A Review on Bioisosterism: A Rational Approach for Drug Design and Molecular Modification

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Running Head: Bioisosterism: A Prime Approach

Keywords: Bioisosterism, Molecular Modelling, Drug Design, Chemistry

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Summary

Several methods for drug designing have been employing from many decades. Development of novel drug molecule with improved with high efficacy, potency and undesirable side effects have been the aim of the scientists. Bioisosterism represents one such approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents. This review will show the role of bioisosterism in the molecular modification as well as in rational drug design and optimization process with the aim to improve pharmacodynamic and pharmacokinetic properties of lead compounds.

Introduction

A lead compound (LC) with a desired pharmacological activity may have associated with it undesirable side effects, characteristics that limit its bioavailability, or structural features which adversely influence its metabolism and excretion from the body. Taking consideration of the structure of lead molecule, it is always the priority of medicinal chemist to design safer drug molecule. Isosterism played good role in designing of desired drugs. Isosteres are molecules or ions with the same number of atoms and the same number of valence electrons. The term isosterism was introduced in 1919 by the physicist Irving Langmuir. [1] This definition has now been broadened to include groups that produce compounds that can sometimes have similar biological activities. The term bioisosterism, introduced by Friedman in 1951[2] is used, when along with physicochemical analogy, compounds share some common biological properties. 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 [3]. The LC should be of a completely well known chemical structure and possess an equally well known mechanism of action. Furthermore, the pathways of metabolic inactivation[4], 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. 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 and also as a tool useful in the molecular modification.

Why Need For Bioisosteric Replacements [5]?

There are many reasons for the use of bioisosterism:

- Greater selectivity for a determined receptor or enzymatic isoform subtype.
- Less side effects and Decreased toxicity
- Improved pharmacokinetics (solubility- hydrophobicity)
- Increased stability
- Simplified synthesis

Background: Development of the isosterism concept

In 1918, **Allen [6]** defined the molecular number of a compound in a same way to the atomic number:
Compare ammonium (NH_4) and sodium (Na) cations as an example. The atomic number of NH_4 cation and Na cation is 11. Thus the molecular number of the NH_4^+ ion can be calculated and compared with Na^+ ion and it is 11. Two compounds, with identical molecular numbers shows at least some similar physical properties.

In 1919, **Langmuir [7]** created the concept of isosterism, compared the physical properties, chemical behavior and reactivity of various molecules possessing atoms or groups with the same number of valence electrons, i.e. isoelectronic. Examples of various atoms and molecules are [8]:

(1) O^{-2}, F^-, Ne, Na^+, Mg^{+2}, Al^{3+}
(2) ClO_4^-, SO_4^{-2}, PO_4^{-3}
(3) N=N and C=O
(4) CO_2 , NO_2; and
(5) N=N=N , N=C=O-

Langmuir concluded from the octet theory that the number and arrangement of electrons in these molecules are the same.
In 1925 gave **Grimm [9, 10] Hydride Displacement Law**, is an early hypothesis to describe bioisosterism, the ability of certain chemical groups to function as or mimic other chemical groups. Atoms anywhere up to four places in the periodic system of groups 4A, 5A, 6A, 7A

before an inert gas change their properties by uniting with one to four hydrogen atoms to their right [11] in such a manner that the resulting combinations behave like pseudoatoms. According to Grimm, each vertical column **(Table 1)** would represent a group of isosteres.

C	N	O	F	Ne	Na
	CH	NH	OH	FH	-
		CH_2	NH_2	OH_2	FH_2^+
			CH_3	NH_3	OH_3^+
				CH_4	NH_4^+

Table 1: Grimm's hydride displacement law

In 1932, **Erlenmeyer** [12] broadened Grimm's classification and redefined isosteres as elements, molecules or ions which present the same number of electrons at the valence level. Examples: elements of the same column on the Periodic Table are isosteres among themselves (e.g. C, Si and Ge) **(Table 2)** and the development of a concept of electronically equivalent rings, later lead to the term ring bioisosterism.

