraphPad Prism software Version 4 (San Diego, California, USA) using non linear regression curve fit for sigmoidal dose response (variable slope).

An in-vitro MAP kinase assay is set up using activated MAP kinase 2/ERK2 (Cat. No. 14-550) obtained from Upstate. TR-FRET detection technology is used for the read out.

The assay buffer solution contains 50 mM Tris pH 7.5, 10 mM MgCl₂, 1 mM DTT, 0.01 % Tween 20, 1 nM activated ERK2, 100 μM ATP and 500 nM long chain biotin-peptide substrate (LCB- FFKNIVTPRTPPP) in a 384 well format. The kinase reaction is stopped after 90 minutes with 10 mM EDTA and Lance detection mix (2 nM Eu-labeled phospho-serine/threonine antibody (Cat. No. AD0176-Perkin Elmer), 20 nM SA-APC (Cat. No. CR130-100-Perkin Elmer) is added. The TR-FRET signal (excitation at 340 nm, emission at 615 nm and 665 nm) is read with 50 μs delay time on Victor3 V fluorimeter. The data is calculated using the ratio of readings at 665nm to 615 nm. The final concentration of DMSO is 2.5 % in the assay. Compounds are screened at 10

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μ M concentration with pre-incubation of the enzymes in the presence of test compound for 45 minutes.

The radioactive filter binding assay is standardized using recombinant human activated BRAF (V599E) kinase (Cat No. 14-557) and kinase dead MEK1 (K97R) (Cat No. 14-737) procured from Upstate. The incorporation of ^{32} P into MEK1 (K97R) by BRAF (V599E) is measured with final assay buffer conditions of 50 mM Tris pH 7.5, 10 mM $MgCl_2$, 1 mM DTT, 100 mM sucrose, 100 μ M sodium orthovanadate, 5 μ M ATP and 2 μ Ci [γ ^{32} P] ATP and 500 mg MEK1 Kinase dead substrate. The enzymatic reaction is stopped after 120 minutes with 8N HCl (hydrochloric acid) and 1 mM ATP. The solution is spotted on P81 filter paper and washed 4 times with 0.75 % orthophosphoric acid and lastly with acetone. The dried P81 filter papers are read in a Micro-beta Trilux scintillation counter. The final concentration of DMSO is 1 % in the assay. Compounds are screened at 10 μ M concentration with pre-incubation of the enzymes in the presence of test compound for 45 minutes.

These assays described above are fully detailed in Han, Shulin, et. al., Bioorganic & Medicinal Chemistry Letters (2005) 15, 5467-5473, and in Yeh, et. al., Clin Cancer Res (2007) 13 (5), 1576-1583.

The cell viability assay in A375 cells is set up in a 96-well plate format using XTT.

XTT is a yellow tetrazolium salt that is cleaved to an orange formazan dye by the mitochondria of metabolically active cells. The procedure allows for rapid determination in a microtitre plate, to give reproducible and sensitive results.

A375 cells are grown in DMEM media containing 10% FBS and 1mM sodium pyruvate. Cells are trypsinized and seeded at 1000 cells/well. After allowing the cells to adhere overnight, compound is added to the wells at the following final concentrations: 10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.001, and 0.0001 μ M. The assay is set up in triplicates for each concentration. DMSO concentrations are kept at 0.5% /well. Three days after compound addition, the XTT assay is performed. Wells are washed once with PBS. 100 μ L of DMEM media without phenol red or FBS is added to each well. A working solution of

XTT containing 1mg/ml XTT and 100 µL of PMS (stock concentration 0.383 mg/ml) per 5ml is prepared. 50 µL of the working solution of XTT is added to each well. Absorbance of the plate is read at 465nm using a Spectramax 190 (Molecular Devices). The absorbance from wells with media and XTT alone, but without cells is considered the blank and subtracted from readings from all wells.

Percentage viability is calculated considering the blank subtracted value from wells treated with DMSO alone as 100% viable. GI50 values are calculated using Graphpad Prism, using non-linear regression curve fit for sigmoidal dose response (variable slope).

The cell viability assay is further described in Scudiero, et. al., Cancer Research (1988) 48, 4827-4833; Weislow, et. al., J. Natl. Cancer Institute, (1989) 81, 577-586; and Roehm, et. al., J. Immunol.Methods [1991]142:257-265.

The compounds of the above Examples were evaluated as inhibitors of the MAP kinase pathway in a BRAF-MEK-ERK enzymatic cascade assay and in the cell viability assay described above. The results are collated in Table 1 below.

TABLE 1

Example No.	IUPAC Name	% inhibition	GI ₅₀ µM
1A	Cyclopropanesulfonic acid [1-benzyl-7-(4-bromo-2-fluorophenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide	70%	-
2A	Cyclopropanesulfonic acid [7-(4-bromo-2-fluorophenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide	100%	0.8
3A	Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide	100%	0.019

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Example No.	IUPAC Name	% inhibition	GI ₅₀ μM
4A	1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide	100%	2.88
5A	1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide	100%	0.293
6A	3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide	100%	1.38
7A	Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide	99%	0.026
8A	2-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide	100%	0.122
9A	1-(2-Hydroxy-ethyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide	100%	0.019
10A	1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide	100%	0.033

Example No.	IUPAC Name	% inhibition	GI ₅₀ μM
11A	1-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide	100%	0.02
12A	1-(3-Hydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide	100%	0.011
13A	3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide	100%	0.122
14A	Cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide	100%	0.016
15A	3-(1,3-dihydroxypropan-2-yl)-N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)cyclobutane-1-sulfonamide	100%	1.53
16A	N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-1-(3-methyloxetan-3-yl)methanesulfonamide	100%	1.30
17A	N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-2-(oxetan-3-yl)ethanesulfonamide	100%	1.73

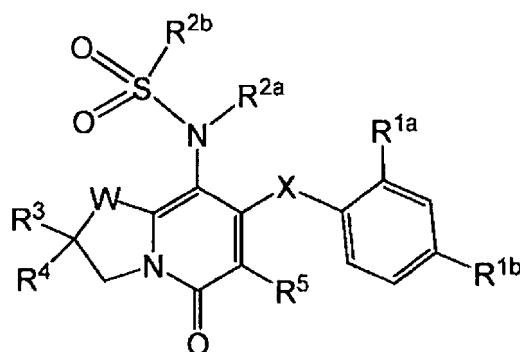
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Example No.	IUPAC Name	% inhibition	GI ₅₀ μM
18A	N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-4-hydroxy-3-(hydroxymethyl)butane-1-sulfonamide	100%	4.26
19A	Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide	100%	0.0003
20A	1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide	100%	0.054
21A	2-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide	100%	0.158
22A	1-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide	97%	0.061
23A	N-[7-(2-Fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-dimethylaminosulfonamide	100%	0.107
24A	Cyclopentanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide	100%	0.192

Example No.	IUPAC Name	% inhibition	GI ₅₀ μM
25A	3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide	100%	0.922
26A	Cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide	100%	0.156
27A	Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide	100%	0.064

What is Claimed is:

1. A compound of Formula (IA)



(IA)

5 wherein

X is -N(R⁶)-, where R⁶ is H or (C₁-C₆)alkyl;

R^{1a} and R^{1b} are each independently selected from hydroxyl, cyano, nitro, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₂-C₆)alkenyloxy, (C₂-C₆)alkynyloxy, halogen, (C₁-C₆)alkyl-C(O)-, -C(O)OH, -C(O)-O(C₁-C₆)alkyl, amino, (C₁-C₆)alkylNH-, di((C₁-C₆)alkyl)N-, (C₁-C₆)alkylNH-C(O)-, di((C₁-C₆)alkyl)N-C(O)-, (C₁-C₆)alkyl-C(O)-NH-, (C₁-C₆)alkyl-C(O)-N((C₁-C₆)alkyl)-, (C₁-C₆)alkyl-SO₂-NH-, (C₁-C₆)alkyl-SO₂-N((C₁-C₆)alkyl)-, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-S(O)-, (C₁-C₆)alkyl-SO₂-, NH₂-SO₂-, (C₁-C₆)alkylNH-SO₂- and di((C₁-C₆)alkyl)N-SO₂-, where each of said (C₁-C₆)alkyl, (C₂-C₆)alkenyl, and (C₂-C₆)alkynyl moieties are optionally substituted by one or more substituents each independently selected from halogen, hydroxyl, (C₁-C₆)alkoxy, amino, (C₁-C₆)alkyl-NH-, di((C₁-C₆)alkyl)N- or cyano;

R^{2a} is H or C₁₋₆-alkyl;

R^{2b} is a chemical moiety selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, NR¹⁰R¹², cycloalkyl, aryl, heterocycloalkyl, or heteroaryl, wherein said chemical moiety is optionally substituted by one to three substituents each independently selected from halogen, cyano, hydroxyl, (C₁-C₆)alkoxy, (C₂-C₆)alkenyloxy, (C₂-C₆)alkynyloxy, (C₁-C₆)alkyl-S-, halo-substituted(C₁-C₆)alkyl, amino, (C₁-C₆)alkylNH-, di((C₁-C₆)alkyl)N-, HC(O)-NH-, (C₁-C₆)alkyl-C(O)-NH-, HC(O)-N(C₁-C₆)alkyl-, (C₁-C₆)alkyl-C(O)-N((C₁-C₆)alkyl)-, monocyclic cycloalkyl or

monocyclic heterocycloalkyl, where said cycloalkyl and said heterocycloalkyl are optionally substituted by one or two substituents each independently selected from halogen, cyano, hydroxyl, (C₁-C₆)alkoxy, (C₂-C₆)alkenyloxy, (C₂-C₆)alkynyloxy, (C₁-C₆)alkyl-S-, C₁₋₆-haloalkyl, amino, (C₁-C₆)alkylNH-, di((C₁-C₆)alkyl)N-, HC(O)-NH-, (C₁-C₆)alkyl-C(O)-NH-, HC(O)-N(C₁-C₆)alkyl-, or (C₁-C₆)alkyl-C(O)-N((C₁-C₆)alkyl)-;

W is NR²², O, or S;

R³ and R⁴ are each independently H, (C₁-C₆)alkyl, halo-substituted(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, or (C₁-C₆)alkoxy;

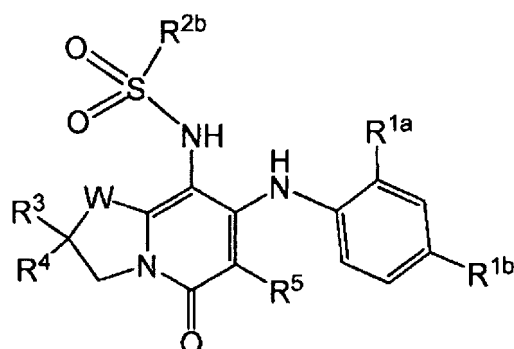
10 R⁵ is H, halogen, (C₁-C₃)alkyl, or halo-substituted(C₁-C₃)alkyl;

R¹⁰ and R¹² are each independently H, or a chemical moiety selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylC(O)-, (C₁-C₆)alkoxy, (C₃-C₁₄)cycloalkyl, (C₆-C₁₄)aryl, 4- to 14-membered cycloheteroalkyl, or 5- to 14-membered heteroaryl, wherein each of said chemical moieties are optionally substituted by one or more substituents each independently selected from halogen, hydroxyl, (C₁-C₆)alkoxy, amino, (C₁-C₆)alkylamino, di-((C₁-C₆)alkyl)amino or cyano; and

R²² is H, or a chemical moiety selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, cycloalkyl, aryl, heterocycloalkyl, aryl-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-aryl-, or diaryl-(C₁-C₆)alkyl-, where each of said chemical moieties is optionally substituted by one or more substituents each independently selected from hydroxyl, cyano, nitro, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₂-C₆)alkenyloxy, (C₂-C₆)alkynyloxy, halogen, (C₁-C₆)alkyl-C(O)-, -C(O)OH, -C(O)-O(C₁-C₆)alkyl, amino, (C₁-C₆)alkylNH-, di((C₁-C₆)alkyl)N-, (C₁-C₆)alkylNH-C(O)-, di((C₁-C₆)alkyl)N-C(O)-, (C₁-C₆)alkyl-C(O)-NH-, (C₁-C₆)alkyl-C(O)-N((C₁-C₆)alkyl)-, (C₁-C₆)alkyl-SO₂-NH-, (C₁-C₆)alkyl-SO₂-N((C₁-C₆)alkyl)-, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-S(O)-, (C₁-C₆)alkyl-SO₂-, NH₂-SO₂-, (C₁-C₆)alkylNH-SO₂- and di((C₁-C₆)alkyl)N-SO₂-, where each of said (C₁-C₆)alkyl, (C₂-C₆)alkenyl, and (C₂-C₆)alkynyl moieties are optionally substituted by one or more substituents each independently selected from halogen, hydroxyl, (C₁-C₆)alkoxy, amino, (C₁-C₆)alkyl-NH-, di((C₁-C₆)alkyl)N-, or cyano;

or a pharmaceutically acceptable salt thereof.

2. A compound of Formula (IB)



(IB)

wherein

R^{1a} and R^{1b} are each independently hydroxyl, cyano, nitro, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, halogen, amino, or (C₁-C₆)alkyl-NH-; R^{2b} is

(i) 3- to 6-membered cycloalkyl, where said cycloalkyl is optionally substituted with hydroxyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, or (C₂-C₆)alkynyl, wherein said (C₁-C₆)alkyl, said (C₂-C₆)alkenyl, and said (C₂-C₆)alkynyl are optionally substituted with 1 to 3 hydroxyl,

(ii) (C₁-C₆)alkyl substituted by a monocyclic 3- to 6-membered cycloalkyl or a monocyclic 3- to 6-membered heterocycloalkyl containing 1 to 3 heteroatoms selected from O, S or N, where said substituted alkyl is optionally substituted with one to three substituents each independently selected from the group consisting of halogen, cyano, hydroxyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-S-, halo-substituted(C₁-C₆)alkyl, amino, (C₁-C₆)alkyl-NH-, di-((C₁-C₆)alkyl)-N-, and (C₁-C₆)alkylC(O)-NH-,

(iii) (C₂-C₆)alkenyl substituted by a monocyclic 3- to 6-membered cycloalkyl or a monocyclic 3- to 6-membered heterocycloalkyl containing 1 to 3 heteroatoms selected from O, S or N, where said substituted alkenyl is optionally substituted with one to three substituents each independently selected from the group consisting of halogen, cyano, hydroxyl, (C₁-

C₆)alkoxy, (C₁-C₆)alkyl-S-, halo-substituted(C₁-C₆)alkyl, amino, (C₁-C₆)alkyl-NH-, di-((C₁-C₆)alkyl)-N-, and (C₁-C₆)alkylC(O)-NH-,

(iv) (C₂-C₆)alkynyl substituted by a monocyclic 3- to 6-membered cycloalkyl or a monocyclic 3- to 6-membered heterocycloalkyl containing 1 to 3 heteroatoms selected from O, S or N, where said substituted alkynyl is optionally substituted with one to three substituents each independently selected from the group consisting of halogen, cyano, hydroxyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-S-, halo-substituted(C₁-C₆)alkyl, amino, (C₁-C₆)alkyl-NH-, di-((C₁-C₆)alkyl)-N-, and (C₁-C₆)alkylC(O)-NH-, or

(v) di((C₁-C₆)alkyl)amine;

R³ is H;

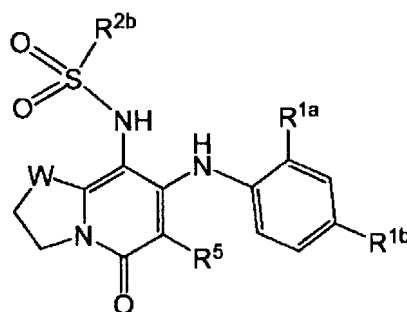
R⁴ is H or methyl;

W is NR²², O, or S, where R²² is H, methyl, ethyl, phenyl, benzyl, or phenethyl;

R⁵ is H, halogen, (C₁-C₃)alkyl, or halo-substituted(C₁-C₃)alkyl; or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 2 wherein R^{1a} and R^{1b} are each independently halogen; or a pharmaceutically acceptable salt thereof.

4. A compound of Formula (IC)



(IC)

wherein

R^{1a} is F;

R^{1b} is Br or I;

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R^{2b} is

(i) 3- to 6-membered cycloalkyl, where said cycloalkyl is optionally substituted with hydroxyl or (C₁-C₆)alkyl, wherein said (C₁-C₆)alkyl is optionally substituted with 1 to 3 hydroxyl,

5 (ii) (C₁-C₆)alkyl, where said (C₁-C₆)alkyl is optionally substituted with oxetanyl or 1 to 3 hydroxyl, or

(iii) -N(CH₃)₂;

W is O, S or N(R²²), where R²² is H or benzyl; and

R⁵ is H, F, Cl, CH₃ or CF₃;

10 or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 4 wherein W is O; or a pharmaceutically acceptable salt thereof.

15 6. A compound selected from the group consisting of

Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

2-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

20 1-(2-Hydroxy-ethyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

25 1-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

1-(3-Hydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

30 Cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-oxazolo[3,2-a]pyridin-8-yl]-amide;

3-(1,3-dihydroxypropan-2-yl)-N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)cyclobutane-1-sulfonamide;

N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-1-(3-methyloxetan-3-yl)methanesulfonamide;

5 N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-2-(oxetan-3-yl)ethanesulfonamide; and

N-(7-(2-fluoro-4-iodophenylamino)-6-methyl-5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyridin-8-yl)-4-hydroxy-3-(hydroxymethyl)butane-1-sulfonamide;

or a pharmaceutically acceptable salt thereof.

10

7. The compound of Claim 4 wherein W is S; or a pharmaceutically acceptable salt thereof.

8. A compound selected from the group consisting of

15 Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

20 2-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

1-Hydroxymethyl-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

N-[7-(2-Fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-dimethylaminosulfonamide;

25 Cyclopentanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;

30 Cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide; and

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Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridin-8-yl]-amide;
or a pharmaceutically acceptable salt thereof.

5 9. The compound of Claim 4 wherein W is NH; or a pharmaceutically acceptable salt thereof.

10. A compound selected from the group consisting of
Cyclopropanesulfonic acid [7-(4-bromo-2-fluoro-phenylamino)-6-methyl-5-
10 oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide;
Cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-methyl-5-
oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide;
1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(4-bromo-2-fluoro-
phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-
15 amide;
1-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [7-(2-fluoro-4-iodo-
phenylamino)-6-methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-
amide; and
3-Hydroxy-cyclobutanesulfonic acid [7-(2-fluoro-4-iodo-phenylamino)-6-
20 methyl-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-a]pyridin-8-yl]-amide;
or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a pharmaceutical composition
comprising a compound according to any one of Claims 1-10, or
25 pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable
excipient.

12. The compound according to any one of claims 1-10 for use in therapy.

30 13. A method of treating a disease, disorder or syndrome associated with
MEK inhibition comprising the step of administering to a subject in need thereof

(i) a compound according to any one of claims 1-10, or pharmaceutically acceptable salt thereof, or

(ii) a pharmaceutical composition of Claim 11.

5 14. The method of Claim 13 wherein said subject is a human and said disease, disorder or syndrome associated with MEK inhibition is cancer.

15. The method of Claim 13 wherein said subject is a human and said disease, disorder or syndrome associated with MEK inhibition is inflammation.

10

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/066659

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D471/04 C07D498/04 C07D513/04 A61K31/4355 A61K31/4365 A61K31/437 A61P29/00 A61P35/00 ADD. According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2010/121646 A1 (NOVARTIS AG [CH]; CHIKKANNA DINESH [IN]; MCCARTHY CLIVE [CH]; MOEBITZ) 28 October 2010 (2010-10-28) claims 1,15,19	1-15
A	WO 2009/064675 A1 (TAKEDA PHARMACEUTICAL [JP]; ADAMS MARK E [US]; DONG QING [US]; KALDOR) 22 May 2009 (2009-05-22) paragraph [0001]; claim 1; example 1	1-15
A	WO 2008/089459 A1 (ARDEA BIOSCIENCES INC [US]; VERNIER JEAN-MICHEL [US]; MADERNA ANDREAS) 24 July 2008 (2008-07-24) claims 1,49	1-15
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *C* earlier document but published on or after the international filing date *I* 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 13 January 2011		Date of mailing of the international search report 19/01/2011
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Gettins, Marc

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2010121646	A1	28-10-2010	NONE	
WO 2009064675	A1	22-05-2009	AR 069462 A1	27-01-2010
			CA 2705452 A1	22-05-2009
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			US 2008255133 A1	16-10-2008
			US 2010331334 A1	30-12-2010

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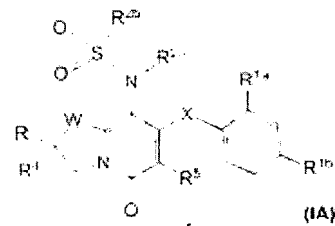
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(54) Título : DERIVADOS DE SULFONAMIDA HETEROCÍCLICOS ÚTILES COMO INHIBIDORES DE MEK



(57) Resumen: La presente invención se refiere a los compuestos de la fórmula (IA), en donde R^{1a}, R^{1b}, X, R^{2a}, R^{2b}, W, R³, R⁴, y R⁵ son como se definen en la presente, así como a las sales farmacéuticamente aceptables de los mismos. Se ha demostrado que los compuestos actúan como inhibidores de MEK, lo cual puede ser útil en el tratamiento de enfermedades hiperproliferativas, como cáncer e inflamación.

WO 2011/054828 A1

DERIVADOS DE SULFONAMIDA HETEROCÍCLICOS ÚTILES COMO
INHIBIDORES DE MEK

CAMPO DE LA INVENCIÓN

5 La invención se refiere a compuestos de sulfonamida heterocíclicos y a composiciones farmacéuticas de los mismos, en particular a compuestos de sulfonamida heterocíclicos que son inhibidores específicos de la actividad de cinasa de MEK. La invención también se refiere al uso de los compuestos y
10 composiciones de los mismos en el manejo de enfermedades hiperproliferativas como cáncer e inflamación.

ANTECEDENTES

Las enfermedades hiperproliferativas como cáncer e inflamación están recibiendo una gran cantidad de atención de la
15 comunidad científica, y existe un fuerte deseo de descubrir compuestos que proporcionen beneficios terapéuticos con respecto al tratamiento de enfermedades hiperproliferativas. En este aspecto, se han hecho esfuerzos para identificar y dirigirse a los mecanismos específicos que tengan una función en la proliferación de las
20 enfermedades.

Un objetivo de interés es la sobre-activación de la cascada de cinasa de proteína activada por mitógeno (MAP), la cual se sabe que tiene una función importante en la proliferación y diferenciación celular. Esta senda se puede activar cuando un factor de crecimiento
25 se enlaza a su cinasa de tirosina receptora. Esta interacción

promueve la asociación de RAS con RAF, e inicia una cascada de fosforilación a través de MEK (cinasa MAP) hasta ERK. Se sabe que la inhibición de esta senda es benéfica en el tratamiento de las enfermedades hiperproliferativas. MEK es un objetivo terapéutico tractivo, debido a que los únicos sustratos conocidos para la fosforilación de MEK son las cinasas MAP, ERK1 y ERK2. La activación constitutiva de MEK/ERK se ha encontrado en muestras de tumores primarios pancreáticos, de colon, pulmón, riñón y ovario.

