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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

Ref. Expediente 14-119-704

TÍTULO SOLICITADO: "INHIBIDORES DE PAK PARA EL TRATAMIENTO DE
LOS TRASTORNOS DE PROLIFERACIÓN CELULAR"PUBLICACIÓN: Gaceta 703 de 21 de agosto de 2014, N° de publicación
960.

PRIORIDAD: US 61/555.902 de 04/11/2011

SOLICITANTE: AFRAXIS HOLDINGS, INC.

APODERADO: JUAN PABLO CADENA SARMIENTO

TRÁMITE: SUSTENTACION DE OPOSICIÓN

TITO NOÉ PARRA MURILLO, mayor de edad y vecino de Bogotá, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 71.168 del Consejo Superior de la Judicatura, obrando en calidad de apoderado general de LABORATORIO FRANCO COLOMBIANO S.A.S. – LAFRANCOL, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito sustentar la oposición presentada, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito insistir en que la solicitud referida a Inhibidores de PAK para el tratamiento de los trastornos de proliferación celular, incumple los requisitos materiales de patentabilidad exigidos para el otorgamiento de patente de invención puesto que incumple los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

II. COMPLEMENTO DE INFORMACIÓN.

A continuación me permito presentar el siguiente complemento de información para demostrar la improcedencia de la obtención de la solicitud de patente en trámite, veamos:

Métodos de tratamiento

Se observa que la solicitante reclama materia que no es considerada patentable:

47. Un método para tratar un trastorno de proliferación celular en un individuo que lo necesita, que comprende administrarle al sujeto una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1.

Así mismo las reivindicaciones dependientes 46 a 82 hacen referencia a este tipo de materia no patentable.

Composición farmacéutica

La solicitante reclama materia carente de claridad y concisión como es el caso de la composición:

46. Una composición farmacéutica que comprende el compuesto de la reivindicación 1 y un excipiente, portador o aglutinante de este farmacéuticamente aceptable.

De acuerdo a lo allí revelado, se observa que se está reclamando una composiciones que no revela sus componentes, sus proporciones y que además parece no tener ningún efecto técnico sorprendente o inesperado.

Además, en la revisión de la descripción se presentan ejemplos de composiciones sin mencionar sus efectos técnicos:

Ejemplo 25: Composiciones farmacéuticas

Ejemplo 25a: Composición parenteral

Ejemplo 25b: Composición oral

Ejemplo 25c: Composición sublingual (cápsula dura)

Ejemplo 25d: Pastilla sublingual de rápida desintegración

Ejemplo 25e: Composición para inhalación

Ejemplo 25f: Composición para gel rectal

Ejemplo 25g: Composición para gel tópico

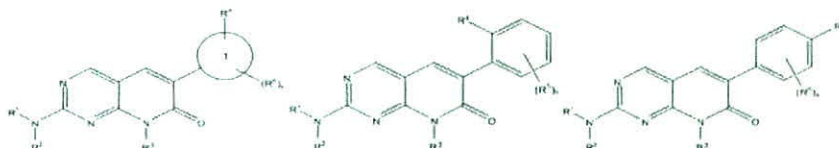
Ejemplo 25h: Composición de solución oftálmica

Ejemplo 25i: Solución nasal en spray

Carencia de concisión, claridad y soporte en la descripción

Se observa que la solicitante reclama una serie de compuestos muy amplia y carente de sustento en la descripción en lo relacionado a efectos sorprendentes o inesperados logrados por estas moléculas:

1. Un compuesto que tiene la estructura de la Fórmula I, Fórmula II o Fórmula III, o una sal o N-óxido de este farmacéuticamente aceptable.



Fórmula I

Fórmula II

Fórmula III;

donde:

el anillo T es un anillo de arilo o heteroarilo;

R^1 es H o alquilo sustituido o no sustituido;

R^2 es alquilo no sustituido o alquilo sustituido con amino, amido, nitro, ariltio, alquilsulfóxido, arilsulfóxido, alquilsulfona, arilsulfona, ariloxi, alkoloxo, amida, éster, alcoilo, ciano, arilo o heteroarilo sustituidos o no sustituidos; alcoxi sustituido o no sustituido; aralcoxi sustituido o no sustituido; heteroalquilo sustituido o no sustituido; cicloalquilo sustituido o no sustituido; cicloalquilalquilo sustituido o no sustituido; heterocicloalquilo sustituido o no sustituido; heterocicloalquilalquilo sustituido o no sustituido; espiro - cicloaquil-heterocicloalquilo; -alquilenosulfonil; -alquilenosulfonil; o -S(=O)₂R⁹;

