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DIRECCIÓN DE NUEVAS CREACIONES

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Bogotá, D.C.,

Abogado
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ASUNTO

Radicación	09 149 835
Trámite	011
Evento	378
Actuación	519
Oficio	15167
Folios	006

Patente de Invención	☑		Patente de Modelo de Utilidad	☐
Vía Nacional				
Vía PCT (Fase Nacional)	☑	Capítulo I ☐	Capítulo II	☐
No. Solicitud Internacional		PCT/GB08/02194		
Fecha de Presentación Internacional		24/Junio/2008		

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 7 a 51	31/Diciembre/2009
Reivindicaciones:	Folios 52 a 54	31/Diciembre/2009
Prioridad:	PCT/GB2007/002390	26/Junio/2007

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486), y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "DERIVADOS DE TIAZOL FUSIONADOS COMO INHIBIDORES DE QUINASA".

El problema planteado en esta solicitud consiste en la necesidad de suministrar compuestos útiles como inhibidores selectivos de PI3 quinasa.

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto de la fórmula (I) sus sales y composiciones que lo contienen.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D 513/04, A61K 31/437, C07D 519/00.

4. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de la reivindicación 15 no es patentable de acuerdo con el Art citado.

5. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)
El uso de las reivindicaciones 12 – 14 no es patentable, de acuerdo con el Art 14.

6. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 y sus dependientes 2 a 9 y 11, reclaman también los solvatos de los cuales no existe soporte en la descripción.

En las Reivindicaciones 1 y sus dependientes, se sugiere una razonable generalización del tipo de compuestos que ha sido sintetizado ó probado, con la actividad biológica que se les atribuye, teniendo en cuenta que sólo están soportadas la sustituciones de R11 y R12 por un grupo metilo, R24 por H, V y W son siempre un átomo de C (según los ejemplos de la descripción).

La reivindicación 10 no esta caracterizada por esta correctamente caracterizada.

7. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación de la Solicitud de Prioridad: Junio 26 de 2007 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Nº	Documento	Título	Fecha de Publicación*
D1	WO2006114606	Fused Thiazole derivatives as kinase inhibitors	Noviembre 2 del 2006
D2	Libro	Foye´s principles of Medicinal Chemistry	2002

D1[1], enseña el compuesto derivado de tiazol fusionado con actividad como inhibidores de quinasa de fórmula (I), sus sale y composiciones que lo contienen.

D2[2] libro se refiere al bioisosterismo como herramienta para la modificación de compuestos.

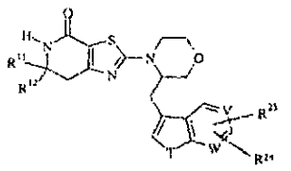
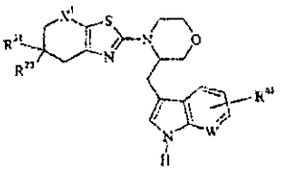
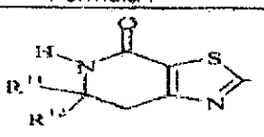
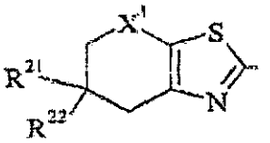
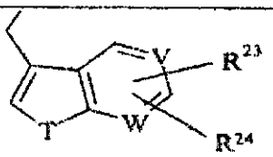
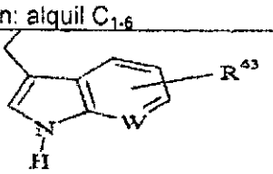
8. **Examen de Patentabilidad** (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en un compuesto de fórmula (I), o una sal o un solvato farmacéuticamente aceptable del mismo.

1http://worldwide.espacenet.com/publicationDetails/biblio?DB=EPODOC&II=0&ND=3&adjacent=true&locale=en_EP&FT=D&date=20061102&CC=WO&NR=2006114606A1&KC=A1
2 Foyer´s principles of Medicinal Chemistry sixth Edition Thomas L. LEMKE, M David A. WILLIAMS, Victoria F.ROCHE, S. William Zito; Classical Bioisosteres, Pág. 50, 2002, (págs. Portada y 49, Fls. 111 y 112).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características **esenciales**	**D1**
 Fórmula I	 Fórmula IIE
 C(O) **N-H** R11 y R12 son: -CH3	 X1= C(O), **C-H** R21 y R22 son: alquil C_{1-6}
 **T=N-alquilC1-6** W=CH V=CH R23=hidrógeno, halógeno, ciano, alquilo C1-6, hidroxialquilo C1-6, trifluorometilo, arilalquiloC1-6, hidroxi, alcoxiC1-6, trifluorometoxi, ariloxi, arilalcoxiC1-6, alquilC1-6tio, alquilC1-6sulfoniloxi, amino, alquilC2-6carbonilamino.	 **N-H** W=CH CH R43= hidrógeno, halógeno, ciano, alquilo C1-6, hidroxialquilo C1-6, trifluorometilo, arilalquiloC1-6, hidroxi, alcoxiC1-6, trifluorometoxi, ariloxi, arilalcoxiC1-6, alquilC1-6tio, alquilC1-6sulfoniloxi, amino, alquilC2-6carbonilamino.

