

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogada
ALICIA LLOREDA RICAURTE

ASUNTO	Radicación	09 025 722
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	009

E 12774

Patente de Invención



Patente de Modelo de Utilidad



Via Nacional



Via PCT (Fase Nacional)



Capítulo I



Capítulo II



No. Solicitud Internacional

PCT/US07/076378

Fecha de Presentación Internacional

21/Febrero/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 29 a 134	12/Marzo/2009
Reivindicaciones:	Folios 135 a 151	12/Marzo/2009
	Folios 185 a 200	29/Abril/2009
	Folios 218 a 241	30/Junio/2010
Prioridad:	US 60/839,018	21/Agosto/2006
	US 60/851,385	13/Octubre/2006

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 ÁCIDO FENOXIFENILACÉTICO 4-

Expediente 09 025 722 1er Art 45

SUSTITUIDOS".

El problema planteado en esta solicitud consiste en la necesidad de suministrar compuestos útiles para tratar y prevenir enfermedades alérgicas tales como asma, rinitis alérgica y dermatitis atópica y otras enfermedades inflamatorias moderadas por prostaglandinas D2(PGD2).

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto de la fórmula (I), su proceso de síntesis y la composición que lo contiene.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07C 233/87, 255/57, 307/06, 311/06, 311/19, 317/14, C07D 213/81, 213/82, 333/16, A61K 31/18, 31/435, 31/165, 31/77, 31/381, 31/10.

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones 13 y 14 repiten la materia de la reivindicación 2 (fórmula Ia), en donde R9 y R10 son H.

5. 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: Agosto 21 de 2006 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Nº	Documento	Título	Fecha de Publicación*
D1	WO2006/014012	Aromatic compound	9 de Febrero de 2006
D2	artículo	Bioisosterism: A Rational Approach in Drug Design	25 de Julio 1996

D1¹ divulga compuestos derivados fenoxifenilacético, los cuales presenten actividad como inhibidores de la producción de colágeno en daños por fibrosis (inflamación modulada por prostaglandinas PDG2), con actividades en IC50 entre 0.0019 y 0.0950 µM.

D2² se refiere al bioisosterismo como herramienta para la modificación de compuestos en agentes activos más seguros y más eficaces clínicamente.

6. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

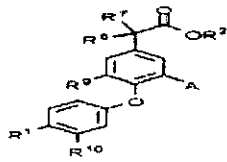
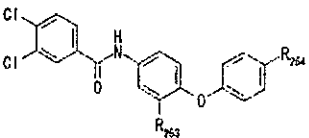
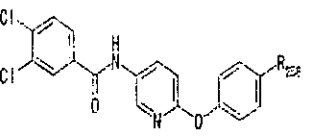
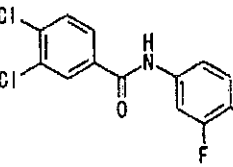
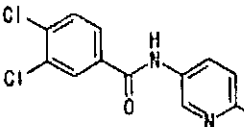
La reivindicación 1 consiste en un compuesto de fórmula (I).

1 [http://patentscope.wipo.int/search/en/detail.jsf?docId=WO2006014012&recNum=1&docAn=JP2005014611&queryString=FP:\(wo2006014012\)&maxRec=1](http://patentscope.wipo.int/search/en/detail.jsf?docId=WO2006014012&recNum=1&docAn=JP2005014611&queryString=FP:(wo2006014012)&maxRec=1).

2 Bioisosterism: A Rational Approach in drug Design, George A. Patani and Edmond J. Lavoie
Chem.Rev.1996.96.3147-3176

Expediente 09 025 722 1er Art 45

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

Características esenciales	D1	
 o una sal del mismo	 R253=F y R254=CH2-COOCH3 compuesto 503	 R258=CH2-COOCH3 compuesto 518
R7 y R8= H	CH2	CH2
R2=H, alquilo C1-6	CH3	CH3
A= H	H	H
R9=H	H	H
R1=Ar¹-L¹-W-L²- L²=-(CR^cR^d)_m- W= -CONR^{3a}-; -NR^{3b}CO- R^{3a} y R^{3b}= H, -CH₃ L¹ = -(CR^aR^b)_n- ; -(CH=CH)- ; -O(CR^aR^b)_n-, a condición que cuando W es -NR^{3b}CO- entonces L¹ no es -(CH=CH)- N y m son independientemente 0,1, o 2. Cada R^a, R^b, R^c, R^d son independientemente H, F, OH, metilo... Ar1= fenilo, naftilo opcionalmente sustituido por Cl, F, ciclopropilo O Ar1 es 1,2,3,4,tetrahidronaftilo opcionalmente sustituido por metoxi, a condición que cuando Ar1 es naftilo o 1,2,3,4,tetrahidronaftilo entonces n=0		
R10= H, F	F	H