La fosforilación de MEK parece aumentar su afinidad y su actividad catalítica hacia ERK, así como su afinidad para ATP. Esta invención describe compuestos que inhiben la actividad de MEK mediante la modulación del enlace de ATP, la asociación de MEK con ERK mediante mecanismos que son competitivos y/o aloestéricos y/o no competitivos.

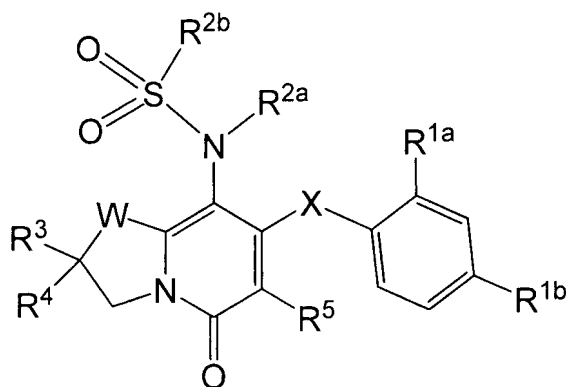
La activación de MEK se ha demostrado en muchos modelos de enfermedad, sugiriendo, por consiguiente, que la inhibición de MEK podría tener un efecto terapéutico potencial en diferentes enfermedades, tales como dolor (véase, por ejemplo, Evidence of efficacy in pain models, descrito en J. Neurosci. 22: 478, 2002; Acta Pharmacol Sin. 26: 789 2005; Expert Opin Ther Targets. 9: 699, 2005; y Mol. Pain. 2:2, 2006); embolia (véase, por ejemplo, Evidence of efficacy in stroke models significant neuroprotection against ischemic brain injury by inhibition of the MEK, descrito en J. Pharmacol. Exp. Ther. 304: 172, 2003; y en Brain Res. 996: 55, 2004); diabetes (véase, por ejemplo, Evidence in diabetic

complications, descrito en Am. J. Physiol. Renal.286, F120 2004); inflamación (véase, por ejemplo, Evidence of efficacy in inflammation models, descrito en Biochem Biophy. Res. Com. 268: 647, 2000); y artritis (véase, por ejemplo, Evidence of efficacy in experimental osteoarthritis and artritis, como se describe en J. Clin. Invest. 116: 163. 2006).

Aunque se ha demostrado que la inhibición de MEK tiene un beneficio terapéutico potencial en varios estudios, todavía sigue existiendo una necesidad de encontrar compuestos que tengan aplicación comercial.

BREVE DESCRIPCIÓN DE LA INVENCION

La invención proporciona un compuesto de sulfonamida de la fórmula (IA):



(IA)

en donde:

X es -N(R⁶)-, en donde R⁶ es H o alquilo (de 1 a 6 átomos de carbono);

R^{1a} y R^{1b} se seleccionan cada uno independientemente a partir

de hidroxilo, ciano, nitro, alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), alquinilo (de 2 a 6 átomos de carbono), alcoxilo (de 1 a 6 átomos de carbono), alqueniloxilo (de 2 a 6 átomos de carbono), alquiniloxilo (de 2 a 6 átomos de carbono), halógeno, alquilo (de 1 a 6 átomos de carbono)-C(O)-, -C(O)OH, -C(O)-O-alquilo (de 1 a 6 átomos de carbono), amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono)-N-, alquilo (de 1 a 6 átomos de carbono)-NH-C(O)-, di-(alquilo (de 1 a 6 átomos de carbono)-N-C(O)-, alquilo (de 1 a 6 átomos de carbono)-C(O)-NH-, alquilo (de 1 a 6 átomos de carbono)-C(O)-N-(alquilo (de 1 a 6 átomos de carbono))-, alquilo (de 1 a 6 átomos de carbono)-SO₂-NH-, alquilo (de 1 a 6 átomos de carbono)-SO₂-N-(alquilo (de 1 a 6 átomos de carbono))-, alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono)-S(O)-, alquilo (de 1 a 6 átomos de carbono)-SO₂-, NH₂-SO₂-, alquilo (de 1 a 6 átomos de carbono)-NH-SO₂- y di-(alquilo (de 1 a 6 átomos de carbono)-N-SO₂-, en donde cada una de dichas fracciones de alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), y alquinilo (de 2 a 6 átomos de carbono) está opcionalmente sustituida por uno o más sustituyentes, cada uno independientemente seleccionado a partir de halógeno, hidroxilo, alcoxilo (de 1 a 6 átomos de carbono), amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono)-N- o ciano;

R^{2a} es H o alquilo de 1 a 6 átomos de carbono;

R^{2b} es una fracción química seleccionada a partir de alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), alquinilo (de 2 a 6 átomos de carbono), $NR^{10}R^{12}$, cicloalquilo, arilo, hetero-cicloalquilo, o heteroarilo, en donde esta fracción química está opcionalmente sustituida por uno a tres sustituyentes, cada uno independientemente seleccionado a partir de halógeno, ciano, hidroxilo, alcoxilo (de 1 a 6 átomos de carbono), alqueniloxilo (de 2 a 6 átomos de carbono), alquiniloxilo (de 2 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono) sustituido por halógeno, amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono)-N-, HC(O)-NH-, alquilo (de 1 a 6 átomos de carbono)-C(O)-NH-, HC(O)-N-alquilo (de 1 a 6 átomos de carbono))-, alquilo (de 1 a 6 átomos de carbono)-C(O)-N-(alquilo (de 1 a 6 átomos de carbono))-, cicloalquilo monocíclico o hetero-cicloalquilo monocíclico, en donde este cicloalquilo y este hetero-cicloalquilo están opcionalmente sustituidos por uno o dos sustituyentes, cada uno independientemente seleccionado a partir de halógeno, ciano, hidroxilo, alcoxilo (de 1 a 6 átomos de carbono), alqueniloxilo (de 2 a 6 átomos de carbono), alquiniloxilo (de 2 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono)-S-, halo-alquilo de 1 a 6 átomos de carbono, amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono)-N-, HC(O)-NH-, alquilo (de 1 a 6 átomos de carbono)-C(O)-NH-, HC(O)-N-alquilo (de 1 a 6 átomos

de carbono))-, o alquilo (de 1 a 6 átomos de carbono)-C(O)-N-(alquilo (de 1 a 6 átomos de carbono))-;

W es NR^{22} , O, o S;

R^3 y R^4 son cada uno independientemente H, alquilo (de 1 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono) sustituido por halógeno, hidroxil-alquilo (de 1 a 6 átomos de carbono), o alcoxilo (de 1 a 6 átomos de carbono);

R^5 es H, halógeno, alquilo (de 1 a 3 átomos de carbono), o alquilo (de 1 a 3 átomos de carbono) sustituido por halógeno;

R^{10} y R^{12} son cada uno independientemente H, o una fracción química seleccionada a partir de alquilo (de 1 a 6 átomos de carbono), alqueno (de 2 a 6 átomos de carbono), alquino (de 2 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono)-C(O)-, alcoxilo (de 1 a 6 átomos de carbono), cicloalquilo (de 3 a 14 átomos de carbono), arilo (de 6 a 14 átomos de carbono), cicloheteroalquilo de 4 a 14 miembros, o heteroarilo de 5 a 14 miembros, en donde cada una de estas fracciones químicas está opcionalmente sustituida por uno o más sustituyentes, cada uno seleccionado independientemente a partir de halógeno, hidroxilo, alcoxilo (de 1 a 6 átomos de carbono), amino, alquilo (de 1 a 6 átomos de carbono)-amino, di-(alquilo (de 1 a 6 átomos de carbono))-amino, o ciano; y

R^{22} es H, o una fracción química seleccionada a partir de alquilo (de 1 a 6 átomos de carbono), alqueno (de 2 a 6 átomos de carbono), alquino (de 2 a 6 átomos de carbono), cicloalquilo, arilo, hetero-cicloalquilo, aril-alquilo (de 1 a 6 átomos de carbono)-, alquilo

(de 1 a 6 átomos de carbono)-aril-, o diaril-alquilo (de 1 a 6 átomos de carbono)-, en donde cada una de estas fracciones químicas está opcionalmente sustituida por uno o más sustituyentes, cada uno independientemente seleccionado a partir de hidroxilo, ciano, nitro,

5 alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), alquinilo (de 2 a 6 átomos de carbono), alcóxido (de 1 a 6 átomos de carbono), alquéníloxido (de 2 a 6 átomos de carbono), alquíníloxido (de 2 a 6 átomos de carbono), halógeno, alquilo (de 1 a 6 átomos de carbono)-C(O)-, -C(O)OH, -C(O)-O-alquilo (de 1 a 6

10 átomos de carbono), amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono)-N-, alquilo (de 1 a 6 átomos de carbono)-NH-C(O)-, di-(alquilo (de 1 a 6 átomos de carbono)-N-C(O)-, alquilo (de 1 a 6 átomos de carbono)-C(O)-NH-, alquilo (de 1 a 6 átomos de carbono)-C(O)-N-(alquilo (de 1 a 6

15 átomos de carbono))-, alquilo (de 1 a 6 átomos de carbono)-SO₂-NH-, alquilo (de 1 a 6 átomos de carbono)-SO₂-N-(alquilo (de 1 a 6 átomos de carbono))-, alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono)-S(O)-, alquilo (de 1 a 6 átomos de carbono)-SO₂-, NH₂-SO₂-, alquilo (de 1 a 6 átomos de carbono)-NH-SO₂- y di-

20 (alquilo (de 1 a 6 átomos de carbono)-N-SO₂-, en donde cada una de dichas fracciones de alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), y alquinilo (de 2 a 6 átomos de carbono) está opcionalmente sustituida por uno o más sustituyentes, cada uno independientemente seleccionado a partir de halógeno,

25 hidroxilo, alcóxido (de 1 a 6 átomos de carbono), amino, alquilo (de 1

a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono)-N-, o ciano; o una sal farmacéuticamente aceptable del mismo.

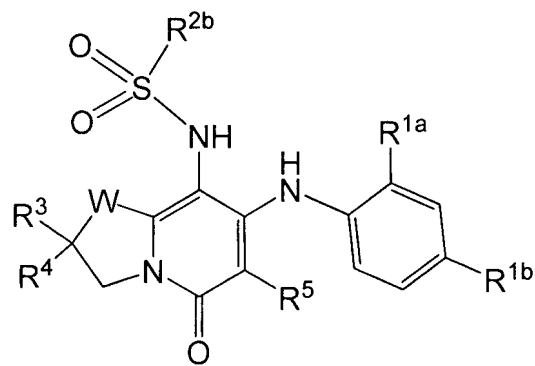
Cuando W es NR^{22} , entonces R^{22} es de preferencia H, alquilo (de 1 a 6 átomos de carbono) (por ejemplo, metilo, etilo, o propilo), alquenilo (de 2 a 6 átomos de carbono) (por ejemplo, etenilo), alquinilo (de 2 a 6 átomos de carbono) (por ejemplo, etinilo), cicloalquilo (por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo), arilo (por ejemplo, fenilo), hetero-cicloalquilo (por ejemplo, piperazinilo, piperidinilo, tetrahidro-furanilo, o morfolinilo), aril-alquilenos (de 1 a 6 átomos de carbono) (por ejemplo, fenil- CH_2 -, fenil- $\text{CH}_2\text{-CH}_2$ -, o fenil- $\text{CH}_2\text{-CH}_2\text{-CH}_2$ -), alquilo (de 1 a 6 átomos de carbono)-aril- (por ejemplo, tolilo), diaril-alquilenos (de 1 a 6 átomos de carbono) (por ejemplo, difenil-CH-); en donde este alquilo, alquenilo, alquinilo, cicloalquilo, arilo, hetero-cicloalquileno, o arilo está opcionalmente sustituido por uno o más grupos, cada uno independientemente seleccionado a partir de la Lista 1. Más preferiblemente, R^{22} es H, metilo, etilo, propilo, ciclopropilo, ciclopentilo, fenilo, bencilo, o fenetilo, en donde este metilo, etilo, propilo, ciclopropilo, ciclopentilo, fenilo, bencilo, o fenetilo está opcionalmente sustituido por uno o más grupos independientemente seleccionados a partir de la Lista 1. Todavía más preferiblemente, R^{22} es H, metilo, etilo, fenilo, bencilo, o fenetilo, en donde este metilo, etilo, fenilo, bencilo, o fenetilo está opcionalmente sustituido por uno o más grupos independientemente seleccionados a partir de

la Lista 1. En una modalidad, R^{22} es H o bencilo. De una manera muy preferible, R^{22} es H.

De preferencia, R^3 y R^4 son cada uno independientemente H, metilo, o etilo. Más preferiblemente, uno de R^3 y R^4 es H, y el otro es metilo. De una manera muy preferible, ambos R^3 y R^4 son H.

De preferencia, R^5 es H, halógeno (de preferencia, flúor o cloro), alquilo (de 1 a 3 átomos de carbono) (de preferencia, metilo), o alquilo (de 1 a 3 átomos de carbono) sustituido por halógeno (de preferencia, trifluoro-metilo). Más preferiblemente, R^5 es flúor, cloro, metilo, o trifluoro-metilo. De una manera muy preferible, R^5 es metilo.

En otra modalidad, se proporciona un compuesto de la fórmula (IB):



(IB)

en donde:

R^{1a} y R^{1b} son cada uno independientemente hidroxilo, ciano, nitro, alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), alquinilo (de 2 a 6 átomos de carbono), alcoxilo

(de 1 a 6 átomos de carbono), halógeno, amino, o alquilo (de 1 a 6 átomos de carbono)-NH-;

R^{2b} es:

(i) cicloalquilo de 3 a 6 miembros, en donde este cicloalquilo
5 está opcionalmente sustituido con hidroxilo, alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), o alquinilo (de 2 a 6 átomos de carbono), en donde este alquilo (de 1 a 6 átomos de carbono), este alquenilo (de 2 a 6 átomos de carbono), y este alquinilo (de 2 a 6 átomos de carbono) están opcionalmente
10 sustituidos con 1 a 3 grupos hidroxilo,

(ii) alquilo (de 1 a 6 átomos de carbono) sustituido por un cicloalquilo monocíclico de 3 a 6 miembros o un heterocicloalquilo monocíclico de 3 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de O, S o N, en donde este alquilo sustituido
15 está opcionalmente sustituido con uno a tres sustituyentes, cada uno independientemente seleccionado a partir del grupo que consiste en halógeno, ciano, hidroxilo, alcoxilo (de 1 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono) sustituido por halógeno, amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono))-N-, y alquilo
20 (de 1 a 6 átomos de carbono)-C(O)-NH-,

(iii) alquenilo (de 2 a 6 átomos de carbono) sustituido por un cicloalquilo monocíclico de 3 a 6 miembros o un heterocicloalquilo monocíclico de 3 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de O, S o N, en donde este alquenilo
25

sustituido está opcionalmente sustituido con uno a tres sustituyentes, cada uno independientemente seleccionado a partir del grupo que consiste en halógeno, ciano, hidroxilo, alcoxilo (de 1 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono) sustituido por halógeno, amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono))-N-, y alquilo (de 1 a 6 átomos de carbono)-C(O)-NH-,

(iv) alquinilo (de 2 a 6 átomos de carbono) sustituido por un cicloalquilo monocíclico de 3 a 6 miembros o un heterocicloalquilo monocíclico de 3 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de O, S o N, en donde este alquinilo sustituido está opcionalmente sustituido con uno a tres sustituyentes, cada uno independientemente seleccionado a partir del grupo que consiste en halógeno, ciano, hidroxilo, alcoxilo (de 1 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono) sustituido por halógeno, amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono))-N-, y alquilo (de 1 a 6 átomos de carbono)-C(O)-NH-, o

(v) di-(alquilo (de 1 a 6 átomos de carbono))-amina;

20 R^3 es H;

R^4 es H o metilo;

W es NR^{22} , O, o S, en donde R^{22} es H, metilo, etilo, fenilo, bencilo, o fenetilo;

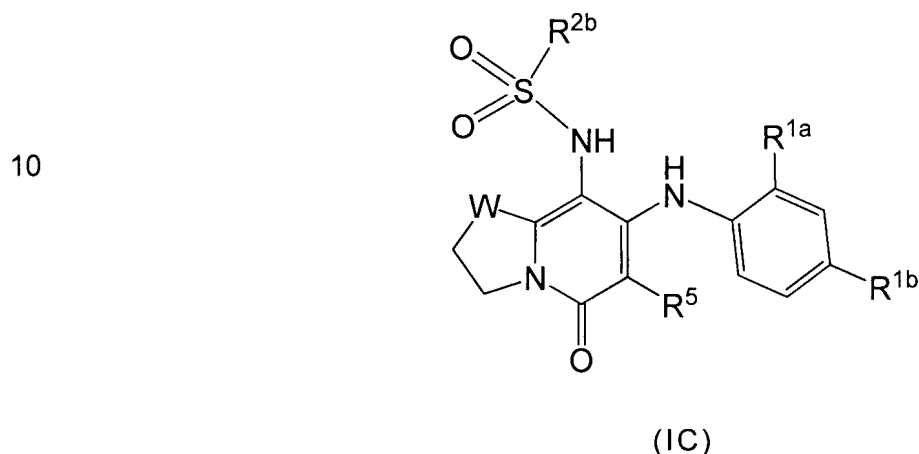
R^5 es H, halógeno, alquilo (de 1 a 3 átomos de carbono),
25 o alquilo (de 1 a 3 átomos de carbono) sustituido por halógeno;

o una sal farmacéuticamente aceptable del mismo.

De preferencia, R^{1a} y R^{1b} son cada uno independientemente halógeno.

5

En todavía otra modalidad, se proporciona un compuesto de la fórmula (IC):



15

en donde:

R^{1a} es F;

R^{1b} es Br o I;

R^{2b} es:

(i) cicloalquilo de 3 a 6 miembros, en donde este cicloalquilo
20 está opcionalmente sustituido con hidroxilo, o alquilo (de 1 a 6 átomos de carbono), en donde este alquilo (de 1 a 6 átomos de carbono) está opcionalmente sustituido con 1 a 3 grupos hidroxilo,

(ii) alquilo (de 1 a 6 átomos de carbono), en donde este alquilo (de 1 a 6 átomos de carbono) está opcionalmente sustituido
25 con oxetanilo o con 1 a 3 grupos hidroxilo, o

(iii) $-N(CH_3)_2$;

W es O, S o $N(R^{22})$, en donde R^{22} es H o bencilo; y

R^5 es H, F, Cl, CH_3 o CF_3 ;

5 o una sal farmacéuticamente aceptable del mismo.

En un aspecto de esta modalidad, W es O. En otro aspecto de esta modalidad, W es S. En todavía otro aspecto de esta modalidad, W es $N(R^{22})$, de preferencia R^{22} es H.

10 Los compuestos representativos adecuados en donde W es O incluyen:

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico;

15 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 2-hidroxi-metil-ciclopropan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-(2-hidroxi-etil)-ciclopropan-sulfónico;

20 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-(2,3-dihidroxi-propil)-ciclopropan-sulfónico;

25 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-hidroxi-metil-ciclopropan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-(3-hidroxi-propil)-ciclopropan-sulfónico;

5 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 3-hidroxi-ciclobutan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclobutan-sulfónico;

10 3-(1,3-dihidroxi-propan-2-il)-N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-ciclobutan-1-sulfonamida;

N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-1-(3-metil-oxetan-3-il)-metan-

15 sulfonamida;

N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-2-(oxetan-3-il)-etan-sulfonamida; y

N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-4-hidroxi-3-(hidroxi-metil)-butan-1-

20 sulfonamida;

o una sal farmacéuticamente aceptable de los mismos.

Los compuestos representativos adecuados, en donde W es S, incluyen:

25 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico;

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[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-(2,3-dihidroxi-propil)-ciclopropan-sulfónico;

5 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 2-hidroxi-metil-ciclopropan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-hidroxi-metil-ciclopropan-sulfónico;

10 N-[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-dimetil-amino-sulfonamida;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopentan-sulfónico;

15 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 3-hidroxi-ciclobutan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclobutan-sulfónico; y

20 [7-(2-fluoro-4-yodo-fenil-amino)-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico;

o una sal farmacéuticamente aceptable de los mismos.

Los compuestos representativos adecuados, en donde W es NH, incluyen:

25 [7-(4-bromo-2-fluoro-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido ciclopropan-

sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico;

5 [7-(4-bromo-2-fluoro-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido 1-(2,3-dihidroxi-propil)-ciclopropan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido 1-(2,3-dihidroxi-propil)-ciclopropan-sulfónico; y

10 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido 3-hidroxi-ciclobutan-sulfónico;

o una sal farmacéuticamente aceptable de los mismos.

15 **Definiciones**

Como se utiliza en la presente, el término "alquilo" se refiere a una fracción de hidrocarburo de la fórmula general: C_nH_{2n+1} . El grupo alcano puede ser recto o ramificado. Por ejemplo, el término "alquilo (de 1 a 6 átomos de carbono)" se refiere a un grupo alifático monovalente recto o ramificado que contiene de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, propilo normal, isopropilo, butilo normal, isobutilo, butilo secundario, butilo terciario, pentilo normal, 1-metil-butilo, 2-metil-butilo, 3-metil-butilo, neopentilo, 3,3-dimetil-propilo, hexilo, 2-metil-pentilo, y similares). De una manera similar,

20 la porción de alquilo (es decir, la fracción de alquilo) de un alcóxido,

25

alquil-amino, dialquil-amino, acilo (es decir, alquil-C(O)-), alquil-amido (es decir, alquil-C(O)-NH-, alquil-C(O)-N-(alquil)-(H)-), tioalquilo (es decir, alquil-S-), alquil-sulfinilo (es decir, alquil-S(O)-), alquil-sulfonilo (es decir, alquil-S(O)₂-), alquil-sulfanil-(alquil-NH-SO₂-), alquil-sulfonamido (alquil-SO₂-NH-), etc. tiene la misma definición que anteriormente. Cuando se indica como "opcionalmente sustituido", el radical de alcano o la fracción de alquilo puede estar insustituída o sustituida con uno o más sustituyentes (en términos generales, uno a tres sustituyentes, excepto en el caso de los sustituyentes de halógeno, tales como los percloro- o perfluoro-alquilos). "Alquilo sustituido por halógeno" se refiere a un grupo alquilo que tiene cuando menos una sustitución de halógeno.

El término "alquenilo" se refiere a una fracción de alquilo que contiene cuando menos una insaturación en el grupo alquilo. El grupo alquenilo puede ser recto o ramificado. Por ejemplo, vinilo, prop-1-enilo, prop-2-enilo, 2-metil-prop-2-enilo, 3-metil-but-2-enilo, y similares.