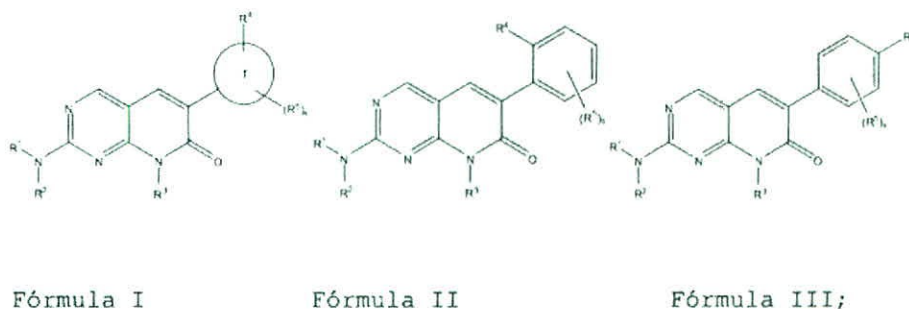
R^3 es H, alquilo sustituido o no sustituido, alcoxi sustituido o no sustituido, amino sustituido o no sustituido, heteroalquilo sustituido o no sustituido, heterocicloalquilo sustituido o no sustituido, cicloalquilo sustituido o no sustituido, cicloalquilalquilo sustituido o no sustituido, heterocicloalquilalquilo sustituido o no sustituido, arilo sustituido o no sustituido, aralquilo sustituido o no sustituido, heteroarilo sustituido o no sustituido o heteroarilalquilo sustituido o no sustituido;

R^4 es heteroarilo sustituido o no sustituido unido al anillo T o el anillo de fenilo mediante un átomo de carbono de R^4 o heterocicloalquilo sustituido o no sustituido unido al anillo T o el anillo de fenilo mediante un átomo de carbono de R^4 ;

cada R^5 es independientemente halógeno, -CN, -NO₂, -OH, -OCF₃, -OCH₂F, -OCF₂H, -CF₃, -SR⁸, -NR¹⁰S(=O)₂R⁹, -S(=O)₂N(R¹⁰)₂, -S(=O)R⁹, -S(=O)₂R⁹, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R¹⁰, -N(R¹⁰)₂, -C(=O)N(R¹⁰)₂, -NR¹⁰C(=O)R¹⁰, -NR¹⁰C(=O)OR¹⁰, -NR¹⁰C(=O)N(R¹⁰)₂, alquilo sustituido o no sustituido, alcoxi sustituido o no

sustituido, heteroalquilo sustituido o no sustituido; o heterocicloalquilo sustituido o no sustituido; o cicloalquilo sustituido o no sustituido; o arilo sustituido o no sustituido; o heteroarilo sustituido o no sustituido; cada R^8 es independientemente H o R^9 ; cada R^9 es independientemente alquilo sustituido o no sustituido, cicloalquilo sustituido o no sustituido, heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido o heteroarilo sustituido o no sustituido; cada R^{10} es independientemente H, alquilo sustituido o no sustituido, cicloalquilo sustituido o no sustituido, heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido o heteroarilo sustituido o no sustituido; o dos R^{10} junto con los átomos a los que están unidos forman un heterociclo; y s es 0-4.

De la observación de la reivindicación principal, tenemos que se reclaman tres tipos diferentes de compuestos o la sal o el N-óxido de este tipo de moléculas, veamos:



lo anterior, sumado a la gran amplitud asignada a la definición de los radicales sustituyentes en esta molécula, le resta claridad y concisión a la materia reclamada.

Por otro lado, la descripción no brinda información suficiente que justifique tal amplitud, como se puede observar los ejemplos que se presentan en la descripción se agrupan en dos:

1. Ejemplos de la síntesis de los compuestos

La primera parte de los ejemplos presentados se refieren a la síntesis de algunos de los compuestos incluidos dentro de la materia reclamada:

Ejemplo 1: Síntesis de 8-etil-6-(2-metil-4-(3-metilpirazin-2-il)fenil)-2-(tetra(hidro-2H-piran-4-ilamino) pirido[2,3-d]pirimidin-7(8H)-ona (9)

En conexión con lo anterior y como se puede ver en la descripción, las tablas 1 a 10 presentan las estructuras de aproximadamente 137 compuestos con algunos datos de la respectiva síntesis, sin embargo, no se observan datos que demuestren efectos sorprendentes obtenidos con estas síntesis.