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque D1 divulga compuestos derivados fenoxifenilacético (ejemplos 503,512 entre otros, Págs. 512 y 514), los cuales presenten actividad como inhibidores de la producción de colágeno en daños por fibrosis (inflamación modulada por prostaglandinas PDG2), con actividades en IC50 entre 0.0019 y 0.0950 µM (pág. 978).

Los compuestos reivindicados difieren de los de D1 en la ubicación del Flúor en el anillo fenil del centro de la molécula, ya que en los reclamados están ubicados en posición meta con respecto al oxígeno del grupo fenoxi y en los compuestos

conocidos están ubicados en posición orto, respecto a este mismo grupo.

No obstante esta diferencia, no se evidencia un efecto sorprendente ó una ventaja de los compuestos reivindicados con respecto a lo divulgado en el estado del arte (compuestos isómeros) en cuanto a la actividad farmacológica.

Cabe resaltar que los datos proporcionados por el solicitante, hacen referencia a ensayos de actividad expresados en IC50 menores de 1 µM (págs. 37 y 38, descripción), los cuales no son mejores que los IC50 de los compuestos isómeros conocidos, por lo tanto se requiere una mayor concentración de los nuevos compuestos (reivindicados de formula I) para lograr un mismo efecto.

De manera que el Problema técnico objetivo a resolver es: ¿Cómo modificar los compuestos derivados fenoxifenilacético conocidos en D1, para lograr compuestos alternativos, con actividad modulada por prostaglandinas PDG₂?

Adicionalmente, el cambio de posición (orto o meta) de sustituyentes como el flúor en diferentes moléculas activas (fármacos) se encuentra divulgado en D2, el cual enseña que el estas sustituciones son bien conocidas en el estado de la técnica. Además el H, F y Cl son isósteros (Págs. 3149 y 3150, Fls. 243 y 244), en donde reemplazar específicamente el H por halógenos como F en un anillo aromático, ha mostrado incremento en la afinidad de unión disminuyendo los valores de IC50 (ej: pág. 3149; Fl.243, Figura 2). Asimismo es conocido en el estado de la técnica³ el bioisosterismo clásico como es el reemplazar un H por un F y un anillo benceno por una piridina (pág.50, Fl.245) con la expectativa de producir el mismo efecto biológico como es el caso de los compuestos 503 y 518, entre otros, de D1.

De manera que tomando en cuenta todo lo anteriormente expuesto, la persona normalmente versada en la materia que pretenda obtener compuestos derivados fenoxifenilacético que modulen la prostaglandinas PDG₂ y que conozca el estado de la técnica, estaría motivado a realizar la modificación bioisostérica de hidrógeno por flúor propuesto en D2, o la de reemplazar un benceno por una piridina, en los compuestos divulgados por D1 llegando así al objeto de la reivindicación , por lo cual el objeto reivindicado no tiene nivel inventivo.

Puesto que las reivindicaciones dependientes 2 a 17 no mencionan características inventivas adicionales, tampoco pueden ser consideradas inventivas.

7. Conclusión

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

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO2006/014012	1-17	Nivel Inventivo
D2	Articulo	1-17	Nivel Inventivo

3 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, Fls. 248 y 249.
Expediente 09 025 722 1er Art 45

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.


JESÚS FERNEL GARCÍA GARCÍA
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha
25 JUL. 2012

Elaborado por: Lyna del Carmen Mordecay Dunoyer
Revisado Por: Gloria Jacqueline Alfonso Rozo
Aprobado por: Jesús Fernel García García.

