

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

2020
Bogotá, D.C.,

Abogado
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-001889- -00006-0000

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Act. 519 TRASLADOINFORME Folios: 1

ASUNTO	Radicación	10-1889
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	005

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

No. Solicitud Internacional PCT/GB2008/050431
Fecha de Presentación Internacional 11 de junio 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 199 a 359	08/enero/2010
Reivindicaciones:	Folios 360 a 378	08/enero/2010
Prioridad:	US 60943440	12/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. Modificaciones no aceptadas (Art 34 D 486 y Art 19, 22 y 34 PCT)

Las modificaciones de las Reivindicaciones 11-38, folios 363-376, no son aceptables porque no se pagó la tasa respectiva. Lo anterior, de acuerdo con requerimiento N° 01272 del 28 de enero de 2011

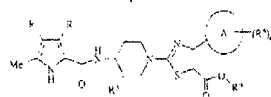
4. Objeto de la invención

Título de la solicitud: "Derivados carboxílicos y alcoxi de 4-sustituido-2-[4-((5-metil-1H-pirrol-2-il)carbonil)amino)-piperidin sustituido-1-il]-1,3-tiazol como inhibidores de la DNA girasa y/o topoisomerasa IV y composiciones farmacéuticas de los mismos" (modificado en el folio 387).

El problema planteado en esta solicitud consiste en suministrar compuestos que presentan actividad antibacteriana para tratar infecciones bacterianas en animales de sangre caliente

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



Compuesto la

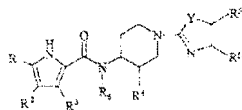
El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D 417/08

5. Determinación del Estado de la Técnica

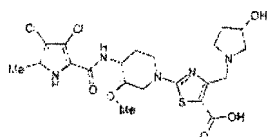
El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: junio 12 de 2007 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación*
D1	WO 2006/087543	Antibacterial piperidine derivatives	24/agosto/2006
D2	Current Medicinal Chemistry, 2005, Vol. 12, No. 1	Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design	2005

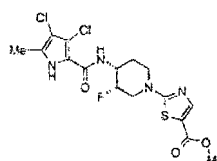
D1:<http://patentscope.wipo.int/search/en/WO2006087543> divulga una serie de compuesto con actividad antibacterial (Pág. 2, Ren. 1-10) derivados del compuesto le (Pág. 241) inhibidores de la DNA girasa (Pág 53, Ren. 3-10) y que da a conocer por medio realizaciones preferidas 380 (Pág. 166) y 426 (Pág. 177) los compuestos.



Compuesto 1e



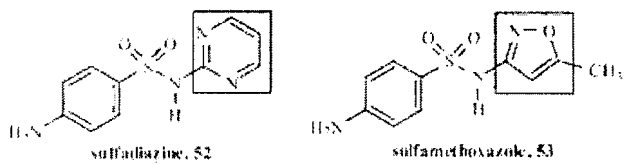
Realización preferida 380



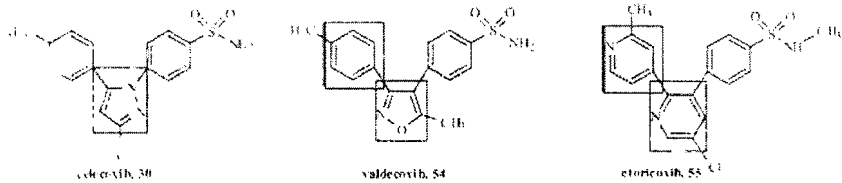
Realización preferida 426

D2: divulga (Pág 1. Int.) que el bioisosterismo es una estrategia de la química medicinal para el diseño racional de nuevos fármacos, el cual a partir de un compuesto líder o base a través de un procesos especial de modificaciones moleculares. El objeto de este proceso es desarrollar nuevas sustancias que son terapéuticamente atractivas y se ha observado una un crecimiento significativo en distintas clases terapéuticas, siendo ampliamente utilizado por la industria farmacéutica para descubrir nuevos análogos de las innovaciones terapéuticas comercialmente atractivos y también como una herramienta útil en el nivel molecular modificación.

Adicionalmente, da a conocer (Pág, 8) algunos grupos heterocíclicos bioisósteros como la diazina y el oxazol para los antibacterianos del grupo de las sulfas



y pirazol, oxazol y piridina para el grupo de la antiinflamatorios del grupo de inhibidores selectivos de la COX-2.

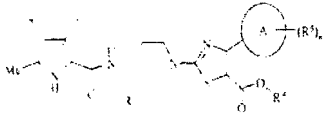
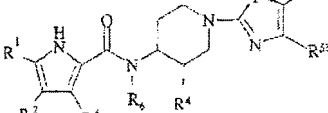


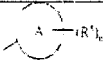
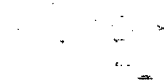
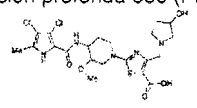
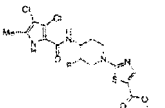
6. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D186)

La reivindicación 1 consiste en compuesto de fórmula (Ia) derivados del ácido 2-((3S,4R)-4-[(3,4-sustituido-5-metil-1H-pirrol-2-il)carbonil]amino}3-sustituidos piperidin-1-il)-1,3-tiazol-4-carbociclil o heterociclil-5-carboxílico inhibidores de la DNA girasa y/o topoisomerasa IV

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

SOLICITUD	D1	D2
Un compuesto de fórmula Ia	Un compuesto de fórmula Ie	Divulga que el bioisosterismo es una estrategia de la química medicinal para el diseño racional de nuevos fármacos y da a conocer grupos heterocíclicos bioisósteros como 1.) la diazina y el oxazol y 2.) pirazol, oxazol y piridina entre otros
 Compuesto Ia	 Compuesto Ie	
R ¹	R ²	
fluoro metilo metoxi etoxi propoxi allyloxy benciloxi	hidrógeno nitro hidroxi halo ciano C ₁₋₄ alquilo C ₁₋₄ alcoxi C ₂₋₄ alquenilo C ₂₋₄ alquinilo C ₁₋₄ alcanoilo C ₁₋₄ alquiloS(O) _a en donde a es 0 a 2 y C ₃₋₆ cicloalquilo; donde R ³ puede ser opcionalmente sustituido	
R ²	R ³	
cloro ciano	hidrógeno nitro hidroxi halo, ciano -C = N-OR 'donde R' es H o C ₁₋₄ alquilo. C ₁₋₄ alquilo C ₁₋₄ alcoxi C ₂₋₄ alquenilo C ₂₋₄ alquinilo C ₁₋₄ alcanoil C ₁₋₄ alquiloS(O) _a en donde a es 0 a 2 y C ₃₋₆ cicloalquilo; donde R ³ puede ser opcionalmente sustituido	

SOLICITUD	D1	
R ³	R ⁴	
Fluoro Metilo Metoxi Etoxi Propoxi Aliloxi benciloxi	Halo carboxi C ₁₋₄ alquilo C ₁₋₄ alcanoilo C ₁₋₄ alcanoiloxi	
Azufre	Y	
	S	
Hidrógeno	R ⁴	
	Hidrógeno	
	R ^{5a}	
es carbociclilo o heterociclilo; donde si dicho heterociclilo contiene nitrógeno un resto-NH- esto puede ser sustituido por R ⁶	Carbociclil-R ¹⁰ o heterociclil-R ¹¹ donde R ¹⁰ o R ¹¹ puede ser sustituido por un grupo seleccionado	
	R ^{5b}	
Donde R ⁴ es hidrógeno o C ₁₋₄ alquilo	Carboxi opcionalmente sustituido C ₁₋₄ alquilo	
REALIZACIONES PREFERIDAS	REALIZACIONES PREFERIDAS	
Realización preferida 114 (Fol. 289) 	Realización preferida 380 (Pág. 166) 	
Realización preferida 61 (Fol. 270) 	Realización preferida 426 (Pág. 177) 	
Correspondiente al compuesto 2-((3S,4R)-4-(((3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino)-3-fluoropiperidin-1-il)-1,3-tiazol-5-carboxilato	Correspondiente a la sal del compuesto 2-((3S,4R)-4-(((3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino)-3-fluoropiperidin-1-il)-1,3-tiazol-5-carboxilato	

El documento D1 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulga compuestos derivados del ácido 2-((3S,4R)-4-(((3,4-sustituidos-5-metil-1H-pirrol-2-il)carbonil]amino)-3-sustituidos piperidin-1-il)-1,3-tiazol-4-carbociclil o heterociclil-5-carboxílico inhibidores de la DNA girasa y/o topoisomerasa IV y por lo tanto útiles para el tratamiento de infecciones bacterianas.

