

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

2020
Bogotá, D.C.,

Abogado

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ASUNTO	Radicación	09-138245
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	021

1 6 7 1 6

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☒	Cap. I	☒
Vía PCT (fase nacional)	☒	Cap. II	☐

No. Solicitud Internacional PCT/EP2008/003473

Fecha de Presentación Internacional 29 de abril de 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 17-239	03 de diciembre de 2009
Reivindicaciones:	Folios 240-292	03 de diciembre de 2009
Prioridad:	DE 10 20070320507.1	12 de julio de 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).

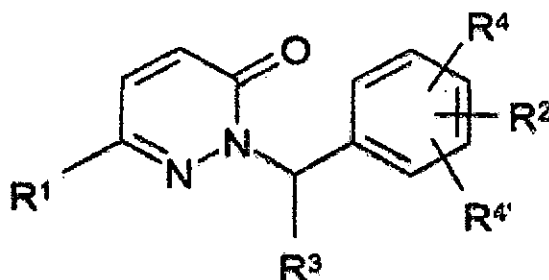
Y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Derivados de piridazinona"

El problema planteado en esta solicitud consiste en la necesidad de proporcionar compuestos útiles como inhibidores, reguladores o moduladores de señales quinasas.

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



El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D 403/14; 413/14; 417/10; 413/10.

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 17-25 no es patentable, de acuerdo con el Art 14.

5. De la Solicitud de Patente

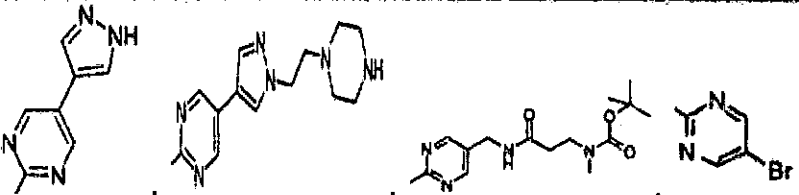
Titulo

El título es muy general y no define adecuadamente el objeto de la solicitud ni su alcance, por lo cual se sugiere cambiar el título de la solicitud por: "Inhibidores de las señales quinasa derivados de la 2-bencilpiridazin-3(2H)-ona".

Reivindicaciones (Art 30 D 486, Art 22 PCT)

El capítulo reivindicatorio no es claro ni conciso cuando utiliza términos tales como:

- Het, Het¹: porque no define el número de miembros que contiene el anillo
- Heterociclo de 6 miembros insaturado, saturado o aromático con 1-4 átomos de N, O y/o S, por el número de combinaciones a que dan lugar y se encuentran soportadas en el capítulo descriptivo.
- Alquilo con 1-10 átomos de C, Alquilo con 1-8 átomos de C: por el número indeterminado de combinaciones a los que pueden dar lugar.
- 1-7 átomos de H pueden estar reemplazados por F, puede estar mono-, di-, tri-, tetra-, o penta sustituido: no son concisas porque no limitan el alcance la reivindicación, ni la definen de manera adecuada.
- Alquilo cíclico 3-7 átomos de C: por el número indeterminado de combinaciones a los que pueden dar lugar.
- La utilización de los términos "m, n, p" se definen como 0, 1, 2, 3, 4: por el número indeterminado de combinaciones a los que pueden dar lugar.
- El uso de términos tales como "derivados": no define las posibles estructuras químicas que lo pueden conformar, lo cual tampoco se puede deducir de la descripción. Se requiere al solicitante para este punto, eliminar este término del alcance del pliego reivindicatorio.
- El uso de términos tales como "solvatos, sales. Tautómeros y estereoisómeros": es falta de claridad debido a que para determinar si un substrato particular formaría solvatos o hidratos requeriría la síntesis del substrato y someterlo a recristalización con una variedad de solventes, temperaturas y humedades y en el capítulo descriptivo no hay un ejemplo de trabajo de cualquier hidrato o solvato formado. Y no hay evidencia de que tales compuestos existan. Se requiere al solicitante para este punto, eliminar este término del alcance del pliego reivindicatorio.

	
R3	H
R4	H
R4'	H

La reivindicación 15 consiste en un proceso para preparar compuestos de fórmula (I), sin embargo, no se encuentra adecuadamente definida ya que no menciona características esenciales de un proceso tales como: condiciones, solventes, uso de catalizadores y temperaturas. Se sugiere al solicitante definir el proceso de manera inequívoca, teniendo en cuenta las observaciones realizadas.

Las reivindicaciones 26 y 27 no son concisas cuando hacen uso de la expresión "otro principio activo medicamentoso", puesto que da lugar a todos aquellos compuestos que tienen actividad farmacológica, lo cual va más allá del alcance de la solicitud. Se sugiere al solicitante restringir las reivindicaciones a aquellos principios activos medicamentosos que se encuentran debidamente soportados en el capítulo descriptivo

6. Determinación del Estado de la Técnica

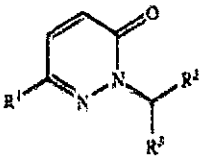
El Estado de la Técnica se determinó con base en la fecha de Presentación de la Solicitud de Prioridad: 12 de julio de 2007

Y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación*
D1	US20080293719	Pyridiazinone Derivatives for the Treatment of Tumours	27 de noviembre de 2008**
D2	Current medicinal chemistry	Bioisosterim: a Useful Strategy for Molecular Modification and Drug Design (volume 12, issue 1, page 23-49)	2005

**Versión Norteamericana de la solicitud internacional WO2007/065518 publicada en fase internacional el 14 de junio de 2007 presentada en estados unidos el 27 de noviembre de 2008.

D1
<http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=2008293719A1&KC=A1&FT=D&ND=3&date=20081127&DB=&locale=en> EP



Divulga compuestos de la fórmula (I) , los cuales tienen actividad inhibidores de tirosina quinasas, en particular, Met-quinasa, y se pueden emplear, entre otras cosas, para el tratamiento de tumores

D2 (folios 590-601)
Bioisosterim: a Useful Strategy for Molecular Modification and Drug Design (volume

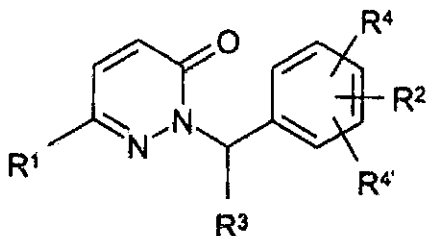
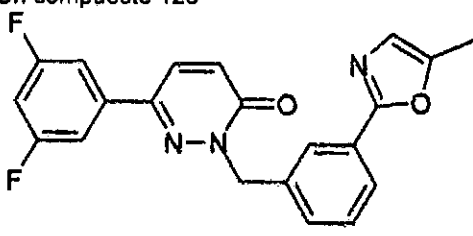
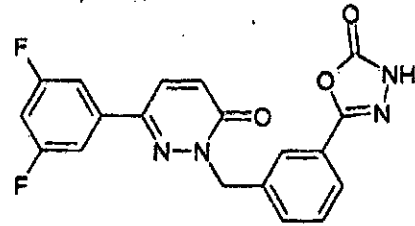
Divulga el Bioisosterismo como una práctica común para desarrollar medicamentos, y modificación de los mismos. Bioisósteros y clásicos y no clásicos.

7. Examen de Patentabilidad (Art 14 D486)

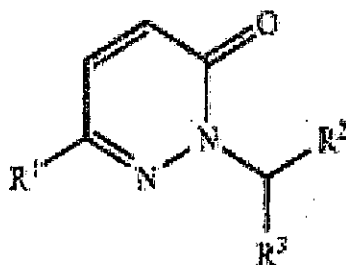
Novedad (Art 16 D486)

La reivindicación 1 consiste un compuesto de fórmula (I)

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

Características esenciales	D1
Un compuesto de fórmula (I) 	Un compuesto 123 
Donde R1 es fenilo di sustituido por halógeno. R3 es hidrógeno, R4 y R4' son Hidrógeno. R2 es un heteroarilo	Un compuesto 123 

Las características **esenciales** de la compuesto de fórmula (I) de la reivindicación 1 hablan sido divulgadas previamente en D1, el cual enseña un compuesto de fórmula



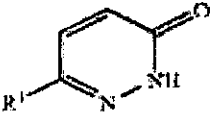
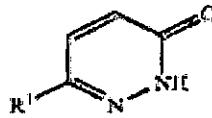
(I) (párrafo 26), específicamente los compuestos 122 y 123 (párrafo 297), donde R1 es un fenilo 2,4 difluoro sustituido R3 es H, y R2 es un 3-(5-metil-1,3-oxazol-2-il)bencil (ejemplo 122) y un [3-(5-oxo-4,5-dihidro-1,3,4-oxadiazol-2-il)bencil (ejemplo 123), lo cual, está de acuerdo con lo afirmado en la reivindicación 1 de la actual solicitud, el radical R1 de D1 puede ser sustituido por un anillo heteroaromático (párrafo 27, compuestos A24, A26, A30, A57), R1 tambien se encuentra sustituido por 1 o varios radicales sustituido por un grupo CN (ejemplo A41), halógenos (ejemplos A40, A37), hidroxilo (ejemplo A29), propiloximorfolin (ejemplo 44), piridina (ejemplo A65), R2 puede ser sustituido por un anillo heteroaromático o arilo (párrafo 28), tales como fenilo, naftilo dada uno de los cuales es sustituido por un arilo o heteroarilo o arilo (párrafo 32)

En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D1.

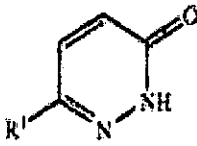
Las reivindicaciones dependientes 2-11, 16, 26 y 27 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no son nuevas.