OK

Bioisosterism: A Rational Approach in Drug Design

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Contents

I. Introduction	3147
II. Classical Bioisosteres	3149
A. Monovalent Atoms or Groups	3149
1. Fluorine vs Hydrogen Replacements	3149
2. Interchange of Hydroxyl and Amino Groups	3150
3. Interchange of Hydroxyl and Thiol Groups	3151
4. Fluorine and Hydroxyl, Amino, or Methyl Groups as Replacements for Hydrogen (Grimm's Hydride Displacement Law)	3152
5. Monovalent Substitutions Involving Chloro, Bromo, Thiol, and Hydroxyl Groups (Erlenmeyer's Broadened Classification of Grimm's Displacement Law)	3154
B. Divalent Isosteres	3155
1. Divalent Replacements Involving Double Bonds	3155
2. Divalent Replacements Involving Two Single Bonds	3155
C. Trivalent Atoms or Groups	3156
D. Tetrasubstituted Atoms	3157
E. Ring Equivalents	3158
1. Divalent Ring Equivalents	3158
2. Trivalent Ring Equivalents	3159
III. Nonclassical Bioisosteres	3160
A. Cyclic vs Noncyclic Nonclassical Bioisosteric Replacements	3160
B. Nonclassical Bioisosteric Replacements of Functional Groups	3165
1. Hydroxyl Group Bioisosteres	3165
2. Carbonyl Group Bioisosteres	3166
3. Carboxylate Group Bioisosteres	3168
4. Amide Group Bioisosteres	3170
5. Thiourea Bioisosteres	3171
6. Halogen Bioisosteres	3172
IV. Conclusion	3172
V. Acknowledgments	3172
VI. References	3172



George Patani graduated with a B.Pharm. in 1992 from the College of Pharmaceutical Sciences, Mangalore University at Manipal, India. In 1996, he received his M.S. in Pharmaceutical Science at Rutgers University under the direction of Professor Edmond J. LaVoie. He is presently pursuing graduate studies in pharmaceuticals. His current research interests are focused on drug design and controlled drug delivery.



Edmond J. LaVoie received his B.S. in Chemistry from Fordham University in 1971 and his Ph.D. in Medicinal Chemistry from S.U.N.Y. at Buffalo under the direction of Dr. Wayne K. Anderson. After postdoctoral study with Dr. S. Morris Kupchan at the University of Virginia, he joined the American Health Foundation in Valhalla, NY. In 1988, he was appointed Professor of Medicinal Chemistry in the College of Pharmacy at Rutgers University. His current research interests are in the design and synthesis of cancer chemotherapeutics and in the elucidation of mechanism(s) of carcinogenesis.

I. Introduction

Years of cumulative research can result in the development of a clinically useful drug, providing either a cure for a particular disease or symptomatic relief from a physiological disorder. A lead compound with a desired pharmacological activity may have associated with it undesirable side effects, characteristics that limit its bioavailability, or structural features which adversely influence its metabolism and excretion from the body. Bioisosterism represents one approach used by the medicinal chemist

for the rational modification of lead compounds into safer and more clinically effective agents. The concept of bioisosterism is often considered to be qualitative and intuitive.¹

The prevalence of the use of bioisosteric replacements in drug design need not be emphasized. This topic has been reviewed in previous years.²⁻⁵ The objective of this review is to provide an overview of bioisosteres that incorporates sufficient detail to enable the reader to understand the concepts being delineated. While a few popular examples of the successful use of bioisosteres have been included, the

divalent atoms or groups; (C) trivalent atoms or groups; (D) tetrasubstituted atoms; and (E) ring equivalents.

Nonclassical isosteres do not obey the steric and electronic definition of classical isosteres. A second notable characteristic of nonclassical bioisosteres is that they do not have the same number of atoms as the substituent or moiety for which they are used as a replacement. Nonclassical bioisosteres can be further divided into groups: (A) rings vs noncyclic structures; and (B) exchangeable groups.

This approach to classifying bioisosteres will be used to review literature examples of those bioisosteric replacements that have provided useful information on the structure-activity relationships associated with various pharmacologically active compounds.

II. Classical Bioisosteres

A. Monovalent Atoms or Groups

Similarities in certain physicochemical properties have enabled investigators to successfully exploit several monovalent bioisosteres. These can be divided into the following groups: (1) fluorine vs hydrogen replacements; (2) amino-hydroxyl interchanges; (3) thiol-hydroxyl interchanges; (4) fluorine, hydroxyl, amino, and methyl group interchanges (Grimm's Hydride Displacement Law); (5) chloro, bromo, thiol, and hydroxyl group interchanges (Erlenmeyer's Broadened Classification of Grimm's Displacement Law).