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto (Ie) del documento D1 corresponden a que 1.) La invención divulga explícitamente un sustituyente carbociclil o heterociclil en la posición 4 del anillo 1,3-tiazol y el documento I refiere estos sustituyentes como parte de un grupo seleccionado para la posición 4 o 5 del anillo 1,3-tiazol. Por lo cual se considera que esta invención es una selección.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: "cómo seleccionar los derivados del ácido 2-((3S,4R)-4-(((3,4-sustituido-5-metil-1H-pirrol-2-il)carbonil]amino)-3-sustituidos-piperidin-1-il)-1,3-tiazol-4-carbociclil o heterociclil-5-carboxílico del compuesto (Ie) conocidos en D1 para obtener inhibidores de la DNA girasa y/o topoisomerasa IV y por lo tanto útiles para el tratamiento de infecciones bacterianas.

El efecto que se logra al seleccionar los derivados del ácido 2-((3S,4R)-4-(((3,4-sustituido-5-metil-1H-pirrol-2-il)carbonil]amino)-3-sustituidos piperidin-1-il)-1,3-tiazol-4-

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carbociclíl o heterociclíl-5-carboxílico del compuesto (Ie) divulgado en D1 es obtener nuevos inhibidores alternativos de la DNA girasa y/o topoisomerasa IV.

Sin embargo, dado que documento D1 refiere que 1.) Los compuestos 2-((3S,4R)-4-(((3,4-sustituido-5-metil-1H-pirrol-2-il)carbonil]amino)3-sustituidos piperidin-1-il)-1,3-tiazol como el compuesto 426 (Pág. 177) son inhibidores de la DNA girasa y/o topoisomerasa IV y por lo tanto útiles para el tratamiento de infecciones bacterianas y el documento D2 indica que el bioisosterismo es una estrategia de la química medicinal para el diseño racional de nuevos fármacos, dando a conocer una serie de grupos heterocíclicos bioisósteros como lo son 1.) La diazina y el oxazol y 2.) El pirazol, el oxazol y la piridina.

En consecuencia, una persona del oficio normalmente versada en la materia, estaría suficientemente motivada para seleccionar los derivados del ácido 2-((3S,4R)-4-(((3,4-sustituido-5-metil-1H-pirrol-2-il)carbonil]amino)3-sutituidos piperidin-1-il)-1,3-tiazol-4-carbociclíl o heterociclíl-5-carboxílico del compuesto (Ie) y obtener inhibidores alternativos de la DNA girasa y/o topoisomerasa IV como lo sugieren el documento D1 o sustituir en la posición 4 del anillo 1,3 tiazol de la realizaciones preferidas 380 y 426 del documento D1 o incluir en la posición 4 del anillo 1,3 tiazol del compuesto 426 (Pág. 177) de acuerdo con lo sugerido el documento D2 un grupo carbociclíl o heterociclíl bioisósteros alternativo al definido en el documento D1 para obtener nuevos inhibidores alternativos dado que esta sustitución o inclusión esta sugerida por los documentos D1 y D2. Por lo cual la reivindicación 1 se considera obvia.

Puesto que los documentos D1 y D2 mencionan todas las características técnicas esenciales de las reivindicaciones dependientes 2-3 y 6-10, estas tampoco se pueden considerar inventivas.

7. Conclusión

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

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO 2006/087543	1-3 y 6-10	Nivel Inventivo
D2	Current Medicinal Chemistry, 2005, Vol. 12, No. 1	1-3 y 6-10	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.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante (60 días) y presentarla por escrito.

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)

28 AGO. 2012

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

Elaborado por: Lenin Roberto Guerrero 
Revisado Por: Consuelo Leguizamón Leguizamón. 
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Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design

Elisa Moreira Lima and Eliezer J. Barreiro*

Laboratório de Avaliação e Síntese de Substâncias Bioativas, C-1 ANSBio, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CUS Cidade Universitária, CP 68009, 21944-900, Rio de Janeiro, R.J., Brazil

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 pharmacophore 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.

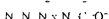
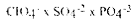
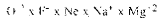
There may be innumerable reasons for the use of bioisosterism to design new drugs, including the necessity to improve pharmacological activity, gain selectivity for a determined receptor or enzymatic isoform subtype, with simultaneous reduction of certain adverse effects, or even optimize the pharmacokinetics 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 1975, 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 pseudocation 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 pseudocations.

In 1932, Grlenmeyer [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 Thorner during the early 50s. Friedman [11], recognizing the usefulness of the concept *isosterism* to design bioactive molecules, defined bioisosteres 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, Thorner [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.

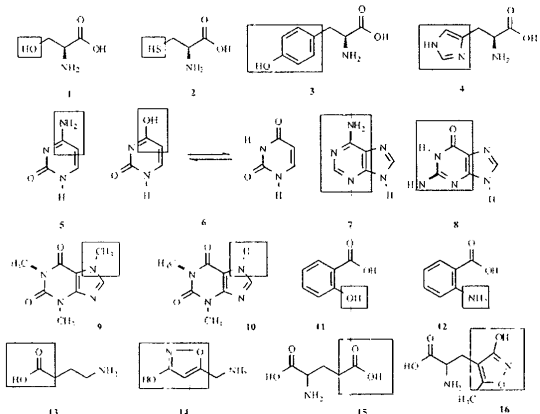
Over the years, innumerable bioisosteric relations have been identified in compounds both natural and synthetic. In nature, we have identified many examples of isosterism as a

Group	Group	Group	Group	Group		
4A	5A	6A	7A	8A		
Nº of e ⁻	6	7	8	9	10	11
	C	N	O	F	Ne	Na ⁺
H ⁺ ↓	CH	NH	OH	FH		
	H ⁺ ↓	CH ₂	NH ₂	OH ₂	FH ₂ ⁺	
		H ⁺ ↓	CH ₃	NH ₃	OH ₃ ⁺	
			H ⁺ ↓	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 (2), purine bases, cytosine (5) and uracil (6), iderine (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).

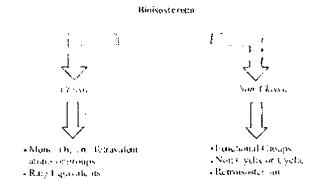


Scheme 1.

*Address correspondence to this author at the Laboratório de Avaliação e Síntese de Substâncias Bioativas (ANSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro (CUS Cidade Universitária), CP 68009, 21944-900, Rio de Janeiro, R.J., Brazil. E-mail: elisapharm@ufrj.br

3. CLASSIFICATION OF BIOISOSTERISM: CLASSIC AND NON CLASSIC

In 1938, Arthur Burger classified and subdivided isosteres into two broad categories: Classic and Non Classic [1]. 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	Retrosynthesis

Table 1 Classic Bioisostere Groups and Atoms

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

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]:

- 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;
- degree of lipidic and aqueous solubility, so as to allow prediction of alteration of the physicochemical properties such as logP and pKa;
- 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;
- conformational factors, including the differential capacity formation of inter- or intramolecular hydrogen bonds.

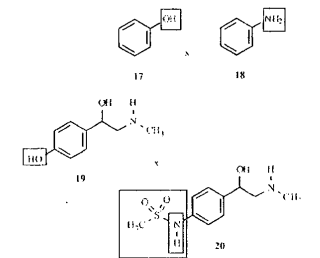
4.1. BIOISOSTERISM AND ALTERATIONS OF PHYSICO-CHEMICAL PROPERTIES

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 (-NH₂⁺), originating from basic aromatic amine function (pKa = 9.39) by another acid (pKa = 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
-C(=O)-	-SO ₂ H	-SO ₂ OHNH ₂	-F	-NHCO-	-ROCO-	-CSNH ₂
-SO ₂ -	-tetrazole					
-SO ₂ NH-	-SO ₂ MH-		-OH			
	-SO ₂ NH ₂		-CH ₂ OH			
-CON-	-2-hydroxyisoxazole					
-CH(CN)-	-2-hydroxychromones		-NH ₂ ONH ₂			
-R-S-R			-NHCS-NH ₂			
-R-O-R	-N-					
-R-N(CN)-	-C(CN)-R'					
			-NH-C(=CHNO ₂)-NH ₂			
			-NH-C(=CHC(=O)-NH ₂)-NH ₂			
-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.

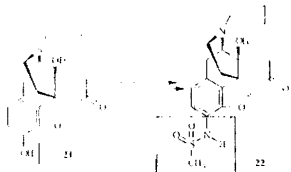
Another classic example of isosteric replacement involving phenol (PhOH), can be found in the search for adrenergic derivatives, structurally related to catecholamines

(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 (pKa = 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-PhNH₂SO₂CH₃ are, in this case, monovalent groups. However, the identified bioisosteric relationship between the PhOH and PhNH₂SO₂CH₃ 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 NH₂SO₂CH₃ 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.