La reivindicación 15 consiste en un procedimiento para elaborar los compuestos de las reivindicaciones 1.-14

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

Características esenciales	D1
Un compuesto de fórmula (II) 	Un compuesto de fórmula (II) 
Reacciona con un compuesto de fórmula (III)	Reacciona con un compuesto de fórmula (III) $R^2-CHL-R^3$
Luego R2 se convierte en otro radical R2, acilando o alquilando el grupo amino	R2 se convierte en otro R2 por acilación del grupo amino
Libera uno de sus derivados funcionales por tratamiento con un agente solvolizante o hidrogenolizante.	Libera uno de sus derivados funcionales por tratamiento con un agente solvolizante o hidrogenolizante.

Las características técnicas esenciales del proceso de la reivindicación 15 fueron previamente divulgadas en D1, porque éste divulga un proceso para preparar un compuesto de fórmula (I) (reivindicación 16), que comprende las etapas Un



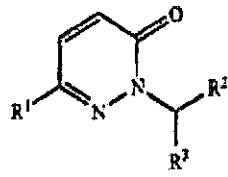
compuesto de fórmula (II), reacciona con un compuesto de formula (III), luego R2 se convierte en otro R2 por acilación del grupo amino, Libera uno de sus derivados funcionales por tratamiento con un agente solvolizante o hidrogenolizante. D1 tambien divulga que R3 es H, y R2 en el ejemplo 123 es un [3-(5-oxo-4,5-dihidro-1,3,4-oxadiazol-2-il)bencil.

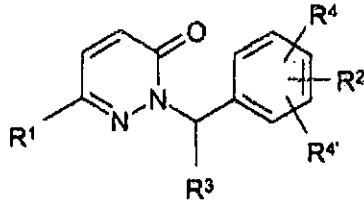
En consecuencia, la reivindicación 15 no es nueva o carece de novedad, según lo divulgado en el documento D1.

Nivel Inventivo (Art18 D486)

La reivindicación 13 consiste en un compuesto de las reivindicaciones 1-12 donde

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

Características esenciales	D1
Un compuesto como el de las reivindicaciones 1-12 donde:	Un compuesto de fórmula (I) 

	
R1 Es arilo o heteroarilo	R1 de D1 puede ser sustituido por un anillo heteroaromático (párrafo 27, compuestos A24, A26, A30, A57).
R2 es pirimidinilo, piperidinilo, piridazinilo, morfolinilo, piperazinilo,	R2 un fenilo sustituido por un Het ¹ o un grupo A (párrafo 28).
R3 es H, Metilo, etilo, propilo	R3 es un hidrógeno o un alquilo C ₁₋₁₀ (párrafos 29-30)
R4 y R4' es H	Sus equivalentes son H

El Documento D1 se considera el estado de la técnica cercano a la invención definida en la reivindicación 13 porque divulgan un compuesto de fórmula (I) donde R1 puede ser sustituido por un anillo heteroaromático o aromático (párrafo 27, compuestos A24, A26, A30, A57, A122, A123), R2 un fenilo sustituido por un Het¹ (párrafo 28), donde Het¹ es un heteroanillo monocíclico, saturado, insaturado o aromático. Que contienen 1 ó 2 N y/u O, que pueden a su vez estar mono-, di-, trisustituidos (párrafo 34), R3 es un hidrógeno o un alquilo C₁₋₁₀ (párrafos 29-30), Y los equivalentes de R4 y R4' son H, R2 es un anillo aromático (ejemplos 122 y 123)

La diferencia entre la invención, definida en la reivindicación 13 y el compuesto de D1 consiste que la reivindicación 1 presenta sustituciones de R2 definidas como: pirimidinilo, piperidinilo, piridazinilo, morfolinilo, piperazinilo,

El efecto que logra el incluir la introducción de los sustituyentes de R2 pirimidinilo, piperidinilo, piridazinilo, morfolinilo, piperazinilo, no queda adecuadamente demostrada, puesto que no se presentan datos comparativos respecto de los compuestos de D1 especialmente los de los ejemplos 123 y 124.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo presentar compuestos alternativos a los compuestos de D1 y que tengan actividad inhibitoria de tirosina quinasa"

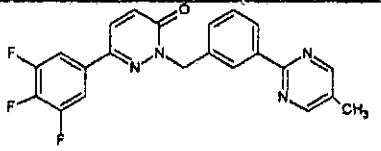
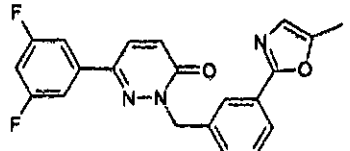
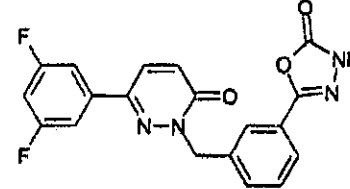
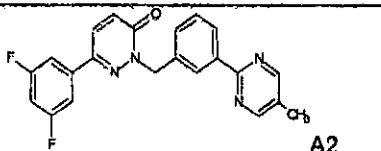
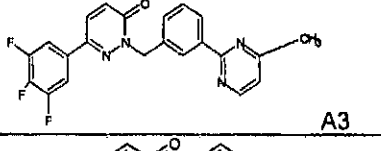
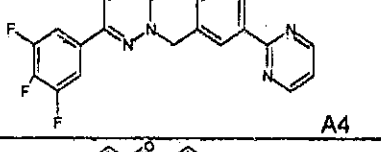
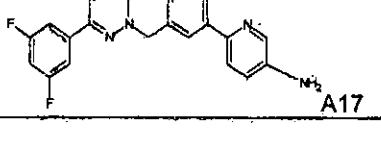
Sin embargo, el documento D1 define que R2 es un anillo aromático como el Fenilo puede ser sustituido por un grupo Het 1 que pueden ser a su vez piperidin-1-il, pirrolidin-1-il, morfolin-4-yl, piperazin-1-il, 1,3-oxazolidin-3-il, imidazolidinil, oxazolil, tiazolil, tienil, furanil or piridil, evidencia de lo cual existen los compuestos de los ejemplo 122 y 123.

En consecuencia, la persona del oficio normalmente versada en la materia, se vería fuertemente motivada a intercambiar los radicales arriba mencionados en los compuestos 122 y 123 por los sugeridos también en D1, para llegar así al objeto de la reivindicación 13 de la solicitud. Por lo cual se considera obvia.

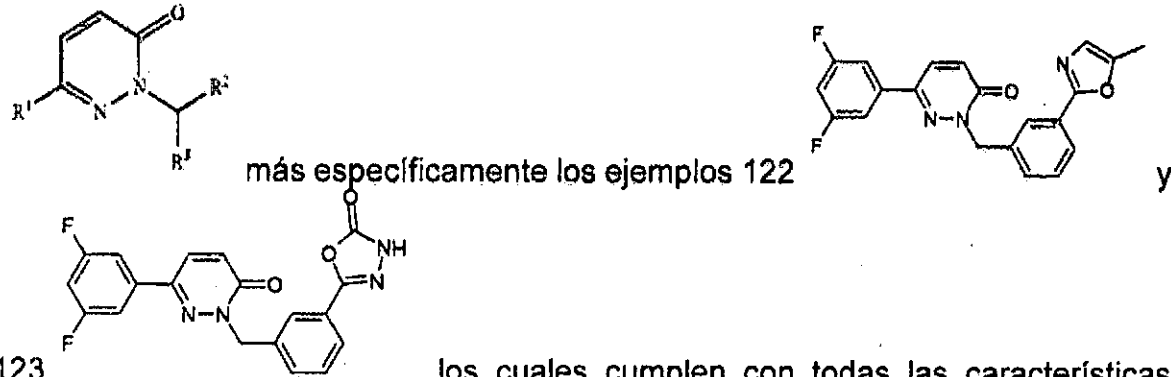
Conclusión:
La reivindicación 13 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18).

La reivindicación 14 consiste en compuestos de acuerdo con reivindicación 1 seleccionados del grupo:

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

Características esenciales	D1	D2
Compuestos específicos de fórmula (I) denominados "A1-A4 y A17"	Compuestos específicos de fórmula (I) ejemplos 122 123	
 A1	 	Divulga el Bioisosterismo como una estrategia exitosa en el desarrollo de nuevos análogos de sustancias que son de interés terapéutico. (introducción) existen bioisosteros clásicos y no clásicos (página 25, esquema 2), divulga que los anillos piridina, pirimidina y oxadiazol son bioisosteros (página 30 figura 2)
 A2		
 A3		
 A4		
 A17		

El Documento D1 se considera el estado de la técnica cercano a la invención definida en la reivindicación 14 porque divulgan un compuesto de fórmula (I)



los cuales cumplen con todas las características esenciales de los compuestos de Formula (I) de la actual solicitud.

La diferencia entre la invención definida en la reivindicación 14 y los ejemplos de D1 consiste que la reivindicación 1 presenta sustituciones de R2 definidas como: pirimidinilo, piridinilo

El efecto que logra el incluir la introducción de los sustituyentes de R2 pirimidinilo, piridinilo, es que proporciona compuestos químicos alternativos a los compuestos de fórmula (I) ya conocidos con anterioridad en D1. Ya que más allá de esto, no se establecen ejemplos comparativos entre la actual invención y la anterioridad D1 que permitan concluir que los compuestos actualmente reivindicados presentan un efecto

técnico mejorado traducido en mejores propiedades farmacéuticas tales como: selectividad, biodisponibilidad, etc.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo presentar compuestos alternativos a los compuestos de D1"

Sin embargo, el documento D2 ya divulga que el bioisosterismo es una estrategia exitosa de amplia difusión en el arte de la síntesis para el desarrollo de nuevos análogos de sustancias ya conocidas que son de interés terapéutico. (folio 590, introducción), que los anillos piridina, pirimidina y oxazol son bioisómeros y que por lo tanto se espera que al intercambiar estos anillos en la estructura, se espera que tenga actividad similar(folio 597, figura 2, página 30, folio 598, numeral 5.2 página 31)

En consecuencia, la persona del oficio normalmente versada en la materia, se vería fuertemente motivada a intercambiar los el anillo oxazol por los anillos piridina o pirimidina en los compuestos 122 y 123 como lo sugiere D2, para llegar así al objeto de la reivindicación 13 de la solicitud. Por lo cual se considera obvia.