NO. OF PERIPHERAL ELECTRONS				
4	**5**	**6**	**7**	**8**
N^+	**P**	**S**	**Cl**	**ClH**
P^+	**As**	**Se**	**Br**	**BrH**
S^+	**Sb**	**Te**	**I**	**IH**
As^+		**PH**	**SH**	**SH_2**
Sb^+			**PH_2**	**PH_3**

Table 2

Friedman [13] defined bioisosters as compounds which fulfill the broadest definitions of isosteres and have the same type of biological activity of bio-receptor, whether through agonist or antagonist actions. More recently this definition has been broadened by Burger as "Compounds

or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties [8].

Later, **Thornber [14] (1979)** put forward a broadening of the term bioisosteres, defined them as groups or molecules which have chemical and physical similarities producing broadly similar pharmacological effects.

Bioisosterism: A plan designed to achieve molecular modeling

The most appropriate application of bioisosterism insist on physical, chemical, electronic and conformational parameters involved in bioisosteric substitution, carefully analyzed so as to predict, although theoretically, any alterations occurs in terms of the pharmacodynamic and pharmacokinetic properties. Following parameters should be appropriately considered while making any bioisosteric replacement [15].

a) Degree of hydrophobocity and aqueous solubility, allows to predict changes in physico-chemical properties such as log P and p Ka, if changes occurs.
b) Size, volume and electronic distribution of the atoms or the considerations on the degree of hybridization, polarizability, bonding angles, inductive and mesomeric effects.
c) Chemical reactivity of the functional groups or bioisosteric structural subunits, mainly to predict significant alterations in the processes of biotransformation.
d) Conformational factors, including the differential capacity formation of inter- or intramolecular hydrogen bonds.

Classification of bioisosterism: Classic & Non Classic

In 1970, Alfred Burger classified and subdivided bioisoteres into two broad categories: Classic and Non- Classic [16].

- 1925 by Grimm: groups that have the same number of valence electrons, but may have a different number of atoms.
- By Erlenmeyer: atoms, ions, or molecules in which the peripheral layers of electrons can be considered to be identical

1. Classical 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-Classical Bioisosteres (Table 2)

- Do not have the same number of atoms and do not fit the steric and electronic rules of the classical isosteres, but do produce similar biological activity.

2.1 Cyclic vs Noncyclic

2.2 Functional groups

2.3 Retroisosterism

Table 1: Classical Bioisosteres Groups and Atoms

1. Univalent atoms and groups

a.	CH_3	NH_2	OH	F	Cl
b.	Cl	PH_2	SH		
c.	Br	Propyl			
d.	I	t-Bu			

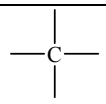
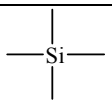
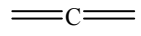
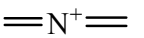
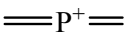
2. Bivalent atoms and groups

a.	$-CH_2-$	-NH-	-O-	-S-	-Se-
b.	$-COCH_2R$	-CONHR	-COOR	-COSR	

3. Trivalent atom and groups

a.	-CH=	-N=
b.	-P=	-As=

4. Tetravalent atom

a.			
b.			

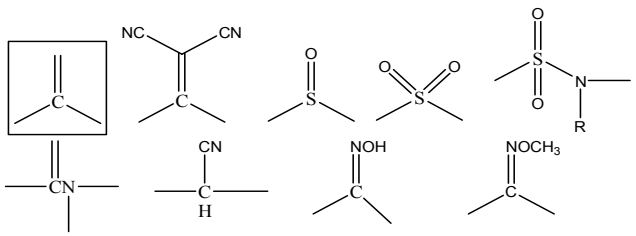
5. Ring equivalent

a.	-CH=CH-	-S- (e.g. benzene, thiophene)		
b.	-CH=	-N= (e.g. benzene, pyridine)		
c.	-O-	-S-	$-CH_2$	-NH-(e.g. tetrahydrofuran, tetrahydrothiophene, cyclopentane, pyrrolidine)

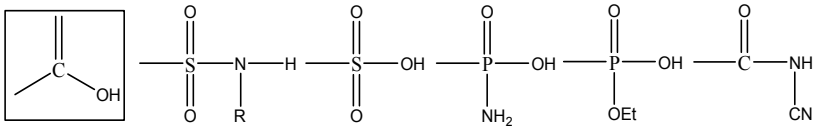
Table 2:

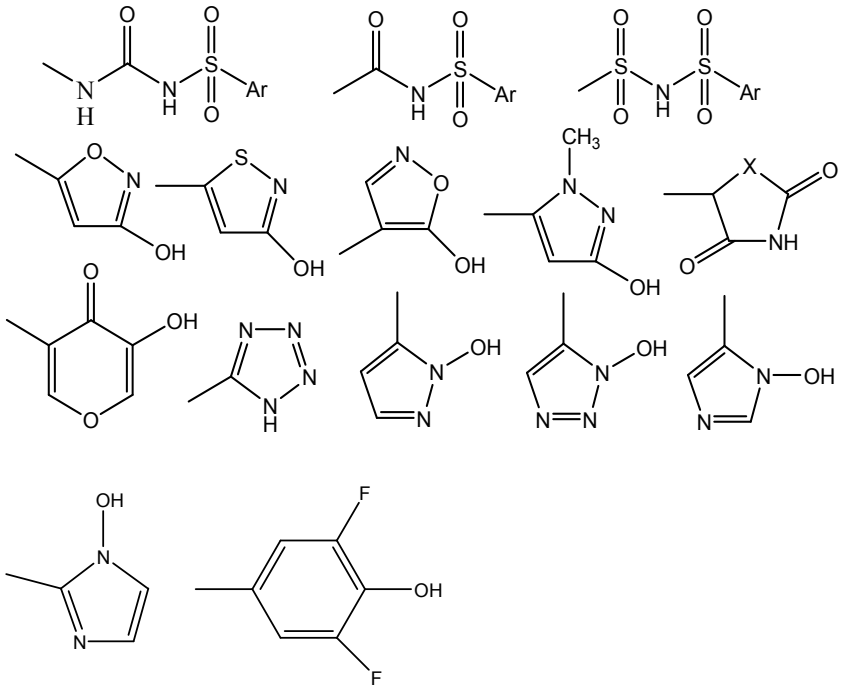
Non-classical isosteres

1. Carbonyl group

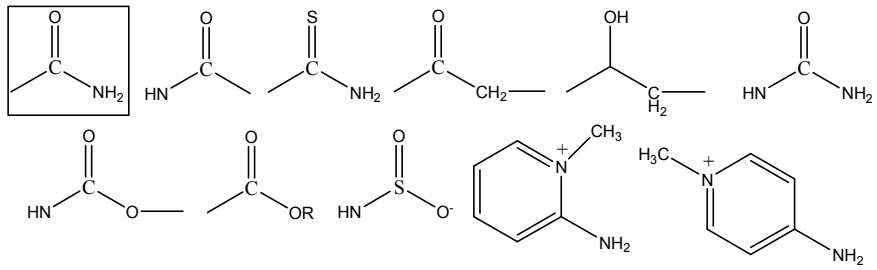


2. Carboxylic acid group

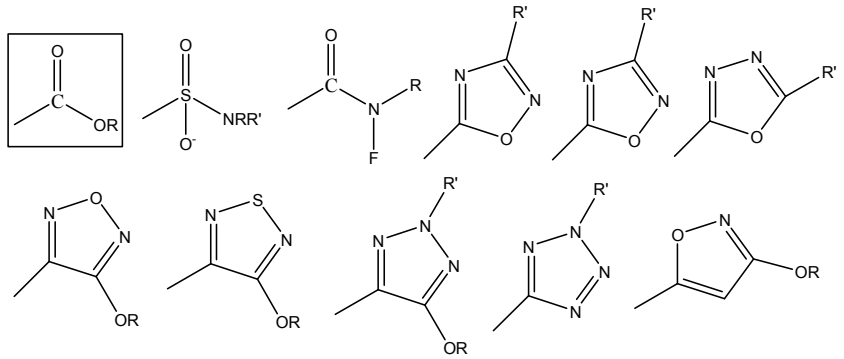




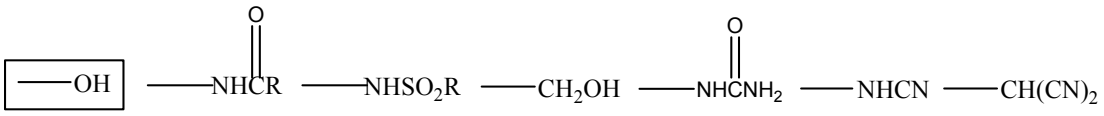
3. Amide group



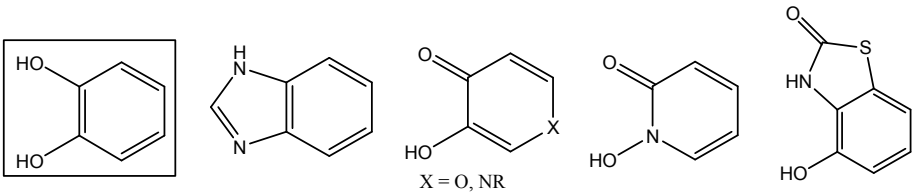
4. Ester group



5. Hydroxyl group



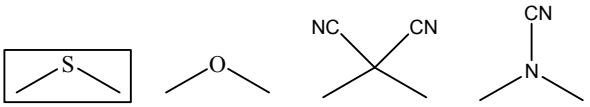
6. Catechol group



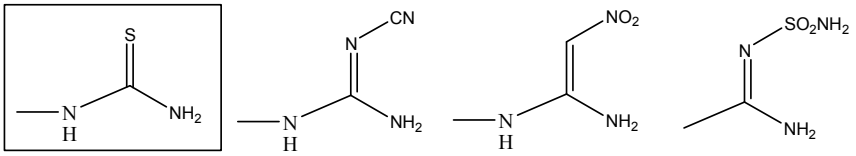
7. Halogen

X CF_3 CN $N(CN)_2$ $C(CN)_3$

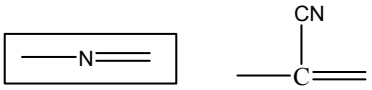
8. Thioether



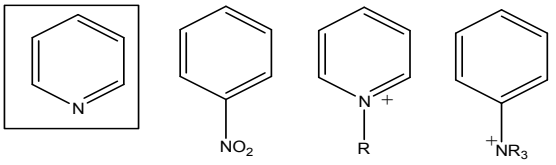
9. Thiourea



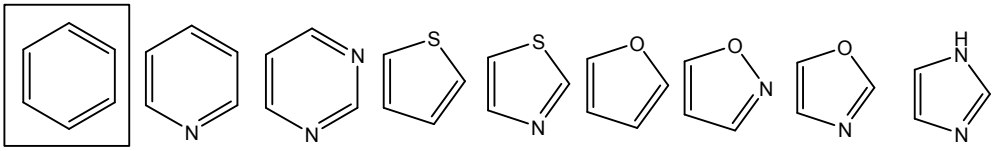
10. Azomethine



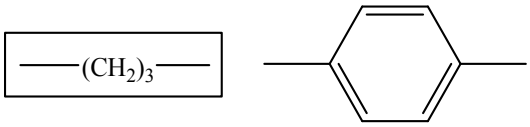
11. Pyridine



12. Benzene



13. Spacer group



Examples of Bioisosterism

(A) Classical Bioisosterism

(i) Bioisosterism of Monovalent Atoms or Groups

These can be divided into the following groups: (a) fluorine vs hydrogen replacements; (b) amino-hydroxyl interchanges; (c) thiol-hydroxyl interchanges; (d) fluorine, hydroxyl, amino, and methyl group interchanges (Grimm's Hydride Displacement Law); (e) chloro, bromo, thiol, and hydroxyl group interchanges (Erlenmeyer's Broadened Classification of Grimm's Displacement Law).

(a) Fluorine vs Hydrogen Replacements

Steric parameters for hydrogen and fluorine are similar, their van der Waal's radii being 1.2 and 1.35 Å, respectively [17]. Thus, difference in electronic effects (fluorine being the most electronegative element in the periodic table) form the major differences in the pharmacological properties of agents where fluorine has been substituted for hydrogen. Due to electronegativity of fluorine, it exerts a strong field and inductive effects (electron-withdrawing effect) on the adjacent carbon atom. Fluorine substitution exerts a diminished electron-withdrawing effect at distal sites. This is commonly referred to as its **mesomeric effect**. The antineoplastic agent 5-fluorouracil (5-FU) [18] is biochemically transformed in vivo into 5-fluoro-2'-deoxyuridylic acid. This biochemically altered form of 5-FU **(1)**, 5-fluoro-2'-deoxyuridylic acid, is ultimately responsible for the inhibition of thymidylate synthase, an enzyme involved in the conversion of uridylic acid to thymidylic acid and critical for DNA synthesis **(Figure 1)**. The increased reactivity of 5-fluoro-2'-deoxyuridylic acid relative to 2'-deoxyuridylic acid is due to the inductive effect of fluorine which results in its covalent binding to thymidylate synthase.