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must be studied in this system (the groups PhOH and $\text{PhNH}_2\text{SO}_2\text{CH}_3$) to obtain 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 bioisosteric, will not necessarily be successful in another therapeutic series, acting through other receptors.*

5. CLASSIC BIOISOSTERISM

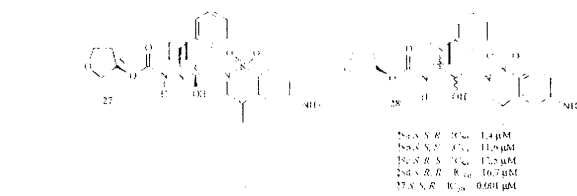
5.1. Bioisosterism of Mono-, Di-, Tri- and Tetravalent Atoms or Groups

In the search for new anti-hypertensive drugs analogous to clonidine (23), with a greater selectivity by I_1 imidazoline receptors (I_1R) and reduced action on α_2 -adrenoceptors, Schiano 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,

overlapped by replacement of the bivalent oxygen atom (O) present in the oxazoline ring by the methylene group (CH_2), in the structure of the new pyridine derivative (25); and between replacement of monovalent groups illustrated by the substitution of hydrogen atoms (H) in C-4 and C-5 of active (25) by the methyl group (CH_3), originating the *oxazoline* 4,5-dimethyl homologue 26 [17]. The *binding* tests with I_1R and α_2 -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 I_1R , and illustrated an example of the success of classic bioisosterism.

To develop new HIV-protease inhibitors, Roche/Novartis and coworkers described the bioisosteric exchange between bivalent groups (Scheme 6), realizing the exchange of the methylene group (CH_2), 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 isosteric was synthesized, and its stereoisomers were duly 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 thiophenyl 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

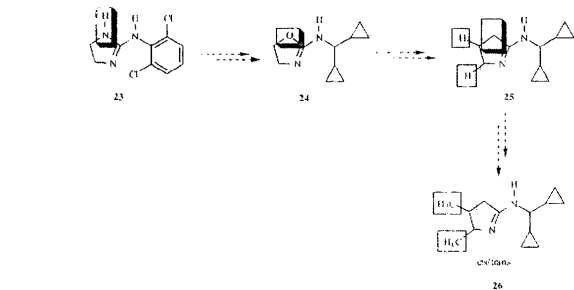


Scheme 6.

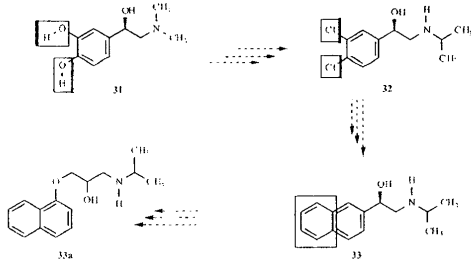
effect of isosteric modifications on the structure of lead compound SC-58125 (29), to improve its pharmacokinetic properties. In spite of the high rate of selectivity by PGHS-2 ($\text{SI} > 1000$) and good inhibitory potential, the derivative SC-58125 (29) exhibited a half-life of over 200 h, thus reflecting 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 bioisosteric 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 bioisosteric 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/Seac 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.

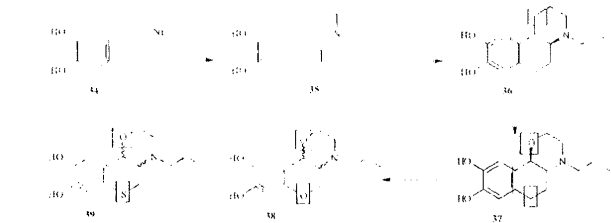
The design of dichloroisoproterenol (32) from isoproterenol (31) is, without a doubt, an unique example of the contribution of the application of bioisosterism to optimize pharmacodynamic and pharmacokinetic properties of new drugs (Scheme 8). The replacement of catecholic hydroxyls, present in isoproterenol (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 5.

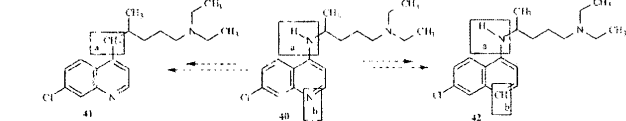


Scheme 8.



Scheme 9.

Furthermore, the discovery of dichloroisoproterenol (32), made feasible the comprehension of the relevance of structural characteristics of the catecholic substituent for adrenergic activity, allowing *a posteriori* the discovery of pronethalol (33), the first selective antagonist for adrenergic receptors for subtype β_2 (pronethalol(33), discontinued during the 1980s, was the precursor of propranolol (33a), a therapeutic innovation which revolutionized the treatment for hypertension. The discoverer, Sir 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.



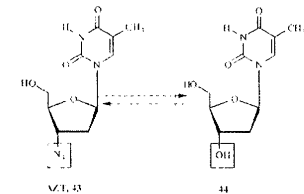
Scheme 10.

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 meta-ene (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 this-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 as to behaves in an inverse relationship between

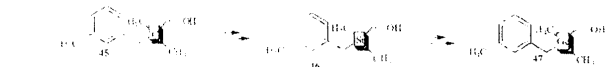
the increase in lipophilicity and the selectivity desired by the D_3 receptors.

To understand the contributions of 4-aminoquinoline subunit present in the structure of the first generation antimalarial chloroquine (CLQ, 49), Chenku 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-aniline*) and N (b; *N-quinoline*) 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

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.

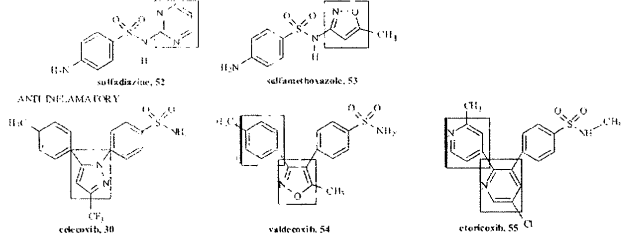


Scheme 12.

(CLQ, $IC_{50} = 80$ μ M; 41 $IC_{50} = 1500$ μ M, 42 $IC_{50} = 500$ μ M). Hence, the isosteric modifications realized reinforced the hypothesis of the importance of N-quinoline interaction process with hemozoin, 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

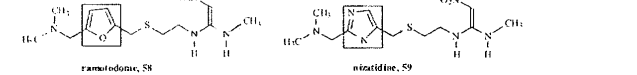
ANTI-BACTERIAL



ANALGESIC



ANTHELMINTIC



MALE FERTILITY ENHANCER

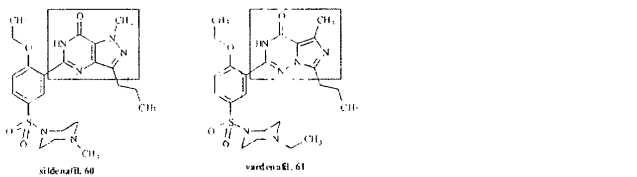


Fig. (2). Examples of drug bioisosterism between drugs belonging to different therapeutic classes.

Furthermore, several authors have used to ascertain the existence of a classic bioisosteric relationship of nucleoside groups between the nucleoside thymine (24) nucleosidic substrate, or the synthesis of DNA and RNA, and *N*-(2'-deoxy-2'-methyl-5-phosphoryl-uracil) (25) (Scheme 11) [34]. Furthermore, although classic bioisosteric relationships between OH and NH groups possess organic electronic differences, easily demonstrated by simple functional analysis.

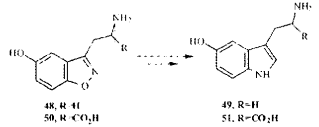
Although applicability of the strategy of molecular modification of a given lead compound through bioisosterism is well consolidated in the pharmaceutical industry, recent studies by Locke and coworkers (Scheme 12) shows that this approach may be used efficiently to optimize the organotopic properties of compounds used in fragrances of industrial interest [25]. In this study, the application of classic bioisosterism of tetrasubstituted atoms, illustrated by exchange of the carbon atom (C), present in the structure of nujanol (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 x Si x Ge, produces bioisosteres 48, 49 and 50, resulting 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, Shovel 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 phosphorus, 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 x Si in the structure of new drugs to be quite limited [25].

5.2. Ring Bioisosterism

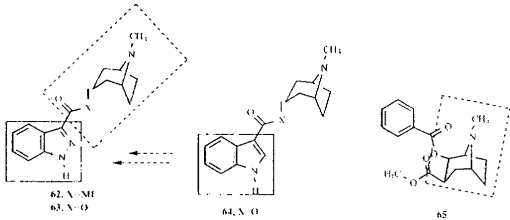
Ring bioisosterism is undoubtedly the most frequent relationship in drugs of different therapeutic classes [8], as can be seen in (Fig. 2) and certain specific examples will be commented upon.

In 1973, Campaigne and coworkers synthesized compound 58 [27] as being a derivative structurally related to serotonin (9), an antiserotonin 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 58 presented no type of serotonininimetic 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.

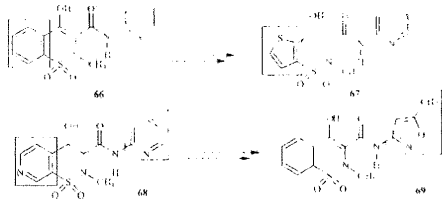


Scheme 13.