2. Ejemplos biológicos

Se observa que la segunda parte de los ejemplos se enfoca hacia los efectos biológicos logrados por algunos compuestos, sin embargo, se observa que la mayoría presenta información acerca de la metodología pero no información contundente que señale el efecto técnico sorprendente o inesperado de los compuestos reclamados, a continuación se muestran los ejemplos de este segundo grupo:

Ejemplo 2: Ensayo de inhibición de PAK in vitro

Ejemplo 11: Ensayo de inhibición de PAK in vitro adicional

Ejemplo 12: Ensayo celular In Vitro p-PAK1(S144) y p-MEK1(S298)

Ejemplo 13: Inhibición del crecimiento de un compuesto de Fórmula I-IV y A-D en varias líneas de células cancerosas

Ejemplo 14: Ensayo clínico del inhibidor PAK en niños, adolescentes y adultos jóvenes

con neurofibromatosis de tipo 1 y neurofibromas plexiformes progresivos

Ejemplo 15: Inhibidores PAK como monoterapia en el tratamiento de neurofibromatosis de tipo 2 - Schwannoma vestibular relacionado

Ejemplo 16: Estudio para evaluar la seguridad, farmacocinética y farmacodinámica de un inhibidor PAK en pacientes con tumores sólidos avanzados e incurables en los cuales las cinasas diana están relacionadas a la patofisiología de la enfermedad

Ejemplo 17: Estudio de un inhibidor PAK de glioblastoma recurrente

Ejemplo 18: Estudio de seguridad y eficacia de un inhibidor

PAK y gemcitabina combinados para pacientes con carcinoma de células renales sarcomatoide metastásico o no extirpable

Ejemplo 19: Monitoreo in vivo de la plasticidad de la espina dendrítica en ratones GFP-M/DN-DISC1 doblemente transgénicos tratados con un compuesto inhibidor de PAK descrito en la presente

Ejemplo 20: Tratamiento de esquizofrenia mediante administración de un compuesto inhibidor PAK descrito en la presente en un modelo animal

Ejemplo 21: Tratamiento de depresión clínica mediante administración de un compuesto inhibidor PAK descrito en la presente en un modelo animal

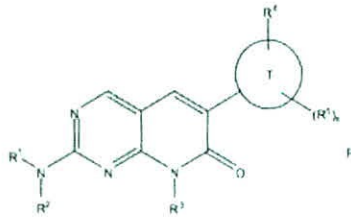
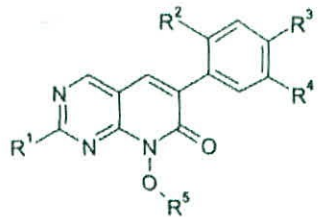
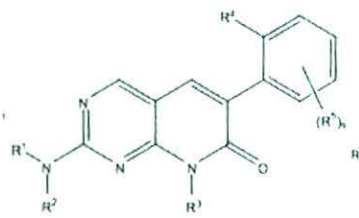
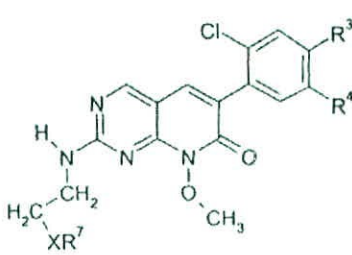
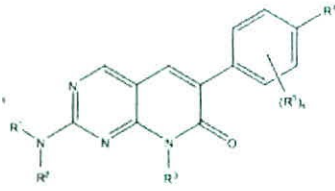
Ejemplo 22: Tratamiento de epilepsia mediante administración de un compuesto inhibidor PAK descrito en la presente en un modelo animal

Ejemplo 23: Tratamiento de deterioro cognitivo leve mediante administración de un inhibidor PAK en un modelo animal

Ejemplo 24: Tratamiento de autismo mediante administración de un inhibidor de PAK en un modelo animal

De lo anterior, podemos decir que: el ejemplo 2 "**Tabla: IC₅₀ de Inhibición de PAK**", describe algunos datos obtenidos por los compuestos representados en el primer grupo de ejemplos, los cuales no son inesperados o sorprendentes a la luz de lo divulgado en el arte anterior, tal como sucede en lo revelado en la Publicación Internacional WO2009130015 - IMPROVED RAF INHIBITORS – publicado en 29.10.2009.