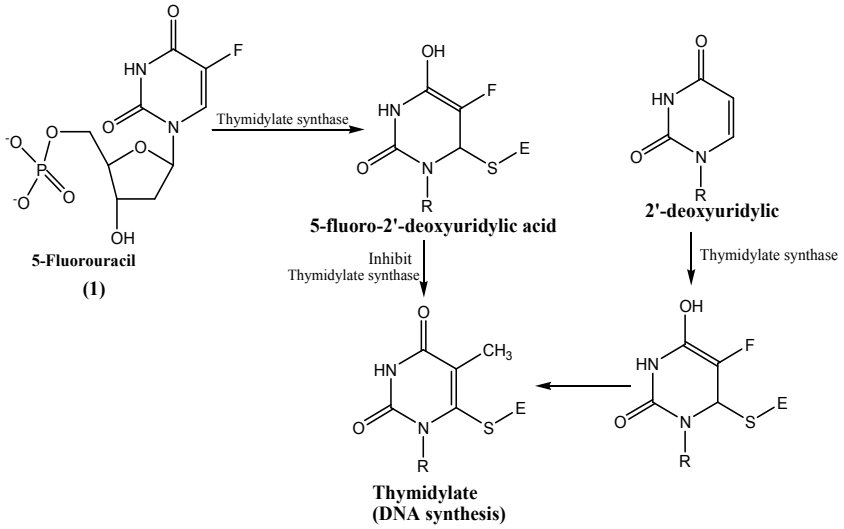


Figure1

Replacement of the hydrogen **(2)** with fluorine **(3)** at the ortho position of the pendent phenyl group of either naphthyl-fused diazepines [19] **(Figure 2)** resulted in enhanced affinity and efficacy for both naphthyl isomers. This greater receptor binding affinity is also due to the inductive effect of the fluorine atom facilitating a stronger interaction with the receptor.

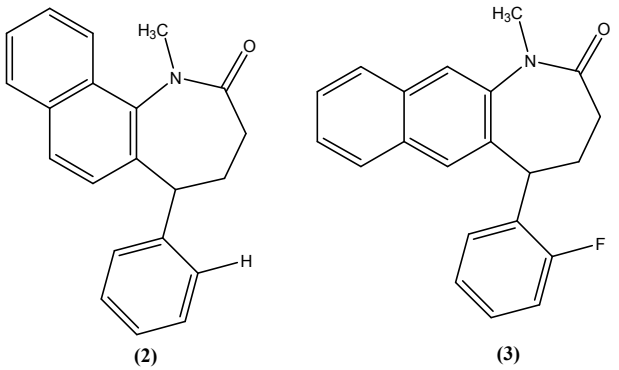
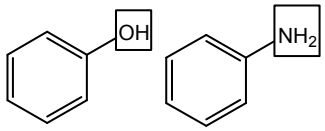


Figure 2

(b) Interchange of Hydroxyl and Amino Groups

The functional groups having similar steric size, spatial arrangement, and the ability to act as either hydrogen bond acceptors or donors is likely responsible for their successful use as bioisosteres. The bioisosteric replacement of aromatic amine present in aniline **(5)** by hydroxyl, forming phenol **(4) (Figure 3)** resulting in a significant change in the acid-base properties of isosteres, with modification of the p Ka of compounds, which is responsible for the distinct

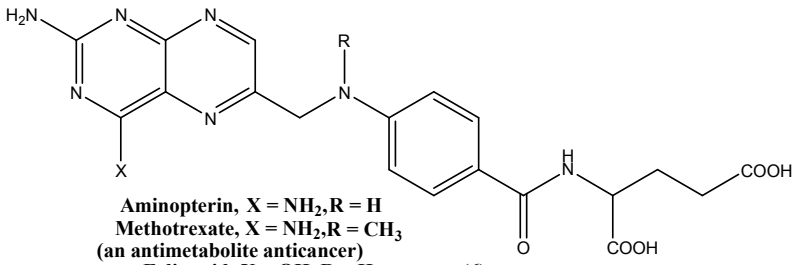
pharmacokinetic profiles among the isosteres. Abolish in the original activity occurs when change in positively charged function ($-NH_3^+$), arise from basic aromatic amine function (p Kb = 9) by another acid (p Ka = 10) present in phenol takes place. [20].