Conclusión:
La reivindicación 13 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18).

8. Conclusión

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

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US20080293719	2-11, 16, 26 y 27	Novedad
		13-14	Nivel inventivo
D2	Current medicinal chemistry Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design	14	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)

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

Elaborado por: Harvey Jaramillo oklt
Revisado Por: Jacqueline Alfonso

Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design

Lidia Moreira Lima and Eliezer J. Barreiro*

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Abstract: This review aims to demonstrate the role of bioisosterism in rational drug design as well as in the molecular modification and optimization process aiming to improve pharmacodynamic and pharmacokinetic properties of lead compounds.

1. INTRODUCTION

Bioisosterism is a strategy of Medicinal Chemistry for the rational design of new drugs, applied with a lead compound (LC) as a special process of molecular modification [1]. The LC should be of a completely well known chemical structure and possess an equally well known mechanism of action, if possible at the level of topographic interaction with the receptor, including knowledge of all of its pharmacophoric group. Furthermore, the pathways of metabolic inactivation [2], as well as the main determining structural factors of the physicochemical properties which regulate the bioavailability, and its side effects, whether directly or not, should be known so as to allow for a broad prediction of the definition of the bioisosteric relation to be used.

The success of this strategy in developing new substances which are therapeutically attractive has observed a significant growth in distinct therapeutic classes, being amply used by the pharmaceutical industry to discover new analogs of therapeutic innovations commercially attractive (*me-too*), and also as a tool useful in the molecular modification.

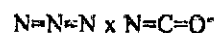
There may be innumerable reasons for the use of bioisosterism to design new drugs, including the necessity to improve pharmacological activity, gain selectivity for a determined receptor or enzymatic isoform subtype - with simultaneous reduction of certain adverse effects -, or even optimize the pharmacokinetics the LC might present.

In this paper, we will discuss bioisosterism as a strategy of molecular modification, showing its importance in building a new series of congeners compounds designed as candidate of new drugs, giving examples of successful cases in distinct therapeutic classes [3-7].

2. BACKGROUND

In 1919, Langmuir [8] studying the chemical behavior and reactivity of determined substances possessing atoms or groups with the same number of valence electrons, *i.e.*

isoelectronic, created the concept of isosterism to define atoms or organic or inorganic molecules which possess the same number and/or arrangement of electrons examples:



In 1925, Grimm [9] formulated the *Hydride Displacement Law*, an empiric rule which states that the addition of a hydrogen atom with a pair of electrons (*i.e.* hydride) to an atom, produces a pseudoatom presenting the same physical properties as those present in the column immediately behind on the Periodic Table of the Elements for the initial atom (Fig. 1), showing that any atom belonging to groups 4A, 5A, 6A, 7A on the Periodic Table change their properties by adding a hydride, becoming isoelectronic pseudoatoms.

In 1932, Erlenmeyer [10] proposed a broadening of the term isosterism, defining isosteres as elements, molecules or ions which present the same number of electrons at the valence level. His contribution includes the proposition that elements of the same column on the Periodic Table are isosteres among themselves (*e.g.* C x Si x Ge) and the creation of a concept of rings electronically equivalent, later broadened to the term ring bioisosterism.

The coining of the term bioisosterism goes back to the pioneer work of Friedman and Thornber during the early 50s. Friedman [11], recognizing the usefulness of the concept *isosterism* to design bioactive molecules, defined bioisosters as compounds which fit the definitions of isosteres and which exercise their biological activity of bioreceptor, whether through agonist or antagonist actions. However, Friedman introduced the term bioisosterism to describe the phenomenon observed between substances structurally related which presented similar or antagonistic biological properties [11]. Later, Thornber [3] proposed a broadening of the term bioisosteres, defining them as sub-units or groups or molecules which possess physicochemical properties of similar biological effects.

Over the years, innumerable bioisosteric relations have been identified in compounds both natural and synthetic. In nature, we have identified many examples of isosterism as a

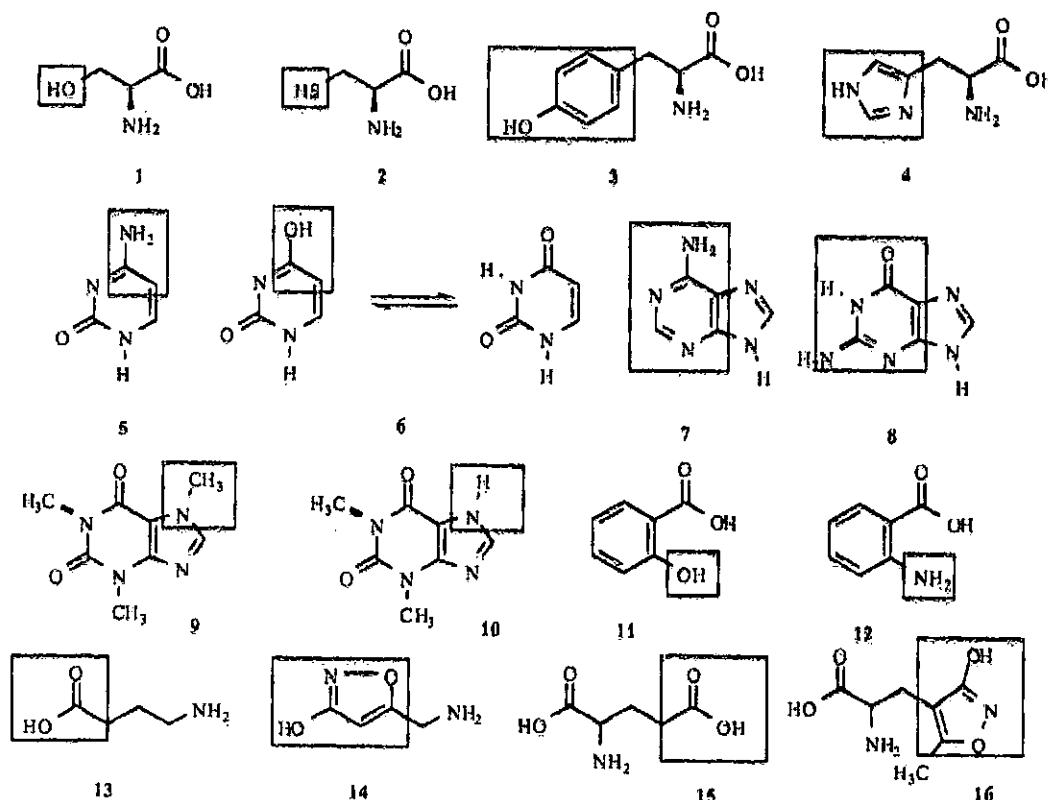
*Address correspondence to this author at the Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro. CCS, Cidade Universitária, CP 68.006, 21944-190, Rio de Janeiro, R.J., Brazil. E-mail: ejb@pharma.ufrj.br

	Group 4A	Group 5A	Group 6A	Group 7A	Group 8A	
N° of e ⁻	6	7	8	9	10	11
	C	N	O	F	Ne	Na ⁺
	H-L	CH	NH	OH	FH	
		H-L	CH ₂	NH ₂	OH ₂	FH ₂ ⁺
			H-L	CH ₃	NH ₃	OH ₃ ⁺
				H-L	CH ₄	NH ₄ ⁺

Fig. (1). Grimm's hydride displacement law.

form of broadening chemodiversity (Scheme 1), striking among which are the classic bioisosteric relation existing between the essential amino acids serine (1) and cysteine (2), tyrosine (3) and histidine (4) among the pyrimidine and purine bases cytosine (5) and uracile (6), adenine (7) and guanine (8); among the xanthines caffeine (9) and theophylline (10); and among the salicylic (11) and anthranilic (12) acids, which originated two important

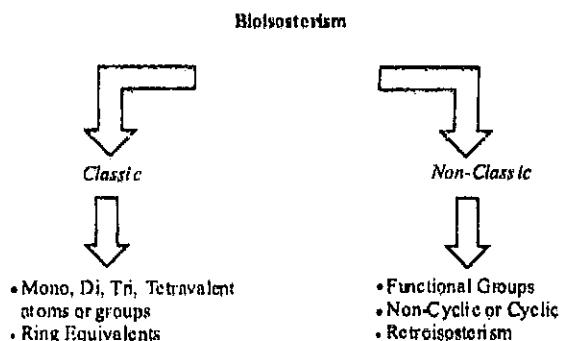
classes of non-steroid anti-inflammatory drugs, e.g. acetylsalicylic acid and mefenamic acids, respectively. Furthermore, examples of the application of non-classic bioisosterism are also found in nature - such as the bioisosteric relationship existing between γ -aminobutyric acid (GABA) (13) and muscimol (14), between the neurotransmitters glutamate (15) and AMPA (16).



Scheme 1.

3. CLASSIFICATION OF BIOISOSTERISM: CLASSIC AND NON-CLASSIC

In 1970, Alfred Burger classified and subdivided bioisosteres into two broad categories: Classic and Non-Classic [12] (Scheme 2).



Scheme 2.

Burger's definition significantly broadened this concept, now denominating those atoms or molecular subunits or functional groups of the same valence and rings equivalents as classic bioisosteres. (Table 1), while non-classic bioisosteres were those which practically did not fit the definitions of the first class (Table 2).