El término "alquileno" se refiere a una fracción de alquilo en donde la fracción contiene dos sitios de enlace. El grupo alquileno puede ser recto (por ejemplo, -(CH₂)-, -(CH₂)₂-, -(CH₂)₃-, o ramificado (por ejemplo, -CH(CH₃)-, -C(CH₃)₂-, -CH₂CH(CH₃)-, -CH(CH₃)-CH₂-, -C(CH₃)₂-CH₂-, etc.). Las fracciones de alquileno adecuadas son iguales a las descritas anteriormente para alquilo, excepto que con dos sitios de enlace en lugar de solamente uno.

El término "alquenileno" se refiere a una fracción de alquenilo

que contiene dos sitios de enlace. Por ejemplo, $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$. Las fracciones de alquenilo adecuadas son iguales a las descritas anteriormente para alquenilo, excepto que con dos sitios de enlace en lugar de solamente uno.

5 El término "arilo" se refiere a las fracciones aromáticas que tienen un solo anillo (por ejemplo, fenilo) o un sistema de anillos fusionados (por ejemplo, naftaleno, antraceno, fenantreno, etc.). Un grupo arilo típico es un anillo carbocíclico aromático de 6 a 14 miembros. Un sistema de anillos aromáticos fusionados también
10 puede incluir un fenilo fusionado con un cicloalquilo parcialmente o completamente saturado. Por ejemplo, 2,3-dihidro-indenilo, 1,2,3,4-tetrahidro-naftalenilo, 1,2-dihidro-naftalenilo, 2,3-dihidro-naftalenilo, 9,10-dihidro-antracenilo, fluorenilo, y similares. Un arilo preferido es fenilo.

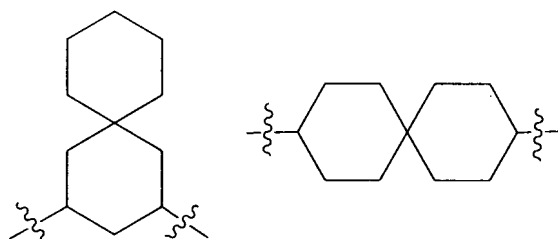
15 El término "arileno" se refiere a una fracción aromática carbocíclica que tiene dos sitios de enlace. Los arilenos adecuados incluyen los grupos descritos anteriormente para una fracción de arilo, excepto que con dos sitios de enlace en lugar de uno. Por ejemplo, 1,2-fenileno, 1,3-fenileno, 1,4-fenileno, 1,3-naftileno, 1,4-naftileno, 1,5-naftileno, 1,6-naftileno, 1,7-naftileno, 2,3-naftileno, 2,4-naftileno, 2,5-naftileno, 2,6-naftileno, 2,7-naftileno, 3,4-naftileno, 3,5-naftileno, 3,6-naftileno, 3,7-naftileno, etc. Los dos sitios de
20 enlace en el sistema de arileno fusionado pueden estar sobre el mismo anillo o en diferentes anillos. Un arileno preferido es fenileno.

25 El término "cicloalquilo" o "cicloalquilo parcialmente o

completamente saturado" se refiere a un anillo carbocíclico que está completamente hidrogenado (por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclo-octilo, etc.) o parcialmente hidrogenado (por ejemplo, ciclopropenilo, ciclobutenilo, ciclopentilo, 5 ciclopenta-1,3-dienilo, ciclohexenilo, ciclohexa-1,3-dienilo, ciclohexa-1,4-dienilo, etc.). A menos que se especifique de otra manera, el anillo carbocíclico puede ser un solo anillo (como se describe anteriormente), un anillo bicíclico (por ejemplo, octahidropentalenilo, biciclo-[1.1.1]-pentanilo, biciclo-[2.1.1]-hexanilo, biciclo-10 [2.1.1]-hex-2-enilo, biciclo-[2.2.1]-hept-2-enilo, biciclo-[2.2.1]-heptanilo, biciclo-[2.2.2]-octanilo, biciclo-[2.2.2]-oct-2-enilo, biciclo-[2.2.2]-octa-2,5-dienilo, etc.) o un anillo espiral (por ejemplo, espiro-[2.2]-pentanilo, etc.), y similares.

El término "cicloalquileno" o "cicloalquileno parcialmente o 15 completamente saturado" se refiere a un anillo carbocíclico que tiene a sea ninguna insaturación en el anillo (completamente hidrogenado) o bien cuando menos una insaturación (parcialmente hidrogenado) sin ser aromático, y contiene dos sitios de enlace. Los sistemas de anillos adecuados incluyen aquéllos descritos anteriormente para un 20 cicloalquilo parcialmente o completamente saturado, excepto que tiene dos sitios de enlace en lugar de uno. Por ejemplo, 1,2-ciclopropilo, 1,2-cicloprop-1-enilo, 1,2-ciclobutilo, 1,3-ciclobutilo, 1,2-ciclobut-1-enilo, 3,4-ciclobut-1-enilo, 3,5-ciclopent-1-enilo, 1,4-ciclopenta-1,3-dienilo, 1,5-ciclopenta-1,3-dienilo, 1,2-ciclopenta-1,3-25 dienilo, 1,3-ciclopenta-1,3-dienilo, etc. A menos que se especifique

de otra manera, el anillo carbocíclico puede ser un solo anillo, un anillo bicíclico, o un anillo espiral, en donde los dos sitios de enlace sobre el anillo bicíclico y el anillo espiral pueden estar en el mismo anillo o en diferentes anillos. Véase, por ejemplo, la siguiente ilustración.



Mismo anillo

Diferente anillo

El término "heterociclo" o "heterociclo parcialmente o completamente saturado" se refiere a un anillo no aromático que está ya sea parcialmente o bien completamente hidrogenado, y que puede existir como un solo anillo, un anillo bicíclico (incluyendo anillos fusionados), o un anillo espiral. A menos que se especifique de otra manera, el anillo heterocíclico es en general un anillo de 3 a 12 miembros que contiene de 1 a 3 heteroátomos (de preferencia 1 ó 2 heteroátomos) independientemente seleccionados a partir de azufre, oxígeno y/o nitrógeno. Los anillos heterocíclicos parcialmente saturados o completamente saturados incluyen grupos tales como epoxilo, aziridinilo, azetidinilo, tetrahidro-furanilo, dihidro-furanilo, dihidro-piridinilo, pirrolidinilo, imidazolidinilo, imidazolinilo, 1H-dihidro-imidazolilo, hexahidro-pirimidinilo, piperidinilo, piperazinilo, pirazolidinilo, 2H-piranilo, 4H-piranilo, 2H-cromenilo, oxazinilo,



morfolino, tiomorfolino, tetrahydro-tienilo, 1,1-dióxido de tetrahydro-tienilo, oxazolidinilo, tiazolidinilo, octahidro-pirroló-[3,2-b]-pirrolilo, y similares. Un anillo heterocíclico parcialmente saturado también incluye grupos en donde el anillo heterocíclico se fusiona con un
5 anillo de arilo o heteroarilo (por ejemplo, 2,3-dihidro-benzo-furanilo, indolinilo (o 2,3-dihidro-indolilo), 2,3-dihidro-benzo-tiofenilo, 2,3-dihidro-benzotiazolilo, 1,2,3,4-tetrahydro-quinolinilo, 1,2,3,4-tetrahydro-isoquinolinilo, 5,6,7,8-tetrahydro-pirido-[3,4-b]-pirazinilo, y similares). Los ejemplos de los anillos en espiral incluyen 2,6-
10 diazaespiro-[3.3]-heptanilo, 3-azaespiro-[5.5]-undecanilo, 3,9-diazaespiro-[5.5]-undecanilo, y similares.

El término "heteroarilo" se refiere a las fracciones aromáticas que contienen cuando menos un heteroátomo (por ejemplo, oxígeno, azufre, nitrógeno, o combinaciones de los mismos) dentro de un
15 sistema de anillo aromático de 5 a 10 miembros (por ejemplo, pirrolilo, piridilo, pirazolilo, indolilo, indazolilo, tienilo, furanilo, benzo-furanilo, oxazolilo, imidazolilo, tetrazolilo, triazinilo, pirimidilo, pirazinilo, tiazolilo, purinilo, bencimidazolilo, quinolinilo, isoquinolinilo, benzo-tiofenilo, benzoxazolilo, 1H-benzo-[d][1,2,3]-
20 triazolilo, y similares.). La fracción heteroaromática puede consistir en un solo anillo o en un sistema de anillos fusionados. Un solo anillo de heteroarilo típico es un anillo de 5 a 6 miembros que contiene de uno a tres heteroátomos independientemente seleccionados a partir de oxígeno, azufre y nitrógeno, y un sistema
25 de anillo de heteroarilo fusionado típico es un sistema de anillo de 9

a 10 miembros que contiene de uno a cuatro heteroátomos independientemente seleccionados a partir de oxígeno, azufre y nitrógeno. El sistema de anillo de heteroarilo fusionado puede consistir en dos anillos de heteroarilo fusionados entre sí, o un
5 heteroarilo fusionado con un arilo (en términos generales, fenilo).

El término "heteroarileno" se refiere a un heteroarilo que tiene dos sitios de enlace en lugar de uno. Los grupos heteroarileno adecuados incluyen aquéllos descritos anteriormente para heteroarilo, que tienen dos sitios de enlace en lugar de uno.

10 A menos que se especifique de otra manera, el término "compuestos de la presente invención" se refiere a los compuestos de las fórmulas (IA), (IB) o (IC), y las sales de los mismos, así como todos los estereoisómeros (incluyendo los diaestereoisómeros y los enantiómeros), los tautómeros, y los compuestos isotópicamente
15 marcados (incluyendo las sustituciones con deuterio), así como las fracciones inherentemente formadas (por ejemplo, polimorfos, solvatos, y/o hidratos).

DESCRIPCIÓN DETALLADA

La presente invención proporciona compuestos y
20 composiciones farmacéuticas de los mismos, que son útiles en el tratamiento de enfermedades, condiciones y/o trastornos modulados por la inhibición de la actividad de cinasa de MEK.

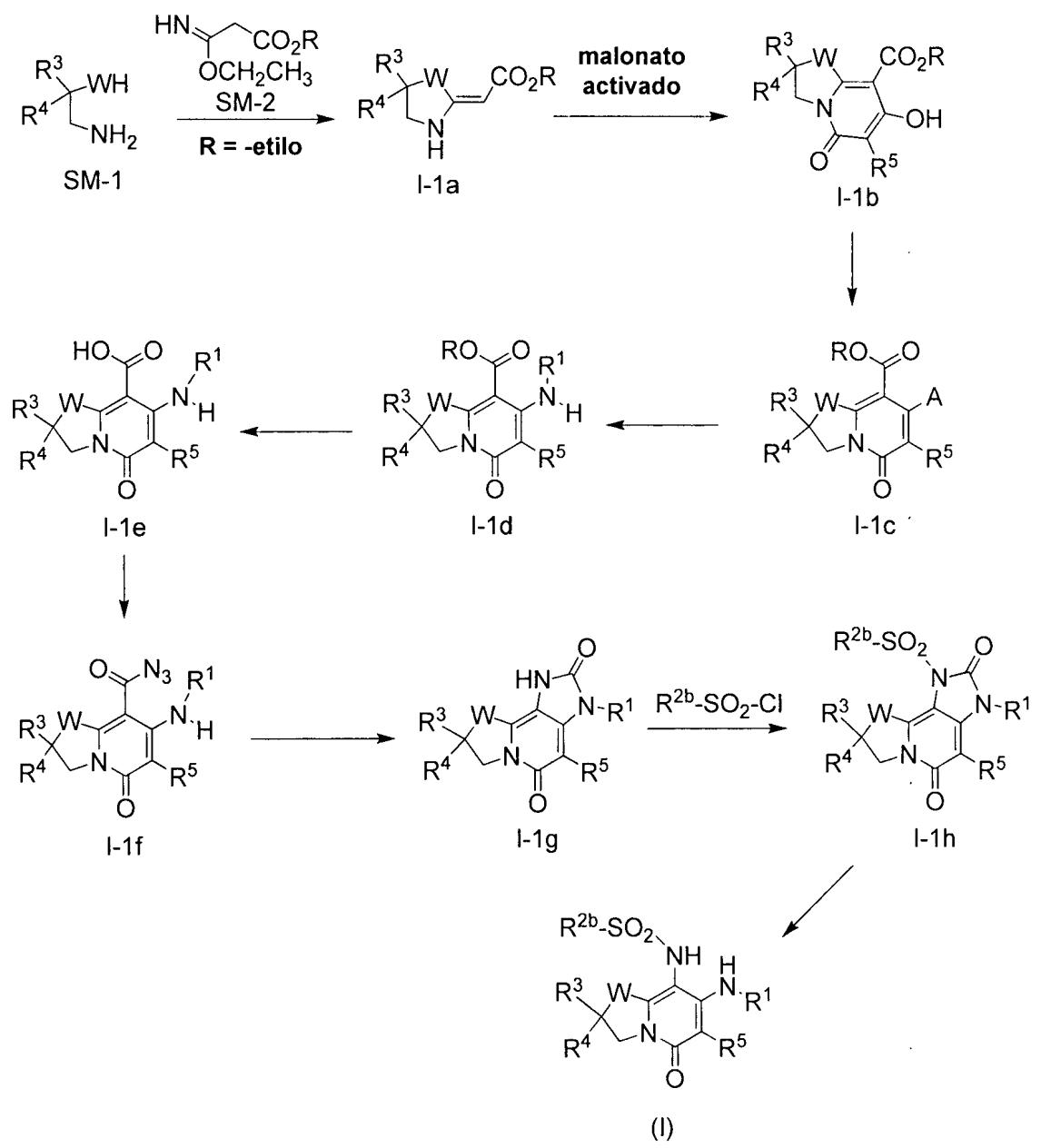
Los compuestos de la presente invención se pueden sintetizar mediante rutas sintéticas que incluyen procesos análogos a aquéllos
25 bien conocidos en la técnica química, en particular a la luz de la

descripción contenida en la presente. Los materiales de partida están generalmente disponibles en las fuentes comerciales, tales como Aldrich Chemicals (Milwaukee, Wis.), o se preparan fácilmente empleando los métodos bien conocidos por los expertos en este campo (por ejemplo, se preparan mediante los métodos generalmente descritos en Louis F. Fieser y Mary Fieser, *Reagents for Organic Synthesis*, Volúmenes 1-19, Wiley, Nueva York (1967-1999 ed.), o *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. ed. Springer-Verlag, Berlín, incluyendo los suplementos (también disponibles por medio de la base de datos en línea Beilstein)).

La invención proporciona, en otro aspecto, un proceso para la preparación de un compuesto de las fórmulas (IA), (IB), y (IC). Para propósitos ilustrativos, los esquemas de reacción ilustrados más adelante proporcionan las rutas potenciales para sintetizar los compuestos de la presente invención, así como los intermediarios clave. Para una descripción más detallada de los pasos de reacción individuales, véase la sección de Ejemplos. Los expertos en este campo apreciarán que se pueden emplear otras rutas sintéticas para sintetizar los compuestos de la invención. Aunque en los esquemas se ilustran los materiales de partida y reactivos específicos, y se discuten más adelante, se pueden sustituir fácilmente por otros materiales de partida y reactivos, para proporcionar una variedad de derivados y/o condiciones de reacción. En adición, muchos de los compuestos preparados mediante los métodos descritos más adelante, se pueden modificar adicionalmente a la luz de esta

divulgación empleando la química convencional bien conocida por los expertos en este campo.

El siguiente Esquema 1 ilustra la manera en que se podrían preparar los compuestos de la presente invención ((1A), (1B), y (1C), en donde R¹ representa el fenilo disustituido).



Esquema 1

El intermediario (I-1a) se puede preparar a partir de la amina deseada (SM-1) poniendo a reflujo con clorhidrato de etoxi-carbonil-etanimidato de etilo (SM-2, en donde R = etilo) en un solvente
5 prótico adecuado (por ejemplo, etanol). El intermediario resultante (I-1a) se puede convertir entonces hasta el intermediario (I-1b) poniendo a reflujo con un malonato activado (por ejemplo, bis-(2,4,6-tricloro-fenil)-éster de ácido malónico) en un solvente no prótico (por ejemplo, xileno). El grupo saliente A se introduce entonces en el
10 intermediario (I-1b) para formar el intermediario (I-1c) mediante el tratamiento del intermediario (I-1b) con un agente halogenante (por ejemplo, oxibromuro de fósforo) ya sea limpio o bien en un solvente no prótico adecuado (por ejemplo, tolueno) a temperaturas en el intervalo de aproximadamente la temperatura ambiente a
15 aproximadamente 140°C. De una manera alternativa, el intermediario (I-1b) se puede hacer reaccionar con fluoruro de nonafluoro-butan-sulfonilo, en la presencia de una base adecuada (por ejemplo, di-isopropil-etil-amina), y un catalizador (por ejemplo, N,N-dimetil-4-amino-piridina), en un solvente no prótico (por ejemplo, dicloro-
20 metano), a aproximadamente la temperatura ambiente, o con N-fenil-trifluoro-metan-sulfonimida en la presencia de una base adecuada (por ejemplo, di-isopropil-etil-amina), en un solvente adecuado (por ejemplo, 1,2-dimetoxi-etano), a temperaturas en el intervalo de aproximadamente la temperatura ambiente hasta la temperatura de
25 reflujo del solvente. De una manera alternativa, el intermediario (I-

1b) se puede tratar con anhídrido de ácido trifluoro-metan-sulfónico en la presencia de una base (por ejemplo, piridina), en un solvente no prótico (dicloro-metano), a temperaturas en el intervalo de aproximadamente -20°C hasta la temperatura ambiente.

5

El intermediario (I-1d) se puede preparar a partir del intermediario (I-1c) mediante la reacción con una anilina apropiada (R^{2b} -NH) utilizando condiciones de acoplamiento de C-N de Buchwald-Hartwig. Las reacciones de Buchwald-Hartwig se pueden

10 llevar a cabo en la presencia de un catalizador (por ejemplo, tris-(dibenciliden-acetona)-dipaladio (0) o acetato de paladio), una base (por ejemplo, fosfato de potasio, terbutóxido de sodio, 1.8-diazobiciclo-[5.4.1]-undec-7-eno, o carbonato de cesio), y un ligando

15 (por ejemplo, 9,9'-dimetil-4,5-bis-(difenil-fosfino)-xanteno, 2,2'-bis-(difenil-fosfino)-1-1'-binaftilo, 2-diciclohexil-fosfino-2'-(N,N-dimetil-amino)-bifenilo, 2-diciclohexil-fosfino-2',6'-(dimetoxi)-bifenilo o tri-butyl-fosfina), en un solvente adecuado (por ejemplo, tolueno, 1,2-dimetoxi-etano, tetrahidrofurano, o dioxano), a una temperatura en el

20 intervalo de aproximadamente la temperatura ambiente hasta la temperatura de reflujo del solvente, o bajo irradiación con microondas a una temperatura en el intervalo de aproximadamente 70°C a aproximadamente 150°C. El intermediario (I-1e) se puede preparar entonces a partir del intermediario (I-1d) mediante la

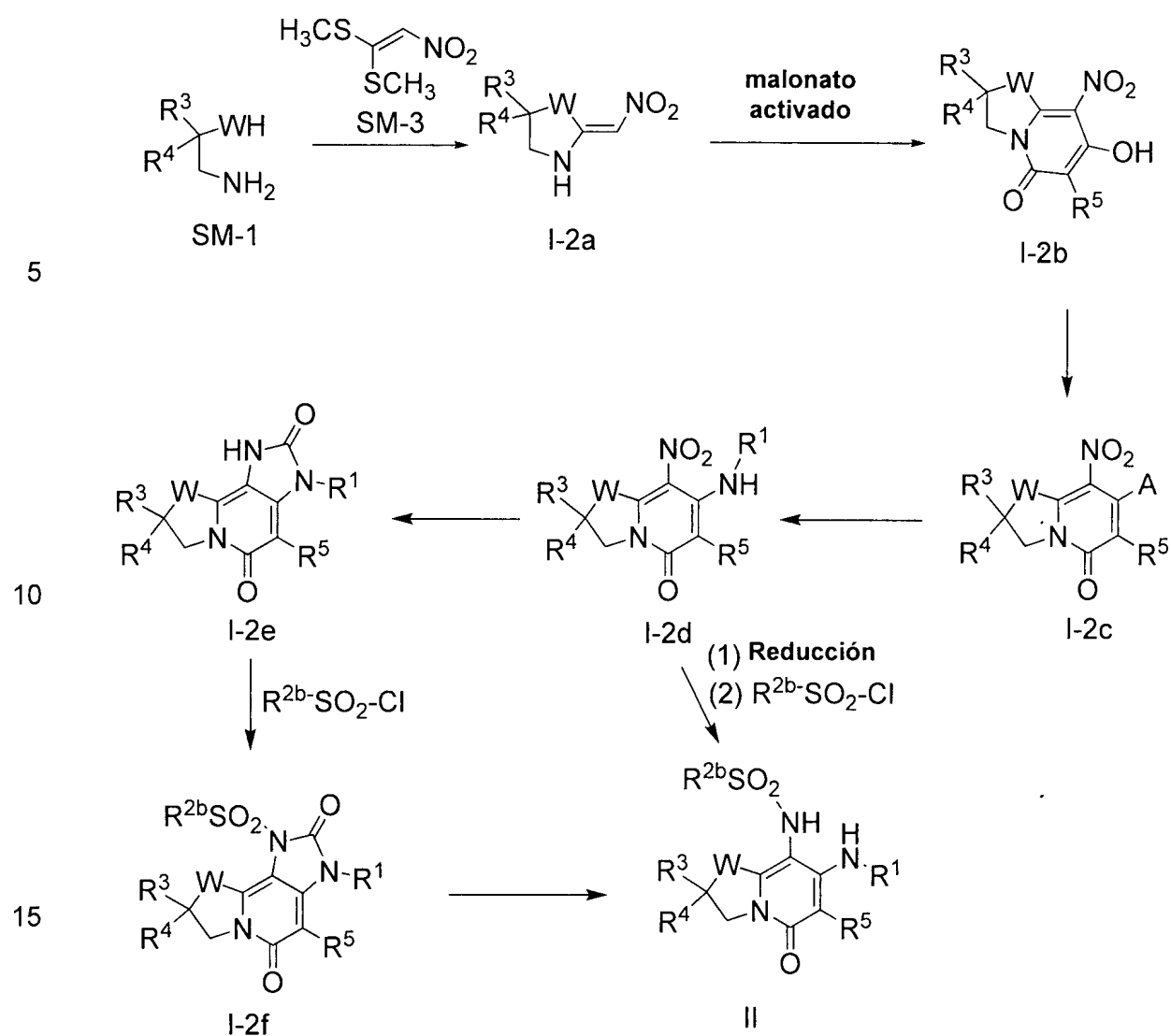
25 reacción con una base fuerte (por ejemplo, hidróxido de sodio) en un solvente prótico (por ejemplo, etanol o metanol), a una temperatura



en el intervalo de aproximadamente la temperatura ambiente hasta la temperatura de reflujo del solvente. El intermediario de acil-azida (I-1f) se puede preparar a partir del intermediario (I-1e) por medio del haluro de ácido (por ejemplo, el tratamiento con un cloruro de ácido
5 empleando condiciones convencionales), seguido por el tratamiento con azida de sodio o difenil-fosforil-azida (DPPA), en la presencia de una amina (por ejemplo, trietil-amina), en un solvente no prótico (por ejemplo, N,N-dimetil-formamida). El intermediario (I-1f) se puede transformar entonces por medio de la reconfiguración de Curtius,
10 para dar el intermediario (I-1g).