Dicha anterioridad anticipa compuestos con un núcleo igual al reclamado, veamos:

Exp. 14-119704	WO2009130015
 Fórmula I	 (I)
 Fórmula II	 (Ia)
 Fórmula III;	

Como se puede observar, la diferencia está en el grupo sustituyente R3 de los compuestos reclamados, pues en el caso de la anterioridad hay un oxígeno que sirve de enlace entre el nitrógeno y el grupo sustituyente R5 (que hace las veces de R3 en la solicitud colombiana), sin embargo, es de notar la gran similitud entre las dos moléculas, y el efecto técnico es también similar:

Exp. 14-119-704	Table: PAK Inhibition IC50			
	Example	PAK1 IC50 (nM)	PAK2 IC50 (nM)	PAK3 IC50 (nM)
				PAK4 IC50 (nM)
	I	B	B	B
	D			
	137	B	A	B
	D			
A, IC50 < 50 nM; B, 50 nM ≤ IC50 ≤ 500 nM; C, 0.5 μM < IC50 < 5 μM; D, IC50 ≥ 5 μM				

WO 2009/130015	Table 3: Inhibition values of exemplary compounds (columns 2 and 3); and inhibition of tumor cell growth (columns 4 and 5)				
	Compound number	Biochemical inhibition [%] C-Raf	Biochemical inhibition [%] p38	CELLULAR IC ₅₀ [μM] HT-29 [B-Raf V600E mutant]	CELLULAR IC ₅₀ [μM] A-431 [B-Raf wildtype]
	3	nd	nd	< 5	> 10
	9	nd	nd	> 10	> 10
	64	>70%	>70%	< 5	> 10
	65	nd	nd	< 10	> 10
	66	nd	nd	< 10	> 10
	67	nd	nd	< 5	< 10

Como se puede ver en la comparación anterior, el efecto técnico alcanzado por los compuestos reclamados no es sorprendente o inesperado a la luz de lo divulgado por WO2009/130015, pues la mayoría de los valores ic50 obtenidos en la anterioridad rondan los 5-10 uM y los de la presente solicitud están entre 50nM hasta 5 uM, de tal forma que no se pude considerar que estos compuestos sean inventivos.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

III. PRUEBAS.

Ruego que se tengan como pruebas de este escrito, los documentos mencionados en el texto del mismo, todos ellos aportados por el suscrito y obrante en el expediente.

- Publicación Internacional WO2009/130015 – *“Improved Raf Inhibitors”* – publicado en 29.10.2009. Portada, páginas 1-7, 25 y 94

Señor Superintendente,

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(54) Title: IMPROVED RAF INHIBITORS

(57) Abstract: The present invention provides derivatives of pyrido[2,3-d]pyrimidin-7-one. These compounds are inhibitors or kinases such as Raf, including compounds that show anti-proliferative activity, including against tumor cells, and are useful in the treatment of diseases including cancer.

WO 2009/130015 A1

Improved Raf Inhibitors

Field of the Invention

The present invention provides derivatives of pyrido[2,3-d]pyrimidin-7-one. These compounds are inhibitors of kinases such as Raf, including compounds that show anti-proliferative activity against cells, including against tumor cells, and are useful in the treatment of diseases including cancer.

Background of the Invention

Kinases are important cellular enzymes that perform essential cellular functions such as regulating cell division and proliferation, and appear to play a decisive role in many disease states such as in disease states that are characterized by uncontrolled proliferation and differentiation of cells. These disease states encompass a variety of cell types and maladies such as cancer, atherosclerosis, and restenosis.

Drugs that target kinases, and especially drugs based on small-molecule chemical compounds that inhibit the activity of kinases, are important medicines that can significantly improve the health, lifespan or quality of life for people throughout the world, including patients suffering from highly debilitating diseases such as cancer. Indeed, the drug "imatinib" (GLEEVEC/GLIVEC; Novartis) is such a drug that inhibits a kinase and is used to successfully treat certain types of cancer including particular types of leukaemia (CML) and gastrointestinal cancer (GIST). Its improved efficacy compared to previous standard treatments for CML, and that it is generally very well tolerated, showing mild side-effects, has lead, among other reasons, for it to have made the cover of TIME magazine where it was described as a "bullet" to combat cancer.

Tyrosine kinases are essential for the propagation of growth factor signal transduction leading to cell cycle progression, cellular proliferation, differentiation, and migration. Tyrosine kinases include cell surface growth factor receptor tyrosine kinases (RTKs) such as FGFR and PDGFR as well as non-receptor tyrosine kinases including c-Src and Lck. Inhibition of these enzymes has been demonstrated to cause antitumor and antiangiogenesis activity (Hamby et al., Pharmacol. Ther, 1999; 82(2-3):169-193).

The molecular mechanisms and signaling pathways that regulate cell proliferation and survival are receiving considerable attention as potential targets for anticancer drug development.

Recently, there has been a notable increase in efforts directed at targeting the MAPK pathway, which integrates proliferative signals that are initiated by a wide array of RTKs and G protein-coupled receptors.