1 Classic Bioisosteres (Table 1)

- 1.1 Monovalent atoms or groups
- 1.2 Divalent atoms or groups
- 1.3 Trivalent atoms or groups
- 1.4 Tetrasubstituted atoms
- 1.5 Ring equivalents

2 Non-Classic Bioisosteres (Table 2)

- 2.1 Cyclic vs Noncyclic
- 2.2 Functional groups
- 2.3 Retroisosterism

Table 1 Classic Bioisostere Groups and Atoms

Monovalent	Divalent	Trivalent	Tetravalent
, -OH, -NH ₂ , -CH ₃ , -OR	-CH ₂ -	=CH-	=C=
-F -Cl, -Br, -I, -SH, -PH ₂	-O-	=N-	=Si=
-Si ₃ , -SR	-S-	=P-	=N ⁺ =
	-Se-	=As-	=P ⁺ =
	-Te-	=Sb-	=As ⁺ =
			=Sb ⁺ =

Many authors have contributed to updating the tables of functional bioisostere groups, which explains why, in that which we refer to as non-classic bioisosterism, we have observed a growing number of bioisosteres described in the literature [6-7].

4. BIOISOSTERISM AS A STRATEGY OF MOLECULAR MODIFICATION

Among the most recent numerous examples used in the strategy of bioisosterism for designing new pharmacotherapeutically attractive substances [6-7,13], there is a significant predominance on non-classic bioisosterism, distributed in distinct therapeutic categories, be they selective receptor antagonist or agonist drugs, enzymatic inhibitors or anti-metabolites. The use of classic bioisosterism for the structural design of new drugs, while less numerous, has also been carried out successfully [6].

The correct use of bioisosterism demands physical, chemical, electronic and conformational parameters involved in the planned bioisosteric substitution, carefully analyzed so as to predict, although theoretically, any eventual alterations in terms of the pharmacodynamic and pharmacokinetic properties which the new bioisosteric substance presents.

Thus being, any bioisosteric replacement should be rigorously preceded by careful analysis of the following parameters [5]:

- a) size, volume and electronic distribution of the atoms or the considerations on the degree of hybridization, polarizability, bonding angles and inductive and mesomeric effects when fitting;
- b) degree of lipidic and aqueous solubility, so as to allow prediction of alteration of the physicochemical properties such as logP and pKa;
- c) chemical reactivity of the functional groups or bioisosteric structural subunits, mainly to predict significant alterations in the processes of biotransformation, including for the eventual alteration of the toxicity profile relative to the main metabolites;
- d) conformational factors, including the differential capacity formation of inter- or intramolecular hydrogen bonds.

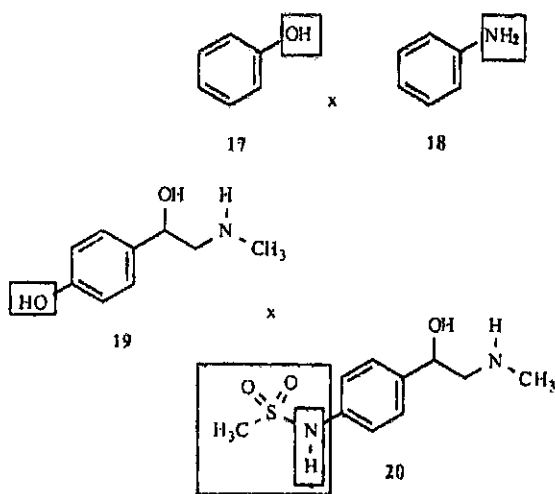
4.1. BIOISOSTERISM AND ALTERATIONS OF PHYSICOCHEMICAL PROPERTIES

Some bioisosteric groups dramatically alter the physicochemical properties of substances and, therefore, their activities. This can be easily understood by comparing classic isosteres resulting from bioisosteric replacement between hydroxyl (-OH) and amine (-NH₂), an example of classic bioisosterism of monovalent groups according to Grimm's Rule. In this case, considering the bioisosteric replacement of aromatic amine present in aniline (18) by hydroxyl, we have phenol (17) (Scheme 3) resulting in a significant change in the acid-base properties of isosteres, with dramatic modification of the pKa of the compounds, which is responsible for the distinct pharmacokinetic profiles among the isosteres in question. Furthermore, in terms of molecular recognition of a given receptor site, we have a change from one positively charged function (-NH₃⁺), originating from basic aromatic amine function (pK_b = 9,30) by another acid (pK_a = 10,0) present in phenol, which may, quite probably, abolish the original activity [14]. Thus, in

Table 2 Non-Classic Bioisosteres

-CO-	-COOH	-SO ₂ NH ₂	-H	-CONH-	-COOR	-CONH ₂
-CO ₂ -	-SO ₃ H	-PO(OH)NH ₂	-F	-NHCO-	-ROCO-	-CSNH ₂
-SO ₂ -	-tetrazole					
-SO ₂ NR-	-SO ₂ NHR -SO ₂ NH ₂		-OH -CH ₂ OH		-catechol	
-CON-	-3-hydroxyisoxazole				-benzimidazole	
-CH(CN)-	-2-hydroxychromones		-NHCONH ₂			C ₄ H ₄ S
R-S-R			-NH-CS-NH ₂			-C ₂ H ₄ N
(R-O-R')	=N-					-C ₆ H ₅
R-N(CN)-	C(CN)=R'		-NH-C(=CHNO ₂)-NH ₂ -NH-C(=CHCN)-NH ₂			-C ₄ H ₄ NH
-halides						
	-CF ₃					
	-CN					
	-N(CN) ₂					
	-C(CN) ₃					

this example, we may predict that the use of bioisosterism, even the classic type, can promote severe alterations of molecular properties, as much in terms of lipidic-aqueous solubility as well as chemical reactivity, among others, which, broadly speaking, is not observed in the same homologue carbonic series. Otherwise, the system's enzymatic capacity for hepatic detoxification of xenobiotics, involving the microsomal mixed function oxidase also called cytochrome P-450 system [14], is distinct in the presence of these functional isosteric groups, which does not allow a simplistic comparison between the lead compound aniline (18) and the hydroxylated isostere (17) in terms of metabolism, altering, therefore, the pharmacokinetic phase as well as the pharmacodynamics of the isosteres.



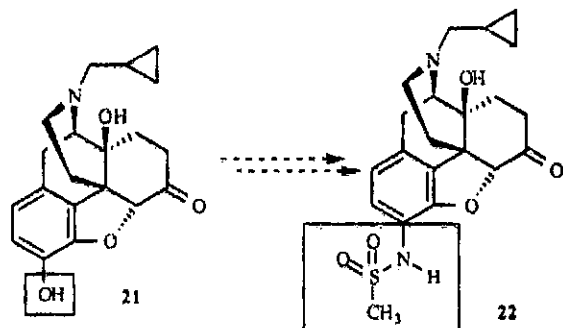
Scheme 3.

Another classic example of isosteric replacement involving phenol (PhOH), can be found in the search for adrenergic derivatives, structurally related to catecholamines

(Scheme 3) [15]. This example illustrates the exchange of phenolic hydroxyl group present in compound 19 with the arilsulfonamide unit in compound 20, through the use of non-classic bioisosterism of functional groups.

The results obtained, carrying out bioassays with these compounds, witness comparable biological activities through the mechanism of equivalent action, allowing us to conclude that both functional groups involved are authentic bioisosteres. This bioisosteric relationship was experimentally evidenced by determining the degree of acidity of these substances. Both compounds are of comparable acidity ($pK_A = 9.1$ and 9.6 respectively), explaining the similarity of biological profile in function of equivalent interactions of both molecules with site receptor, possibly through ionic bonding, in the presence of a similar acidity or even through hydrogen bonding [15]. Furthermore, both acidic groups, i.e. R-PhOH and R-PhNHSO₂CH₃ are, in this case, monovalent groups. However, the identified bioisosteric relationship between the PhOH and PhNHSO₂CH₃ groups, confirmed for adrenergic derivatives 19 and 20, is not extensive to other bioreceptors in which the process of molecular recognition is distinct. An example of how isostere groups can, in certain systems, not maintain a bioisosteric relationship, previously defined in another bioreceptor, is well illustrated with the analyses of 21 and 22, described by McCurdy and coworkers (Scheme 4) [16]. The structural design of 3-sulfonamido compound 22, targeting the attainment of new bonds for opioid receptors, was based on the structural data of lead compound 21, which point to the relevance of phenolic hydroxyl as site of molecular recognition. This way, the replacement OH by the NHSO₂CH₃ group would respect the acidic properties and the characteristics donor and/or acceptor H-bonds as evidenced by the previous work of Larsen and Lish (1964). Nonetheless, the determination of the pharmacological properties of arilsulfonamide derivative 22, evidenced the absence of affinity by the opioid receptors, *in vitro* models,

indicating that in this system the groups PhOH and PhNHSO₂CH₃ are not bioisosteres, despite their great structural similarity.



Scheme 4.

Thus, when bioisosteric replacement occurs in functional groups involved in the pharmacophore subunit of a certain bioactive substance, the relative activity of the resulting compounds may be dramatically modified. However, bioisosteric replacement which successfully occurs in a series of compounds acting as a type of bioreceptor, will not necessarily be successful in another therapeutic series, acting through other receptors.