El grupo R^{2b} -sulfonilo se puede introducir en el intermediario (I-1g) para formar el intermediario (I-1h) mediante el tratamiento con el cloruro de sulfonilo deseado (R^{2b} -SO₂-Cl), en un solvente adecuado
15 (por ejemplo, dicloro-metano), en la presencia de una base (por ejemplo, trietil-amina, di-isopropil-etil-amina o piridina). El compuesto final (I) se prepara entonces hidrolizando el intermediario (I-1h). Por ejemplo, el intermediario (I-1h) se calienta en la presencia de una base fuerte (por ejemplo, hidróxido de sodio), en un solvente
20 prótico acuoso (por ejemplo, etanol/agua).

El siguiente Esquema 2 proporciona un procedimiento alternativo para la preparación de los compuestos de la presente invención ((1A), (1B), y (IC), en donde R^1 representa el fenilo
25 disustituido).



Esquema 2

El intermediario (I-2a) se puede preparar a partir de la amina deseada (SM-1) mediante el tratamiento con cantidades equimolares de 1,1-bis-(tioalquil)-2-nitro-etileno en un solvente polar (por ejemplo, metanol, etanol, acetonitrilo, tetrahidrofurano, agua, o mezclas de los mismos), a temperaturas hasta la temperatura de reflujo del solvente. Se puede utilizar un aceptor de protones (por ejemplo, NaOH, carbonato de sodio, o trietil-amina) en la reacción.

20

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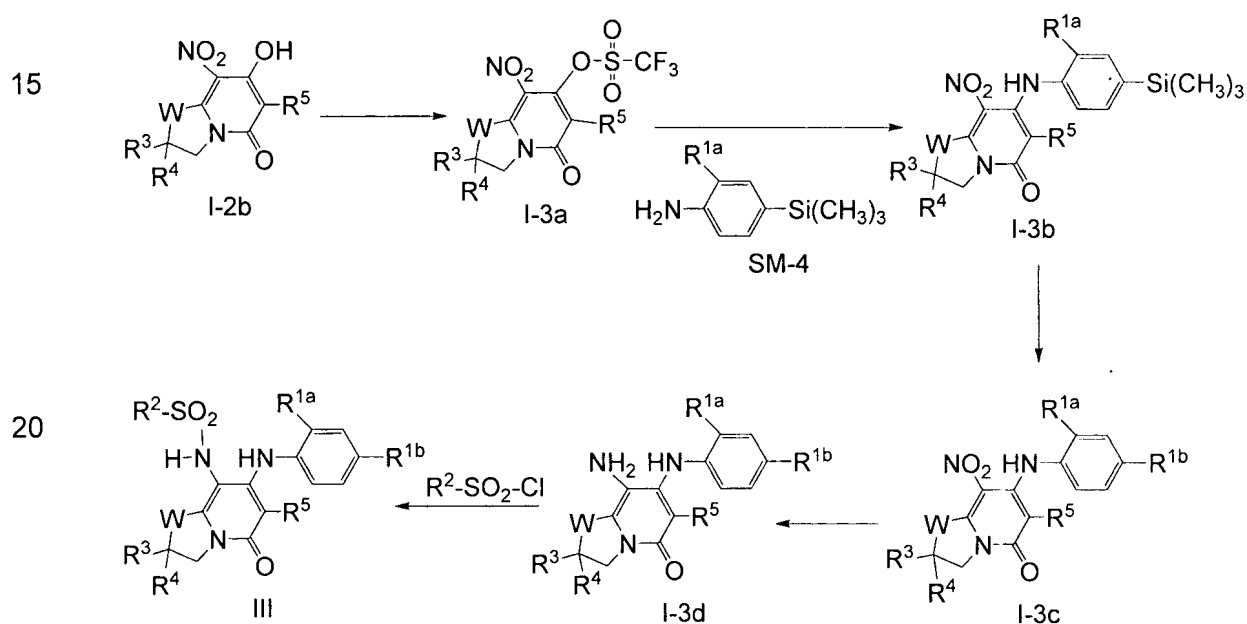
El intermediario (I-2b) se puede preparar entonces empleando condiciones análogas a aquéllas descritas en el esquema I anterior, para la preparación del intermediario (I-1b). De una manera similar, los intermediarios (I-2c), y (I-2d) se pueden preparar utilizando las condiciones descritas anteriormente en el esquema I para la preparación de intermediarios (I-1c) y (I-1d), respectivamente. Como una alternativa, el intermediario (I-2d) también se puede preparar a partir del intermediario (I-2c) empleando las condiciones de reducción convencionales. Por ejemplo, el tratamiento con Fe/NH₄Cl en un solvente (por ejemplo, tetrahidrofurano), seguido por la reacción con trifosgeno, en un solvente no prótico (por ejemplo, N,N-dimetil-formamida).

El intermediario (I-2d) se puede convertir directamente en un compuesto de la presente invención (II) empleando condiciones de reducción convencionales, bien conocidas por los expertos en este campo, seguido por el tratamiento con el cloruro de sulfonilo deseado (R^{2b}-SO₂-Cl), en un solvente adecuado (por ejemplo, dicloro-metano), en la presencia de una base (por ejemplo, trietil-amina, di-isopropil-etil-amina o piridina).

De una manera alternativa, el grupo nitro del intermediario (I-2d) se puede reducir primero hasta un grupo amino, seguido por el tratamiento con N,N'-carbonil-di-imidazol (CDI) o trifosgeno en la presencia de trietil-amina (TEA), para producir el intermediario de imidazolona (I-2e). El intermediario (I-2e) se puede hacer reaccionar entonces con el cloruro de sulfonilo deseado (R^{2b}-SO₂-Cl) en un

solvente adecuado (por ejemplo, piridina o N,N-dimetil-formamida), en la presencia de una base (por ejemplo, trietil-amina, di-isopropil-etil-amina o piridina), para producir el intermediario de sulfonamida (I-2f). Entonces se puede producir el producto final (II) empleando
 5 procedimientos análogos a aquéllos descritos anteriormente en el Esquema I. Por ejemplo, el intermediario (I-2f) se calienta en la presencia de una base fuerte (por ejemplo, hidróxido de sodio) en un solvente prótico acuoso (por ejemplo, etanol/agua).

El siguiente Esquema 3 ilustra la preparación de los
 10 compuestos de la fórmula (IA), en donde X es $-N(R^6)-$, en donde R^6 es H (referido en el Esquema 3 como (III)). Cuando R^3 y R^4 son ambos H, entonces el Esquema 3 también ilustra la manera en que se podrían preparar los compuestos de las fórmulas (IB) y (IC).



25 El grupo OH del intermediario (I-2b) se puede convertir hasta



un éster trifílico mediante la reacción con anhídrido trifílico, en la presencia de una base (por ejemplo, trietil-amina). El intermediario resultante (I-3a) se puede hacer reaccionar entonces con una aril-amina deseada (SM-4) empleando condiciones bien conocidas por los expertos en este campo (por ejemplo, condiciones de Buchwald-Hartwig), para formar el intermediario (I-3b). Las condiciones preferidas de las reacciones de Buchwald-Hartwig incluyen hacer reaccionar el intermediario (I-3a), y la amina deseada (SM-4), en la presencia de un catalizador (por ejemplo, $\text{Pd}(\text{OAc})_2$), una base (por ejemplo, carbonato de cesio), y un ligando (por ejemplo, 2,2'-bis-(difenil-fosfino)-1,1'-binaftilo (BINAP)), en la presencia de un solvente adecuado (por ejemplo, dioxano).

El grupo trimetil-sililo del intermediario (I-3b) es entonces reemplazado con el sustituyente deseado empleando los procedimientos bien conocidos por los expertos en este campo. Por ejemplo, el grupo trimetil-sililo puede ser sustituido por yoduro mediante la reacción del intermediario (I-3b) con monoclóruo de yodo y tetrafluoro-borato de plata en dicloro-metano seco, bajo una atmósfera inerte, a temperaturas reducidas (por ejemplo, a aproximadamente -50°C). El intermediario (I-3d) se puede preparar entonces a partir del intermediario (I-3c) reduciendo el grupo nitro, empleando los procedimientos bien conocidos por los expertos en este campo. Por ejemplo, el intermediario (I-3c) se puede tratar con un agente reductor (por ejemplo, ditionita de sodio o cloruro estanoso) en la presencia de un ácido (por ejemplo, ácido

clorhídrico). El compuesto final (III) se puede preparar entonces empleando procedimientos análogos a aquéllos descritos en los Esquemas 1 y 2. Por ejemplo, el intermediario (I-3d) se hace reaccionar con el cloruro de sulfonilo deseado ($R^2\text{-SO}_2\text{-Cl}$), en un
5 solvente adecuado (por ejemplo, piridina o N,N-dimetil-formamida), en la presencia de una base (por ejemplo, trietil-amina, di-isopropil-etil-amina o piridina).

Los compuestos e intermediarios descritos en los esquemas anteriores se pueden aislar por sí mismos, o como sus sales correspondientes. Por ejemplo, muchos de los compuestos
10 representados por las fórmulas (IA), (IB), y (IC) son capaces de formar sales de adición de ácido, en particular sales de adición de ácido farmacéuticamente aceptables. Las sales de adición de ácido farmacéuticamente aceptables del compuesto de las fórmulas (IA),
15 (IB), o (IC) incluyen aquéllas de los ácidos inorgánicos, por ejemplo, ácidos halohídricos, tales como ácido clorhídrico, ácido bromhídrico o ácido yodhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico; y de los ácidos orgánicos, por ejemplo, los ácidos monocarboxílicos alifáticos, tales como ácido fórmico, ácido acético, ácido propiónico y
20 ácido butírico, los hidroxí-ácidos alifáticos, tales como ácido láctico, ácido cítrico, ácido tartárico o ácido málico, los ácidos dicarboxílicos, tales como ácido maleico o ácido succínico, los ácidos carboxílicos aromáticos, tales como ácido benzoico, ácido p-cloro-benzoico, ácido difenil-acético o ácido trifenil-acético, los
25 hidroxí-ácidos aromáticos, tales como ácido o-hidroxí-benzoico,

ácido p-hidroxi-benzoico, ácido 1-hidroxi-naftalen-2-carboxílico ó
ácido 3-hidroxi-naftalen-2-carboxílico, y los ácidos sulfónicos, tales
como ácido metan-sulfónico o ácido bencen-sulfónico. Estas sales se
pueden preparar a partir de los compuestos de las fórmulas (IA),
5 (IB), o (IC) mediante los procedimientos de formación de sales
conocidos.

Los compuestos de las fórmulas (IA), (IB), o (IC) que contienen
grupos ácidos, por ejemplo carboxilo, también son capaces de formar
sales con bases, en particular bases farmacéuticamente aceptables,
10 tales como aquéllas bien conocidas en la materia; las sales
adecuadas incluyen las sales de metales, en particular las sales de
metales alcalinos o de metales alcalinotérreos, tales como las sales
de sodio, potasio, magnesio o calcio, o las sales con amoníaco o con
aminas orgánicas farmacéuticamente aceptables o bases
15 heterocíclicas, tales como etanolaminas, bencil-aminas o piridina.
Estas sales se pueden preparar a partir de los compuestos de las
fórmulas (IA), (IB), o (IC) mediante los procedimientos de formación
de sales conocidos.

Será reconocido por los expertos en la materia que los
20 compuestos de la presente invención pueden contener centros
quirales y, como tales, pueden existir en diferentes formas
isoméricas. Como se utiliza en la presente, el término "isómeros" se
refiere a diferentes compuestos que tienen la misma fórmula
molecular, pero que difieren en el arreglo y la configuración de los
25 átomos. También, como se utiliza en la presente, el término "un

isómero óptico" o "un estereoisómero", se refiere a cualquiera de las diferentes configuraciones estereoisoméricas que pueden existir para un compuesto dado de la presente invención, e incluye los isómeros geométricos. Se entiende que un sustituyente se puede unir en un
5 centro quiral de un átomo de carbono. Por consiguiente, la invención incluye los enantiómeros, diaestereómeros o racematos del compuesto.

"Enantiómeros" son un par de estereoisómeros que son imágenes de espejo uno del otro, que no se pueden superponer. Una
10 mezcla de 1:1 de un par de enantiómeros es una mezcla "racémica". El término se utiliza para designar una mezcla racémica donde sea apropiado.

"Diaestereoisómeros" son los estereoisómeros que tienen cuando menos dos átomos asimétricos, pero que no son imágenes de
15 espejo uno del otro. La estereoquímica absoluta se especifica de acuerdo con el sistema de Cahn-Ingold-Prelog R-S. Cuando un compuesto es un enantiómero puro, la estereoquímica en cada átomo de carbono quiral se puede especificar mediante cualquiera de *R* o *S*. Los compuestos resueltos cuya configuración absoluta se
20 desconozca, se pueden designar como (+) o (-), dependiendo de la dirección (dextrógira o levógira) en que roten la luz polarizada en el plano a la longitud de onda de la línea de sodio D. Algunos de los compuestos descritos en la presente contienen uno o más centros asimétricos o ejes, y, por consiguiente, pueden dar lugar a los
25 enantiómeros, diaestereómeros, y otras formas estereoisoméricas

que se puedan definir en términos de estereoquímica absoluta, como (R) o (S).

A menos que se especifique de otra manera, los compuestos de la presente invención pretenden incluir todos los posibles isómeros, incluyendo mezclas racémicas, formas ópticamente puras, y mezclas de intermediarios. Los isómeros (R) y (S) ópticamente activos se pueden preparar utilizando sintones quirales o reactivos quirales, o se pueden resolver empleando técnicas convencionales. Si el compuesto contiene un doble enlace, el sustituyente puede estar en la configuración E o Z. Si el compuesto contiene un dicioalquilo sustituido, el sustituyente de cicloalquilo puede tener una configuración *cis* o *trans*. También se pretende incluir todas las formas tautoméricas.

Los compuestos de la invención que contienen grupos capaces de actuar como donadores y/o aceptores para los enlaces de hidrógeno pueden ser capaces de formar co-cristales con formadores de co-cristales adecuados. Estos co-cristales se pueden preparar a partir de los compuestos de la presente invención mediante procedimientos de formación de co-cristales conocidos. Estos procedimientos incluyen molienda, calentamiento, co-sublimación, co-fusión, o contacto en solución de los compuestos de la presente invención con el formador de co-cristales bajo condiciones de cristalización, y el aislamiento de los co-cristales formados de esta manera. Los formadores de co-cristales adecuados incluyen aquéllos descritos en la Publicación Internacional Número WO 2004/078163.

Por consiguiente, la invención proporciona además co-cristales, los cuales comprenden un compuesto de la presente invención.

Los compuestos de la presente invención incluyen compuestos isotópicamente marcados en donde uno o más átomos son reemplazados por átomos que tienen el mismo número atómico, pero una masa atómica o número de masa diferente de la masa atómica o número de masa usualmente encontrado en la naturaleza.

Los ejemplos de los isótopos adecuados para incluirse en los compuestos de la invención comprenden los isótopos de hidrógeno, tales como ^2H y ^3H , de carbono, tales como ^{11}C , ^{13}C y ^{14}C , de cloro, tales como ^{36}Cl , de flúor, tales como ^{18}F , de yodo, tales como ^{123}I y ^{125}I , de nitrógeno, tales como ^{13}N y ^{15}N , de oxígeno, tales como ^{15}O , ^{17}O y ^{18}O , de fósforo, tales como ^{32}P , y de azufre, tales como ^{35}S .

La sustitución con isótopos más pesados, tales como deuterio, es decir, ^2H , puede proporcionar ciertas ventajas terapéuticas resultantes de la mayor estabilidad metabólica, por ejemplo, un aumento de la vida media *in vivo* o requerimientos de dosificación reducida, y, por consiguiente, se puede preferir en algunas circunstancias.

Los compuestos isotópicamente marcados de la presente invención se pueden preparar en términos generales mediante técnicas convencionales conocidas para los expertos en este campo o mediante procesos análogos a aquéllos descritos en las Secciones de ejemplos y preparaciones acompañantes, utilizando un reactivo isotópicamente marcado apropiado en lugar del reactivo no marcado



previamente empleado.

Los compuestos de la presente invención pueden existir en formas no solvatadas así como solvatadas con solventes farmacéuticamente aceptables, tales como agua, etanol, y similares, y se pretende que la invención abarque las formas tanto solvatadas como no solvatadas. Para los propósitos de la presente invención, los solvatos (incluyendo los hidratos) se consideran como composiciones farmacéuticas, por ejemplo, un compuesto de las fórmulas (IA), (IB), o (IC) (o una sal farmacéuticamente aceptable del mismo) en combinación con un excipiente, en donde el excipiente sea un solvente.

La presente invención también se refiere a una composición farmacéutica, la cual comprende un compuesto de la presente invención y excipientes farmacéuticamente aceptables.

Los excipientes adecuados incluyen en términos generales aglutinantes, anti-adherentes, desintegrantes, rellenos, diluyentes, saborizantes, colorantes, derrapantes, lubricantes, conservadores, absorbentes y edulcorantes o combinaciones de los mismos.

Una formulación típica se prepara mediante la mezcla de un compuesto de la presente invención y un vehículo, diluyente o excipiente. Los vehículos, diluyentes y excipientes adecuados son bien conocidos por los expertos en este campo, e incluyen materiales tales como carbohidratos, ceras, polímeros solubles en agua y/o hinchables por agua, materiales hidrofílicos o hidrofóbicos, gelatina, aceites, solventes, agua, y similares. El vehículo, diluyente o

excipiente particular utilizado dependerá de los medios y del propósito para el que se esté aplicando el compuesto de la presente invención. Los solventes se seleccionan en términos generales basándose en los solventes reconocidos por la persona experta en la materia como seguros (GRAS) para administrarse a un mamífero. En general, los solventes seguros son solventes acuosos no tóxicos, tales como agua y otros solventes no tóxicos que sean solubles o miscibles en agua. Los solventes acuosos adecuados incluyen agua, etanol, propilenglicol, polietilenglicoles (por ejemplo, PEG400, PEG300), etc., y mezclas de los mismos. Las formulaciones también pueden incluir uno o más reguladores del pH, agentes estabilizantes, tensoactivos, agentes humectantes, agentes lubricantes, emulsionantes, agentes de suspensión, conservadores, antioxidantes, agentes opacificantes, derrapantes, auxiliares de procesamiento, colorantes, edulcorantes, agentes perfumantes, agentes saborizantes, y otros aditivos conocidos para proporcionar una presentación elegante del fármaco (es decir, un compuesto de la presente invención o una composición farmacéutica del mismo), o para ayudar en la elaboración del producto farmacéutico (es decir, el medicamento).

Las formulaciones se pueden preparar empleando procedimientos convencionales de disolución y mezcla. Por ejemplo, la sustancia de fármaco a granel (es decir, el compuesto de la presente invención o la forma estabilizada del compuesto (por ejemplo, complejo con un derivado de ciclodextrina u otro agente de

formación de complejo conocido)) se disuelve en un solvente adecuado, en la presencia de uno o más de los excipientes. El compuesto de la presente invención típicamente se formula en formas de dosificación farmacéutica para proporcionar una dosificación fácilmente controlable del fármaco, y para dar al paciente un producto elegante y fácilmente manejable.

La composición se formula en general en diferentes formas de dosificación seleccionadas a partir de un grupo que comprende tabletas, trociscos, grageas, suspensiones acuosas u oleosas, ungüento, parche, gel, loción, dentífrico, cápsula, emulsión, cremas, aspersión, gotas, polvos o gránulos dispersables, emulsión en cápsulas de gel duras o blandas, jarabes y elixires.

La composición farmacéutica (o formulación) para su aplicación, se puede empacar en una variedad de formas dependiendo del método empleado para administrar el fármaco. En términos generales, un artículo para distribución incluye un recipiente que tiene depositado en el mismo la formulación farmacéutica en una forma apropiada. Los recipientes adecuados son bien conocidos por los expertos en este campo, e incluyen materiales tales como frascos (de plástico y de vidrio), bolsitas, ampollitas, bolsas de plástico, cilindros metálicos, y similares. El recipiente también puede incluir un ensamblaje a prueba de forzaduras para impedir el acceso indiscreto al contenido del paquete. En adición, el recipiente tiene depositado sobre el mismo una etiqueta que describe el contenido del recipiente. La etiqueta también puede incluir

advertencias apropiadas.

Los compuestos de la presente invención son útiles como tratamiento profiláctico al igual que como productos terapéuticos para las enfermedades o condiciones relacionadas con la
5 hiperactividad de MEK, así como para las enfermedades o condiciones moduladas por la senda de Raf/Ras/Mek.

Por consiguiente, como un aspecto adicional, la invención se refiere a un método para el tratamiento de una enfermedad o condición relacionada con la hiperactividad de MEK, o de una
10 enfermedad o condición modulada por la cascada de MEK, el cual comprende la administración de un cantidad terapéutica efectiva de un compuesto de las fórmulas (IA), (IB) o (IC), o de una sal farmacéuticamente aceptable del mismo.

Como un aspecto adicional, la invención se refiere a un método
15 para el tratamiento de las enfermedades proliferativas, tales como cáncer, el cual comprende la administración de una cantidad efectiva de un compuesto de la presente invención.