1. Fluorine vs Hydrogen Replacements

The substitution of hydrogen by fluorine is one of the more commonly employed monovalent isosteric replacements. Steric parameters for hydrogen and fluorine are similar, their van der Waal's radii being 1.2 and 1.35 Å, respectively.¹³ Thus, the difference in the electronic effects (fluorine being the most electronegative element in the periodic table) is often the basis for the major differences in the pharmacological properties of agents where fluorine has been substituted for hydrogen. Due to its electronegativity, fluorine exerts strong field and inductive effects on the adjacent carbon atom. Fluorine substitution, in general, exerts a diminished electron-withdrawing effect at distal sites. However, fluorine can donate a lone pair of electrons by resonance. This is commonly referred to as its mesomeric effect. The opposing resonance and field effects can nearly cancel. The pharmacological differences can be attributed to the influence of the electron-withdrawing effect that the fluorine substitution causes on interaction with either a biological receptor or enzyme, as well as its effect on the metabolic fate of the drug.

The antineoplastic agent 5-fluorouracil (5-FU) represents a classical example of how fluorine substitution of a normal enzyme substrate can result in a derivative which can alter select enzymatic processes. In this instance, 5-FU is biochemically transformed *in vivo* into 5-fluoro-2'-deoxyuridylic acid. Its close similarity to uracil allows this fluoro derivative to be a successful mimetic. This biochemically altered

form of 5-FU, 5-fluoro-2'-deoxyuridylic acid, is ultimately responsible for the inhibition of thymidylate synthase, an enzyme involved in the conversion of uridylic acid to thymidylic acid and critical for DNA synthesis (Figure 1). The increased reactivity of 5-fluoro-2'-deoxyuridylic acid relative to 2'-deoxyuridylic acid is due to the inductive effect of fluorine which results in its covalent binding to thymidylate synthase.

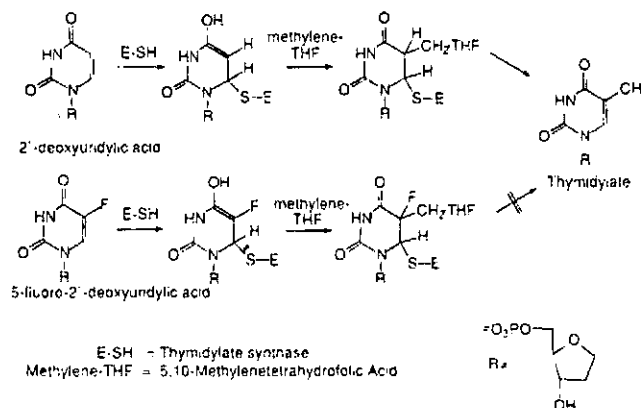


Figure 1.

The application of the monovalent substitution of a fluorine atom for a hydrogen atom can also be seen in a more recent study with naphthyl-fused diazepines, which were employed as agonistic probes of the pharmacophore of benzodiazepine receptors.¹¹ Replacement of the hydrogen with fluorine at the *ortho* position of the pendent phenyl group of either naphthyl-fused diazepines, as illustrated in Figure 2, resulted in enhanced affinity and efficacy for both naphthyl isomers (Table 4). This greater receptor binding affinity could again be attributed to the inductive effect of the fluorine atom facilitating a stronger interaction with the receptor.

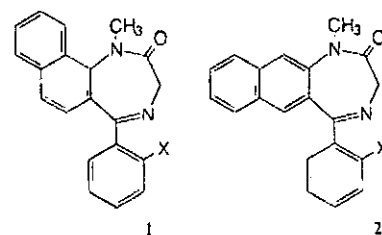


Figure 2.

Table 4. Benzodiazepine Receptor Binding Affinity for Naphthyl-Fused Diazepines

compound	X	IC ₅₀ (nM) ^a
1a	H	1000
1b	F	260
2a	H	1000
2b	F	55

^a *In vitro* potency of the compound to displace [³H]flunitrazepam from the benzodiazepine receptor.