The MAPK signal cascade includes a G protein, known as Ras, that works upstream of a core module consisting of three kinases: Raf, MEK1/2 and ERK1/2. In this signal cascade, Raf (a serine/threonine kinase) phosphorylates and thus activates MEK1/2, which in turn ultimately leads to the activation of ERK1/2. Understanding of Raf function in Ras signaling is complicated by the fact that in mammals Raf is encoded by a gene family consisting of three genes (A-raf, B-raf and C-raf (raf-1)) which encode highly conserved 68 to 74 kD proteins (Daum et al., Trends Biochem. Sci. 1994, 19: 474-480) sharing highly conserved amino-terminal regulatory regions and catalytic domains at the carboxyl terminus. Raf proteins are normally cytosolic but are recruited to the plasma membrane by the small G-protein Ras, with this being an essential step for Raf activation by growth factors, cytokines, and hormones. Raf activation at the membrane occurs through a highly complex process involving conformation changes, binding to other proteins, binding to lipids, and phosphorylation and dephosphorylation of some residues.

Raf kinases, and particularly B-Raf, have long been considered attractive targets for drug discovery and therapeutic intervention due to their importance as potential checkpoints for cancer-related signal transduction (Tuveson et al., Cancer Cell, 2003, 4: 95-98; Strumberg and Seeber, Onkologie, 2005, 28: 101-107; Beeram et al., J. Clin. Oncol. 2005, 23: 6771-6790).

The importance of the MAPK signalling cascade for the proliferation and survival of tumor cells has recently increased following the discovery of a number of activating mutations of B-Raf in human tumors. Activating Raf mutations have been identified in melanoma, thyroid, colon, and other cancers (Davies et al., Nature, 2002, 417: 949-954; Cohen et al., J. Natl. Cancer Inst., 2003, 95: 625-627; Mercer and Pritchard, Biochim Biophys Acta, 2003, 1653: 25-40; Oliveira et al., Oncogene, 2003, 22: 9192-9196; Pollock et al., Nat. Genet. 2003, 33: 19-20; Domingo et al., Genes Chromosomes Cancer 2004, 39: 138-142; Shih and Kurman, Am. J. Pathol., 2004, 164: 1511-1518). Therefore, in addition to a role in controlling tumors with Ras mutations or activated growth factor receptors, inhibitors of Raf kinases harbor therapeutic potential for tumors carrying a B-Raf oncogene (Sharma et al., Cancer Res. 2005, 65: 2412-2421).

A variety of agents have been discovered to interfere with Raf kinases, including antisense oligonucleotides and small molecules. These inhibitors prevent the expression of Raf protein, block Ras/Raf interaction, or obstruct its kinase activity. Down-regulation of B-Raf activity by siRNA led to decreased tumorigenic potential of 1205 Lu cells (Sharma et al., Cancer Research, 2005, 65: 2412-2421), and by the kinase inhibitor BAY43-9006 (Sorafenib) led to inhibition of the growth of melanoma cells (Panka et al., Cancer Research., 2006, 66: 1611-9). Raf inhibitors that are currently undergoing clinical evaluation show promising signs of anti-cancer efficacy with a very tolerable safety profile. Most advanced is the Raf inhibitor Sorafenib (Nexavar®), which has been in clinical testing for the treatment of metastatic renal cell carcinoma (Ratain et al., Proc. Am. Soc. Clin. Oncol. (ASCO Meeting Abstract), 2004, 23: Abstract 4501; Motzer et al., J. Clin. Oncol. 2006, 24: 16-24) and which was approved in 2007 by the EMEA for the treatment of patients with advanced renal cell carcinoma. (RCC), or kidney cancer, who have failed prior interferon alfa or interleukin-2 based therapy or are considered unsuitable for such therapy, and by the FDA for use in patients with a form of liver cancer known as hepatocellular carcinoma, when the cancer is inoperable.

The family of mitogen-activated protein (MAP) kinases are proline-directed serine/threonine kinases that activate their substrates by dual phosphorylation. The kinases are activated by a variety of signals including nutritional and osmotic stress, UV light, growth factors, endotoxin and inflammatory cytokines. One group of MAP kinases is the p38 kinase group that includes various isoforms (e. g., p38a, p39ss, p38 or p388).

The p38 kinases are responsible for phosphorylating and activating transcription factors as well as other kinases, and are activated by physical and chemical stress, proinflammatory cytokines, and bacterial lipopolysaccharides.

More importantly, the products of the p38 phosphorylation have been shown to mediate the production of inflammatory cytokines, including TNF, IL-1, and cyclooxygenase-2. These cytokines have been implicated in numerous disease states and conditions. For example, TNF- α is a cytokine produced primarily by activated monocytes and macrophages. Its excessive or unregulated production has been implicated as playing a causative role in the pathogenesis of rheumatoid arthritis. More recently, inhibition of TNF production has been shown to have broad application in the treatment of inflammation, inflammatory bowel disease, multiple sclerosis and asthma.