(4) **(5)**

Figure 3

An example where change in biological activity occurs when hydroxyl group is replaced by amino group is represented by 4-amino-4-deoxy derivative [16], aminopterin and its N^{10}-methyl derivative methotrexate (amethopterin) **(Figure 4) (6)**, an anti-metabolite anticancer.

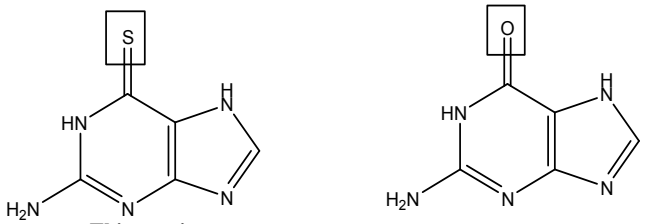


Aminopterin, X = NH_2,R = H
Methotrexate, X = NH_2,R = CH_3
(an antimetabolite anticancer)
Folic acid, X = OH, R = H **(6)**

Figure 4

(c) Thiol-hydroxyl interchanges

This replacement is based on the ability of both these functional groups to be hydrogen bond acceptors or donors. A classical illustration of this replacement is shown by guanine **(8)** and 6-thioguanine **(7)** (both are purine analogous) **(Figure 5)** [21]. 6-Thioguanine act as substrate by the salvage pathway associated with purine biosynthesis, allows for its transformation into 6-thioguanylic acid by hypoxanthine-guanine phosphoribosyltransferase (HGPRT).

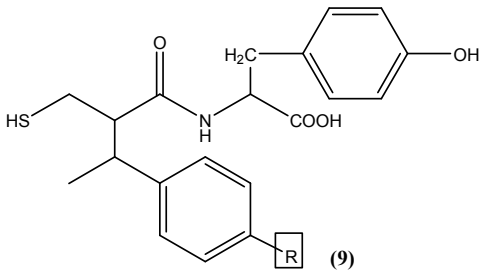


Thioguanine **Guanine**
(7) **(8)**

Figure 5

(d) Fluorine, hydroxyl, amino, and methyl group interchanges

By inhibition of epithelial neutral endopeptidase (NEP) that cause inactivation of endogenous atrial natriuretic peptide (ANP), effects of diuretic and natriuretic effects can be mediated. Inhibition of angiotensin II formation occurs by inhibition of endothelial angiotensin-converting enzyme (ACE). A series of dual metallopeptidase inhibitors **(9)** have been designed on the basis of the characteristics of the active sites of both enzymes. Monovalent substitution by fluorine, hydroxyl, and amino in place of hydrogen has been used in the design of these metallopeptidase inhibitors **(Fig. 6)** [22].



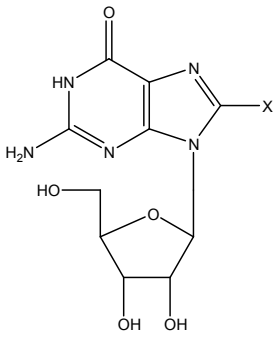
(9)

Fig. 6

Optically pure N-[2-(mercaptomethyl)-3-phenylbutanoyl] amino acids act as dual inhibitors of NEP and ACE. Substitution with isosteres (-F, -OH, -NH_2) resulted in retention of activity. However due to increase in the effective van der Waal's radii of the isosteric substituents resulted in a decrease in activity, thus with these bioisosteres, no significant alteration in preferential activity with either of the peptidases, ACE or NEP observed.