Another good illustration of this monovalent bioisosteric replacement is observed in a recent series of anti-inflammatory corticosteroid analogues (3, Figure 3).¹⁵ In this study, the topical anti-inflammatory activity of two pairs of structurally similar corticosteroids were compared. Their relative anti-inflammatory activity was normalized to fluocinolone acetonide, which was assigned a potency of 100. Table

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Table 2.9 Classical Biosorters (Groups Within the Row Can Replace Each Other)

Monovalent biosorters

F, H
OH, SH
F, OH, NH, CH, OH, SH
Cl, Br, CF₃

Divalent biosorters

—CH₂—, —C(=O)—, —CH=CH—, —C(=O)—, —C(=O)—

Trivalent atoms or groups

—NH—, —N=, —P=, —As=

Tetravalent atoms

—C—, —Si—, —Ge—, —Sn—, —Pb—

Ring biosorters



still produce the same biological effects. (If this did not occur, the use of insulin in treating diabetes would have had to wait another 60 years for recombinant DNA technology to allow production of human insulin.)

What may be a successful biosorteric replacement for a given molecule interacting with a particular receptor quite often has no effect or abolishes biological activity in another. Thus, the use of biosorteric replacement (classical or nonclassical) in drug design is highly dependent on the biological system being investigated. No hard-and-fast rules exist to determine what biosorteric replacement is going to work with a given molecule, although as the following tables and examples demonstrate, some generalizations are possible. The medicinal chemist, however, must still rely on experience and intuition to decide the best approach to use when applying this strategy.

Each category of biosorters can be further subdivided as shown below, and examples are provided in Table 2.10:

I. Classical biosorters

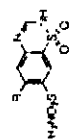
- Monovalent atoms and groups
- Divalent atoms and groups
- Trivalent atoms and groups
- Tetravalent atoms
- Ring equivalents

II. Nonclassical biosorters

- Exchangeable groups
- Range versus nonexchange structure

Classical Biosorters

Substitution of hydrogen by fluorine is one of the most common monovalent biosorteric replacements. Sterically, hydrogen and fluorine are quite similar, with their van



R =	Cl	Br	CF ₃
σ	-0.23	-0.23	-0.54
π	-0.71	-0.86	-0.82
E_s	-0.97	-1.15	-2.49

Fig. 2.34. Isosteric replacement of chlorine in thiazide diuretics. Comparison of physicochemical properties of the substituents.

der Waals' radii being 1.2 and 1.35 Å, respectively. Because fluorine is the most electronegative element in the periodic table, any differences in biological activity resulting from replacement of hydrogen with fluorine can be attributed to this property.

A classic example of hydrogen replacement by fluorine is the replacement of the amineoplastic agent 2-fluoranthracene from urea. Another example is shown in Figure 2.33, in which the chlorine of chlorothiazide has been replaced with bromine or a trifluoromethyl group. For each of the substituents, the electronic (where σ^+ is electron withdrawing and σ^- is electron donating) and hydrophobic (π) properties of each group are maintained relatively constant, but the size of each group varies significantly, as indicated by the Taft steric parameter (E_s).

Figure 2.35 shows an example of classical biosorteric substitution of an amino group for a hydroxyl group in folic acid. The amino group is capable of mimicking the tautomeric forms of folic acid and providing the appropriate hydrogen bonds to the enzyme active site.

A trivalent biosorteric replacement study was done by Galsbol et al. (37) with a series of o-tolophthal analogues (Fig. 2.36). o-Tolophthalol has been shown to exchange

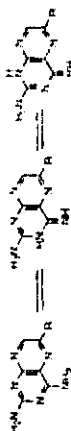
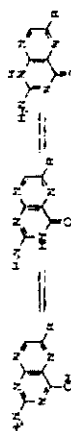
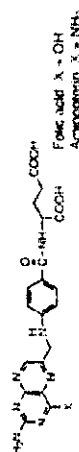


Fig. 2.35. Isosteric replacement of OH by NH₂ in folic acid and possible tautomers of folic acid and aminopterin.

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245

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Sanjay Kumar

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1. The first step is to identify the problem or question that needs to be answered. This involves understanding the context and the specific information required.

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1. Introduction

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III. Life Examples of mechanical chemistry

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2.1.5.2. *Staphylococcus aureus*

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