TNF has also been implicated in viral infections, such as HIV, influenza virus, and herpes virus including herpes simplex virus type-1 (HSV-1), herpes simplex virus type-2 (HSV-2), cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein Barr virus, human herpes virus-6 (HHV-6), human herpes virus-7 (HHV-7), human herpes virus-8 (HHV-8), pseudorabies and rhinotracheitis, among others.

Similarly, IL-1 is produced by activated monocytes and macrophages, and plays a role in many pathophysiological responses including rheumatoid arthritis, fever and reduction of bone resorption.

Additionally, p38 has been implicated in stroke, Alzheimer's disease, osteoarthritis, lung injury, septic shock, angiogenesis, dermatitis, psoriasis and atopic dermatitis, see, e.g., J. Exp. Opin. Ther. Patents, (2000) 10(1).

The inhibition of the above-mentioned cytokines by inhibition of the p38 kinase can be of benefit in controlling, reducing and/or alleviating one or more of these disease states.

Despite the progress that has been made, the search continues for low molecular weight kinase inhibitor compounds, especially compounds that inhibit Raf kinases, that are useful for treating a wide variety of diseases, including cancer, tumors and other proliferative disorders or diseases including restenosis, angiogenesis, diabetic retinopathy, psoriasis, surgical adhesions, macular degeneration, and atherosclerosis, or other disorders or diseases mentioned above. Thus, a strong need exists to provide compositions, pharmaceuticals and/or medicaments with kinase inhibitory activity, particularly inhibitory activity against one or more Raf kinases, or with anti-proliferative activity against cells such as tumour cells. Such compositions, pharmaceuticals and/or medicaments may possess not only such activity, but may also exert tolerable, acceptable or diminished side effects in comparison to other anti-proliferative agents. Furthermore, the spectrum of tumors or other diseases responsive to treatment with such compositions, pharmaceuticals and/or medicaments may be broad. The active ingredients of such compositions, pharmaceuticals and/or medicaments may be suitable in the mentioned indication as single agent, and/or in combination therapy, be it in connection with other therapeutic agents, with radiation, with operative/surgical procedures, heat treatment or any other treatment known in the mentioned indications.

It is known that specific classes of pyrido[2,3-d]pyrimidines, substituted in a specific manner, have pharmacologically useful properties. In particular, specific derivatives of

pyrido[2,3-d]pyrimidin-7-one are known to possess anti-proliferative activity. These compounds however are structurally dissimilar from the compounds of the present invention.

WO 96/34867 discloses 2-substituted and 2,8-disubstituted 6-aryl-pyrido[2,3-d]pyrimidin-7-ones and 7-imino derivatives thereof, that are shown to inhibit tyrosine kinases and to have certain activity in tumor models (see also US 5,620,981 and US 5,733,914). WO 01/55147 discloses 5,6-disubstituted 2,7-diamino-pyrido[2,3-d]pyrimidines having similar activities. WO 01/70741 discloses substituted 2-amino-5-(alkyl,aryl)-pyrido[2,3-d]pyrimidin-7-ones, that are shown to have Cdk inhibitor activity. WO 02/18380 discloses 8-unsubstituted and 8-substituted 2-amino-6-aryl-pyrido[2,3-d]pyrimidin-7-ones, that are shown to inhibit protein kinases, including p38. WO 02/18380 and WO 03/088972 disclose 2,4,8-trisubstituted pyrido[2,3-d]pyrimidin-7-ones, that are shown to inhibit kinases and are thus able to inhibit the production of various cytokines. WO 02/064594 discloses 8-unsubstituted and 8-substituted 2-amino-6-(amino,oxy)-pyrido[2,3-d]pyrimidin-7-ones and 7-imino derivatives thereof, that are shown to inhibit protein kinases, including p38. WO 03/062236 discloses 2-(pyrid-2-yl)amino-pyrido[2,3-d]pyrimidin-7-ones (optionally substituted at positions 5, 6 and/or 8), that are shown to be potent inhibitors of Cdk 4. WO 03/066630 discloses 6-(monocyclyl)-pyrido[2,3-d]pyrimidin-7-ones (optionally substituted at positions 2, 4 and/or 5), that are shown to be inhibitors of Cdks, and that showed activity in an ischemic stroke model. WO 2004/063195 discloses derivatives of 2-amino-8-methyl-6-phenyl-pyrido[2,3-d]pyrimidin-7-one that are shown to inhibit Bcr-Abl kinase.