Applying classic bioisosterism in the design of new serotonin receptor (5-HT₂) antagonists Fludzinski and coworkers (Scheme 14) described the obtention of new indazolyl compounds 62 and 63 with important antagonistic properties of receptor 5-HT₂ [28]. These two substances were developed as bioisosteres of 64, a compound which possesses as main structural characteristic the hybrid



Scheme 14.



Scheme 15.

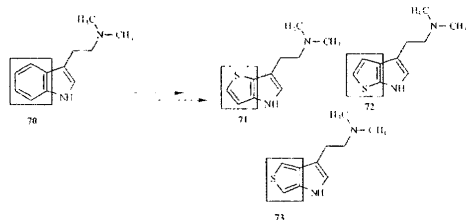
character between serotonin (49), represented by the indole ring substituted in C-3, and cocaine (65), represented by the nature of the substituent in C-3, a known antagonist of receptors 5-HT₂ [29]. The bioisosteric relationship of these two nuclei was proven. In this case, by the results obtained in bioassays which showed for 67 a rate of selectivity by the receptors 5-HT₂ superior to that of 64, when administered intravenously as well as orally, showing that the indole 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 amide 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, piroxican 66 being the main representative of this class of 1,1-dioxibenzene-1,2-thiazine (BTA) synthetics.

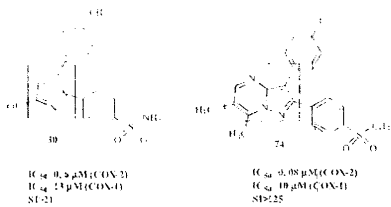
Applying the strategy of ring bioisosterism, Binder proposed tenoxican 67, the newest member of the class of arylthiazine-1,1-dioxides, where the benzothiazine nucleus

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 (*i.e.* 68) [33]. Being differentiated from other bioisosteres developed by structural alterations in the heteroaromatic ring, present in the carboxamide unit, whose representative is isoxican 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.



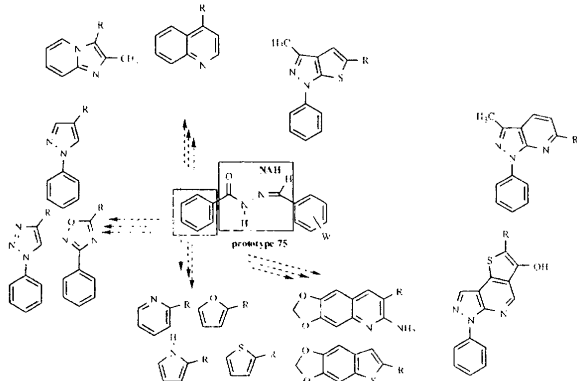
Scheme 17.

considering the possible regioisomers involved in this replacement. Studies by Blar and coworkers have illustrated very well this type of replacement, in which the phenyl ring of the indole 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*]pyridine rings present in compounds 30 and 74, respectively. The exchange of the pyrazolic ring, present in celecoxib (30), by the pyrazolo[1,5-*a*]pyridine system in 74, resulted in an optimization of the pharmacodynamic properties of 30, although it compromised its oral bioavailability.

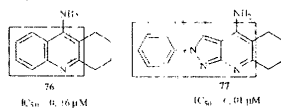
The use of ring bioisosterism may serve for designing congeneric series of lead compound candidates for new drugs, in view of the detailed study of the distinct hydrophobic contributions resulting from rings equivalents. This strategy has revealed itself as a fundamental tool in designing new *me-too* drugs, *i.e.* therapeutic copy *travels* (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.

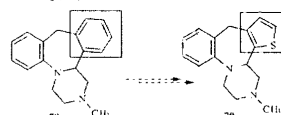
18) [36], in an effort to correlate the differences found in the profile of antiplatelet, analgesic and anti-inflammatory activities, of each new heterocyclic system studied, with its respective electronic characteristics.

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 guanidine nuclei in 76 and pyrazolo-pyridine in 77, which have shown a similar inhibitory capacity for rat brain cholinesterases.

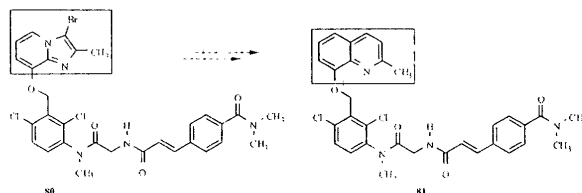


Scheme 19.

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, Wathney 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 thiophene 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, as distinct pharmacological activities, allowing for a generalization on the bioisosteric relationship between heterocyclic nuclei of five atoms and benzene ring [40].



Scheme 20.



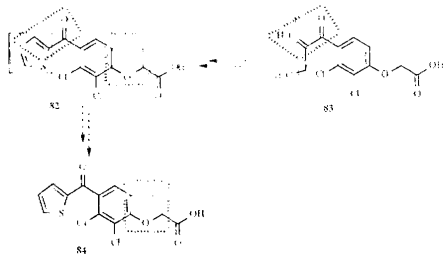
Scheme 21.

The recognition of the importance of bradykinin in the processes of pain, inflammation, hemostasis 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, Abe and coworkers described the attainment of 2-methylimidazo[1,2-*a*]pyridine derivatives, highlighting the derivative FR16344 as lead compound (80) (Scheme 21) [41]. Later, these authors proposed the bioisosteric exchange of 2-methylimidazo[1,2-*a*]pyridine ring, present in compound 80, by the 2-methylquinoline substituent, 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 phenoxycetic class, in which etacrine 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 an activity superior to 82, Hoffman and coworkers applied non-classic bioisosterism represented by *ring-closing*, or *anellation*, 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 bioisoster of 83 (Scheme 22). The structure of 84 was defined based on the anellation of the phenoxycetic chain (a) of 83, which, in turn, arose by the replacement of the ethylene 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 anellation in the ethylene chain of 82 had been proposed previously by Thuillier [43-44], who described the synthesis of 83 as being an acid equivalent to etacrine 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



Scheme 22.

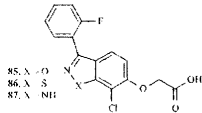
83, its uric potential being even greater. Furthermore, the introduction of the thiophene ring in 83 to replace the ethylamide subunit of 82, eliminates Michael's acceptor site present in the structure of etoxime acid 182, responsible for the hepatotoxic effects of this drug.

Still on the subject of diuretics related to etacrine acid (82), Shutske and coworkers later developed the synthesis of new aryl-benzisoxazole/oxyacetic acids (e.g., 85) [45], based on the probable bioisosteric relationship existing between the aryl-benzisoxazole unit and the 2-acyl-thiophenyl moiety present in acid 83 [46] (Scheme 22). This illustrative example is sufficient to show the potential of the strategy of non-classic bioisosterism for designing molecular modifications in substances of pharmacological interest.

Shutske and coworkers successfully explored the possibility of integrating the thiophenacyl group of 83 into one aryl-benzisoxazole nucleus, respecting the basic pharmacophore of this class of agents, so as to assure, at least theoretically, an action through a similar mechanism, *i.e.*, through molecular recognition by the same site receptor. In this example, the authors introduced a factor of conformational restriction in 85, typical of non-classic bioisosterism of the *locking ring* type. Later, the same authors [47] used classic bioisosteric ring to design structurally new heterocyclic diuretic compounds from 85, possessing, now, the indazole ring in 87 and benzisothiazole in 86 (Scheme 23).

Innumerable other examples can illustrate the validity of the use of this strategy in discovering new bioactive agents which are more therapeutically attractive. A classic example

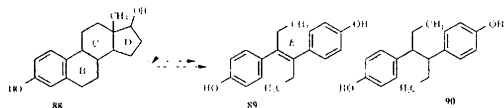
is represented by the discovery of the estrogenic properties of *trans*-diethylstilbestrol 88 [48], illustrating the application of non-classic ring opening bioisosterism. This example shows that the molecular design of 89 could be carried out from the opening of rings B and C of the steroidal skeleton of estradiol 88 (Scheme 24). However, in analogy to what was observed for estradiol (88), the activity of 89 is dependent on the configurational aspects, such that, the diastereoisomer *E* presents an estrogen profile significantly superior to the diastereoisomer *Z*, with reduced estrogen activity also being observed for the dihydrogenated compound 90 (Scheme 24).



Scheme 23.

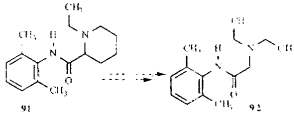
Another example of the application of non-classic bioisosterism can be illustrated by the discovery in 1957 of lidocaine 92 from mepivacaine 91 (Scheme 25), contributing to the design of the important anesthetic agent with predominant antiarrhythmic properties, identified *a posteriori*.