Los documentos D1 y D2 constituyen el estado de la técnica cercano a la invención porque D1, da a conocer el compuesto de fórmula IIE (pág.31) sus sales, solvatos y enantiómeros (págs.2, 5 y 6), además de sus composiciones farmacéuticas (reivindicación 16, pág.140).

El compuesto, objeto de esta solicitud se diferencia del conocido en D1, en que este incluye un átomo de N en el anillo de ciclohexanona para formar la piridinona.

El hecho de incluir un átomo de N en el anillo de ciclohexanona para formar la piridinona, en el compuesto que se daba a conocer en D1, no causa un efecto sorprendente.

Por tanto, el Problema Técnico Objetivo consiste en ¿cómo modificar el compuesto según D1, para logar un compuesto alternativo con la misma actividad que el conocido?.

Es importante mencionar que en la descripción de la presente solicitud se observan valores de IC50 para la inhibición de la actividad de PI3Kα y/o PI3Kβ, y/o PI3Kγ y/o PI3Kδ humanas de 50μM o mejores (pág.18, Fl.24), que al compararlos con los resultados de actividad del compuesto de D1, que también son inhibidores de la actividad de PI3Kα y/o PI3Kβ y/o PI3Kγ y/o PI3Kδ humanas, se comprueba que son exactamente iguales por tener un IC50 de 50μM o mejores (enzyme inhibition assays pág.40).

No obstante D2 muestra que es posible cambiar un grupo CH2 por un grupo NH (tabla 2.8, pág.49) con la expectativa de mantener la misma actividad en el

compuesto reivindicado.

En consecuencia, la reivindicación es obvia, porque la persona del oficio normalmente versada en la materia enfrentada al problema de "¿cómo modificar el compuesto según D1, para logar un compuesto alternativo con la misma actividad que el conocido?", incluiría el grupo NH que se revela en D2 en el compuesto que se enseña en D1, logrando de esta forma el compuesto reivindicado.

Por lo cual el compuesto de la Reivindicación 1 carece de Nivel Inventivo.

Puesto que las reivindicaciones dependientes 2 a 9 y 11 no mencionan características que las hagan inventivas, tampoco tienen nivel inventivo.

9. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO2006114606	1-9 y 11	Nivel Inventivo
D2	Libro	1-9 y 11	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.

JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

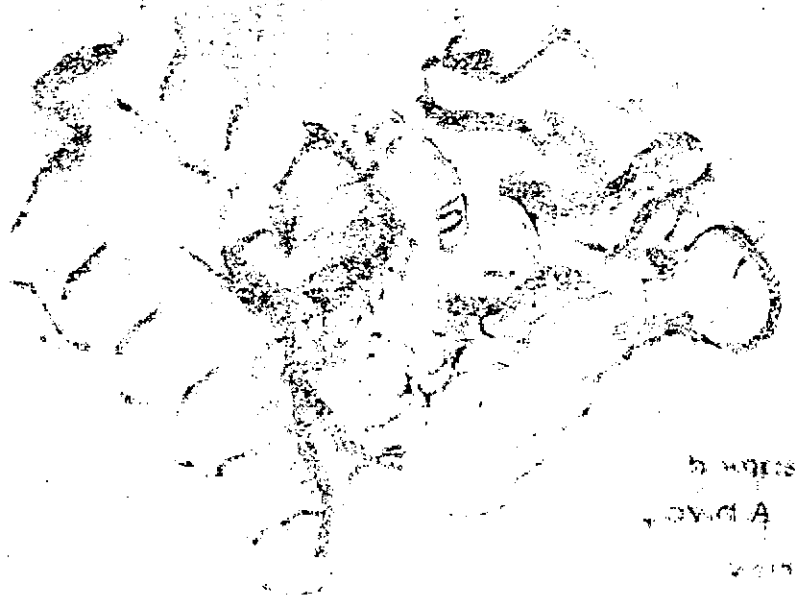
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MEDICINAL CHEMISTRY

SIXTH EDITION



THOMAS L. LEMKE

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FOYE'S Principles of Medicinal Chemistry

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Cover image courtesy of Wavefunction, Inc. The ribbon display (green and red) is tyrosine kinase. The "active site" for tyrosine kinase is shown as tube display with a stick-style electrostatic potential map (a charge distribution map), with the drug imatinib shown in the "active site" with a solid-color style electrostatic potential map (where the colors toward red depict negative potentials; colors toward blue depict positive potentials; and colors such as yellow, orange, green, and violet depict intermediate values). Imatinib (a 2-phenyl amino pyrimidine derivative, a.k.a. CGP57148B, ST1571 or Gleevec®) is a selective inhibitor of several tyrosine kinases that binds in the ATP-binding pocket of tyrosine kinase and blocks the activities of Abl, c-kit, and PDGFR. It is used for treating chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs), and a number of other malignancies.