In particular, PCT publication WO 03/062236 discloses 2-(pyrid-2-yl)amino-pyrido[2,3-d]pyrimidin-7-ones and 2-(pyrid-2-yl)amino-dihydropyrido[2,3-d]pyrimidin-7-ones (optionally substituted at positions 5, 6 and/or 8), as potent and selective inhibitors of Cdk 4 (and Cdk 6), and compares certain such compounds to their C2-phenylamino analogues, as disclosed in WO 98/33798 and WO 01/70741. The generic Markush structure disclosed and claimed in WO 03/062236 includes, amongst other suggested substituents at the nitrogen in position 8, a generically described substituent being "C₁ to C₈ alkoxy". WO 07/136465 discloses certain 6-(alkoxy-aminocarbonylphenyl)-pyrido[2,3-d]pyrimidin-7-ones for treating diseases and disorders associated with abnormal kinase activities. The generic Markush structure disclosed and claimed in WO 07/136465 includes, amongst other suggested substituents at the nitrogen in position 8, a generically described substituent -O-R⁷, with -R⁷ including "C₁₋₈ alkyl".

Summary of the Invention

We have invented a class of 8-substitued pyrido[2,3-d]pyrimidin-7-ones that includes compounds that exhibit surprising properties, including activity as inhibitors of a number of protein kinases such as C- and B-Raf, or p38, and anti-proliferative activity against cells such as
5 tumour cells. Such derivatives of pyrido[2,3-d]pyrimidin-7-ones provide an opportunity to develop new and effective therapies for diseases associated with kinase de-regulation or cellular proliferation, such as cancer or inflammatory disorders.

Compounds of the present invention are specific derivatives of pyrido[2,3-d]pyrimidin-7-one, as discussed in greater detail below. In analogy to certain pyrido[2,3-d]pyrimidin-7-ones
10 previously described, the compounds of the present invention are suitable for further pre-clinical or clinical research and development towards the treatment of a variety of disorders and diseases including cancer, proliferative, degenerative, inflammatory and other disorders and diseases. The present invention provides effective therapies and therapeutics for particularly debilitating diseases such as cancer and other diseases and disorders including those listed herein.

One aspect of the invention relates to 8-oxy-pyrido[2,3-d]pyrimidin-7-ones having a structure represented by formula (I) presented below, or tautomeric or stereoisomeric forms thereof, which are useful as kinase inhibitors and thus useful for treating disorders or diseases
15 mentioned herein, including proliferative disorders or diseases such as cancer, and inflammatory disorders or diseases.

In another aspect, the invention relates to pharmaceutical compositions, including a
20 pharmaceutically acceptable diluent, excipient or carrier and an amount, such as a therapeutically effective amount, of such kinase inhibitor, e.g., which is expected to ameliorate the effects of disorders or diseases mentioned herein, including proliferative disorders or diseases such as cancer, and inflammatory disorders or diseases.

Another aspect of the invention relates to a pharmaceutical package, including such
25 pharmaceutical composition, and instructions which indicate that said pharmaceutical composition may be used for the treatment of a patient suffering from a disorder or disease mentioned herein, including proliferative disorders or diseases such as cancer, and inflammatory disorders or diseases.

In another aspect, the invention relates to methods that involve administering to or
30 contacting a subject, a cell, a tissue, an organ or an organism with a therapeutically effective

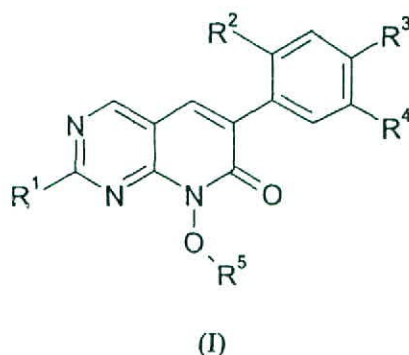
amount of a compound or pharmaceutical composition disclosed herein. These methods include, but are not limited to, prophylaxis and/or treatment of a disorder or disease mentioned herein, including proliferative disorders or diseases such as cancer, and inflammatory disorders or diseases.

5 In another aspect, the invention relates to uses of the compounds of the present invention for the preparation of a medicament for the treatment of a disorder or disease mentioned herein, including proliferative disorders or diseases such as cancer.

In another aspect, the invention relates to uses of the compounds of the present invention for the preparation of a medicament for the treatment of an inflammatory disorder or disease.

10 Another aspect of the invention relates to methods of synthesizing the compounds of the present invention, and to intermediates for such compounds.