5. CLASSIC BIOISOSTERISM

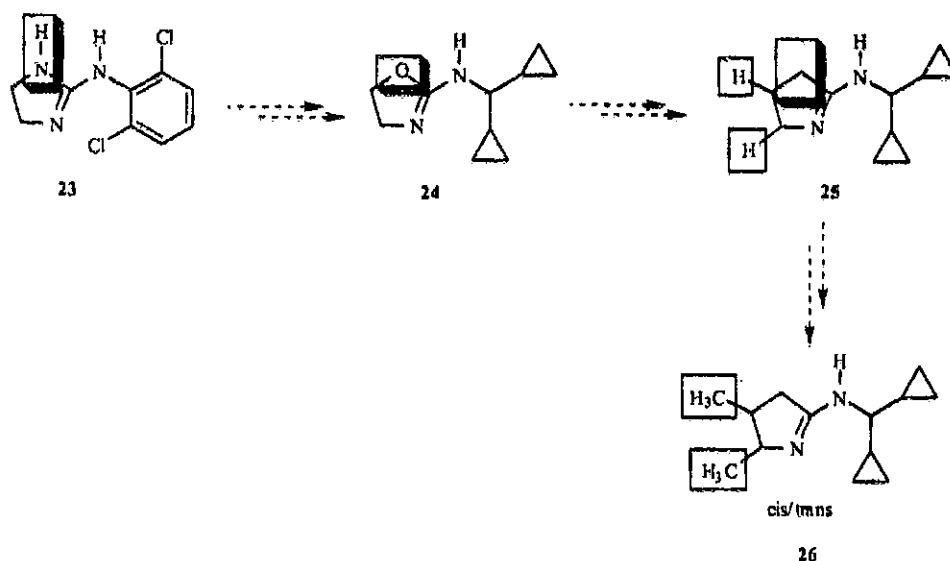
5.1. Bioisosterism of Mono-, Di-, Tri- and Tetravalent Atoms or Groups

In the search for new anti-hypertensive drugs analogous to clonidine (23), with a greater selectivity by I₁ imidazoline receptors (I₁R) and reduced action on α₂-adrenoceptors, Schann and coworkers described the attainment of new candidates for anti-hypertensive drugs designed by molecular modifications in the structure of the lead compound rilmenidine (24) (Scheme 5) [17]. These modifications were based on classic bioisosterism of bivalent groups,

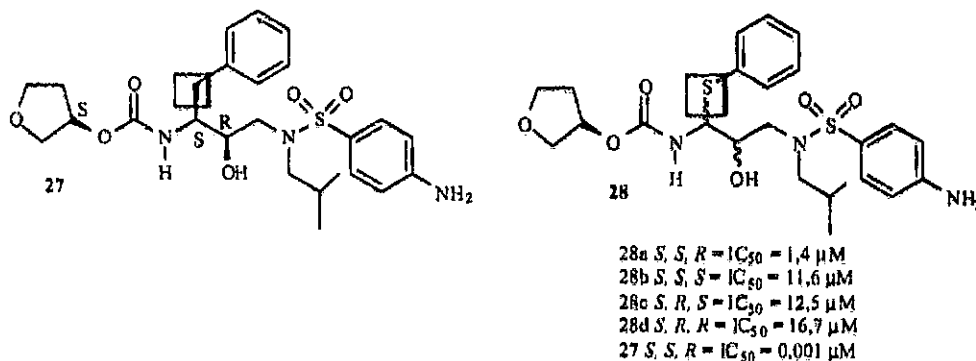
exemplified by replacement of the bivalent oxygen atom (O) present in the oxazoline ring, by the methylene group (CH₂), in the structure of the new pyrroline derivative (25); and between replacement of monovalent groups illustrated by the substitution of hydrogen atoms (H) in C-4 and C-5 of derivative (25) by the methyl group (CH₃), originating the *cis/trans*-4,5-dimethyl homologue 26 [17]. The binding tests with I₁R and α₂-adrenoceptors evidence that the modifications occurring in the structure of rilmenidine (24), allow the attainment of derivatives with affinities comparable to lead compound (24), although with a superior selectivity for I₁R, and illustrated an example of the success of classic bioisosterism.

To develop new HIV-protease inhibitors, Rocheblave and coworkers described the bioisosteric exchange between bivalent groups (Scheme 6), realizing the exchange of the methylene group (CH₂), present in the structure of the lead compound amprenavir (27), for the sulfur atom (S) in 28 [18]. Knowing, *a priori*, that this isosteric replacement could induce several modifications in terms of size, shape, electronic distribution, chemical reactivity, lipophilicity and hydrogen bonding capacity, this new isostor was synthesized, and its stereoisomers were duely separated by HPLC and tested as recombinant HIV protease inhibitors. The results obtained revealed that the four diastereoisomers tested were only weak inhibitors of recombinant HIV protease, while the diastereoisomer (28a), of the same absolute configuration as the lead compound amprenavir (27), being *ca.* 1400 less potent than 27. These results could be explained by the high sensitivity to hydrolysis of thioisoster 28a-d. In fact, the half-life value found for thiophenoxy derivative 28a-d was 10 min, while amprenavir (27) was recovered unchanged after 1440 min.

Another illustration of the application of classic bioisosterism can be found in the works of Penning and coworkers (Scheme 7) [19]. Continuing the research to find new anti-inflammatory drugs acting through the selective inhibition of prostaglandin-H synthase-2 (PGHS-2) or cyclooxygenase-2 (COX-2), the authors investigated the

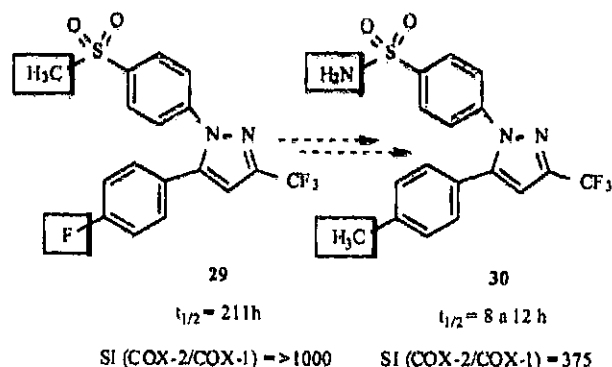


Scheme 5.



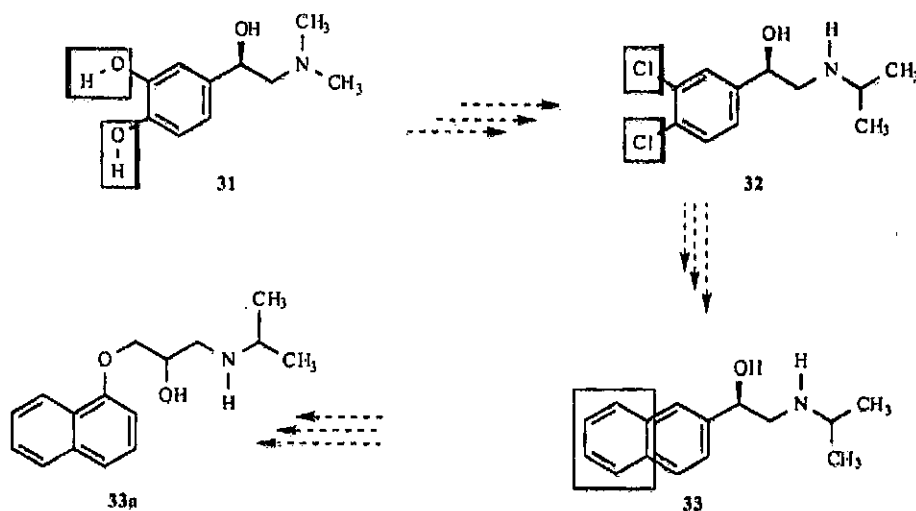
Scheme 6.

effect of isosteric modifications on the structure of lead compound SC-58125 (29), to improve its pharmacokinetic properties. In spite of the high rate of selectivity by PGHS-2 ($SI > 1000$) and good inhibitory potential, the derivative SC-58125 (29) exhibited a half-life of over 200 h, thus reflecting its low susceptibility in the presence of the complex enzyme involved in the hepatic metabolism of xenobiotics. Hence, the authors suggested two classic bioisosteric monovalent group replacements, represented by replacing the methyl group, (CH_3) by the NH_2 group and exchanging the fluorine atom (F) with the CH_3 group (Scheme 7). Both isosteric replacements suggested allow introducing into the structure of the new bioisostere of SC-58125, vulnerable soft metabolic sites taking advantage of the effect of the first passage through reactions of conjugation with glucuronic acid and the benzylic hydroxylation catalyzed by CYP450, respectively. This new bioisostere optimized by SC-58125, *i.e.* celecoxib (30), of a half-life of from 8-12 h, was introduced on the Brazilian market in 1999 by Pfizer/Searle Laboratories to treat rheumatoid arthritis and other inflammatory conditions, being the first non-steroidal anti-inflammatory drug (NSAID) acting selectively upon the inducible isoform prostaglandin-H synthase (*i.e.*, PGHS-2) and, therefore, without the irritating gastric effects typical of the first generation NSAIDs [20].

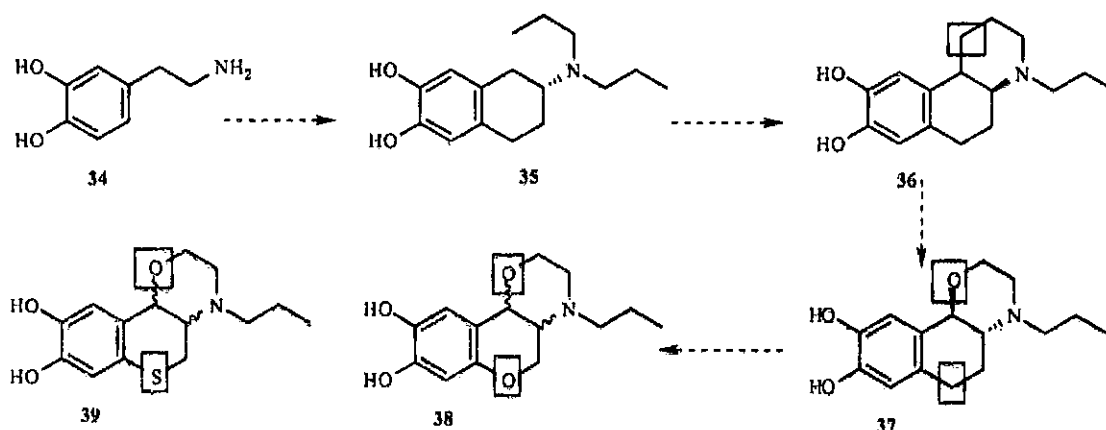


Scheme 7.