Exploring the bioisosteric relationship between the benzoyl and benzisoxazole groups, Strupczewski and coworkers of Hoechst-Roussel Laboratories [49], developed



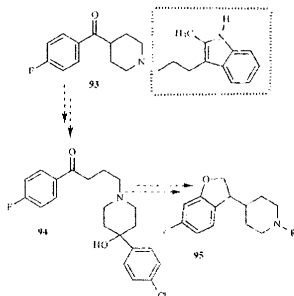
Scheme 24.

a new series of neuroleptic compounds of series 4-benzoylpiperidine, in which 93 (1H-99) is one of the main representatives. This substance is structurally related to haloperidol 94, the main representative of the butyrophenones, a class of neuroleptics discovered by Janssen [50], in which, conceptually, the C-2, C-3 and C-4 carbon atoms of the butyrolactone chain of 94 are contained in the piperidine moiety of 93, thus representing a non-classic bioisostere of 94 (Scheme 26). These authors further developed compound 92, in which a benzisoxazole moiety bioisosterically replaces the 4-benzoyl moiety represented by the 4-fluorobenzoyl unit in 93.



Scheme 25.

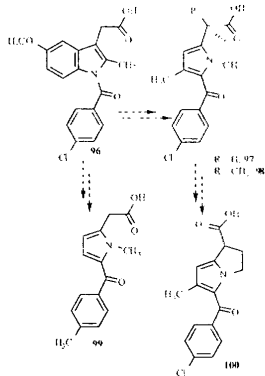
In the class of non-steroid anti-inflammatory drugs (NSAIDs) other examples were found of the use of the strategy of cyclic non-classical bioisosterism. In 1987, Muchowsky and coworkers [51], developed the synthesis of a new NSAID called cetopac (100) designed from the cyclic non-classical bioisosterism strategy, exploring the ring closing between the acetic acid unit and the *N*-CH₃ moiety of lead compound tolmetin (99) (Scheme 27) [52], a well known NSAID of the heteroarylacetic acid class [53]. Tolmetin (99), in turn, was developed by molecular modification of the indomethacin structure 96, an important representative of the 3-indolylacetic acid class with anti-inflammatory properties developed by Shoen and coworkers at Merck, Sharp and Dohme Laboratories in 1962 [54], applying the inverse principle, *i.e.*, noncyclic nonclassical bioisosteric replacement.



Scheme 26.

In tolmetin (99) the indole subunit of indomethacin was replaced by the pyrrole ring carrying the benzoyl unit in C-2,

as the bioequivalent of the *para*-chlorobenzoyl unit in 96. This same approach was taken by Carlson and Wong [55] to develop cetopac (97) (Scheme 27) [56], another NSAID agent of the pyrrole 3-acetic acid class. This compound is an active enantiomer, presenting as the only structural difference the presence of the methyl group in C-3, and may, therefore, be considered a homolog of 99.

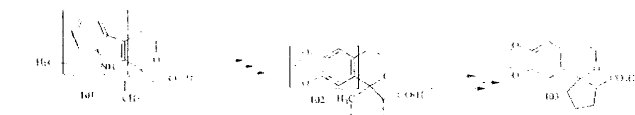


Scheme 27.

In 1973, Carlson and Wong demonstrated that homologation of the acetic chain of 97 leads to a new anti-inflammatory derivative, α -methylbenzene acetic acid 98 (Scheme 28), belonging to the propionic acid series, a class favored by Shen [55], in the light of studies on the relationship between the chemical structure of aryl and heteroarylacetic derivatives, as presenting a profile of anti-inflammatory properties greater than those of the acetic series. Substance 98, in fact, was seen to possess anti-inflammatory properties greater than 99 and was even able to reduce adverse effects on the gastrointestinal tract, corroborating the previous observations made by Shen.

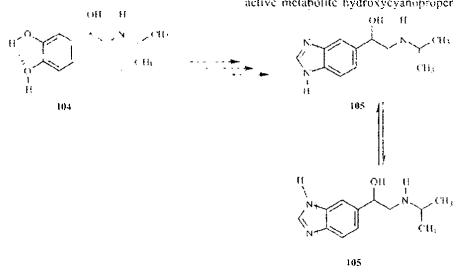
Considering this data, we may observe that compound 100, belonging to the 5-acyl-1, 2-dihydro-3H-pyrrol-(1,2-*a*)-pyrrolyl carboxylic acid family, represents, at the same time, a bioisostere of 99 and 97 (Scheme 27), by *anelation* of the main pharmacophore unit of this family and is a new lead compound of the NSAIDs.

In 1995, Cabral and Barreiro (Scheme 28) applied non-classic ring bioisosterism as a strategy for molecular modification [56], to obtain analogs conformationally restricted to etodolac (101), an important drug with anti-inflammatory, analgesic and antipyretic properties. In this study it was possible to observe the optimization of the analgesic properties of the *aprio*-isochroman-1-yl acid derivative (103) when compared to lead compounds (102) and (102).



Scheme 28.

A supplementary example of bioisosterism may be found in the work by Arnett and coworkers [57]. These authors developed the synthesis of compound 105, exploring the bioisosteric relationship existing between the benzimidazole rings and catechol substituents (Scheme 29), based on isoproterenol (104), a compound with β -adrenergic activity. Compound 105 proved to be a bioisostere of 104, presenting a pharmacological profile comparable to this level of β -adrenoceptors. In this case it is important to point out that the tautomerism of the benzimidazole ring present in 105, mimics, with a single proton, the catecholic group present in 104.



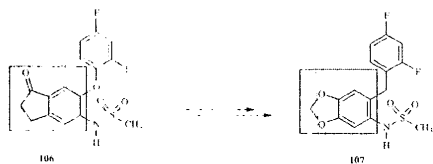
Scheme 29.

In a similar context, Barreiro and coworkers described the non-classic bioisosteric relationship between the indanone ring, present in the structure of the prototype flusolide (106) and benzodioxole unit present in compound 107 (Scheme 30) [58,58]. The results obtained from this study allow us to identify a new molecular standard of prostaglandin H-

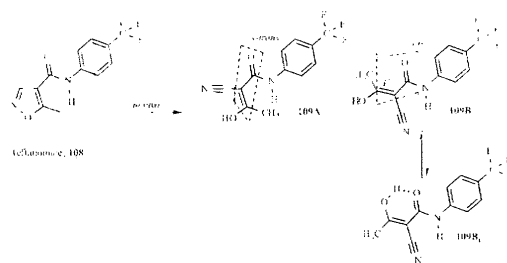
synthase-2 (COX-2) inhibitors, as well as to demonstrate the electronic similarities existing between the indanone and benzodioxole rings, suggesting similar profiles of supramolecular interaction with the enzyme involved in the pharmacological response of the flusolide and the derivative (ASSBio 3-1 (107), possessing the benzodioxole moiety from salrole, an abundant natural allobene present in *Piper spp* and *Ocotea spp*.

Leflunomide (108), an isoxazole immunosuppressor drug that can prevent antibody-mediated rejection in heart xenotransplantation, is a pro-drug metabolized *in vivo* in its active metabolite hydroxycyanopropenamide (109). In this

way, knowledge of the physical, chemical, conformational and configurational characteristics of this metabolite are essential to lead to the design of new immunosuppressive drugs, acting through mechanisms of action common to leflunomide (108). Among the conformational and configurational possibilities, relative to the α,β -unsaturated



Scheme 30.

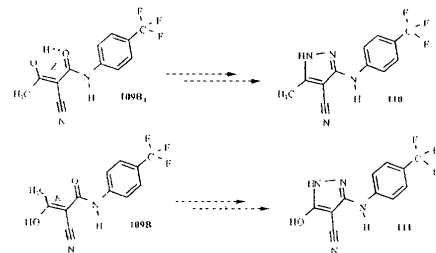


Scheme 31.

carbonyl system, referring to the double bond geometry, possible for the functionalized hydroxycyanopropenamide (109), the *syn* conformer (109B) and *Z*-configuration derivative (109B1), were found in X ray crystallography studies (Scheme 31). The presence of this single diastereoisomer might be due to the stabilization from the formation of intramolecular hydrogen bonds involving hydrogen in the enolic system with the oxygen of amide function [59]. In an effort to corroborate with this experimental evidence, and to correlate it with the eventual bioactive conformation of hydroxycyanopropenamide (109), Papageorgiou and coworkers proposed modifications in the structure of metabolite 109B and 109B1, applying non-classic strategies of ring closing bioisosterism (Scheme 32). In this study it was possible to design two novel pyrazoles analogs (110 and 111) conformationally restricted which mimic the diastereoisomers *E* and *Z* of hydroxycyanopropenamide (109). The pharmacological results obtained with compounds 110 and 111 demonstrated that only derivative 110, whose structure was equivalent to diastereoisomer *Z* of 109 was active in the bioassays realized. Furthermore, X-ray studies carried out with the

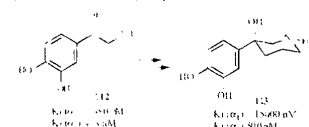
pyrazole derivative 110 demonstrated the existence of a single tautomer relative to the pyrazole ring, evidencing the similarity of the spatial arrangement between compounds 109 (B1) and 110. In summary, this study allowed for identification of a new bioisosteric relationship between the pyrazole ring and the hydroxycyanopropenamide substituent, as well as validating the elucidation of the bioactive conformation of the active metabolite of leflunomide (108).