Los ejemplos de los cánceres incluyen, pero no se limitan a: angiosarcoma, fibrosarcoma, rabdomiosarcoma, liposarcoma,
20 mixoma, rabdomioma, fibroma, lipoma, teratoma; carcinoma broncogénico, carcinoma de células escamosas, carcinoma microcelular no diferenciado, carcinoma macrocelular no diferenciado, carcinoma alveolar (bronquiolar), adenoma bronquial, linfoma, hanlartoma condromatoso, inesotelioma, carcinoma
25 esofágico de células escamosas, leiomiosarcoma, adenocarcinoma



ductal, insulinoma, glucagonoma, gastrinoma, vipoma, tumores
carcinoides de estómago e intestino delgado, adenocarcinoma,
sarcoma de Kaposi, leiomioma, hemangioma, lipoma, neurofibroma,
fibroma, adenoma tubular, adenoma vellosa, hamartoma, tumor de
5 Wilm [nefroblastoma], leucemia, carcinoma de células escamosas de
vejiga y uretra, carcinoma de células de transición, adenocarcinoma,
seminoma, teratoma, carcinoma embrionario, teratocarcinoma,
coriocarcinoma, carcinoma de células intersticiales, fiamplicoma,
tumores adenomatoides, hepatoma (carcinoma hepatocelular),
10 colangiocarcinoma, hepatoblastoma, adenoma hepatocelular,
hemangioma, sarcoma osteogénico (osteosarcoma), histiocitoma
fibroso maligno, condrosarcoma, sarcoma de Ewing, linfoma maligno
(sarcoma de células de retículo), mieloma múltiple, cordoma tumoral
de células gigantes malignas, osteocronfoma (exostosis
15 osteocartilaginosas), condroma benigno, condroblastoma,
condromixofibroma, osteoma osteoide y tumores de células gigantes,
osteoma, granuloma, xantoma, osteítis deformante, meningioma,
meningiosarcoma, gliomatosis, astrocitoma, meduloblastoma, glioma,
ependimoma, germinoma [pinealoma], glioblastoma multiforme,
20 oligodendroglioma, schwannoma, retinoblastoma, tumores
congénitos, neurofibroma de médula espinal, meningioma, glioma,
cáncer endometrial, carcinoma cervical, displasia cervical pre-
tumoral, carcinoma de ovario, cistadenocarcinoma ceroso,
cistadenocarcinoma mucinoso, tumores de células tecales-
25 granulosa, tumores de células de Sertoli-Leydig, disgerminoma,

teratoma maligno, carcinoma intraepitelial, adenocarcinoma, melanoma, carcinoma vaginal de células claras, sarcoma botrioide (rabdomyosarcoma embrionario), carcinoma de trompas de Falopio, leucemia mieloide aguda y crónica, leucemia linfoblástica aguda, 5 leucemia linfocítica crónica, enfermedades mielo-proliferativas, mieloma múltiple, síndrome mielodisplásico, enfermedad de Hodgkin, linfoma no de Hodgkin, linfoma maligno, melanoma maligno, carcinoma de células basales, lunares, nevos displásicos, angioma, dermatofibroma, queloides, soriasis, y neuroblastoma.

10 Los compuestos de la presente invención también pueden ser útiles en el tratamiento de otras enfermedades o condiciones relacionadas con la hiperactividad de MEK. Por consiguiente, como un aspecto adicional, la invención se refiere a un método para el tratamiento de un trastorno seleccionado a partir de: rechazo de 15 xeno-injerto (trasplante de células, piel, extremidades, órganos o médula ósea); osteoartritis; artritis reumatoide; fibrosis quística; complicaciones de diabetes (incluyendo retinopatía diabética y nefropatía diabética); hepatomegalia; cardiomegalia; embolia (tal como embolia isquémica focal aguda e isquemia cerebral global); 20 insuficiencia cardíaca; choque séptico; asma; trastorno pulmonar obstructivo crónico; enfermedad de Alzheimer; y dolor crónico o neuropático.

El término "dolor crónico", para los propósitos de la presente invención, incluye, pero no se limita a, dolor idiopático, y dolor 25 asociado con alcoholismo crónico, deficiencia de vitaminas, uremia,

o hipotiroidismo. El dolor crónico está asociado con numerosas condiciones, incluyendo, pero no limitándose a, inflamación, y dolor post-operativo.

Como se utiliza en la presente, el término "dolor neuropático" está asociado con numerosas condiciones, las cuales incluyen, pero no se limitan a, inflamación, dolor post-operatorio, dolor de extremidad fantasma, dolor por quemadura, gota, neuralgia trigeminal, dolor herpético y post-herpético agudo, causalgia, neuropatía diabética, avulsión del plexo, neuroma, vasculitis, infección viral, lesión por aplastamiento, lesión por constricción, lesión del tejido, amputación de extremidad, y lesión de nervio entre el sistema nervioso periférico y el sistema nervioso central.

Los compuestos de la invención también pueden ser útiles como agentes antivirales para el tratamiento de infecciones virales, tales como VIH, virus de hepatitis B (HBV), virus de papiloma humano (HPV), citomegalovirus (CMV), y virus Epstein-Barr (EBV).

Los compuestos de la invención también pueden ser útiles en el tratamiento de restenosis, soriasis, dermatitis alérgica por contacto, enfermedad autoinmune, aterosclerosis y enfermedades inflamatoria del intestino, por ejemplo, enfermedad de Crohn y colitis ulcerativa.

En ciertas instancias, puede ser conveniente administrar el compuesto de la presente invención en combinación con cuando menos un agente farmacéutico (o terapéutico) adicional (por ejemplo, un agente contra el cáncer o la terapia auxiliar típicamente empleada

en la quimioterapia). El compuesto de la presente invención se puede administrar ya sea simultáneamente con, o antes o después de, uno o más agentes terapéuticos diferentes. De una manera alternativa, el compuesto de la presente invención se puede
5 administrar por separado, por la misma o diferente vía de administración, o juntos en la misma composición farmacéutica que los otros agentes.

Por ejemplo, un compuesto de la presente invención se puede administrar de una manera simultánea, en secuencia o por separado
10 en combinación con uno o más agentes seleccionados a partir de agentes de quimioterapia, por ejemplo, inhibidores mitóticos, tales como Docetaxel (vendido bajo el nombre comercial Taxotere® por Sanofi-Aventis), taxano, un alcaloide vinca, paclitaxel, vincristina, vinblastina, vinorelbina o vinflunina, y otros agentes contra el cáncer,
15 por ejemplo, cisplatina, 5-fluoro-uracilo o 5-fluoro-2-4(1H,3H)-pirimidinadiona (5FU), flutamida o gemcitabina.

Estas combinaciones pueden ofrecer ventajas significativas, incluyendo actividad sinérgica, en la terapia.

Un compuesto de la presente invención también se puede
20 utilizar con ventaja en combinación con otros compuestos anti-proliferativos. Estos compuestos anti-proliferativos incluyen, pero no se limitan a, inhibidores de aromatasa; anti-estrógenos; inhibidores de topoisomerasa I; inhibidores de topoisomerasa II; compuestos activos en microtúbulos; compuestos alquilantes; inhibidores de
25 desacetilasa de histona, tales como LBH589; compuestos que

inducen los procesos de diferenciación celular; inhibidores de ciclo-oxigenasa; inhibidores de MMP; inhibidores de mTOR, tales como RAD001; anti-metabolitos anti-neoplásicos; compuestos de platina; compuestos que dirigen/reducen una actividad de cinasa de proteína o de lípido y otros compuestos anti-angiogénicos; compuestos que dirigen, reducen, o inhiben la actividad de una fosfatasa de proteína o de lípido; agonistas de gonadorelina; anti-andrógenos; inhibidores de amino-peptidasa de metionina; bisfosfonatos; modificadores de la respuesta biológica; anticuerpos anti-proliferativos; inhibidores de heparanasa; inhibidores de las isoformas oncogénicas Ras; inhibidores de telomerasa; inhibidores de proteasoma; compuestos utilizados en el tratamiento de malignidades hematológicas; compuestos que dirigen, reducen, o inhiben la actividad de Flt-3, tales como PKC412; inhibidores de Hsp90, tales como 17-AAG (17-alil-amino-geldanamicina, NSC330507), 17-DMAG (17-dimetil-amino-etil-amino-17-desmetoxi-geldanamicina, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 de Conforma Therapeutics y AUY922; temozolomida (TEMODAL); inhibidores de proteína de huso de cinesina, tales como SB715992 o SB743921 de GlaxoSmithKline, o pentamidina/clorpromazina de CombinatoRx; inhibidores de PI3K, tales como BEZ235; inhibidores de RAF, tales como RAF265; aglutinantes de EDG, compuestos contra la leucemia, inhibidores de reductasa de ribonucleótido, inhibidores de descarboxilasa de S-adenosil-metionina, anticuerpos anti-proliferativos, u otros compuestos quimioterapéuticos. Además, de una manera alternativa

o en adición, se pueden utilizar en combinación con otros planteamientos de tratamiento de tumores, incluyendo cirugía, radiación ionizante, terapia fotodinámica, implantes, por ejemplo, con corticosteroides, hormonas, o se pueden utilizar como radio-sensibilizantes. También, en el tratamiento anti-inflamatorio y/o anti-proliferativo, se incluye la combinación con fármacos anti-inflamatorios. También es posible la combinación con sustancias de fármaco antihistamínicas, fármacos broncodilatadores, fármacos anti-inflamatorios no esteroideos (NSAID), o antagonistas de los receptores de quimiocina.

El término "inhibidor de aromatasa", como se utiliza en la presente, se refiere a un compuesto que inhibe la producción de estrógeno, es decir, la conversión de los sustratos androstenodiona y testosterona hasta estrona y estradiol, respectivamente. El término incluye, pero no se limita a, esteroides, en especial atamestano, exemestano y formestano y, en particular, no esteroides, en especial amino-glutetimida, rogletimida, pirido-glutetimida, trilostano, testolactona, quetoconazol, vorozol, fadrozol, anastrozol y letrozol. El exemestano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada AROMASIN. El formestano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada LENTARON. El fadrozol se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada AFEMA. El anastrozol se puede administrar, por

ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ARIMIDEX. El letrozol se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FEMARA o FEMAR. La amino-glutetimida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ORIMETEN. Una combinación de la invención que comprenda un agente quimioterapéutico que sea un inhibidor de aromatasa, es en particular útil para el tratamiento de los tumores positivos para el receptor de hormonas, por ejemplo, tumores de mama.

El término "anti-estrógeno", como se utiliza en la presente, se refiere a un compuesto que antagoniza el efecto de los estrógenos al nivel del receptor de estrógeno. El término incluye, pero no se limita a, tamoxifeno, fulvestrant, raloxifeno y clorhidrato de raloxifeno. El tamoxifeno se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada NÓLVADEX. El clorhidrato de raloxifeno se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada EVISTA. El fulvestrant se puede formular como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número 4,659,516 o se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FASLODEX. Una combinación de la invención que comprenda un agente quimioterapéutico que sea un anti-estrógeno es en particular útil para el tratamiento de los tumores

positivos para el receptor de estrógeno, por ejemplo, tumores de mama.

El término "anti-andrógeno", como se utiliza en la presente, se refiere a cualquier sustancia que sea capaz de inhibir los efectos biológicos de las hormonas androgénicas e incluye, pero no se limita a, nilutamida (vendida bajo los nombres comerciales Nilandron® y Anandron®, flutamida (vendida bajo el nombre comercial Fulexin^{MR}), bicalutamida (CASODEX), que se puede formular, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número 4,636,505.

El término "agonista de gonadorelina", como se utiliza en la presente, incluye, pero no se limita a, abarelix, goserelina y acetato de goserelina. La goserelina se da a conocer en la Patente de los Estados Unidos de Norteamérica Número US 4,100,274 y se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ZOLADEX. El abarelix se puede formular, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número US 5,843,901.

El término "inhibidor de topoisomerasa I", como se utiliza en la presente, incluye, pero no se limita a, topotecano, gimatecano, irinotecano, camptotecina y sus análogos, 9-nitro-camptotecina y el conjugado de camptotecina macromolecular PNU-166,148 (el compuesto A1 de la Publicación Internacional Número WO99/17804). El irinotecano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada

CAMPTOSAR. El topotecano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada HYCAMTIN.

El término "inhibidor de topoisomerasa II", como se utiliza en la presente, incluye, pero no se limita a, las antraciclinas, tales como doxorubicina (incluyendo la formulación liposomal, por ejemplo, CAELYX), daunorrubicina, epirubicina, idarrubicina y nemorrubicina, las antraquinonas mitoxantrona y losoxantrona, y las podofilotoxinas etoposida y teniposida. La etoposida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ETOPOPHOS. La teniposida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada VM 26-BRISTOL. La doxorubicina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ADRIBLASTIN o ADRIAMYCIN. La epirubicina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FARMORUBICIN. La idarrubicina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ZAVEDOS. La mitoxantrona se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada NOVANTRON.

El término "compuesto activo en microtúbulos" se refiere a los compuestos estabilizantes de microtúbulos y desestabilizantes de microtúbulos, y a los inhibidores de la polimerización de

microtubulina, incluyendo, pero no limitándose a, taxanos, por ejemplo, paclitaxel y docetaxel, alcaloides vinca, por ejemplo, vinblastina, en especial sulfato de vinblastina, vincristina, en especial sulfato de vincristina, y vinorelbina, discodermolidas, colquicina, y epotilonas y derivados de las mismas, por ejemplo, epotilona B o D o derivados de las mismas. El paclitaxel se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, TAXOL. El docetaxel se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada TAXOTERE. El sulfato de vinblastina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada VINBLASTIN R.P.. El sulfato de vincristina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FARMISTIN. La discodermolida se puede obtener, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número US 5,010,099. También se incluyen los derivados de epotilona que se dan a conocer en las Patentes Números WO 98/10121, US 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 y WO 00/31247. Se prefieren en especial Epotilona A y/o B.

El término "compuesto alquilante", como se utiliza en la presente, incluye, pero no se limita a, ciclofosfamida, ifosfamida, melfalano o nitrosourea (BCNU o Gliadel). La ciclofosfamida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada CICLOSTIN. La

ifosfamida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada HOLOXAN.

El término "inhibidores de desacetilasa de histona" o "inhibidores de HDAC" se refiere a los compuestos que inhiben la desacetilasa de histona, y que poseen una actividad anti-proliferativa. Esto incluye compuestos tales como butirato de sodio, LDH589 que se da a conocer en la Publicación Internacional Número WO 02/22577, en especial N-hidroxi-3-[4-[(2-hidroxi-etil)[2-(1H-indol-3-il)-etil]-amino]-metil]-fenil]-2E-2-propenamida, N-hidroxi-3-[4-[[[2-(2-metil-1H-indol-3-il)-etil]-amino]-metil]-fenil]-2E-2-propenamida y las sales farmacéuticamente aceptables del mismo, en especial la sal de lactato. Además incluye en especial el ácido hidroxámico de suberoil-anilida (SAHA), MS275, FK228 (anteriormente FR 901228), tricostatina A, y los compuestos que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número US 6,552,065, en particular la N-hidroxi-3-[4-[[[2-(2-metil-1H-indol-3-il)-etil]-amino]-metil]-fenil]-2E-2-propenamida, o una sal farmacéuticamente aceptable de la misma.

El término "anti-metabolito anti-neoplásico" incluye, pero no se limita a, 5-Fluoro-uracilo o 5-FU, capecitabina, gemcitabina, compuestos desmetilantes del ADN, tales como 5-azacitidina y decitabina, metotrexato y edatrexato, y antagonistas del ácido fólico, tales como pemetrexed. La capecitabina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca

comercial registrada XELODA. La gemcitabina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada GEMZAR.

El término "compuesto de platina", como se utiliza en la presente, incluye, pero no se limita a, carboplatina, cisplatina, cisplatino y oxaliplatina. La carboplatina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada CARBOPLAT. La oxaliplatina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ELOXATIN.

El término "compuestos que dirigen/reducen una actividad de cinasa de proteína o de lípido"; o una "actividad de fosfatasa de proteína o de lípido"; o "compuestos anti-angiogénicos adicionales", como se utiliza en la presente, incluye, pero no se limita a, los inhibidores de cinasa de proteína tirosina y/o de cinasa de serina y/o treonina, o inhibidores de cinasa de lípido, por ejemplo,

a) compuestos que dirigen, reducen, o inhiben la actividad de los receptores del factor de crecimiento derivado de plaquetas (PDGFR), tales como los compuestos que dirigen, reducen, o inhiben la actividad de PDGFR, en especial los compuestos que inhiben al receptor del factor de crecimiento derivado de plaquetas, por ejemplo, un derivado de N-fenil-2-pirimidin-amina, por ejemplo, imatinib, SU101, SU6668 y GFB-111;

b) compuestos que dirigen, reducen, o inhiben la actividad de los receptores del factor de crecimiento de fibroblastos (FGFR);

c) compuestos que dirigen, reducen, o inhiben la actividad del receptor del factor de crecimiento tipo insulina I (IGF-IR), tales como los compuestos que dirigen, reducen, o inhiben la actividad de IGF-IR, en especial los compuestos que inhiben la actividad de cinasa del receptor de IGF-I, tales como los compuestos que se dan a conocer en la Publicación Internacional Número WO 02/092599, o anticuerpos que se dirigen al dominio extracelular del receptor de IGF-I o sus factores de crecimiento;

d) compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasa de tirosina receptora Trk, o inhibidores de efrina B4;

e) compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasa de tirosina receptora Axl;

f) compuestos que dirigen, reducen, o inhiben la actividad de la cinasa de tirosina receptora Ret;

g) compuestos que dirigen, reducen, o inhiben la actividad de la cinasa de tirosina receptora Kit/SCFR, es decir, las cinasas de tirosina receptoras C-kit - (parte de la familia de PDGFR), tales como los compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasa de tirosina receptora c-Kit, en especial los compuestos que inhiben al receptor c-Kit, por ejemplo, imatinib;

h) compuestos que dirigen, reducen, o inhiben la actividad de los miembros de la familia c-Abl, sus productos de fusión genética (por ejemplo, cinasa BCR-Abl) y mutantes, tales como los compuestos dirigen, reducen, o inhiben la actividad de los miembros

de la familia c-Abl y sus productos de fusión genética, por ejemplo, un derivado de N-fenil-2-pirimidin-amina, por ejemplo, imatinib o nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 a partir de ParkeDavis; o dasatinib (BMS-354825);

5 i) compuestos que dirigen, reducen, o inhiben la actividad de los miembros de la familia de cinasas de serina/treonina de la cinasa C de proteína (PKC) y Raf, los miembros de la familia MEK, SRC, JAK, FAK, PDK1, PKB/Akt, y Ras/MAPK, y/o los miembros de la familia de cinasa dependiente de ciclina (CDK), y son en especial
10 los derivados de estaurosporina que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número US 5,093,330, por ejemplo, midostaurina; los ejemplos de compuestos adicionales incluyen, por ejemplo, UCN-01, safingol, BAY 43-9006, Briostatina 1, Perifosina; Ilmofosina; RO 318220 y RO 320432; GO 6976; Isis 3521;
15 LY333531/LY379196; compuestos de isoquinolina, tales como aquéllos que se dan a conocer en la Publicación Internacional Número WO 00/09495; FTIs; BEZ235 (un inhibidor de PI3K) o AT7519 (un inhibidor de CDK);

 j) compuestos que dirigen, reducen, o inhiben la actividad
20 de los inhibidores de cinasa de proteína tirosina, tales como los compuestos que dirigen, reducen, o inhiben la actividad de los inhibidores de cinasa de proteína tirosina, incluyendo mesilato de Imatinib (GLEEVEC) o tirfostina. Una tirfostina es de preferencia un compuesto de bajo peso molecular (peso molecular < 1500), o una
25 sal farmacéuticamente aceptable del mismo, en especial un

compuesto seleccionado a partir de la clase de benciliden-malonitrilo, o de la clase de compuestos de S-aril-bencen-malonitrilo o de quinolina de bisustrato, más especialmente cualquier compuesto seleccionado a partir del grupo que consiste en Tirfostina A23/RG-50810; AG 99; Tirfostina AG 213; Tirfostina AG 1748; Tirfostina AG 490; Tirfostina B44; enantiómero de Tirfostina B44 (+); Tirfostina AG 555; AG 494; Tirfostina AG 556, AG957, y adafostina (adamantil-éster del ácido 4-[(2,5-dihidroxifenil)metil]amino}benzoico; NSC 680410, adafostina);

- 10 k) compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasas de tirosina receptoras del factor de crecimiento epidérmico (EGFR, ErbB2, ErbB3, ErbB4 como homo- o hetero-dímeros) y sus mutantes, tales como los compuestos que dirigen, reducen, o inhiben la actividad de la familia de receptores
- 15 del factor de crecimiento epidérmico, que son en especial los compuestos, proteínas o anticuerpos que inhiben a los miembros de la familia de cinasa de tirosina receptora del factor de crecimiento epidérmico, por ejemplo, el receptor de EGF, ErbB2, ErbB3 y ErbB4, o que se enlazan con el factor de crecimiento epidérmico o con los
- 20 ligandos relacionados con el factor de crecimiento epidérmico, y son en particular los compuestos, proteínas, o anticuerpos monoclonales genérica y específicamente dados a conocer en la Publicación Internacional Número WO 97/02266, por ejemplo, el compuesto del Ejemplo 39, o en las Patentes Números EP 0 564 409, WO 99/03854,
- 25 EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US

5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 y, en especial, WO 96/30347 (por ejemplo, el compuesto conocido como CP 358774), WO 96/33980 (por ejemplo, el compuesto ZD 1839) y WO 95/03283 (por ejemplo, el compuesto ZM105180); por
5 ejemplo, trastuzumab (Herceptin^{MR}), cetuximab (Erbix^{MR}), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 o E7.6.3, y derivados de 7H-pirrólo-[2,3-d]-pirimidina, los cuales se dan a conocer en la Publicación Internacional Número WO 03/013541; y

10 I) compuestos que dirigen, reducen, o inhiben la actividad del receptor c-Met, tales como compuestos que dirigen, reducen, o inhiben la actividad de c-Met, en especial compuestos que inhiben la actividad de cinasa del receptor c-Met, o anticuerpos que se dirigen al dominio extracelular de c-Met o que se enlazan con HGF;

15 Otros compuestos anti-angiogénicos incluyen los compuestos que tienen otro mecanismo para su actividad, por ejemplo, no relacionados con la inhibición de cinasa de proteína o de lípido, por ejemplo, talidomida (THALOMID) y TNP-470.

20 Los compuestos que dirigen, reducen, o inhiben la actividad de una fosfatasa de proteína o de lípido son, por ejemplo, los inhibidores de fosfatasa 1, fosfatasa 2A, o CDC25, por ejemplo, ácido ocadaico o un derivado del mismo.

 Los compuestos que inducen los procesos de diferenciación celular son, por ejemplo, ácido retinoico, tocoferol o tocotrienol.

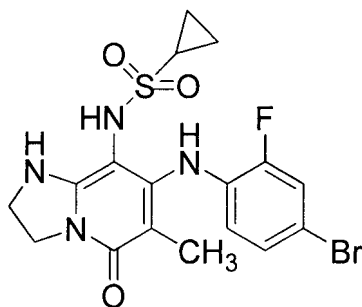
25 El término "inhibidor de ciclo-oxigenasa", como se utiliza en la

etilo al 100 por ciento). La mezcla de reacción se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se concentró para proporcionar el producto crudo. La purificación mediante cromatografía en columna sobre gel de sílice (acetato de etilo al 80 por ciento en hexano), seguida por HPLC de preparación, proporcionó 30 miligramos del producto (6 por ciento de rendimiento).