The design of dichloroisoproterenol (32) from isoproterenol (31) is, without a doubt, an unique example of the contribution of the application of bioisosterism to optimize pharmacodynamic and pharmacokinetic properties of new drugs (Scheme 8). The replacement of catecholic hydroxyls, present in isoproterenol (31), by the monovalent chloro (Cl) group in the structure of dichloroisoproterenol (32), represented a useful strategy to obtain new analogs with half-lives greater than the lead compound 31, since this bioisosteric replacement allows blocking one of the main sites of metabolism of this catecholamine derivative.



Scheme 8.

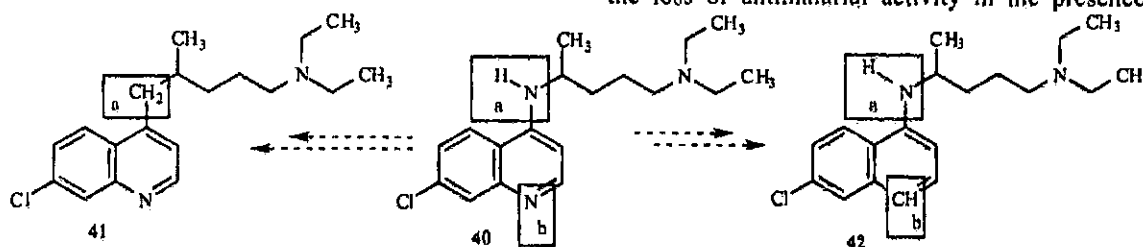


Scheme 9.

Furthermore, the discovery of dichloroisoproterenol (32), made feasible the comprehension of the relevance of structural characteristics of the catecholic subunit for adrenergic activity, allowing *a posteriori* the discovery of pronethalol (33), the first selective antagonist for adrenergic receptors for subtype β . Pronethalol (33), discontinued during the 1980s, was the precursor of propranolol (33a), a therapeutic innovation which revolutionized the treatment for hypertension. The discoverer, *Str* James Black, received the Nobel Prize in Medicine for this feat and his discovery was the lead compound for innumerable other more selective adrenergic β_1 antagonists.

the increase in lipophilicity and the selectivity desired by the D_3 receptors.

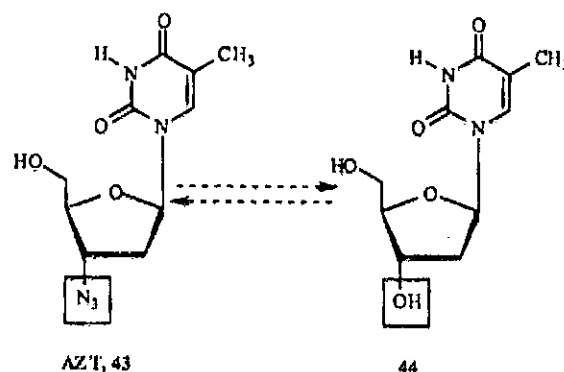
To understand the contributions of 4-aminoquinoline subunit present in the structure of the first generation antimalarial chloroquine (CLQ, 40), Cheruku and coworkers described the attainment and determination of the pharmacological profile of modified analogs of CLQ (Scheme 10) [22]. In this study, the authors carried out the classic bioisosteric exchange of NH (a; *NH-anilinic*) and N (b, *N-quinolinic*) with the CH_2 and CH groups in the structure of compounds 41 and 42, respectively, observing the loss of antimalarial activity in the presence of the



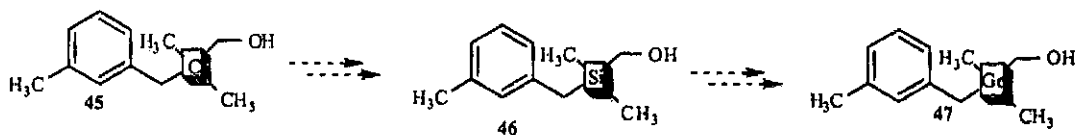
Scheme 10.

The bioisosteric replacement of the bivalent oxygen (O) atom by sulfur (S) results in a significant alteration in lipophilicity, and may be used in the design of new drugs to act upon the central nervous system (CNS). Van Vliete and coworkers (Scheme 9), in their search for selective agonists of dopaminergic receptors, subtype 3 (D_3), molecular target for the design of anti-psychotic drugs, realized modifications in the hexahydronaphthoxazine system present in lead compound 36, an analog conformationally restricted to dopamine (34), of high potency and low selectivity [21]. These structural modifications, based on the bioisosteric exchange of the methylene (CH_2) group in 37, by oxygen (O) and sulfur (S) atoms in compounds 38 and 39, respectively, allow identification of two new dopamine analogs. The coefficient of partition of thio-isostere (39, $\log D = 1.62$) compared to oxo-isostere (38, $\log D = 1.13$), showed a significant increase in lipophilicity, a typical consequence of the bioisosteric replacement carried out. However, the determination of selectivity by the different subtypes of dopaminergic receptors, assayed by the *binding test*, leads us to believe in an inverse relationship between

modifications realized. Carbo-isosteres 41 and 42 were inactive due to the inhibition of *Plasmodium falciparum* NK 54 or K1 strains, even in concentrations over 3000 nM (CLQ, $IC_{50} = 8.5$ and 150 nM, respectively), and also proved to be unable to inhibit the formation of hemozoin



Scheme 11.

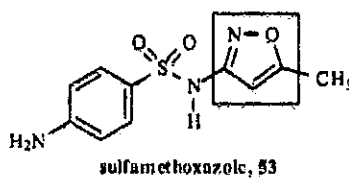
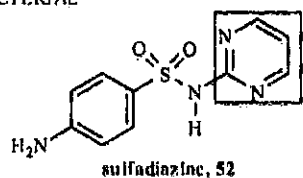


Scheme 12.

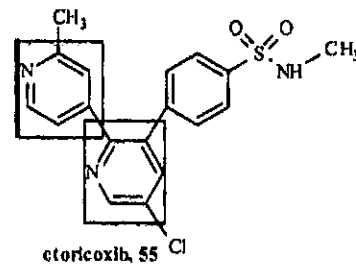
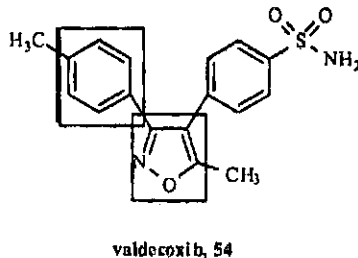
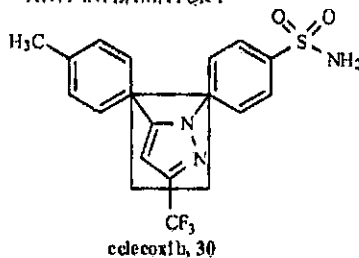
(CLQ $IC_{50} = 80 \mu M$; 41 $IC_{50} = 1500 \mu M$; 42 $IC_{50} > 2500 \mu M$). Hence, the isosteric modifications realized reinforced the hypothesis of the importance of *N*-quinolinic interaction process with hematin, the molecular target of antimalarial action of 4-aminoquinoline drugs.

Zidovudine (AZT, 43), an important chemotherapeutic resource available for the treatment of acquired human immunodeficiency syndrome, was discovered from the properties identified in nucleosides isolated from seaweed. The structural analysis of AZT (43), a powerful inhibitor of

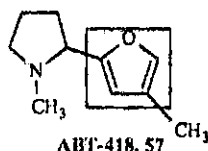
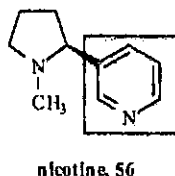
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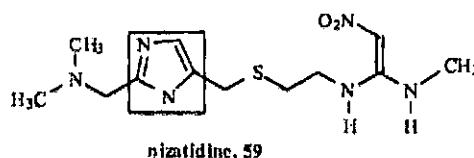
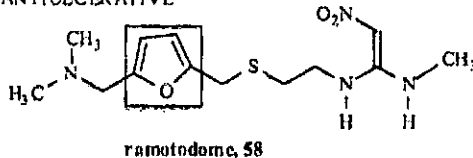
ANTI-INFLAMMATORY



ANALGESIC



ANTIULCERATIVE



MALE ERECTILE DYSFUNCTION

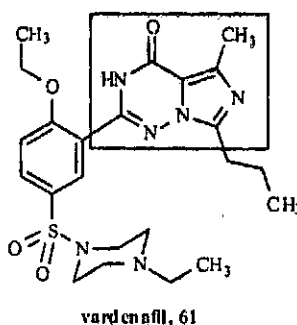
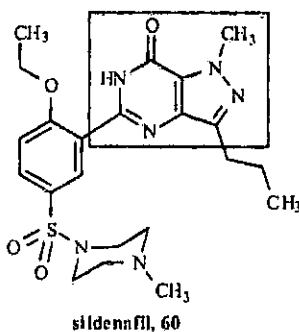


Fig. (2). Examples of ring bioisosterism between drugs belonging to different therapeutic classes.

transcriptase reverse enzyme, enables us to ascertain the existence of a classic bioisosteric relationship of monovalent groups between the nucleoside thymine (44) (endogenous substrate for the synthesis of DNA and RNA) and AZT, exemplified by the presence of the hydroxyl (OH) unit in 44 and azido (N_3) group present in 43 (Scheme 11) [23]. Furthermore, although classic monovalent isosteres, the OH and N_3 groups possess dramatic electronic differences, easily demonstrated by simple functional analysis.

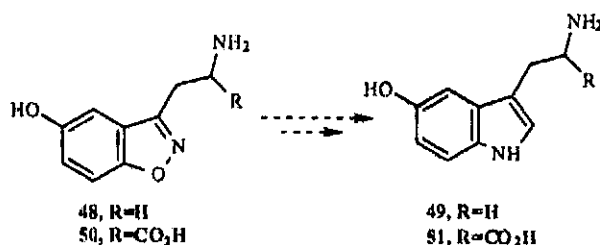
Although applicability of the strategy of molecular modification of a given lead compound through bioisosterism is well consolidated in the pharmaceutical industry, recent studies by Tacke and coworkers (Scheme 12) shows that this approach may be used efficiently to optimize the organoleptic properties of compounds used in fragrances of industrial interest [24]. In this study, the application of classic bioisosterism of tetrasubstituted atoms, illustrated by exchange of the carbon atom (C), present in the structure of majantol (45), by silicon atoms (Si) and germanium (Ge) in 46 and 47, respectively, allows the identification of new standards of fragrances of synthetic origin. Although this isosteric exchange is rare in drugs, the modification of molecular volume by the substitution $C \times Si \times Ge$, producing bioisosteres 45, 46 and 47, results in conformational and electronic similarities evidenced by diffraction and X-ray studies and the determination of electrostatic potential through the Program GAUSSIAN 98.