It is important to point out that the greatest conformational restriction ever reached by way of a anelation process may annul the possibility that the newly derived molecule adopt the bioactive conformation necessary for its molecular recognition by a determined bioreceptor, resulting in the loss of activity when compared to the acyclic lead compound. This concept may be well illustrated by the works of Macchia and coworkers who described the attainment of piperidinol (DDP3, 113) from noradrenaline (112) (Scheme 33), applying the strategy of anelation or ring closing [60]. In this study, the authors observed an expressive loss of affinity by the α_1 and α_2 adrenoceptors observed for the DDP3 derivative (113), attributed to the



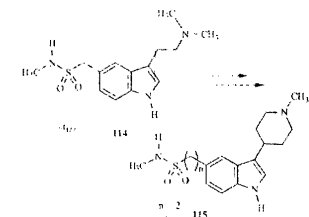
Scheme 32.

process of *in vitro* and *in vivo* hydroxyethylamine substrate, compared to one from line (12) [14].



Scheme 33.

The molecular design of naratriptan (115) from the lead compound sumatriptan (114) (Scheme 34), the first agonist of serotonin receptors of subtype 5HT_{1D} commercialized for the treatment of migraine, illustrates how an increase in molecular volume from a ring process may be explored as a subterfuge of metabolic protection, to obtain new lead compounds with more appropriate half-lives [61]. In fact, the introduction of the hexahydroindole ring in the naratriptan structure (115) resulted in protection by steric blocking of carbon α -amine from oxidative actions of hepatic metabolism, which act as an analog of monoamine oxidases (like MAO), producing the corresponding indolyl-acetic acid derivative.



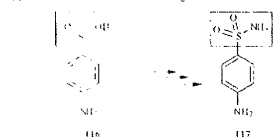
Scheme 34.

6.2. Non-Classic Bioisosterism of Functional Groups

The landmark of the recognition of the importance of the bioisosterism of functional groups is the discovery of the antibacterial properties of sulfanilamide (117). Sulfanilamide (117), an active metabolite of Protonsil® [62], revolutionized chemotherapy during the 30s and the later elucidation of its mechanism of molecular action allowed evidence of the similarity of its structure with *para*-aminobenzoic acid (PABA, 116). These similarities, based on electronic and conformational aspects, as well as the physicochemical properties such as pKa and log P, denote an authentic bioisosteric relationship existing between the sulfonamide (SO₂NH₂) and carboxylic acid functionalities (CO₂H) [63] (Scheme 35).

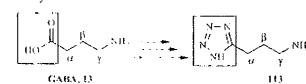
Diverse functional groups are known for their bioisosteric relationships with the carboxylate group. Some examples of the bioisosteric replacement of -COOH by a tetrazole group

are shown (14). An illustrative example is described in the synthesis of 118, a tetrazole bioisostere of γ -aminobutyric acid (GABA, 13), which presents important selective inhibitory properties of GABA transaminase (GABA-T) (Scheme 36) [64] presenting a potential pharmacotherapeutic application as an antiepileptic agent.



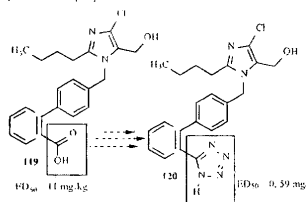
Scheme 35.

The tetrazole group mimics the carboxylate group, principally in terms of its physicochemical properties related to acidity, although the former be more stable and lipophilic. These differences allows this bioisostere to present a greater possibility of overcoming the blood-brain barrier, with the type of tropism favorable to the desired activity.



Scheme 36.

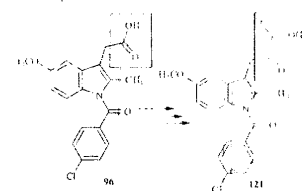
Another more recent example of the bioisosteric relationship existing between tetrazole and carboxylic acid groups may be seen by comparing the structures of losartan (120), angiotensin receptors antagonist approved in 1995 to treat hypertension with the lead compound EXP 7711 (119) (Scheme 37) [66].



Scheme 37.

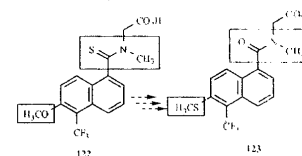
Derivatives possessing a hydroxyamic-acid instead of a carboxylic acid function have been developed as carboxylate bioisosteres. Among other examples, compounds with anti-allergic properties presenting this function have been synthesized [67-68]. While in certain cases the metabolic lability of -CONHOH function, has been demonstrated, which would merely characterize a pro-drug effect [69], hydroxyamic derivative 121 (Scheme 38), designed by

modifications in indoracillin (96) has proved to be metabolically stable, evidencing the non-classic bioisosteric relationship existing between these two groups: -COOH vs. -C(=NHOH)-



Scheme 38.

The discovery of oxatolrestat 122 [70], designed as a classic bioisostere of tolrestat 122 (Scheme 39) a potent aldose reductase inhibitor [71], illustrates the non-classic bioisosteric relationship between the functional groups thioamide (CS-NH-) and amide (CO-NH-).

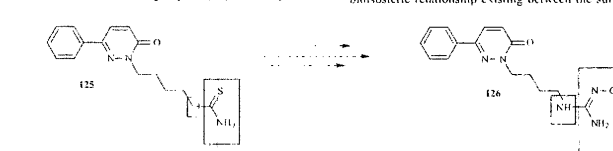


Scheme 39.

Tolrestat 122, currently undergoing clinical assays for its use to treat complications arising from diabetes, may also illustrate the classic bioisosteric relationship between the monovalent groups -OMe (122) and -SMe (123). Significant differences as to the metabolism of these molecules may be expected, however, in view of the possibility that sulfur undergoes specific metabolic oxidation.

Other common examples of amide function bioisosteres include the "retro-amide" groups, i.e.: A-CONH-B $\rightarrow$ A-NHCO-B and alkylidene (-CH=CH₂) [4,72].

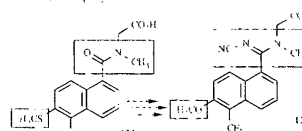
Wrobel and coworkers used the principle of non-elastic bioisosterism of functional groups to propose the synthesis



Scheme 40.

of analog 124, from modifications in the lead compound oxatolrestat 122 (Scheme 40) [70], identifying the bioisosteric relationship between the thioamide and cyanoamide functions.

This same type of bioisosteric relationship between the thiocarbonyl (-C=S-) and cyanoamide (-C(=N)-CN) groups was reported during the development of cimetidine by G. J. Lina and coworkers [71].



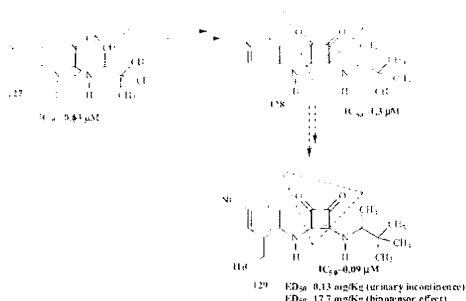
Scheme 40.

The same type of bioisosterism was further used by Yamazaki and coworkers to develop pyridazinone derivatives 125 and 126 (Scheme 41), which present a similar spectrum of antileukemic activity, while also presenting a classic bioisosteric relationship between the substituents of the alkyl chain represented by the replacement of -CH₂- with -NH- group [73].

In the quest for new selective agonists of potassium channels Batera and coworkers carried out modifications in the structure of anti-hypertensive lead compound pinacidil (127) (Scheme 42) [74]. These authors described the replacement of the *N*-cyanoguanidine template, present in pinacidil (127), with a 1,2-diaminocyclobutene-3,4-dione moiety afforded a novel series of potent bladder-selective agonists of the K_{ATP} channel 128 and 129, as a novel drug candidate to treat urge urinary incontinence.

Another important example of non-classic bioisosterism of functional groups may be exemplified by the isosteric relationship existing between the sulfonylhydrazone and acylhydrazone functions, identified in studies by Lina and coworkers (Scheme 43) [75]. In this work, the authors demonstrated that the acylhydrazone function (CONHN-CH) may be efficiently replaced by the sulfonylhydrazone function (SO₂NHN-CH) to design new anti-inflammatory and analgesic candidates, despite the subtle differences between the pKa of these groups.

During research to obtain new diuretics, analogs of torasemide (132), Wouters and coworkers demonstrated the bioisosteric relationship existing between the sulfonylurea



Scheme 42.