^1H RMN (DMSO-D_6 , 300 MHz) δ : 8.4-8.35 (br s, 1H), 7.5 (dd, 1H), 7.4-7.25 (m, 5H), 7.2 (d, 1H), 6.5 (t, 1H), 5.0 (d, 1H), 4.8 (d, 1H), 4.1-4.0 (m, 1H), 3.9 (d, 1H), 3.6-3.5 (m, 1H), 2.3 (d, 1H), 1.6 (s, 3H), 1.3 (s, 1H), 0.9-0.7 (m, 4H), 0.5-0.4 (m, 1H). LCMS: 98.98 por ciento, $m/z = 547(\text{M}+1)$ HPLC: 97.95 por ciento.

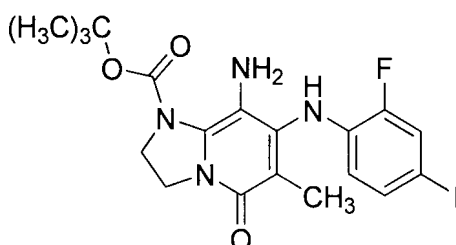
Ejemplo 2

Síntesis de [7-(4-bromo-2-fluoro-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico (2A):



(2A)

Se agregó tribromuro de boro (20 miligramos, 0.0001 moles) a una solución agitada de [1-bencil-7-(4-bromo-2-fluoro-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del

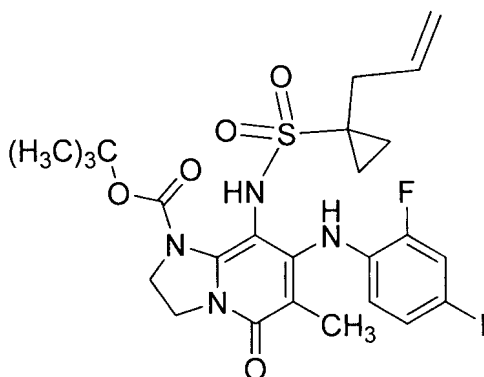


5 Se agregó zinc (296 miligramos, 0.005 moles) a una solución agitada del terbutil-éster del ácido 7-(2-fluoro-4-yodo-fenil-amino)-6-metil-8-nitro-5-oxo-2,3-dihidro-5H-imidazo-[1,2-a]piridin-1-carboxílico (400 miligramos, 0.0008 moles), y NH_4Cl (322 miligramos, 0.006 moles) en agua y tetrahidrofurano (15 mililitros). La mezcla

10 resultante se agitó a temperatura ambiente durante 30 minutos. La reacción se monitoreó mediante TLC (acetato de etilo al 100 por ciento). La mezcla de reacción se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se lavó con una solución saturada de NaHCO_3 y se concentró, para proporcionar 350

15 miligramos del producto crudo, el cual se utilizó en el siguiente paso sin mayor purificación.

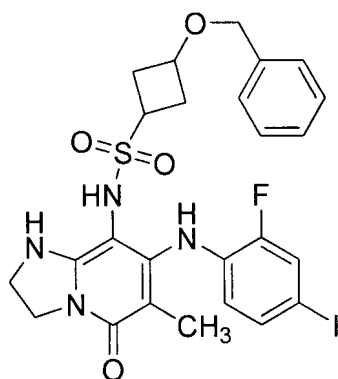
Síntesis del intermediario de terbutil-éster del ácido 8-(1-allyl-ciclopropan-sulfonil-amino)-7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-imidazo-[1,2-a]piridin-1-carboxílico (I-5d):



Empleando las mismas condiciones de reacción y de procesamiento como se describen para la preparación del intermediario (I-5d), el terbutil-éster del ácido 8-amino-7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-imidazo-[1,2-a]-piridin-1-carboxílico (I-5c: 350 miligramos, 0.7 milimoles) en piridina (3 mililitros) se hizo reaccionar con cloruro de 3-benciloxi-ciclobutan-sulfonilo (273 miligramos, 1.05 milimoles), para proporcionar el producto crudo. La purificación mediante cromatografía en columna sobre gel de sílice (acetato de etilo al 80 por ciento en hexano) proporcionó 250 miligramos del producto (45.3 por ciento de rendimiento).

^1H RMN (400 MHz, DMSO- D_6): δ 7.68-7.64 (br s, 1H), 7.58 (d, 1H), 7.50 (s, 1H), 7.40-7.24 (m, 6H), 6.35 (t, 1H), 4.32 (s, 2H), 4.30-4.00 (m, 4H), 3.80 (t, 1H), 3.51-3.40 (m, 1H), 2.30-2.20 (br s, 2H), 2.10-1.90 (m, 2H), 1.70 (s, 3H), 1.50 (s, 9H).

Síntesis del intermediario de [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido 3-benciloxi-ciclobutan-sulfónico (I-6b):

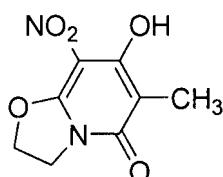


Se agregó clorhidrato de dioxano (3 mililitros) al terbutil-éster

mililitros de agua, y el producto resultante se filtró. El filtrado se concentró adicionalmente, y esto fue seguido por la adición de acetona. La mezcla de reacción se puso a reflujo durante 1 hora, se enfrió a temperatura ambiente, y se filtró. La capa de acetona se concentró para proporcionar 4.1 gramos del producto crudo, el cual se utilizó en el siguiente paso sin mayor purificación.

^1H RMN (300 MHz, DMSO- D_6): δ 9.9 (s, 1H), 6.6 (s, 1H), 4.6 (t, 2H), 3.7 (t, 2H).

Síntesis del intermediario de 7-hidroxi-6-metil-8-nitro-2,3-dihidro-oxazolo-[3,2-a]-piridin-5-ona (I-7b):



La 2-nitro-metilen-oxazolidina (3 gramos, 23.0 milimoles) se agregó en porciones a una solución agitada del bis-(2,4,6-tricloro-fenil)-éster del ácido 2-metil-malónico (12 gramos, 25.15 milimoles) en Xileno (50 mililitros), bajo una atmósfera de nitrógeno, durante un período de 1 hora a 125°C. La mezcla resultante se calentó a 125°C durante 5 horas. La mezcla de reacción se monitoreó mediante TLC (acetato de etilo al 50 por ciento en hexano). La mezcla de reacción se concentró, y el concentrado se purificó mediante cromatografía en columna sobre gel de sílice (acetato de etilo al 60 por ciento en hexano), para proporcionar 1.5 gramos del producto (30 por ciento de rendimiento).

^1H RMN (300 MHz, DMSO- D_6): δ 11.1 (s, 1H), 5.0 (t, 2H), 4.2

120

(0.24 gramos, 1.06 milimoles) a la 7-(2-fluoro-4-yodo-fenil-amino)-6-metil-8-nitro-2,3-dihidro-oxazolo-[3,2-a]-piridin-5-ona (0.15 gramos, 0.347 milimoles) en etanol (5 mililitros). La mezcla resultante se calentó a reflujo durante 2 horas. La reacción se monitoreó mediante
5 TLC (acetato de etilo al 100 por ciento). La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con acetato de etilo, se basificó con una solución saturada de bicarbonato, y se filtró a través de Celite. La capa orgánica se lavó con una solución de salmuera, se secó sobre Na_2SO_4 y se concentró, para proporcionar
10 0.08 gramos del producto crudo, el cual se utilizó en el siguiente paso sin mayor purificación.

Síntesis del compuesto del título: [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico (7A):

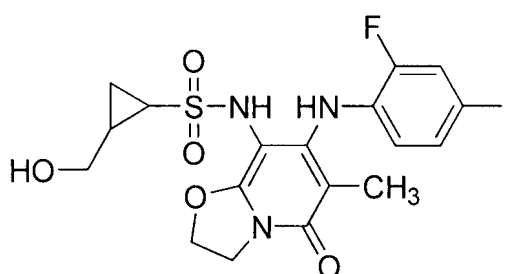
15 Se agregó cloruro de ciclopropan-sulfonilo (50 miligramos, 0.35 milimoles) a una solución de la 8-amino-7-(2-fluoro-4-yodo-fenil-amino)-6-metil-2,3-dihidro-oxazolo-[3,2-a]-piridin-5-ona (1-7f: 80 miligramos, 0.199 milimoles) en piridina seca (1 mililitro) a 0°C. La mezcla resultante se agitó a temperatura ambiente durante 1 hora.
20 La reacción se monitoreó mediante TLC (acetato de etilo al 100 por ciento). La mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica se lavó con agua, una solución de salmuera, se secó sobre Na_2SO_4 y se concentró. La purificación mediante cromatografía en columna sobre gel de sílice (metanol al 1.5 por
25 ciento en dicloro-metano) proporcionó 3 miligramos del producto (3

por ciento de rendimiento).

^1H RMN (300 MHz, CDCl_3): δ 7.3-7.4 (m, 1H), 6.85 (s, 1H), 6.35 (t, 1H), 5.7 (s, 1H), 4.8 (t, 2H), 4.35 (t, 2H), 1.75 (s, 3H), 0.9-1.1 (m, 4H).

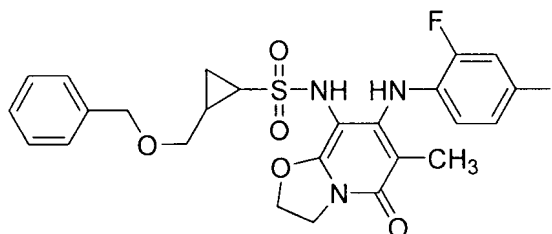
5 **Ejemplo 8**

Síntesis de [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 2-hidroxi-metil-ciclopropan-sulfónico (8A):



(8A)

15 Síntesis del intermediario de [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 2-benciloxi-metil-ciclopropan-sulfónico (I-8a):



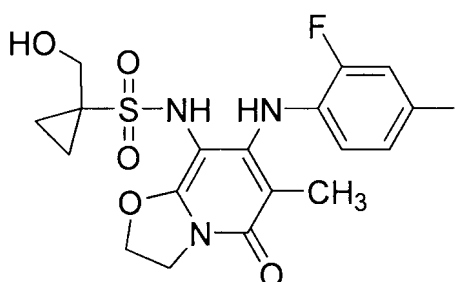
20 Empleado las mismas condiciones de reacción y de procesamiento como se describen para la preparación del Ejemplo 7A, la 8-amino-7-(2-fluoro-4-yodo-fenil-amino)-6-metil-2,3-dihidro-oxazolo-[3,2-a]-piridin-5-ona (I-7f: 0.08 gramos, 0.0002 moles) en

ciento de rendimiento).

^1H RMN (300 MHz, CDCl_3): δ 7.4-7.25 (m, 3H), 6.9 (s, 1H), 6.32 (t, 1H), 5.3 (s, 1H), 4.8 (t, 2H), 4.35 (t, 2H), 4.1-3.9 (m, 1H), 3.6-3.4 (m, 3H), 2.25-2.30 (m, 1H), 1.75 (s, 3H), 0.8-0.7 (m, 5H). LCMS: 97.5 por ciento, m/z = 580.1 (M+1) HPLC: 97.67 por ciento.

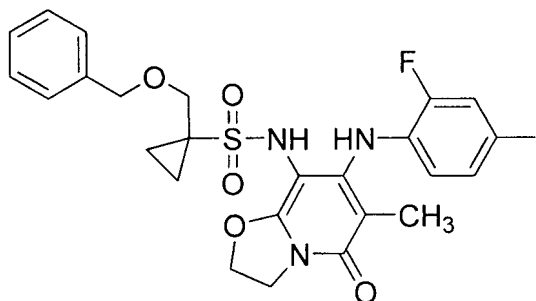
Ejemplo 11

Síntesis de [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]piridin-8-il]-amida del ácido 1-hidroxi-metil-ciclopropan-sulfónico (11A):

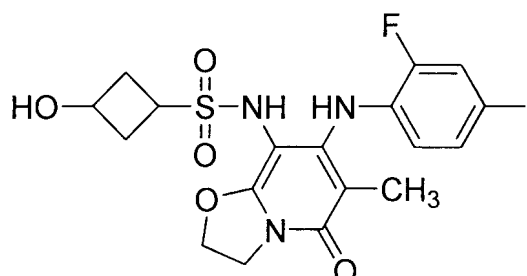


(11A)

Síntesis del intermediario de [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]piridin-8-il]-amida del ácido 1-benciloxi-metil-ciclopropan-sulfónico (I-11a):

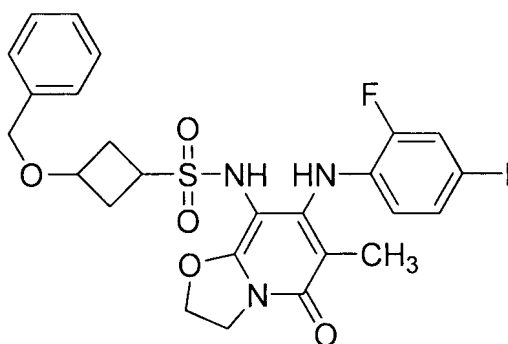


Empleando las mismas condiciones de reacción y de procesamiento como se describen para la preparación del Ejemplo

ciclobutan-sulfónico (13A):

(13A)

Síntesis del intermediario de 3-benciloxi-[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclobutan-sulfónico (I-13a):



Empleando las mismas condiciones de reacción y de procesamiento como se describen para la preparación del Ejemplo 7A, la 8-amino-7-(2-fluoro-4-yodo-fenil-amino)-6-metil-2,3-dihidro-oxazolo-[3,2-a]-piridin-5-ona (I-7f: 0.53 gramos, 1.0 milimoles) en piridina (4 mililitros) se hizo reaccionar con cloruro de 3-benciloxi-ciclobutan-sulfonilo (0.179 miligramos, 1.2 milimoles), para proporcionar el producto crudo. La purificación mediante cromatografía en columna sobre gel de sílice (metanol al 2 por ciento en dicloro-metano) proporcionó 195 miligramos del producto (23.8 por ciento de rendimiento).

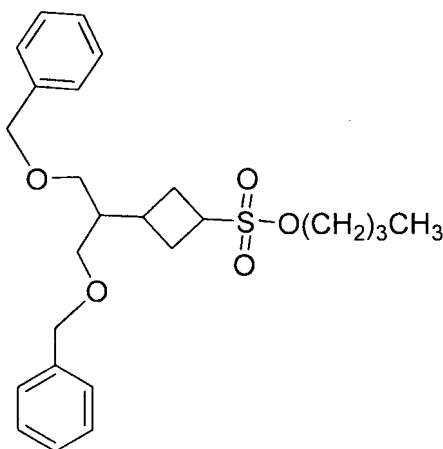
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(0.2 gramos, 0.575 milimoles) en tetrahidrofurano (5 mililitros), y la masa de reacción resultante se agitó a temperatura ambiente durante la noche. La reacción se monitoreó mediante TLC (acetato de etilo al 100 por ciento). La mezcla de reacción se apagó con HCl 1N y se extrajo utilizando acetato de etilo. La capa orgánica se lavó con una solución de salmuera, se secó sobre Na₂SO₄ anhidro, y se concentró. La purificación mediante cromatografía en columna sobre gel de sílice (acetato de etilo al 70 por ciento en hexano) proporcionó 0.13 gramos del producto (74 por ciento de rendimiento).

¹H RMN (CDCl₃, 300 MHz): δ 4.2 (t, 2H), 3.9-3.6 (m, 4H), 2.5-2.4 (m, 2H), 2.4-2.3 (m, 2H), 2.1-1.9 (m, 3H), 1.7-1.6 (m, 2H), 1.5-1.4 (q, 2H), 1.0-0.9 (t, 3H).

LCMS: 99 por ciento, m/z = 266 (M+1).

Síntesis de 3-(1,3-bis-(benciloxi)-propan-2-il)-ciclobutan-1-sulfonato de butilo (I-15d):



Empleando las mismas condiciones de reacción, de procedimiento y procesamiento como se describen para el intermediario I-25a (más adelante), el 3-(1,3-dihidroxi-propan-2-il)-

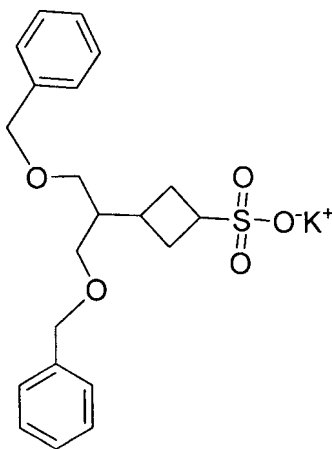
ciclobutan-1-sulfonato de butilo (0.13 gramos, 0.489 milimoles) se hizo reaccionar con bromuro de bencilo (0.13 mililitros, 1.075 milimoles), NaH al 60 por ciento (60 miligramos, 1.467 milimoles), y tetrahidrofurano (5 mililitros), para proporcionar el producto crudo.

5 La purificación mediante cromatografía en columna sobre gel de sílice (acetato de etilo al 8 por ciento en hexano) proporcionó 0.07 gramos del producto (78 por ciento de rendimiento).

¹H RMN (CDCl₃, 300 MHz): δ 7.4-7.2 (m, 10H), 4.5-4.4 (d, 4H), 4.2-4.1 (t, 2H), 3.5-3.4 (d, 4H), 3.6-3.8 (m, 1H), 2.5-2.3 (m, 5H), 2.0-1.9 (m, 1H), 1.7-1.6 (m, 2H), 1.4-1.3 (m, 2H), 1.0-0.9 (t, 3H). LCMS: 10 87 por ciento, m/z = 446 (M+1).

Síntesis del intermediario de 3-(1,3-bis-(benciloxi)-propan-2-il)-ciclobutan-1-sulfonato de potasio (I-15d):

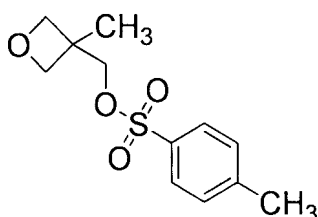
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Empleando las mismas condiciones de reacción, de procedimiento y procesamiento como se describen para el intermediario I-25b (más adelante), el 3-(1,3-bis-(benciloxi)-propan-2-il)-ciclobutan-1-sulfonato de butilo (0.1 gramos, 0.22 milimoles) se 25 hizo reaccionar con KSCN (24 miligramos, 0.24 milimoles), y una

Síntesis del intermediario de 4-metil-bencen-sulfonato de (3-metil-oxetan-3-il)-metilo (I-16a):



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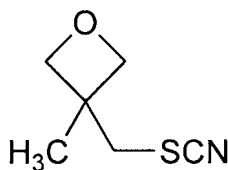
Se agregó cloruro de p-toluen-sulfonilo (5.6 gramos, 29.41 milimoles) a una solución enfriada de (3-metil-oxetan-3-il)-metanol (2 gramos, 19.60 milimoles) en piridina (25 mililitros) a 0°C, y la masa de reacción resultante se agitó a 0°C durante 2 horas. La reacción se monitoreó mediante TLC (acetato de etilo al 20 por ciento en hexano). La masa de reacción se vertió en agua helada, se agitó durante 30 minutos, el sólido formado se recolectó mediante filtración, se lavó con agua, y se secó bajo presión reducida, para proporcionar 2.5 gramos del producto (50 por ciento de rendimiento).

15

^1H RMN (CDCl_3 , 300 MHz): δ 7.8 (d, 2H), 7.4 (d, 2H), 4.4 (m, 4H), 4.1 (s, 2H), 2.5 (s, 3H), 1.3 (s, 3H). LCMS: 99.13 por ciento, m/z = 256 ($M+1$).

20

Síntesis del intermediario de 3-metil-3-(tiocianato-metil)-oxetano (I-16b):



Se agregó KSCN (0.75 gramos, 7.81 milimoles) a una solución de 4-metil-bencen-sulfonato de (3-metil-oxetan-3-il)-metilo (1 gramo,

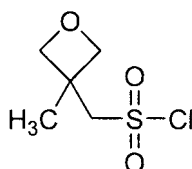
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3.90 milimoles) en etanol (25 mililitros), y la masa de reacción resultante se calentó a 85°C durante la noche. La reacción se monitoreó mediante TLC (acetato de etilo al 30 por ciento en hexano). La masa de reacción se concentró bajo presión reducida, para proporcionar 1.7 gramos del producto crudo, el cual se utilizó para el siguiente paso sin mayor purificación.

Síntesis del intermediario de cloruro de (3-metil-oxetan-3-il)-metan-sulfonilo (I-16c):

10



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Se purgó con gas de cloro a través de una solución enfriada de 3-metil-3-(tiocianato-metil)-oxetano (1.7 gramos) en agua (10 mililitros) a 0°C durante 30 minutos. La reacción se monitoreó mediante TLC (acetato de etilo al 30 por ciento en hexano). La masa de reacción se extrajo utilizando éter. La capa de éter se lavó con una solución de bisulfato de sodio, una solución de bicarbonato de sodio, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida, para proporcionar 0.3 gramos del producto crudo, el cual se utilizó para el siguiente paso sin mayor purificación.

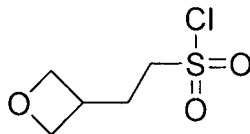
¹H RMN (CDCl₃, 300 MHz): δ 4.7 (d, 2H), 4.5-4.4 (d, 2H), 4.2 (s, 2H), 1.7 (s, 3H).

25

Síntesis del compuesto del título; N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-1-(3-metil-oxetan-3-il)-metan-sulfonamida (16A):

Empleando las mismas condiciones de reacción, de procedimiento y procesamiento como se describen para la preparación del intermediario (I-16b), el 4-metil-bencen-sulfonato de 2-(oxetan-3-il)-etilo (1 gramo, 3.90 milimoles) se hizo reaccionar con KSCN (0.75 gramos, 7.81 milimoles) en etanol (20 mililitros), para proporcionar 1.7 gramos del producto crudo, el cual se utilizó para el siguiente paso sin mayor purificación.

Síntesis del intermediario de cloruro de 2-(oxetan-3-il)-etan-sulfonilo (I-17c):



Empleando las mismas condiciones de reacción, de procedimiento y procesamiento como se describen para la preparación del intermediario (I-16c), el 3-(2-tiocianato-etil)-oxetano (1 gramo) en agua (10 mililitros) se purgó con gas de cloro durante 30 minutos, para proporcionar 0.4 gramos del producto (56 por ciento de rendimiento) el cual fue hacia la siguiente reacción con purificación y caracterización.

Síntesis del compuesto del título; N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-2-(oxetan-3-il)-etan-sulfonamida (17A):

Empleando las mismas condiciones de reacción y de

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procedimiento como se describen para la preparación del Ejemplo 7A, la 8-amino-7-(2-fluoro-4-yodo-fenil-amino)-6-metil-2,3-dihidro-oxazolo-[3,2-a]-piridin-5-ona (l-7f: 0.2 gramos, 0.673 milimoles) se hizo reaccionar con cloruro de 2-(oxetan-3-il)-etan-sulfonilo (0.18
5 gramos, 1.009 milimoles) en piridina seca (3 mililitros), para proporcionar el producto crudo. La purificación mediante HPLC de preparación, seguida por cromatografía por evaporación instantánea en columna (metanol al 3 por ciento en cloroformo) proporcionó 20 miligramos del compuesto (17A) (9 por ciento de rendimiento), y 3
10 miligramos del sub-producto hidrolizado (compuesto (17B)).