More recently Showell and Mills reported that one of the advantages of classic bioisosterism application of tetrasubstituted atoms involving the replacement of the carbon atom (C) by the silicon (Si) atom in the structure of existing drugs, based on the possibility of designing new drug-like candidates that have beneficial biological properties and a clear intellectual property position [25]. In fact, according to Steele, in 2001, less than 1% of patent applications related to compounds containing phosphorous, silicon or other less common elements of the periodic table [26]. However, although this may seem attractive, the differences in atomic size, electronegativity and lipophilicity between C and Si atoms, associated with the instability of Si-H bonds, in physiological conditions prove the applicability of isosteric exchange $C \times Si$ in the structure of new drugs to be quite limited [25].

5.2. Ring Bioisosteres

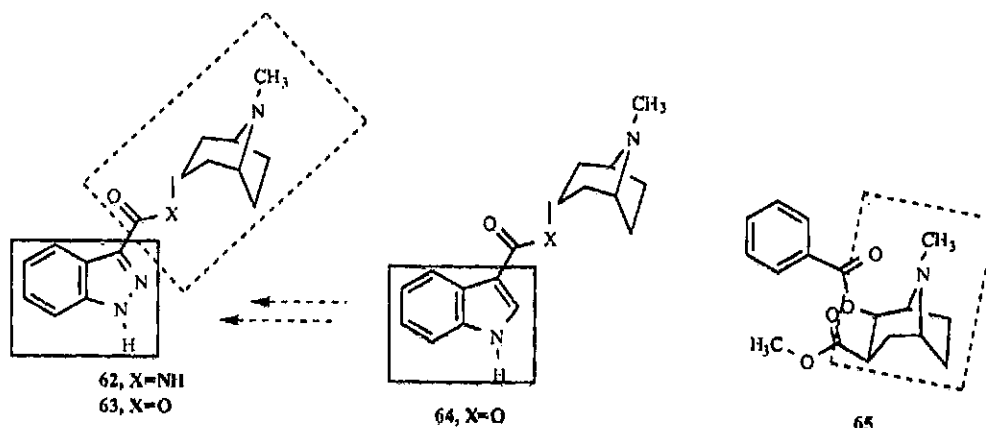
Ring bioisosterism, is undoubtedly the most frequent relationship in drugs of different therapeutic classes [8], as can be seen in (Fig. 2), and certain specific examples will be commented upon.

In 1973, Campaigne and coworkers synthesized compound 48 [27] as being a derivative structurally related to serotonin 49, an autacoid with the function of mediator in different physiological phenomena (Scheme 13). These authors based their findings on the probable classic bioisosteric relationship existing between the benzisoxazole and indole rings present in 48 and 49, respectively. The results of these pharmacological assays showed that compound 48 presented no type of serotoninomimetic activity, not even anti-serotonin, when tested on rat uterus preparations. In contrast, derivative 50, presenting the same benzisoxazole nucleus in replacing the indole ring of 51, showed activity when tested with substrate for serotonin decarboxylase enzyme, dependent on 5-hydroxytryptophan 51 (Scheme 13), an indolic compound which is the natural substrate of the enzyme involved in serotonin biosynthesis. This example highlights the bioisosteric relationship existing between the benzisoxazole rings and the indole nucleus in 50 and 51, respectively, depending on the receptor site involved.

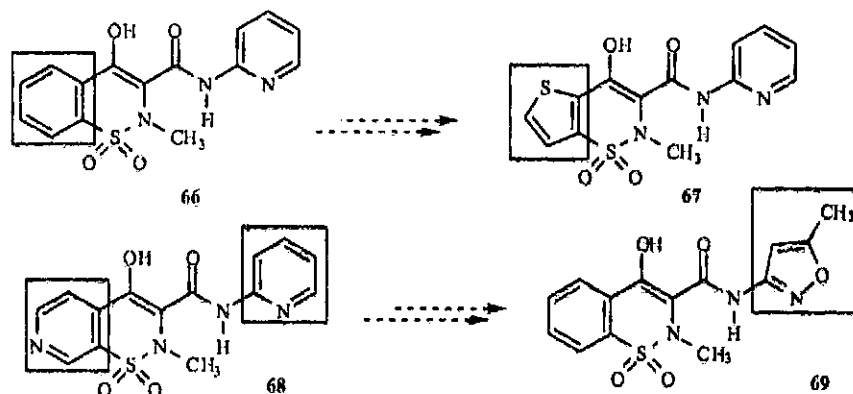


Scheme 13.

Applying classic bioisosterism in the design of new serotonin receptor (5-HT₃) antagonists Fludzinski and coworkers (Scheme 14) described the obtention of new indazolyl compounds 62 and 63 with important antagonistic properties of receptor 5-HT₃ [28]. These two substances were developed as bioisosteres of 64, a compound which possesses as main structural characteristic the hybrid



Scheme 14.



Scheme 15.

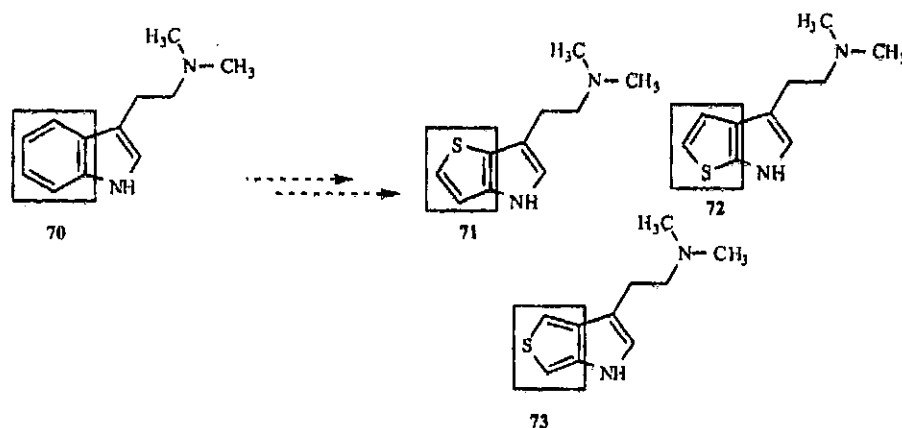
character between serotonin (49), represented by the indole ring substituted in C-3, and cocaine (65), represented by the nature of the substituent in C-3, a known antagonist of receptors 5-HT₃ [29]. The bioisosteric relationship of these two nuclei was proven. In this case, by the results obtained in bioassays which showed for 62 a rate of selectivity by the receptors 5-HT₃ superior to that of 64, when administered intravenously as well as orally, showing that the indazole and indole moieties, when substituted equivalently, possessing the same electronic properties and the same standard of aromaticity, may be considered bioequivalent at the level of interactions with the same receptor. However, compound 62 showed a profile of activity superior to 63, administered *p.o.*, indicating that the amidic bond present in chain 62 is responsible for a more favorable oral bioavailability.

The application of ring bioisosterism was also successfully explored by Binder and coworkers (Scheme 15) [30] in developing new non-steroid anti-inflammatory agents of the oxican group [31]. This class of NSAID was discovered by Lombardino and collaborators [32], at Pfizer Laboratories in England, piroxicam 66 being the main representative of this class of 1,1-dioxibenzene-1,2-thiazine (BTA) synthetics.

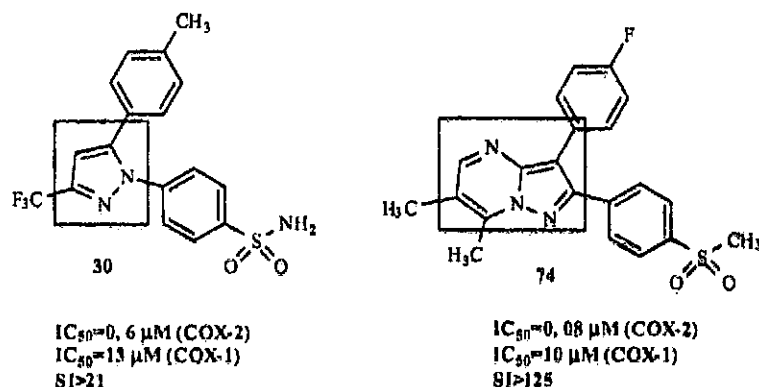
Applying the strategy of ring bioisosterism, Binder proposed tenoxicam 67, the newest member of the class of arylthiazine-1,1-dioxides, where the benzothiazine nucleus

of 66 was replaced by the thienothiazine moiety (Scheme 15) [30]. This example represents the bioisosteric relationship existing between aromatic heterocyclic rings and the phenyl group. The profile of pharmacotherapeutic activity of 67 proved to be comparable to that of 66, being able to be administered in single daily doses of 20 mg, because of its long plasmatic half-life, a desirable quality for cases of arthritis as well as osteoarthritis. Both derivatives act by the same mechanism of action, at the same receptor level, *i.e.* cyclooxygenase, an enzyme involved in arachidonic acid metabolism. It is noteworthy that other ring bioisosteres at the structural subunit level represented by the BTA nucleus may possess the same pharmacotherapeutic profile as 66 and 67 (*cf.* 68) [33], being differentiated from other bioisosteres developed by structural alterations in the heteroaromatic ring, present in the carboxamide unit, whose representative is isoxicam 69, which possesses 5-methylisoxazole ring as equivalent of the pyridine ring present in compounds 66 and 67 (Scheme 15). This derivative was recently taken off the market due to the dermatologic reactions it provoked.