(e) Monovalent Substitutions Involving Chloro, Bromo, Thiol, and Hydroxyl Groups

The classification of the chloro, bromo and thiol group together is based on their similarity in their number of peripheral electrons as defined by Erlenmeyer. An example is illustrated by guanosine analogues having a monovalent isosteric replacements. C8-substituted guanosine analogues **(Fig. 7) (10)** stimulate polyclonal immunoglobulin secretion and in the presence of antigen enhanced the magnitude of the anti-TNP plaque-forming cell (Anti-TNP PFC) antibody response to antigen TNP-Ficoll when evaluated in vitro by cultured with antigen and adjuvant. [23] B- lymphocytes were incubated with 1.0 mM of the guanosine analogues in presence or absence of type 2 antigen TNP-Ficoll.



(10)

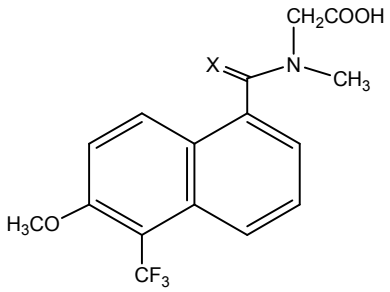
Fig. 7

(ii) Divalent Isosteres

Divalent isosteres can be classified into two subgroups: (a) Those divalent bioisosteres which involve the interchange of atoms that are involved in a double bond, such as in the series; C=**C**, C=**N**, C=**O**, and C=**S** and (b) those divalent isosteres where substitution of a different atom results in the alteration of two single bonds such as in the series; C-**C**-C, C-**NH**-C, C-**O**-C, and C-**S**-C.

(a) Divalent bioisosteres which involve the interchange of atoms that are involved in a double bond

The replacement of C=S with C=O in Tolrestat **(Fig. 8),** an aldose reductase inhibitor **(11)** for the treatment of diabetic neuropathy, resulted in oxo-Tolrestat, which retained activity both in vitro and in vivo [24].



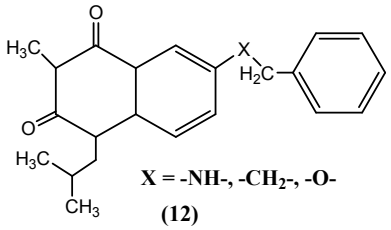
Tolrestat, X = C=S
Oxotolrestat, X =C=O
(11)

Fig. 8

(b) Divalent Replacements Involving Two Single Bonds

These divalent bioisosteres are attached to two different substituents, the chemical and polar differences are less pronounced. Example of divalent bioisosteric linkers shown in the study of

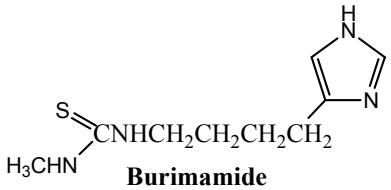
inhibitors of the nuclear factor of activated T cells (NFAT)-mediated transcription of β-galactosidase. [25] Some of the bioisosteric analogues of quinazolinediones **(Figure 9)** as potential immunosuppressive agents by their ability to inhibit β-galactosidase expression has been evaluated. Both -NH- and -CH_2- bioisosteric linkers have similar bond angles and electronegativities result in analogues which retain activity. Use of an oxygen atom as a bioisosteric linker, which has smaller bond angle and much greater electronegativity, results in an analogue **(12)** with increased potency.



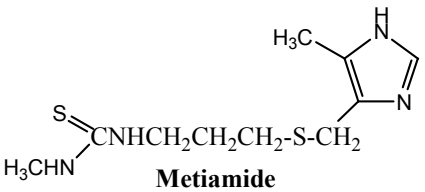
(12)

Figure 9

Burimamide antagonise the effects of histamine on isolated cardiac and uterine muscle in vitro, and to antagonise histamine-stimulated acid secretion inside the body [26]. This pattern of pharmacological effects is not achieved by conventional, tertiary amine, anti-histaminic drugs (of which mepyramine is typical) and has led to the definition of burimamide as an H_2-receptor antagonist and mepyramine as an H_1-receptor antagonist [27]. Although burimamide has sufficient pharmacological activity [28] but seemed to lack the combination of specific activity with adequate oral bioavailability. Therefore it needs to modify the structure of burimamide. In the side carbon chain of burimamide **(13)**, electron withdrawing bivalent sulphur atom was introduced [29] which reduce the ring p Ka. The resulting compound, metiamide **(14)** had excellent oral absorption and was ten times more active than burimamide (**Figure 10).**



Burimamide
(13)



Metiamide
(14)

Figure 10

(iii) Trivalent Atoms or Groups

A classical trivalent bioisosteric replacement is -CH= with -N=. This replacement when applied to cholesterol **(15)** resulted in 20, 25-diazacholesterol **(16) (Figure 11)** which is a potent

inhibitor of cholesterol biosynthesis. [30] The greater electronegativity of the nitrogen atom could be responsible for the biological activity of this bioisostere.