¹H RMN (300 MHz, CD₃OD): δ 7.5 (d, 1H), 7.4 (d, 1H), 6.4 (t, 1H), 4.9-4.8 (m, 4H), 4.4 (m, 4H), 3.1 (m, 3H), 2.2 (m, 2H), 1.8 (s, 3H). LCMS: 100 por ciento, m/z = 549.8 (M+1). HPLC: 95.97 por ciento.

15 Sub-producto del Ejemplo 17A: N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-4-hidroxi-3-(hidroxi-metil)-butan-1-sulfonamida (18A):

¹H RMN (300 MHz, CD₃OD): δ 7.5 (d, 1H), 7.4 (d, 1H), 6.5 (t, 1H), 4.8 (t, 2H), 4.4 (t, 2H), 3.6-3.4 (m, 4H), 3.2 (m, 2H), 1.9 (m, 2H),
20 1.8 (s, 3H), 1.75 (m, 1H). LCMS: 89 por ciento, m/z = 568 (M+1). HPLC: 90.96 por ciento.

Ejemplo 19

Síntesis de [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico (19A):
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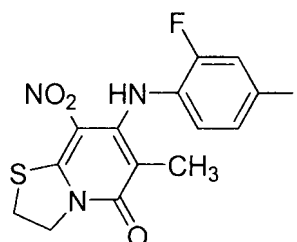
135

milimoles), fosfato de potasio (0.7 gramos, 3.75 milimoles), y Xantphos (87 miligramos, 0.15 milimoles) en tolueno (30 mililitros) a 110°C durante 3 horas, para proporcionar el producto crudo. La purificación mediante cromatografía en columna sobre gel de sílice (acetato de etilo al 30 por ciento en hexano) proporcionó 0.75 gramos del producto (76 por ciento de rendimiento).

^1H RMN (300 MHz, CDCl_3): δ 9.0-8.9 (br s, 1H), 7.3-7.1 (m, 2H), 6.8-6.6 (t, 1H), 4.7-4.5 (t, 2H), 3.4-3.3 (t, 2H), 1.8-1.7 (s, 3H), 0.3-0.2 (s, 9H).

LCMS: 97.55 por ciento, m/z = 393.9 (M+1).

Síntesis del intermediario de 7-(2-fluoro-4-yodo-fenil-amino)-6-metil-8-nitro-2,3-dihidro-tiazolo-[3,2-a]-piridin-5-ona (I-19e):



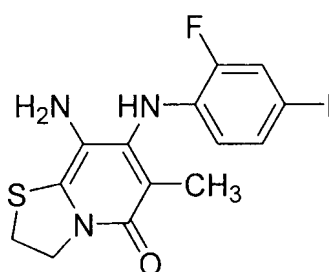
La 7-(2-fluoro-4-trimetil-silanil-fenil-amino)-6-metil-8-nitro-2,3-dihidro-tiazolo-[3,2-a]-piridin-5-ona (0.5 gramos, 1.27 milimoles) en dicloro-metano (10 mililitros) se agregó al tetrafluoro-borato de plata (0.74 gramos, 3.81 milimoles) en dicloro-metano (10 mililitros) previamente desgasificado con nitrógeno a -60°C, y la mezcla resultante se agitó a -60°C durante 30 minutos. Esto fue seguido por la adición de monoclورو de yodo (1.3 mililitros, 1.399 milimoles), y se continuó la agitación durante 30 minutos adicionales de -60°C a -50°C. La reacción se monitoreó mediante TLC (acetato de etilo al 50

por ciento en hexano). La mezcla de reacción se diluyó con dicloro-
 metano, se apagó con una solución de tiosulfato de sodio, se filtró a
 través de Celite, y el filtrado se extrajo con dicloro-metano. La capa
 orgánica se lavó con una solución de NH_3 , una solución de salmuera,
 5 se secó sobre Na_2SO_4 y se concentró. La purificación mediante
 cromatografía en columna sobre gel de sílice (acetato de etilo al 40
 por ciento en hexano) proporcionó 0.45 gramos del producto (80 por
 ciento de rendimiento).

^1H RMN (300 MHz, CDCl_3): δ 8.9 (s, 1H), 7.5-7.4 (d, 1H), 7.4-
 10 7.3 (d, 1H), 6.5 (t, 1H), 4.8-4.6 (t, 2H), 3.5-3.3 (t, 2H), 1.8-1.7 (s, 3H)
 LCMS: 98.6 por ciento, m/z = 445.9 (M-1).

Síntesis del intermediario de 8-amino-7-(2-fluoro-4-yodo-fenil-
 amino)-6-metil-2,3-dihidro-tiazolo-[3,2-a]-piridin-5-ona (I-19f):

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Se agregaron HCl concentrado (0.3 mililitros) y $\text{SnCl}_2 \cdot \text{H}_2\text{O}$
 20 (0.15 gramos, 0.671 milimoles) a la 7-(2-fluoro-4-yodo-fenil-amino)-6-
 metil-8-nitro-2,3-dihidro-tiazolo-[3,2-a]-piridin-5-ona (0.1 gramos,
 0.22 milimoles) en etanol (3 mililitros). La mezcla resultante se
 calentó a reflujo durante 2 horas. La reacción se monitoreó mediante
 TLC (acetato de etilo al 100 por ciento). La mezcla de reacción se
 25 enfrió a temperatura ambiente, se diluyó con dicloro-metano, se

basificó con una solución saturada de bicarbonato, y se filtró a través de Celite. El filtrado se extrajo con dicloro-metano. La capa orgánica se lavó con una solución de salmuera, se secó sobre Na_2SO_4 y se concentró, para proporcionar 0.09 gramos del producto (90 por ciento de rendimiento).

^1H RMN (300 MHz, CDCl_3): δ 7.4-7.3 (d, 1H), 7.2-7.1 (d, 1H), 6.3-6.2 (t, 1H), 5.8 (s, 1H), 4.5 (t, 2H), 3.4-3.3 (t, 2H), 2.8-2.6 (br s, 2H), 1.8-1.7 (s, 3H).

LCMS: 89.9 por ciento, m/z = 417.9 ($M+1$).

Síntesis del compuesto del título; [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico (19A):

Se agregó cloruro de ciclopropan-sulfonilo (34 miligramos, 0.23 milimoles) a una solución de 8-amino-7-(2-fluoro-4-yodo-fenil-amino)-6-metil-2,3-dihidro-tiazolo-[3,2-a]-piridin-5-ona (0.09 gramos, 0.21 milimoles) en piridina (1 mililitro) a 0°C . La mezcla resultante se agitó a temperatura ambiente durante la noche. La reacción se monitoreó mediante TLC (metanol al 5 por ciento en CHCl_3). La mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica se lavó con HCl 2N, una solución de salmuera, se secó sobre Na_2SO_4 y se concentró. La purificación mediante cromatografía en columna sobre gel de sílice (metanol al 1 por ciento en CHCl_3), seguida por HPLC de preparación, proporcionó 25 miligramos del producto (22 por ciento de rendimiento).

^1H RMN (300 MHz, CD_3OD): δ 7.5-7.4 (d, 1H), 7.4-7.3 (d, 1H),

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Empleando las mismas condiciones de reacción y de procesamiento como se describen para la preparación del Ejemplo 19A, la 8-amino-7-(2-fluoro-4-yodo-fenil-amino)-6-metil-2,3-dihidro-tiazolo-[3,2-a]-piridin-5-ona (I-19f: 0.2 gramos, 0.048 milimoles) en piridina (2 mililitros) se hizo reaccionar con cloruro de 1-benciloxi-metil-ciclopropan-sulfonilo (137 miligramos, 0.52 milimoles), para proporcionar el producto crudo. La purificación mediante cromatografía en columna sobre gel de sílice (acetato de etilo al 50 por ciento en hexano) proporcionó 0.21 gramos del producto (70 por ciento de rendimiento).

^1H RMN (300 MHz, CDCl_3): δ 7.4-7.3 (d, 1H), 7.25-7.1 (d, 7H), 6.3-6.2 (t, 1H), 6.1 (s, 1H), 4.6-4.5 (t, 4H), 3.9-3.8 (s, 2H), 3.4-3.3 (t, 2H), 1.7 (s, 3H), 1.5-1.4 (t, 1H), 1.3-1.2 (t, 2H), 1.0-0.9 (t, 1H). LCMS: 100 por ciento, $m/z = 642$ (M+1).

HPLC: 90.5 por ciento.

Síntesis del compuesto del título; [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-hidroximetil-ciclopropan-sulfónico (22A):

Empleando las mismas condiciones de reacción y de procesamiento como se describen para la preparación del Ejemplo 21A, la [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-benciloxi-metil-ciclopropan-sulfónico (0.2 gramos, 0.321 milimoles) se hizo reaccionar con $\text{BF}_3 \cdot \text{OEt}_2$ (0.79 mililitros, 6.24 milimoles) y etano-tiol (0.2 mililitros, 3.21 milimoles). La mezcla resultante se agitó a 40°C

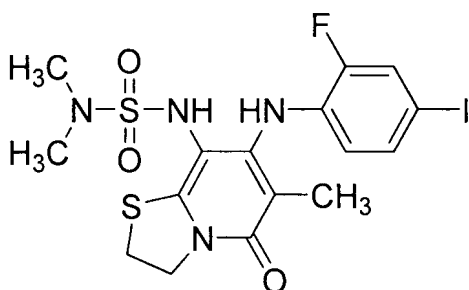
durante 6 horas. La purificación mediante cromatografía en columna sobre gel de sílice (metanol al 2 por ciento en CHCl_3) proporcionó 100 miligramos del producto (55 por ciento de rendimiento).

^1H RMN (300 MHz, CD_3OD): δ 7.6-7.3 (dd, 2H), 6.6-6.5 (t, 1H), 4.6-4.5 (t, 2H), 4.0-3.8 (s, 2H), 3.5-3.4 (t, 2H), 1.65 (s, 3H), 1.4-1.2 (m, 2H), 0.9-0.8 (t, 2H).

LCMS: 100 por ciento, m/z = 551.7 ($M+1$). HPLC: 94.13 por ciento.

Ejemplo 23

Síntesis de N-[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-dimetil-amino-sulfonamida (23A):

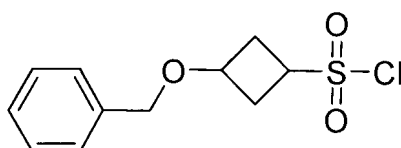


(23A)

Empleando las mismas condiciones de reacción y de procesamiento como se describen para la preparación del Ejemplo 19A, la 8-amino-7-(2-fluoro-4-yodo-fenil-amino)-6-metil-2,3-dihidro-tiazolo-[3,2-a]-piridin-5-ona (I-19f: 0.2 gramos, 0.048 milimoles) en piridina (2 mililitros) se hizo reaccionar con cloruro de dimetil-amino-sulfonilo (76 miligramos, 0.528 milimoles), para proporcionar el producto crudo. La purificación mediante cromatografía en columna

^1H RMN (DMSO- d_6 , 300 MHz): δ 7.4-7.2 (bs, 5H), 4.4-4.3 (s, 2H), 3.9-3.7 (m, 1H), 2.9-2.7 (m, 1H), 2.4-2.2 (m, 2H), 2.1-1.9 (m, 2H). LCMS: 99.03 por ciento, m/z = 280 (M+1).

Síntesis del intermediario de cloruro de 3-(benciloxi)-ciclobutan-1-sulfonilo (I-25c):

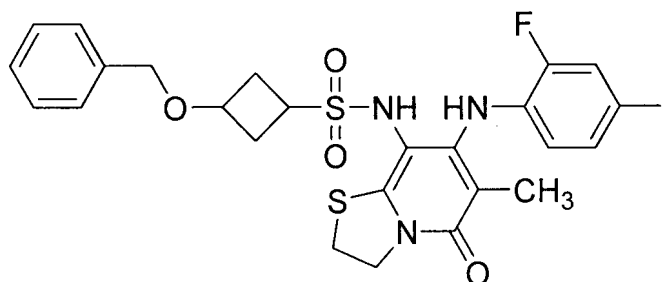


Se agregó POCl_3 (0.34 mililitros, 3.558 milimoles) a una
 10 solución enfriada de 3-(benciloxi)-ciclobutan-1-sulfonato de potasio
 (0.5 gramos, 1.779 milimoles) en dicloro-metano seco (10 mililitros) a
 0°C. Esto fue seguido por la adición lenta de di-isopropil-etil-amina
 (0.65 mililitros, 3.558 milimoles), y se agitó la mezcla de reacción
 resultante a 0°C durante 2 horas. La reacción se monitoreó mediante
 15 TLC (acetato de etilo al 20 por ciento en hexano). La mezcla de
 reacción se extrajo con dicloro-metano. La capa orgánica se lavó con
 agua, una solución de salmuera, se secó sobre Na_2SO_4 y se
 concentró. La purificación mediante cromatografía en columna sobre
 gel de sílice (acetato de etilo al 8 por ciento en hexano) proporcionó
 20 0.15 gramos del producto (38 por ciento de rendimiento).

^1H RMN (CDCl_3 , 300 MHz): δ 7.4-7.1 (m, 5H), 4.5 (s, 2H), 4.1-3.9 (m, 2H), 2.9-2.6 (m, 4H).

Síntesis del intermediario de 3-benciloxi-[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]piridin-8-il]-amida
 25 del ácido ciclobutan-sulfónico (I-25d):

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Empleando las mismas condiciones de reacción y de procesamiento como se describen para la preparación del Ejemplo 19A, la 8-amino-7-(2-fluoro-4-yodo-fenil-amino)-6-metil-2,3-dihidro-tiazolo-[3,2-a]-piridin-5-ona (1-19f: 0.15 gramos, 0.35 milimoles) en piridina (2 mililitros) se hizo reaccionar con cloruro de 3-benciloxi-ciclobutan-sulfonilo (0.1 gramos, 0.39 milimoles), para proporcionar el producto crudo. La purificación mediante cromatografía en columna sobre gel de sílice (acetato de etilo al 50 por ciento en hexano) proporcionó 0.1 gramos del producto (43 por ciento de rendimiento).

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^1H RMN (300 MHz, CDCl_3): δ 7.4-7.2 (m, 7H), 6.9-6.8 (s, 1H), 6.3-6.2 (t, 1H), 4.6-4.5 (t, 2H), 4.45 (s, 2H), 4.0-3.5 (t, 1H), 3.5-3.4 (m, 4H), 2.7-2.5 (m, 4H), 1.8 (s, 3H). LCMS: 85 por ciento, m/z = 641.9 ($M+1$).

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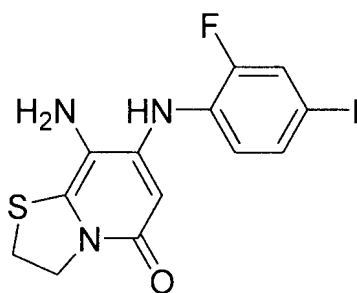
Síntesis del compuesto del título; [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 3-hidroxi-ciclobutan-sulfónico (25A):

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Se agregó BCl_3 1M (0.46 mililitros, 0.468 milimoles) a una solución de 3-benciloxi-[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclo-

^1H RMN (300 MHz, CDCl_3): δ 9.4 (s, 1H), 7.6-7.5 (t, 2H), 7.2-7.1 (t, 1H), 5.5-5.4 (s, 1H), 4.7-4.5 (t, 2H), 3.5-3.3 (t, 2H). LCMS: 94.84 por ciento, m/z = 433.7 ($M+1$).

Síntesis del intermediario de 8-amino-7-(2-fluoro-4-yodo-fenil-amino)-2,3-dihidro-tiazolo-[3,2-a]-piridin-5-ona (I-27d):



Empleando las mismas condiciones de reacción y de procesamiento como se describen para la preparación del intermediario (I-19f), la 7-(2-fluoro-4-yodo-fenil-amino)-8-nitro-2,3-dihidro-tiazolo-[3,2-a]-piridin-5-ona (0.08 gramos, 0.181 milimoles) en etanol (2 mililitros) se hizo reaccionar con $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ (0.12 gramos, 0.541 milimoles), y HCl concentrado (0.5 mililitros), para proporcionar 0.08 gramos del producto crudo, el cual se utilizó en el siguiente paso sin mayor purificación. LCMS: 59 por ciento, m/z = 403.9 ($M+1$).

Síntesis del compuesto del título; [7-(2-fluoro-4-yodo-fenil-amino)-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico (27A):

Empleando las mismas condiciones de reacción y de procesamiento como se describen para la preparación del Ejemplo 19A, la 8-amino-7-(2-fluoro-4-yodo-fenil-amino)-2,3-dihidro-tiazolo-

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[3,2-a]-piridin-5-ona (0.08 gramos, 0.199 milimoles) en piridina (1 mililitro) se hizo reaccionar con cloruro de ciclopropil-sulfonilo (33 miligramos, 0.238 milimoles), para proporcionar el producto crudo. La purificación mediante HPLC de preparación, proporcionó 20 miligramos del producto (20 por ciento de rendimiento).

^1H RMN (300 MHz, DMSO- D_6): δ 9.0 (s, 1H), 7.8-7.7 (d, 1H), 7.6-7.5 (d, 2H), 7.2-7.1 (t, 1H), 5.1 (s, 1H), 4.4-4.2 (t, 2H), 3.5-3.3 (t, 2H), 2.9-2.7 (m, 1H), 1.0-0.8 (m, 4H). LCMS: 97.87 por ciento, m/z = 507.9 (M+1). HPLC: 99.35 por ciento.

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DATOS FARMACOLÓGICOS

La utilidad de los compuestos de la presente invención se pueden demostrar empleando cualquiera de los siguientes procedimientos de prueba:

Se utiliza un ensayo de cascada de BRAF-MEK-ERK para evaluar los efectos de los compuestos como inhibidores de la senda de cinasa MAP. Se establece un ensayo de cascada enzimática utilizando la cinasa BRAF activada humana recombinante (V599E) (Número de Catálogo 14-557), la cinasa MEK1 inactiva de longitud completa humana (Número de Catálogo 14-706), y las enzimas de cinasa MAP inactiva de longitud completa humana / ERK2 (Número de Catálogo 14-536) procuradas por Upstate. Se emplea la tecnología de detección TR-FRET (transferencia de energía de resonancia de fluorescencia resuelta en el tiempo) para la lectura. La solución del regulador de ensayo contiene Tris 50 mM, pH de 7.5, MgCl_2 10 mM, DTT 1 mM, Tween 20 al 0.01 por ciento, BRAF

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activada 0.1 nM, MEK1 inactiva 2 nM, ERK2 inactiva 10 nM, ATP 100 μ M, y sustrato de biotina-péptido de cadena larga 500 nM (LCB-FFKNIVTPRTPPP) en un formato de 384 pozos. La reacción de cinasa se interrumpe después de 90 minutos con EDTA 10 mM y se
5 agregan la mezcla de detección Lance (anticuerpo de fosfo-serina/treonina marcado con Eu 2 nM (Número de Catálogo AD0176 - Perkin Elmer), y SA-APC 20 nM (Número de Catálogo CR130-100 - Perkin Elmer). La señal de TR-FRET (Excitación a 340 nanómetros, Emisión a 615 nanómetros y a 665 nanómetros) se lee con un tiempo
10 de retraso de 50 microsegundos en un fluorímetro Victor3 V. Los datos se calculan utilizando la proporción de lecturas de 665 nanómetros a 615 nanómetros. La concentración final de sulfóxido de dimetilo es del 2.5 por ciento en el ensayo. Los compuestos se rastrean en una concentración de 10 μ M con la incubación previa de
15 las enzimas en la presencia del compuesto de prueba durante 45 minutos.

Cada IC_{50} individual se determina utilizando una curva de respuesta a la dosis de 10 puntos generada por el software GraphPad Prism, Versión 4 (San Diego, California, EUA), utilizando
20 el ajuste de curva de regresión no lineal para la respuesta a la dosis sigmoidea (inclinación variable).

Se establece un ensayo de cinasa MAP *in vitro* utilizando la cinasa MAP activada 2 / ERK2 (Número de Catálogo 14-550) obtenida en Upstate. Se utiliza la tecnología de detección TR-FRET
25 para la lectura.

Weislow y colaboradores, J. Natl. Cancer Institute, (1989) 81, 577-586; y Roehm y colaboradores, J. Immunol. Methods [1991] 142: 257-265.

Los compuestos de los Ejemplos anteriores se evaluaron como inhibidores de la senda de cinasa MAP en un ensayo de cascada enzimática BRAF-MEK-ERK y en el ensayo de viabilidad celular descrito anteriormente. Los resultados se cotejan en la siguiente Tabla 1.