Sixth Edition

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Table 2.8. Grimm's Hydride Displacement "Law"

C	N	O	F	Ne
	CH	NH	OH	FH
		CH$_2$	NH$_2$	OH$_2$
			CH$_3$	NH$_3$

valence electrons for each group of atoms within a column. Within each column, the groups are considered to be "pseudoatoms" with respect to one another. Thus, NH_2 is considered to be isosteric to OH, and so on. This early view of isosterism did not consider the actual location, motion, and resonance of electrons within the orbitals of these functional group replacements. Careful observation of this table reveals that some groups do share similar physicochemical properties, but others have very different properties, despite having the same number of valence electrons. For example, OH and NH_2 share similar hydrogen-bonding properties and, therefore, should be interchangeable if that is the only criterion necessary. The NH_2 group is basic, however, whereas the OH is neutral. Hence, at physiological pH, the NH_2 group would be in its protonated, or conjugate acid, form and give the molecule a positive charge. If OH is being substituted by NH_2, the additional positive charge could have a significant effect on the overall physicochemical properties of the molecule in which it is being introduced. The difference in physicochemical properties of the CH_2 group relative to the OH and NH_2 groups is even greater. In addition to basicity and acidity, this "law" fails to take into account other important physicochemical parameters, such as electronegativity, polarizability, bond angles, size, shape of molecular orbitals, electron density, and partition coefficients, all of which contribute significantly to the overall physicochemical properties of a molecule.

Instead of considering only partial structures, Hinsberg (34) applied the concept of isosterism to entire molecules. He developed the concept of "ring equivalents"—that is, groups that can be exchanged for one another in aromatic ring systems without drastic changes in physicochemical properties relative to the parent structure. Benzene, thiophene, and pyridine illustrate this concept (Fig. 2.33). A $-CH{=}CH-$ group in benzene is replaced by the divalent sulfur, -S-, in thiophene, and a $-CH{=}$ is replaced by the trivalent $-N{=}$ to give pyridine. The physical properties of benzene and thiophene

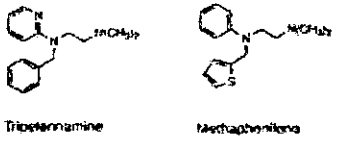


Fig. 2.33. Isosteric substitution of thiophene for benzene and benzene for pyridine.

are very similar. For example, the boiling point of benzene is 81.1°C and that of thiophene is 84.4°C (at 760 mm Hg). Pyridine, however, deviates, with a boiling point of 115 to 116°C. Hinsberg therefore concluded that divalent sulfur (-S- or thioether) must resemble $-CH{=}CH-$ in shape, and these groups were considered to be isosteric. Note that hydrogen atoms are ignored in this comparison. Today, this isosteric relationship is seen in many drugs (e.g., H_1-receptor antagonists) (Fig. 2.33).

Bioisosterism

It is difficult to relate biological properties to physicochemical properties of individual atoms, functional groups, or entire molecules, because many physicochemical parameters are involved simultaneously and, therefore, are difficult to quantitate. Simple relationships as described above often do not hold up across the many types of biological systems seen with medicinal agents. That is, what may work as an isosteric replacement in one biological system (or a given drug receptor, enzyme, etc.) may not work in another system. Because of this, it was necessary to introduce the term "bioisosterism" to describe functional groups related in structure and having similar biological effects. Friedman (35) introduced the term bioisosterism and defined it as follows: "Bioisosteres are (functional) groups or molecules that have chemical and physical similarities producing broadly similar biological properties." Recently, Burger (36) expanded this definition to take into account biochemical views of biological activity: "Bioisosteres are compounds or groups that possess near equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties such as hydrophobicity. Bioisosteric compounds affect the same biochemically associated systems as agonist or antagonists and thereby produce biological properties that are related to each other." The key point is that the same pharmacologic target is influenced by bioisosteres as agonists or antagonists. What may work as a bioisosteric group in one biological system may not have similar effects on another.

Classical and Nonclassical Bioisosteres

Bioisosteric groups can be subdivided into two categories: classical and nonclassical bioisosteres. Functional groups that satisfy the original conditions of Langmuir and Grimm are referred to as classical bioisosteres. Nonclassical bioisosteres do not obey steric and electronic definitions of classical bioisosteres and do not necessarily have the same number of atoms as the substituent they replace. A wider set of compounds and functional groups are encompassed by nonclassical bioisosteres that produce, at the molecular level, qualitatively similar agonistic or antagonistic responses. In animals, many hormones, neurotransmitters, and so on with very similar structures and biological actions can be classified as bioisosteres. An example would be the insulins isolated from various mammalian species. Even though these insulins may differ by several amino acid residues, they