The similarity between the physicochemical properties of the benzene (PE = 80 °C) and thiophene (PE = 84 °C) rings is well fundamented and was used to create the concept of ring bioisosterism or ring equivalents. However, the exchange of the phenyl ring by the thiophene ring in the structure of bicyclic derivatives, should be carried out



Scheme 16.



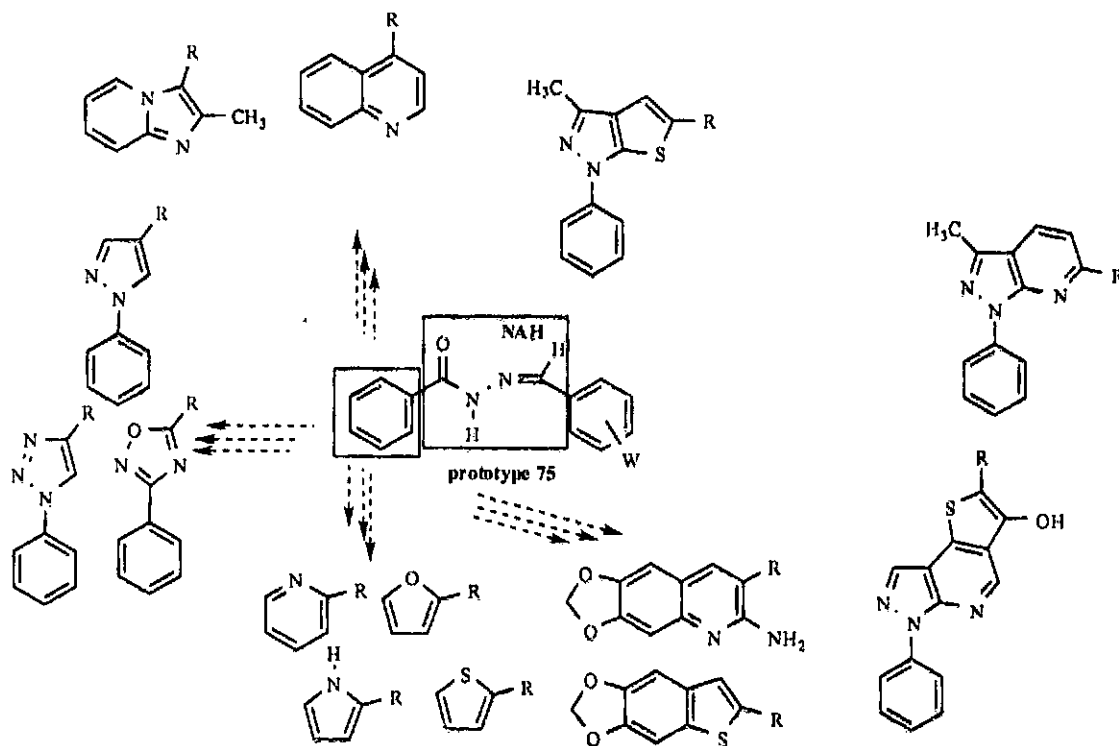
Scheme 17.

considering the possible regioisomeres involved in this replacement. Studies by Blair and coworkers have illustrated very well this type of replacement, in which the phenyl ring of the indolic nucleus, present in the structure of lead compound, *N,N*-dimethyltryptamine (70) was replaced by the thiophene ring, giving rise to the isomeric systems thieno[3,2-*b*]pyrrole (71), thieno[2,3-*b*]pyrrole (72), thieno[4,3-*b*]pyrrole (73) (Scheme 16) [34]. However, the results described by these authors show that with the exception of the thieno[4,3-*b*]pyrrole system (73), of unstable and difficult preparation, the other heterocyclic isomeric systems are authentic bioisosteres of the indole ring, presenting affinity and selectivity by the serotonin receptors similar to lead compound 70.

Concerning the non-steroid anti-inflammatory drugs (NSAIDs), Almansa and coworkers (Scheme 17) [35]

described the existing bioisosteric relationship between the pyrazolo and pyrazolo[1,5-*a*]pyrimidine rings present in compounds 30 and 74, respectively. The exchange of the pyrazolic ring, present in celecoxib (30), by the pyrazolo[1,5-*a*]pyrimidine system in 74, resulted in an optimization of the pharmacodynamic properties of 30, although it compromised its oral bioavailability.

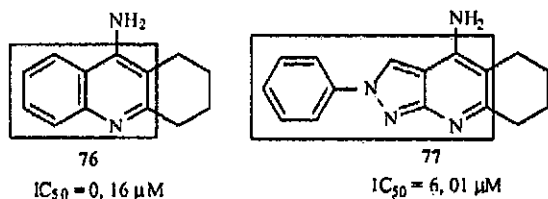
The use of ring bioisosterism may serve for designing congeneric series of lead compound candidates for new drugs, in view of the detailed study of the distinct hydrophobic contributions resulting from rings equivalents. This strategy has revealed itself as a fundamental tool in designing new *me-too* drugs, i.e. therapeutic copy (*vide* Figure 2). In a recent study, Barreiro and coworkers described the application of ring bioisosterism for designing functionalized *N*-acylhydrazones (NAH) derivatives (Scheme



Scheme 18.

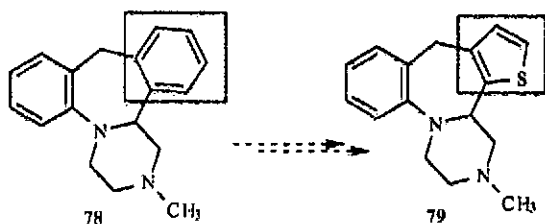
18) [36], in an effort to correlate the alterations found in the profile of anti-platelet, analgesic and anti-inflammatory activities, of each new hetero-aromatic system studied, with its respective electronic characteristics.

More recently, Barreiro and coworkers (Scheme 19) described the attainment of new selective acetylcholinesterase (AChE) inhibitors designed by modifications in the structure of the lead compound tacrine (76) [37]. These modifications allow for identification of a new bioisosteric relationship existing between the quinoline nuclei in 76 and pyrazolo-pyridine in 77, which have shown a similar inhibitory capacity for rat brain cholinesterases.

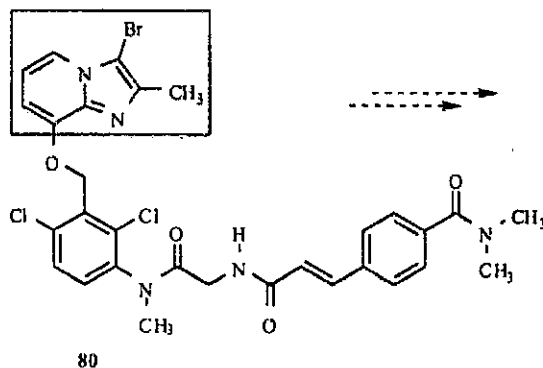


Scheme 19.

In the field of antidepressives, bioisosteric ring replacement of a determined lead compound also permits the discovery of new agents of therapeutic interest. In 1983, Wathley and coworkers developed, at Ciba-Geigy Laboratories, compound 79 as a bioisoster of mianserine 78 (Scheme 20) [38]. As principal structural characteristic, this substance possesses the thiophenic ring integrated to the cyclic unit of this representative of atypical antidepressive agents, which act as serotonin receptors (5-HT) antagonists [39]. Once again, this example illustrates the equivalency of the benzene and thiophene rings, in distinct pharmacological activities, allowing for a generalization on the bioisosteric relationship between heterocyclic nuclei of five atoms and benzene ring [40].



Scheme 20.



Scheme 21.

The recognition of the importance of bradykinin in the processes of pain, inflammation, rhinitis and hypertension, has shown the relevance of bradykinin receptors as a new target for therapeutic intervention. Although many bradykinin receptors antagonists have been described in the literature, its peptidic characteristics have limited its therapeutic applications. Seeking non-peptidic bradykinin receptors antagonists, Abc and coworkers described the attainment of 2-methylimidazo[1,2-*a*]pyridine derivatives, highlighting the derivative FR167344 as lead compound (80) (Scheme 21) [41]. Later, those authors proposed the bioisosteric exchange of 2-methylimidazo[1,2-*a*]pyridine ring, present in compound 80, by the 2-methylquinoline subunit, identifying the new derivative FR175657 (81), as a potent bradykinin receptors antagonists of non-peptidic structure.

6 – NON-CLASSIC BIOISOSTERISM

6.1. Cyclic vs Non-Cyclic

In the category of diuretic substances of the phenoxyacetic class, in which osacrinic acid 82 is the main representative, we have found innumerable examples of the use of non-classic bioisosterism in the discovery of new drugs. To develop new diuretic substances, with uric activity superior to 82, Hoffman and coworkers applied non-classic bioisosterism represented by *ring-closing*, or anelation, as a strategy to choose definitions of new lead compounds for diuretic drugs [42]. These authors working at Merck, Sharp and Dohme Laboratories, proposed compound 84 as a bioisostere of 83 (Scheme 22). The structure of 84 was defined based on the anelation of the phenoxyacetic chain (a) of 83, which, in turn, arose by the replacement of the ethylenone function present in 82 by the thiophene nucleus of 83, including all four carbon atoms of the replacement of 82, there being a clear correspondence between the carbons with sp^2 hybridization in 82 and 84. This type of anelation in the ethylenone chain of 82 had been proposed previously by Thuillier [43-44], who described the synthesis of 83 as being an acid equivalent to osacrinic acid (82) in terms of its diuretic properties, while with superior uric properties. In fact, this last compound represents one of the first examples of bioisosteres of 82, obtained by application of non-classic bioisosteric strategies. Compound 84, proposed and synthesized by Hoffman, presented a profile comparable to