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TABLA 1

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Ej. No.	Nombre IUPAC	% Inhibición	GI ₅₀ μM
1A	[1-bencil-7-(4-bromo-2-fluoro-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico	70%	-
2A	[7-(4-bromo-2-fluoro-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico	100%	0.8
3A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido	100%	0.019

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Ej. No.	Nombre IUPAC	% Inhibición	GI ₅₀ μM
	ciclopropan-sulfónico		
4A	[7-(4-bromo-2-fluoro-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido 1-(2,3-dihidroxi-propil)-ciclopropan-sulfónico	100%	2.88
5A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido 1-(2,3-dihidroxi-propil)-ciclopropan-sulfónico	100%	0.293
6A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido 3-hidroxi-ciclobutan-sulfónico	100%	1.38
7A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico	99%	0.026

	Ej. No.	Nombre IUPAC	% Inhibición	GI ₅₀ μM
5	8A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 2-hidroxi-metil-ciclopropan-sulfónico	100%	0.122
10	9A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-(2-hidroxi-etil)-ciclopropan-sulfónico	100%	0.019
15	10A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-(2,3-dihidroxi-propil)-ciclopropan-sulfónico	100%	0.033
20	11A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-hidroxi-metil-ciclopropan-sulfónico	100%	0.02
25	12A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-	100%	0.011

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Ej. No.	Nombre IUPAC	% Inhibición	GI ₅₀ μM
	(3-hidroxi-propil)-ciclopropan-sulfónico		
13A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 3-hidroxi-ciclobutan-sulfónico	100%	0.122
14A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclobutan-sulfónico	100%	0.016
15A	3-(1,3-dihidroxi-propan-2-il)-N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-ciclobutan-1-sulfonamida	100%	1.53
16A	N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-1-(3-metil-oxetan-3-il)-metan-sulfonamida	100%	1.30
17A	N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-	100%	1.73

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Ej. No.	Nombre IUPAC	% Inhibición	GI ₅₀ μM
	[3,2-a]-piridin-8-il)-2-(oxetan-3-il)- etan-sulfonamida		
18A	N-(7-(2-fluoro-4-yodo-fenil-amino)-6- metil-5-oxo-3,5-dihidro-2H-oxazolo- [3,2-a]-piridin-8-il)-4-hidroxi-3-(hidroxi- metil)-butan-1-sulfonamida	100%	4.26
19A	[7-(2-fluoro-4-yodo-fenil-amino)-6- metil-5-oxo-2,3-dihidro-5H-tiazolo- [3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico	100%	0.0003
20A	[7-(2-fluoro-4-yodo-fenil-amino)-6- metil-5-oxo-2,3-dihidro-5H-tiazolo- [3,2-a]-piridin-8-il]-amida del ácido 1- (2,3-dihidroxi-propil)-ciclopropan- sulfónico	100%	0.054
21A	[7-(2-fluoro-4-yodo-fenil-amino)-6- metil-5-oxo-2,3-dihidro-5H-tiazolo- [3,2-a]-piridin-8-il]-amida del ácido 2- hidroxi-metil-ciclopropan-sulfónico	100%	0.158

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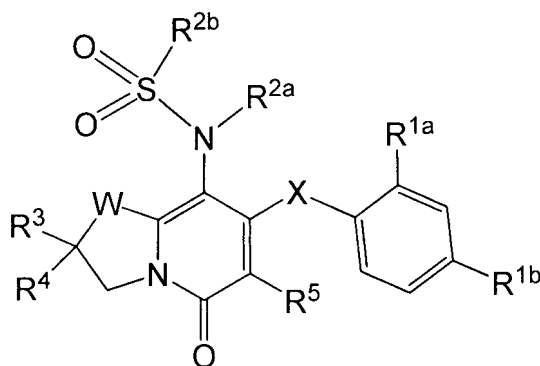
Ej. No.	Nombre IUPAC	% Inhibición	GI ₅₀ μM
22A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-hidroxi-metil-ciclopropan-sulfónico	97%	0.061
23A	N-[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-dimetil-amino-sulfonamida	100%	0.107
24A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopentan-sulfónico	100%	0.192
25A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 3-hidroxi-ciclobutan-sulfónico	100%	0.922
26A	[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclobutan-sulfónico	100%	0.156

Ej. No.	Nombre IUPAC	% Inhibición	GI ₅₀ μM
27A	[7-(2-fluoro-4-yodo-fenil-amino)-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico	100%	0.064

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REIVINDICACIONES

1. Un compuesto de la fórmula (IA):



(IA)

en donde:

X es -N(R⁶)-, en donde R⁶ es H o alquilo (de 1 a 6 átomos de carbono);

R^{1a} y R^{1b} se seleccionan cada uno independientemente a partir de hidroxilo, ciano, nitro, alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), alquinilo (de 2 a 6 átomos de carbono), alcoxilo (de 1 a 6 átomos de carbono), alqueniloxilo (de 2 a 6 átomos de carbono), alquiniloxilo (de 2 a 6 átomos de carbono), halógeno, alquilo (de 1 a 6 átomos de carbono)-C(O)-, -C(O)OH, -C(O)-O-alquilo (de 1 a 6 átomos de carbono), amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono)-N-, alquilo (de 1 a 6 átomos de carbono)-NH-C(O)-, di-(alquilo (de 1 a 6 átomos de carbono)-N-C(O)-, alquilo (de 1 a 6 átomos de carbono)-C(O)-NH-, alquilo (de 1 a 6 átomos de carbono)-C(O)-N-(alquilo (de 1 a 6 átomos de carbono))-, alquilo (de

1 a 6 átomos de carbono)-SO₂-NH-, alquilo (de 1 a 6 átomos de carbono)-SO₂-N-(alquilo (de 1 a 6 átomos de carbono))-, alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono)-S(O)-, alquilo (de 1 a 6 átomos de carbono)-SO₂-, NH₂-SO₂-, alquilo (de 1 a 6 átomos de carbono)-NH-SO₂- y di-(alquilo (de 1 a 6 átomos de carbono)-N-SO₂-, en donde cada una de dichas fracciones de alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), y alquinilo (de 2 a 6 átomos de carbono) está opcionalmente sustituida por uno o más sustituyentes, cada uno independientemente seleccionado a partir de halógeno, hidroxilo, alcóxilo (de 1 a 6 átomos de carbono), amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono)-N- o ciano;

R^{2a} es H o alquilo de 1 a 6 átomos de carbono;

15 R^{2b} es una fracción química seleccionada a partir de alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), alquinilo (de 2 a 6 átomos de carbono), NR¹⁰R¹², cicloalquilo, arilo, hetero-cicloalquilo, o heteroarilo, en donde esta fracción química está opcionalmente sustituida por uno a tres sustituyentes, cada uno independientemente seleccionado a partir de halógeno, ciano, hidroxilo, alcóxilo (de 1 a 6 átomos de carbono), alqueniloxilo (de 2 a 6 átomos de carbono), alquiniloxilo (de 2 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono) sustituido por halógeno, amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de

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carbono)-N-, HC(O)NH-, alquilo (de 1 a 6 átomos de carbono)-
C(O)NH-, HC(O)N-alquilo (de 1 a 6 átomos de carbono))-, alquilo (de
1 a 6 átomos de carbono)-C(O)-N-(alquilo (de 1 a 6 átomos de
carbono))-, cicloalquilo monocíclico o hetero-cicloalquilo
5 monocíclico, en donde este cicloalquilo y este hetero-cicloalquilo
están opcionalmente sustituidos por uno o dos sustituyentes, cada
uno independientemente seleccionado a partir de halógeno, ciano,
hidroxilo, alcóxido (de 1 a 6 átomos de carbono), alquinoxilo (de 2 a
6 átomos de carbono), alquinoxilo (de 2 a 6 átomos de carbono),
10 alquilo (de 1 a 6 átomos de carbono)-S-, halo-alquilo de 1 a 6 átomos
de carbono, amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-
(alquilo (de 1 a 6 átomos de carbono)-N-, HC(O)-NH-, alquilo (de 1 a
6 átomos de carbono)-C(O)-NH-, HC(O)-N-alquilo (de 1 a 6 átomos
de carbono))-, o alquilo (de 1 a 6 átomos de carbono)-C(O)-N-
15 (alquilo (de 1 a 6 átomos de carbono))-;

W es NR²², O, o S;

R³ y R⁴ son cada uno independientemente H, alquilo (de
1 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono)
sustituido por halógeno, hidroxialquilo (de 1 a 6 átomos de
20 carbono), o alcóxido (de 1 a 6 átomos de carbono);

R⁵ es H, halógeno, alquilo (de 1 a 3 átomos de carbono),
o alquilo (de 1 a 3 átomos de carbono) sustituido por halógeno;

R¹⁰ y R¹² son cada uno independientemente H, o una
fracción química seleccionada a partir de alquilo (de 1 a 6 átomos de
25 carbono), alqueno (de 2 a 6 átomos de carbono), alquino (de 2 a 6

átomos de carbono), alquilo (de 1 a 6 átomos de carbono)-C(O)-, alcóxido (de 1 a 6 átomos de carbono), cicloalquilo (de 3 a 14 átomos de carbono), arilo (de 6 a 14 átomos de carbono), cicloheteroalquilo de 4 a 14 miembros, o heteroarilo de 5 a 14 miembros, en donde
 5 cada una de estas fracciones químicas está opcionalmente sustituida por uno o más sustituyentes, cada uno independientemente seleccionado a partir de halógeno, hidróxido, alcóxido (de 1 a 6 átomos de carbono), amino, alquilo (de 1 a 6 átomos de carbono)-amino, di-(alquilo (de 1 a 6 átomos de carbono))-amino, o ciano; y

10 R^{22} es H, o una fracción química seleccionada a partir de alquilo (de 1 a 6 átomos de carbono), alquénido (de 2 a 6 átomos de carbono), alquínido (de 2 a 6 átomos de carbono), cicloalquilo, arilo, hetero-cicloalquilo, aril-alquilo (de 1 a 6 átomos de carbono)-, alquilo (de 1 a 6 átomos de carbono)-aril-, o diaril-alquilo (de 1 a 6 átomos
 15 de carbono)-, en donde cada una de estas fracciones químicas está opcionalmente sustituida por uno o más sustituyentes, cada uno independientemente seleccionado a partir de hidróxido, ciano, nitró, alquilo (de 1 a 6 átomos de carbono), alquénido (de 2 a 6 átomos de carbono), alquínido (de 2 a 6 átomos de carbono), alcóxido (de 1 a 6
 20 átomos de carbono), alquénilóxido (de 2 a 6 átomos de carbono), alquínilóxido (de 2 a 6 átomos de carbono), halógeno, alquilo (de 1 a 6 átomos de carbono)-C(O)-, -C(O)OH,

-C(O)-O-alquilo (de 1 a 6 átomos de carbono), amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6
 25 átomos de carbono)-N-, alquilo (de 1 a 6 átomos de carbono)-NH-

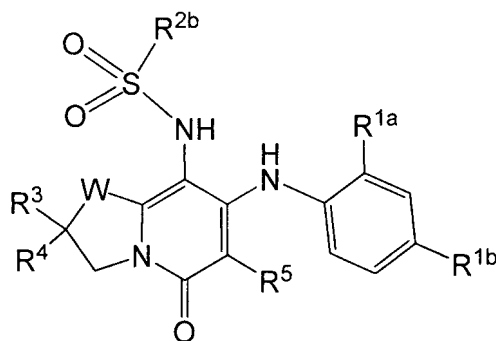
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C(O)-, di-(alquilo (de 1 a 6 átomos de carbono)-N-C(O)-, alquilo (de 1 a 6 átomos de carbono)-C(O)-NH-, alquilo (de 1 a 6 átomos de carbono)-C(O)-N-(alquilo (de 1 a 6 átomos de carbono))-, alquilo (de 1 a 6 átomos de carbono)-SO₂-NH-, alquilo (de 1 a 6 átomos de carbono)-SO₂-N-(alquilo (de 1 a 6 átomos de carbono))-,

alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono)-S(O)-, alquilo (de 1 a 6 átomos de carbono)-SO₂-, NH₂-SO₂-, alquilo (de 1 a 6 átomos de carbono)-NH-SO₂- y di-(alquilo (de 1 a 6 átomos de carbono)-N-SO₂-, en donde cada una de dichas fracciones de alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), y alquinilo (de 2 a 6 átomos de carbono) está opcionalmente sustituida por uno o más sustituyentes, cada uno independientemente seleccionado a partir de halógeno, hidroxilo, alcoxilo (de 1 a 6 átomos de carbono), amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono)-N-, o ciano;

o una sal farmacéuticamente aceptable del mismo.

2. Un compuesto de la fórmula (IB):



(IB)

en donde:

R^{1a} y R^{1b} son cada uno independientemente hidroxilo, ciano, nitro, alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), alquinilo (de 2 a 6 átomos de carbono); alcoxilo (de 1 a 6 átomos de carbono), halógeno, amino, o alquilo (de 1 a 6 átomos de carbono)-NH-;

R^{2b} es:

(i) cicloalquilo de 3 a 6 miembros, en donde este cicloalquilo está opcionalmente sustituido con hidroxilo, alquilo (de 1 a 6 átomos de carbono), alquenilo (de 2 a 6 átomos de carbono), o alquinilo (de 2 a 6 átomos de carbono), en donde este alquilo (de 1 a 6 átomos de carbono), este alquenilo (de 2 a 6 átomos de carbono), y este alquinilo (de 2 a 6 átomos de carbono) están opcionalmente sustituidos con 1 a 3 grupos hidroxilo,

(ii) alquilo (de 1 a 6 átomos de carbono) sustituido por un cicloalquilo monocíclico de 3 a 6 miembros o un heterocicloalquilo monocíclico de 3 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de O, S o N, en donde este alquilo sustituido está opcionalmente sustituido con uno a tres sustituyentes, cada uno independientemente seleccionado a partir del grupo que consiste en halógeno, ciano, hidroxilo, alcoxilo (de 1 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono) sustituido por halógeno, amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono))-N-, y alquilo (de 1 a 6 átomos de carbono)-C(O)-NH-,

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(iii) alqueno (de 2 a 6 átomos de carbono) sustituido por un cicloalquilo monocíclico de 3 a 6 miembros o un heterocicloalquilo monocíclico de 3 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de O, S o N, en donde este alqueno sustituido está opcionalmente sustituido con uno a tres sustituyentes, cada uno independientemente seleccionado a partir del grupo que consiste en halógeno, ciano, hidroxilo, alcoxilo (de 1 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono) sustituido por halógeno, amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono))-N-, y alquilo (de 1 a 6 átomos de carbono)-C(O)-NH-,

(iv) alquino (de 2 a 6 átomos de carbono) sustituido por un cicloalquilo monocíclico de 3 a 6 miembros o un heterocicloalquilo monocíclico de 3 a 6 miembros que contiene de 1 a 3 heteroátomos seleccionados a partir de O, S o N, en donde este alquino sustituido está opcionalmente sustituido con uno a tres sustituyentes, cada uno independientemente seleccionado a partir del grupo que consiste en halógeno, ciano, hidroxilo, alcoxilo (de 1 a 6 átomos de carbono), alquilo (de 1 a 6 átomos de carbono)-S-, alquilo (de 1 a 6 átomos de carbono) sustituido por halógeno, amino, alquilo (de 1 a 6 átomos de carbono)-NH-, di-(alquilo (de 1 a 6 átomos de carbono))-N-, y alquilo (de 1 a 6 átomos de carbono)-C(O)-NH-, o

(v) di-(alquilo (de 1 a 6 átomos de carbono))-amina;

R^3 es H;

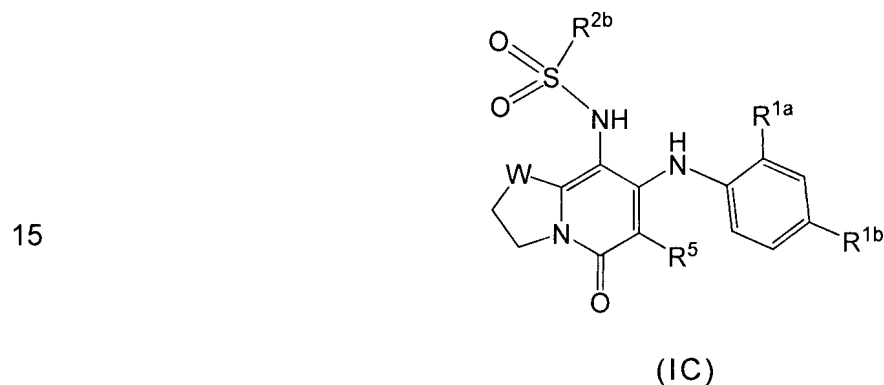
R^4 es H o metilo;

W es NR^{22} , O, o S, en donde R^{22} es H, metilo, etilo, fenilo, bencilo, o fenetilo;

5 R^5 es H, halógeno, alquilo (de 1 a 3 átomos de carbono), o alquilo (de 1 a 3 átomos de carbono) sustituido por halógeno; o una sal farmacéuticamente aceptable del mismo.

3. El compuesto de la reivindicación 2, en donde R^{1a} y R^{1b} son cada uno independientemente halógeno; o una sal farmacéuticamente aceptable del mismo.

4. Un compuesto de la fórmula (IC):



en donde:

R^{1a} es F;

20 R^{1b} es Br o I;

R^{2b} es:

(i) cicloalquilo de 3 a 6 miembros, en donde este cicloalquilo está opcionalmente sustituido con hidroxilo o alquilo (de 1 a 6 átomos de carbono), en donde este alquilo (de 1 a 6 átomos de carbono) está opcionalmente sustituido con 1 a 3 grupos hidroxilo,

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(ii) alquilo (de 1 a 6 átomos de carbono), en donde este alquilo (de 1 a 6 átomos de carbono) está opcionalmente sustituido con oxetanilo o 1 a 3 hidroxilo, o

(iii) $-N(CH_3)_2$;

5 W es O, S o N(R²²), en donde R²² es H o bencilo; y
R⁵ es H, F, Cl, CH₃ o CF₃;
o una sal farmacéuticamente aceptable del mismo.

5. El compuesto de la reivindicación 4 en donde W es O; o una sal farmacéuticamente aceptable del mismo.

10 6. Un compuesto seleccionado a partir del grupo que consiste en:

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico;

15 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 2-hidroxi-metil-ciclopropan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-(2-hidroxi-etil)-ciclopropan-sulfónico;

20 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-(2,3-dihidroxi-propil)-ciclopropan-sulfónico;

25 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-hidroxi-metil-ciclopropan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-(3-hidroxi-propil)-ciclopropan-sulfónico;

5 [7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido 3-hidroxi-ciclobutan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-oxazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclobutan-sulfónico;

10 3-(1,3-dihidroxi-propan-2-il)-N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-ciclobutan-1-sulfonamida;

N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-1-(3-metil-oxetan-3-il)-metan-sulfonamida;

15 N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-2-(oxetan-3-il)-etan-sulfonamida; y

20 N-(7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-3,5-dihidro-2H-oxazolo-[3,2-a]-piridin-8-il)-4-hidroxi-3-(hidroxi-metil)-butan-1-sulfonamida;

o una sal farmacéuticamente aceptable de las mismas.

7. El compuesto de la reivindicación 4, en donde W es S; o una sal farmacéuticamente aceptable del mismo.

8. Un compuesto seleccionado a partir del grupo que
25 consiste en:

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-(2,3-dihidroxi-propil)-ciclopropan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 2-hidroxi-metil-ciclopropan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 1-hidroxi-metil-ciclopropan-sulfónico;

N-[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-dimetil-amino-sulfonamida;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopentan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido 3-hidroxi-ciclobutan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclobutan-sulfónico; y

[7-(2-fluoro-4-yodo-fenil-amino)-5-oxo-2,3-dihidro-5H-tiazolo-[3,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico;

o una sal farmacéuticamente aceptable de las mismas.

9. El compuesto de la reivindicación 4, en donde W es NH; o una sal farmacéuticamente aceptable del mismo.

10. Un compuesto seleccionado a partir del grupo que consiste en:

[7-(4-bromo-2-fluoro-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido ciclopropan-sulfónico;

[7-(4-bromo-2-fluoro-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido 1-(2,3-dihidroxi-propil)-ciclopropan-sulfónico;

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido 1-(2,3-dihidroxi-propil)-ciclopropan-sulfónico; y

[7-(2-fluoro-4-yodo-fenil-amino)-6-metil-5-oxo-1,2,3,5-tetrahidro-imidazo-[1,2-a]-piridin-8-il]-amida del ácido 3-hidroxi-ciclobutan-sulfónico;

o una sal farmacéuticamente aceptable de las mismas.

11. Una composición farmacéutica, la cual comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10, o una sal farmacéuticamente aceptable del mismo, y un excipiente farmacéuticamente aceptable.

12. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10, para utilizarse en terapia.

13. Un método para el tratamiento de una enfermedad,

15X

trastorno o síndrome asociado con la inhibición de MEK, el cual comprende el paso de administrar a un sujeto que lo necesite:

- (i) un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10, o una sal farmacéuticamente aceptable del mismo, o
- (ii) una composición farmacéutica de la reivindicación 11.

14. El método de la reivindicación 13, en donde el sujeto mencionado es un ser humano, y la enfermedad, trastorno o síndrome asociado con la inhibición de MEK es cáncer.

15. El método de la reivindicación 13, en donde el sujeto mencionado es un ser humano, y la enfermedad, trastorno o síndrome asociado con la inhibición de MEK es inflamación.

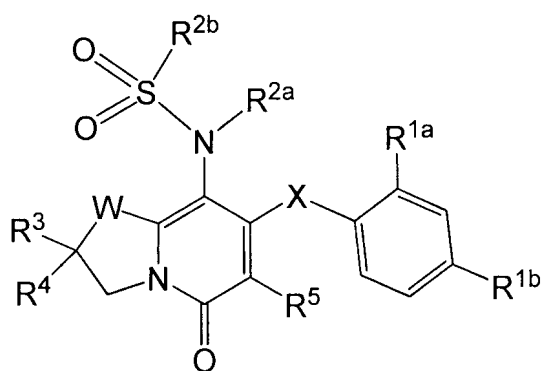
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RESUMEN

La presente invención se refiere a los compuestos de la fórmula (IA):



(IA)

en donde R^{1a}, R^{1b}, X, R^{2a}, R^{2b}, W, R³, R⁴, y R⁵ son como se definen en la presente, así como a las sales farmacéuticamente aceptables de los mismos. Se ha demostrado que los compuestos actúan como inhibidores de MEK, lo cual puede ser útil en el tratamiento de enfermedades hiperproliferativas, como cáncer e inflamación.

* * * * *

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 53897-WO-PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2010/066659	International filing date (day/month/year) 02/11/2010	(Earliest) Priority Date (day/month/year) 04/11/2009
Applicant NOVARTIS AG		

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 43.6bis(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:

HETEROCYCLIC SULFONAMIDE DERIVATIVES USEFUL AS MEK INHIBITORS

5. With regard to the **abstract**,

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

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/066659

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 C07D498/04 C07D513/04 A61K31/4355 A61K31/4365
A61K31/437 A61P29/00 A61P35/00

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2010/121646 A1 (NOVARTIS AG [CH]; CHIKKANNA DINESH [IN]; MCCARTHY CLIVE [CH]; MOEBITZ) 28 October 2010 (2010-10-28) claims 1,15,19	1-15
A	WO 2009/064675 A1 (TAKEDA PHARMACEUTICAL [JP]; ADAMS MARK E [US]; DONG QING [US]; KALDOR) 22 May 2009 (2009-05-22) paragraph [0001]; claim 1; example 1	1-15
A	WO 2008/089459 A1 (ARDEA BIOSCIENCES INC [US]; VERNIER JEAN-MICHEL [US]; MADERNA ANDREAS) 24 July 2008 (2008-07-24) claims 1,49	1-15

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

13 January 2011

Date of mailing of the international search report

19/01/2011

Name and mailing address of the ISA/

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Authorized officer

Gettins, Marc

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/066659

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010121646 A1	28-10-2010	NONE	
WO 2009064675 A1	22-05-2009	AR 069462 A1 CA 2705452 A1 EP 2227469 A1 PE 09982009 A1 US 2009124595 A1	27-01-2010 22-05-2009 15-09-2010 12-08-2009 14-05-2009
WO 2008089459 A1	24-07-2008	AU 2008206045 A1 CA 2675358 A1 CN 101663279 A CO 6210813 A2 CR 10939 A EA 200900959 A1 EC SP099525 A EP 2121620 A1 JP 2010516698 T US 2008255133 A1 US 2010331334 A1	24-07-2008 24-07-2008 03-03-2010 20-10-2010 13-11-2009 26-02-2010 30-11-2009 25-11-2009 20-05-2010 16-10-2008 30-12-2010



No. 12-073066-00000-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 159

PATENTE DE INVENCION ☐

MODELO DE UTILIDAD ☐

Art 33 Decisión 486/00

☐	Indicación que se solicita una patente.
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Descripción de la invención
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)
Completa ☐	Incompleta ☐

PATENTE DE INVENCION PCT ☐

MODELO DE UTILIDAD PCT ☐

Art.33 Decisión 486/00, Circular Única

☐	Indicación que se solicita una PCT
☐	Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
Completa ☐	Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

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

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

☐	Indicación que se solicita un esquema de trazado
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica de un esquema de trazado
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