Accordingly, the present invention provides compounds having a structure represented by the general formula (I)



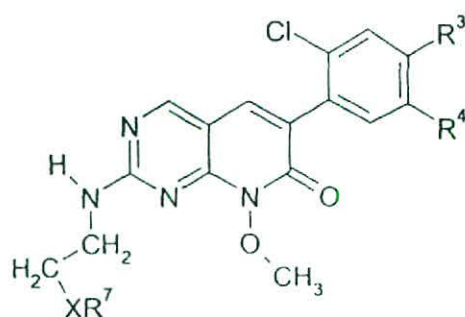
15

or any tautomeric form thereof, wherein

R¹ is selected from hydrogen, -NH₂, and substituted or unsubstituted: -NH-C₁-₆-alkyl, -NH-cycloalkyl, -NH-heterocycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-C₁-₆-alkylene-OR⁷, and -NH-C₁-₆-alkylene-NR⁷₂;

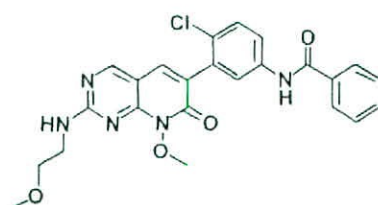
20 R² is selected from hydrogen, -halogen, -methyl, -CH₂F, -CHF₂, -CF₃, -O-methyl, -O-CH₂F, -O-CHF₂, and -O-CF₃;

one of R³ and R⁴ is hydrogen, and the other is -NH-C(=O)-(NH)ₓ-(CH₂)ᵧ-R⁶, wherein x and y are independently selected from 0 and 1;



(Ia)

or any tautomeric or stereoisomeric form thereof, wherein X is selected from -O- and -NR⁷-, and wherein R³, R⁴, and R⁷ are as defined above, provided, however, that compound (A) is excluded:



(A)

In certain embodiments, X is -NR⁷-. In particular such embodiments, both R⁷ are methyl.

In other certain embodiments, R³ is hydrogen and R⁴ is -NH-C(=O)-(NH)_x-(CH₂)_y-R⁶, wherein x and y are independently selected from 0 and 1, and R⁶ is as defined above. In a particular embodiment, y is 0.

In other certain embodiments, R⁴ is hydrogen and R³ is -NH-C(=O)-(NH)_x-(CH₂)_y-R⁶, wherein x and y are independently selected from 0 and 1, and R⁶ is as defined above. In certain embodiments, x is 0. In other embodiments, y is 0. In particular embodiments, x and y are 0.

In certain embodiments of Formula I, the compound is selected from:

4-Chloro-N-{4-chloro-3-[2-(2-dimethylamino-ethylamino)-8-methoxy-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-6-yl]-phenyl}-3-trifluoromethyl-benzamide

5-tert-Butyl-2H-pyrazole-3-carboxylic acid {4-chloro-3-[2-(2-dimethylamino-ethylamino)-8-methoxy-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-6-yl]-phenyl}-amide

66	D: 4.37	640 (321)	194, 253, 343
67	D: 4.82	731 (366)	198, 253 343

Table 3: Inhibition values of exemplary compounds (columns 2 and 3); and inhibition of tumor cell growth (columns 4 and 5)

Compound number	Biochemical inhibition [%] C-Raf	Biochemical inhibition [%] p38	CELLULAR IC ₅₀ [μM] HT-29 [B-Raf V600E mutant]	CELLULAR IC ₅₀ [μM] A-431 [B-Raf wildtype]
3	nd	nd	< 5	> 10
9	nd	nd	> 10	> 10
10	>70%	>70%	< 5	> 10
11	nd	nd	< 10	> 10
12	nd	nd	< 10	> 10
13	nd	nd	< 10	> 10
14	nd	nd	< 5	> 10
15	nd	nd	< 5	> 10
16	>70%	>70%	< 5	> 10
17	>70%	>70%	< 5	> 10
18	>70%	>70%	< 10	> 10
19	nd	nd	?	?

20	nd	nd	> 10	> 10
21	nd	nd	< 5	> 10
22	nd	nd	< 5	> 10
23	>70%	>70%	< 5	> 10
24	>70%	>70%	< 5	> 10
25	nd	nd	< 5	> 10
26	>70%	>70%	< 10	> 10
27	>70%	>70%	< 5	< 10
28	>70%	>70%	< 5	> 10
29	nd	nd	< 10	> 10
30	>70%	>70%	< 5	> 10
31	~70%	>70%	< 5	< 10
32	>70%	>70%	< 5	< 10
33	nd	nd	> 10	> 10
34	nd	nd	< 10	> 10
35	nd	nd	< 5	> 10
36	nd	nd	> 10	> 10
37	>70%	>70%	< 5	< 10
38	nd	nd	> 10	> 10
39	>70%	>70%	< 5	> 10
40	nd	nd	> 10	> 10
4	>70%	>70%	< 10	> 10
41	>70%	>70%	< 5	< 10
42	>70%	>70%	< 5	< 10