(132), sulfonamido-urea (133), sulfonamido-urea (134) and sulfonamido-urea (135) functionalities (Scheme 44) [76]. These authors demonstrated that while these groups present similar electronic and geometric properties, determined by X-ray crystallography and similar acidity (pK_a 6.0 to 6.7), compounds 132, 133, 134 and 135 each possess a distinct lipophilicity, expressed in $\log P$ values (Scheme 44). The pharmacological results obtained for compounds 132, 133, 134 and 135 *in vivo* show that their diuretic potency is inversely proportional to their lipophilicity, a fact which may be explained considering that the diuretic activity of these molecules is the result of inhibition of the $Na^+ K^+ 2Cl^-$ cotransporter located on the luminal membrane of the thick ascending limb of the loop of Henle, and that the glomerular filtration process is generally enhanced for hydrophilic compounds, while tubular reabsorption is increased for lipophilic compounds.

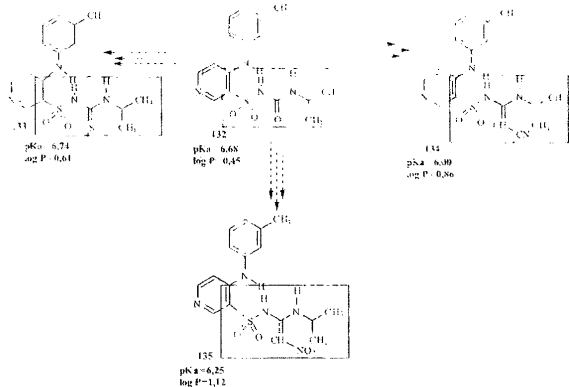
The importance of ionotropic receptors of glutamate (Glu), the principal excitatory neurotransmitter in rapid synaptic signal pathways, as well as in processes of learning and memory are well characterized and the deficits within the glutamatergic signaling pathways in Alzheimer's patients may, in part, explain the loss of cognitive function of this disease. However, the use of glutamate to treat Alzheimer's disease is limited because of its inadequate pharmacokinetic properties in the biophase. Thus being, diverse research groups have sought to design new analogs of glutamate (Glu) with a half-life and lipophilicity superior to Glu. Recently, Stensbol and coworkers proposed replacement of

the carboxylic acid group, present in Glu (15) with 3-hydroxy-1,2,5-thiadiazole (136), 1-hydroxy-1,2,3-triazole (137), 1-hydroxyimidazole (138) and 1-hydroxypyrazole (139) groups (Scheme 45), observing that with the exception of the imidazole derivative (138), all the other compounds presented similar affinity for AMPA receptors, without, however, showing significant affinity for the other glutamate ionotropic receptors, *i.e.* NMDA and kainate receptors [77]. The absence of activity of the derivative containing the 1-hydroxyimidazole ring (138) may be explained by the basicity of this compound. Actually, the experimental determination of pK_a value of the *N*-hydroxy group of 138 was found to be at least three pK_a units higher than those found for the 3-hydroxy-1,2,5-thiadiazole, 1-hydroxy-1,2,3-triazole and 1-hydroxypyrazole substituents.

In developing of new drug candidates to treat cerebrovascular ischemia designed as (*R,S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)-propionic acid (AMPA) receptors antagonists, Jimoneli and coworkers described the attainment of imidazo[1,2-*a*]indeno-[1,2-*c*]pyrazine-2-substituted derivatives (Scheme 46) [78]. These authors proposed the exchange of the carboxylic acid function in C-2 (140) by the phosphonic acid (141), tetrazole (142) and *N*-methylsulfonylcarboxamide groups (143) (Scheme 46). The results obtained show that all of the isosteres studied present affinity for the AMPA receptors, in varying degrees. However, the selectivity measured by way of AMPA and NMDA receptors is significantly affected by the replacements realized, such that the tetrazole derivative (142)



Scheme 43.



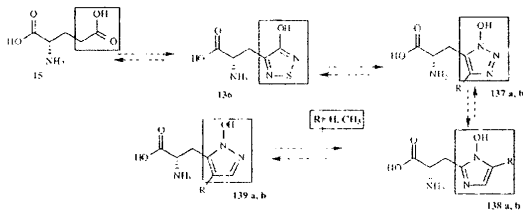
Scheme 44.

proves to be approximately 10 times more selective than the corresponding carboxylic acid derivative (140).

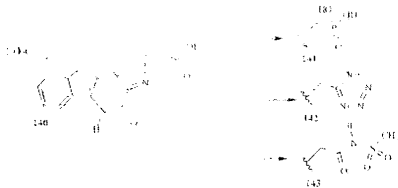
In 2001 Habeeb and coworkers described the design and synthesis of new analogs for celecoxib and rofecoxib, non-steroid anti-inflammatory drugs of second generation, reporting for the first time the bioisosteric relationship existing between methylsulfonamide, methylsulfone and azido functional groups (Scheme 47) [79]. Actually, many authors have reported obtaining new PGHS-2 inhibitors, using both classic as well as non-classic bioisosteric strategies. The bioisosterism of methylsulfonamide ($CH_3SO_2NH_2$), sulfonamide ($-SO_2NHCH_3$) and methylsulfone (CH_3SO_2-) functions, for example, is well characterized within the class of selective PGHS-2 inhibitors, as are its contributions to other pharmacodynamic

and pharmacokinetic factors [58]. The results obtained from the studies by Habeeb and coworkers revealed that the azido group (N_3) is capable of realizing electrostatic interactions (ion-ion) with amino acid residues from the active site of PGHS, (the example of Arg₃₁₅ residue), being, however, an authentic bioisostere of methylsulfonamide and methylsulfone functions, presenting comparable molecular volume and electrostatic potential.

Quinuclidine (148), designed by modifications in the natural alkaloid structure arcolfine (147), is an important non-selective muscarinic (M1 and M2) receptors agonist with marginal actions on nicotinic ganglionic receptors. However, the low selectivity associated with low therapeutic index and inadequate bioavailability, have annulled its use for treating Alzheimer's disease. In an effort to optimize the



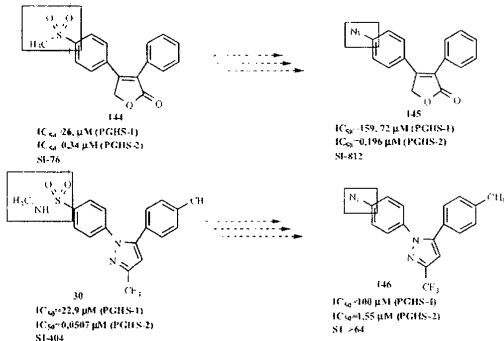
Scheme 45.



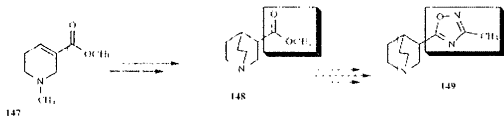
Scheme 46.

pharmacotherapeutic profile of quinacridone (148). Ordel and coworkers proposed the exchange of the methyl ester group, present in 148, with the 3-methyl-1,2,3-oxadiazole group in the structure of compound 149 (Scheme 48) [80], being able to identify electrostatic similarities between the methyl-oxadiazole and methyl ester groups, as well as in the profile of muscarinic agonist activity of these derivatives. However, the metabolic stability of methyl-oxadiazole bioisostere (149) was greater than that found for the quinacridone lead compound (148), conferring to compound 149 a better oral bioavailability.

Another successful example of a bioisosteric replacement of an ester functionality with an oxadiazole moiety, for improving the metabolic stability, can be illustrated in the development of cyclin-dependent kinase 2 (CDK2) inhibitors as anticancer agents. Despite the potent CDK2 inhibitory activity found for compound 2-amino-5-thio-substituted thiazole (150), it lacks cellular activity in cell proliferation assays due to hydrolysis of the ethyl ester to the corresponding carboxylic acid, that is completely devoid of CDK2 inhibitory activity. In an attempt to increase the cellular stability of 150, Kuri and coworkers realized the

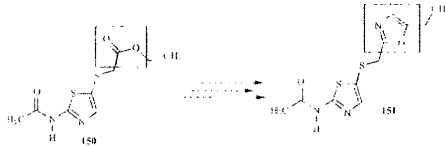


Scheme 47.



Scheme 48.

replacement of the ethyl ester with a bioisosteric oxazole moiety led to compound 151 (Scheme 49), which is metabolically stable against esterase, maintains the selectivity and shows increased CDK2 inhibitory potency as well as potent antiproliferative activity in cancer cell lines [77].



Scheme 49.

Nonetheless, bioisosteric replacement of the ester with oxazole and other heteroaromatics may not be universally effective, as demonstrated by Dhanak and coworkers in the design and synthesis of a series of highly selective and potent phenylalanine derived CCR2 antagonists as anti-inflammatory agents (Scheme 50). While compound 152 was highly effective in blocking both the binding and the

their search for GABA aminotransferase inhibitors, the enzyme responsible for GABA catabolism. Ota and coworkers proposed structural modifications in the enzymatic substrate, i.e. GABA based on the application of non-classic bioisosterism of functional groups [82]. In this study, the authors carried out the exchange of the carboxylic



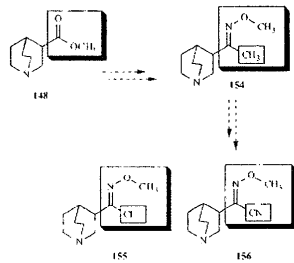
Scheme 50.

functional activity of a number of CCR2 agonists, compound 153 lacks all CCR2 affinity which suggests a more subtle role for the ester moiety that the heterocycles were unable to mimic [7].

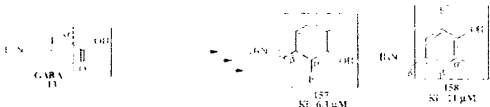
To identify non-aromatic bioisosteres, alternatives of carboxylic esters, Bromidge and coworkers described the synthesis and determination of the affinity of ketoxime ethers derivatives (154-156) for muscarinic receptors in rat cerebral cortex (Scheme 51) [81]. In this study it was possible to confirm the bioisosteric relationship existing between the methyl ester (148) and (*h*)-ketoxime ethers (154) functions, and the later use of additional classic bioisosteric exchanges of monovalent groups, led to the attainment of optimized compound 156 (Scheme 51), which present a pKa value inferior to that found for lead compound 154, resulting in a decrease in basicity, facilitating the passage through the blood-brain-barrier.

The application of the strategy of functional group bioisosterism in drug designing can be well illustrated by planning new anti-convulsant agents, structurally related to γ -aminobutyric acid (GABA), an inhibitory neurotransmitter of low molecular weight. GABA's polar and hydrophilic nature makes its use impossible for treating epilepsy, in view of its rapid inactivation and excessively low logP. In

measuring the conversion of [¹⁴C] α -ketoglutarate to [¹⁴C]glutamate, and both were poor substrate. These results suggest that the 2,6-difluorophenyl group may be an authentic lipophilic bioisostere of carboxylic acids.



Scheme 51.

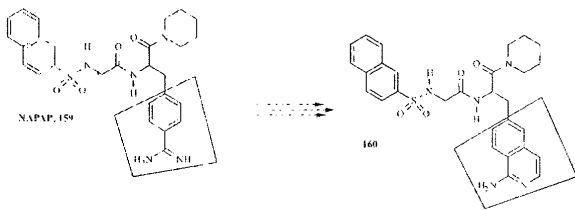


Scheme 52.

The antithrombotic activity reached by way of thrombin inhibition has moved to be of landmark therapeutic relevance, in view of the recent FDA approval of argatroban approved to treat thromboembolic disorders [83]. However, the great challenge of this class of therapeutic drugs is in obtaining lead compounds of adequate oral bioavailability. NAPAP (159) (Scheme 53) is a high affinity reversible inhibitor of thrombin (K_i 6 nM) and low oral bioavailability. Many studies have suggested that the inadequate pharmacokinetic properties of NAPAP (159) and its structurally related derivatives is due to the elevated basicity of the benzamidine function (160, pK_a 12). To deal

absorption ($Caco-2$) [85]. Nonetheless, the inherent basicity of this function (160, pK_a 7.5) is sufficient to guarantee ionic interactions with aspartic/serine acid residue present at the thrombin catalytic site and facilitate membrane permeability. Thus, replacement of the highly basic benzamidine moiety in NAPAP (159) with 1-aminoguanidine yielded new thrombin inhibitor and confirming a new existing bioisosteric relationship between these functions.

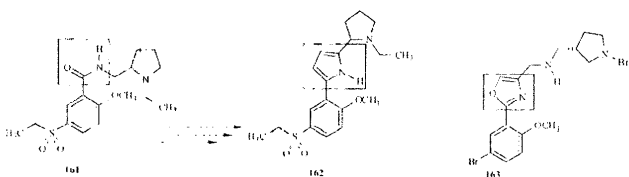
In the course of searching for high affinity dopamine D3 receptor antagonists, conformationally restricted benzamide



Scheme 53.

with these pharmacokinetic limitations, Rewinkel and coworkers proposed the bioisosteric exchange of the benzamidine group by the 1-aminoquinoline function (Scheme 53) [84]. In this study the authors demonstrated that the lower basicity of the 1-aminoquinoline group (pK_a 7.5) conferred a greater absorption to compound (160) determined using cell monolayers as a model for intestinal

isosteres, such as pyrroles, oxazoles, and thiazoles were investigated by Einsiedel and coworkers (Scheme 54). Replacement of the amide suboptimal (161) by a pyrrole ring led to compound 162 which maintained affinity for the dopamine D3 receptor and introduced modest selectivity over the dopamine D2 receptor. Replacement of the benzamide with oxazole subunit resulted in compound 163.

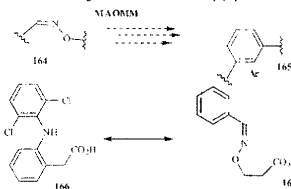


Scheme 54.

which exhibits dopamine D3 and dopamine D4 binding affinities comparable to those of the atypical neuroleptics sulpiride and clozapine, respectively [7].

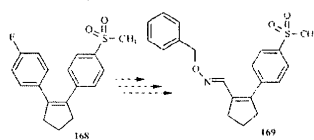
6.3. The Versatility of Non-Classical Bioisosterism

A spectacular example of non-classical bioisosterism may be illustrated by the work of Macchia and coworkers, involving the bioisosteric relationship between the benzene ring (164) and the methylenecarboxy methyl moiety (MAOMM, 164) (Scheme 55) [86]. These authors, studying the synthesis of new non-steroid anti-inflammatory agents of easy synthetic access, prepared substance 167 possessing the MAOMM function as bioequivalent to the benzene ring (164). The results observed in the anti-inflammatory activity of 167 and derivatives, in comparison with standard diclofenac (166), an aryl-acetic acid anti-inflammatory drug, prove this amazing bioisosteric relationship [6].



Scheme 55.

More recently, Balsamo and coworkers described the attainment of new selective inhibitors of PGHS-2 isoform, applying bioisosterism as a strategy of molecular modification [87]. This study also illustrates the non-classical bioisosteric relationship between aromatic rings and the methylenecarboxy methyl moiety (MAOMM) (Scheme 56). However, it must be considered that introducing the oxime-ether (O-N CH-) subunit in 169 introduces incoherent molecular characteristics in the structure of lead compound SC 57666 (168).

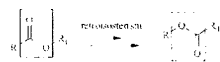


Scheme 56.

6.4. Retroisosterism

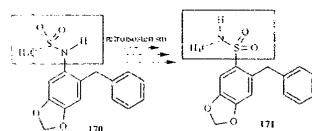
Retroisosterism is based on the inversion of a determined functional group present in the lead compound structure, producing an isostere with the same function (Scheme 57). This strategy, just as the other bioisosteric strategies

concerned on in this paper, aims to optimize the pharmacotherapeutic properties of the original lead compound, thus aiding in optimizing the profile of interaction with the bioreceptor in designing drugs with half-lives more adequate for therapeutic use and may even be used in the attempt to avoid the formation of potentially toxic metabolite intermediates.



Scheme 57.

In a recent study, Lases and coworkers described the existing retroisosteric relationship between the methanesulfonylamine and methanesulfonamide functions (Scheme 58) present in the structures of new selective COX-2 inhibitor lead compounds 170 and 171 [88]. This type of retroisosteric relationship confers metabolic susceptibility and distinct pK_a values between compounds 170 and 171, while the greatest activity found for the methanesulfonamide derivative 170 may be explained considering the profile of interaction of this group with the Arg₅₁₃ and Ser₅₁₅ amino acid residues present at the catalytic site of COX-2, favored in 170 when compared to the 171 retroisostere.



Scheme 58.

Based on studies of molecular modeling, Barreiro and coworkers proposed two new molecular standards, exemplified by compounds 172 and 173 as new candidates for second generation anti-inflammatory drugs. The molecular design of 173 from the lead compound 172 (Scheme 59), was realized applying the strategy of retroisosterism [14] and aimed to minimize the possibility of electrophilic species formation (176) (Scheme 59), potentially toxic, obtained by the action of enzymatic pool involved in the metabolism of xenobiotics. Furthermore, the use of retroisosterism for derivative 173 enables the formation of intramolecular hydrogen bonds, which confer greater conformational restriction allowing the prediction that derivatives 172 and 173 will present pharmacokinetic concerning the process of metabolism and pharmacodynamics distinct profiles.

Among the different categories of 5-lipoxygenase inhibitors (5-LOX), the hydroxamic acids stand out acting through the formation of complexes with the Fe³⁺ ion present at the catalytic site of 5-LOX. It has been shown that although many hydroxamic acids are potent inhibitors of the enzyme *in vitro*, they fail to produce significant inhibition *in vivo*. This dichotomy between *in vitro* vs *in vivo* pharmacological results can be explained based on pharmacokinetic studies realized with different hydroxamic