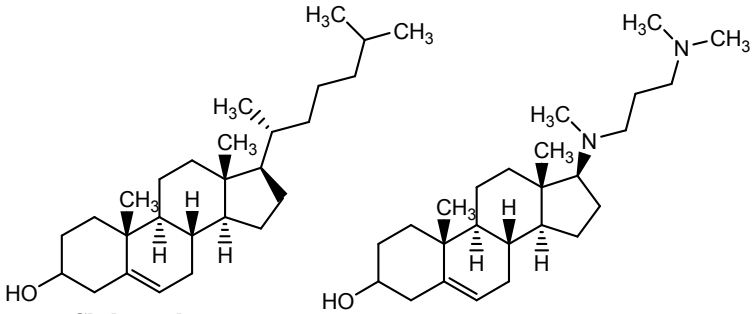


Figure 11

Replacement of -P= (bond angle C-P-C = 100 ± 4^0) with -As= (bond angle C-As-C = 96 ± 5^0) [31] is another example. Arsenicals have received considerable attention due to their therapeutic significance. The oxidation of arsenic compounds to arsenoxides is important in the bioactivation of a number of chemotherapeutic arsenicals. One of the first drugs used clinically was arsphenamine. Oxophenarsine metabolite of arsphenamine contribute to its activity against the syphilis organism. Due to the lack of selective toxicity associated with these arsenicals, analogy is drawn to prontosil **(17) (Figure 12)** which is found to be metabolized to p-aminobenzenesulfonamide **(18)**. Prontosil is inactive against microorganisms in vitro but active in vivo.

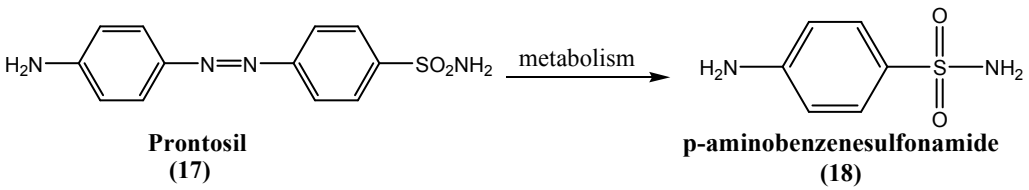
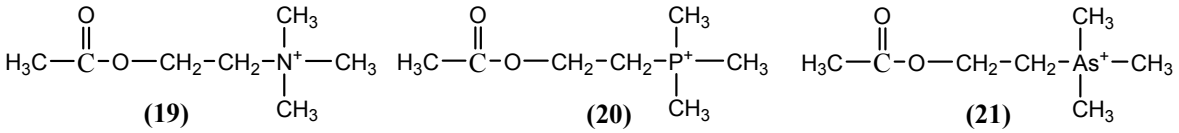


Figure 12

(iv) Tetrasubstituted Atoms

A classical illustration of tetrasubstituted isosteres involves replacement of the quaternary ammonium group **(19)** in case of cholinergic agonists **(Figure 13)** [32] with the phosphonium **(20)** and arsonium **(21)** analogues. Such replacements resulted in less potent analogues with greater toxicity. Activity decreased as size of the onium ion increased. The decreased potency and greater toxicity of these higher elements has diminished interest in replacements of this type for the development of direct-acting cholinergic agonists.



(19) **(20)** **(21)**

Figure 13

(v) Ring Equivalents

The use of the classical bioisosteres benzene, thiophene, and pyridine resulted in analogues with retention of biological activity within different series of pharmacological agents. Ring bioisosterism, is the most frequent relationship in drugs of different therapeutic classes [33], as can be seen in **(Fig. 14)**, and certain specific examples will be commented upon.

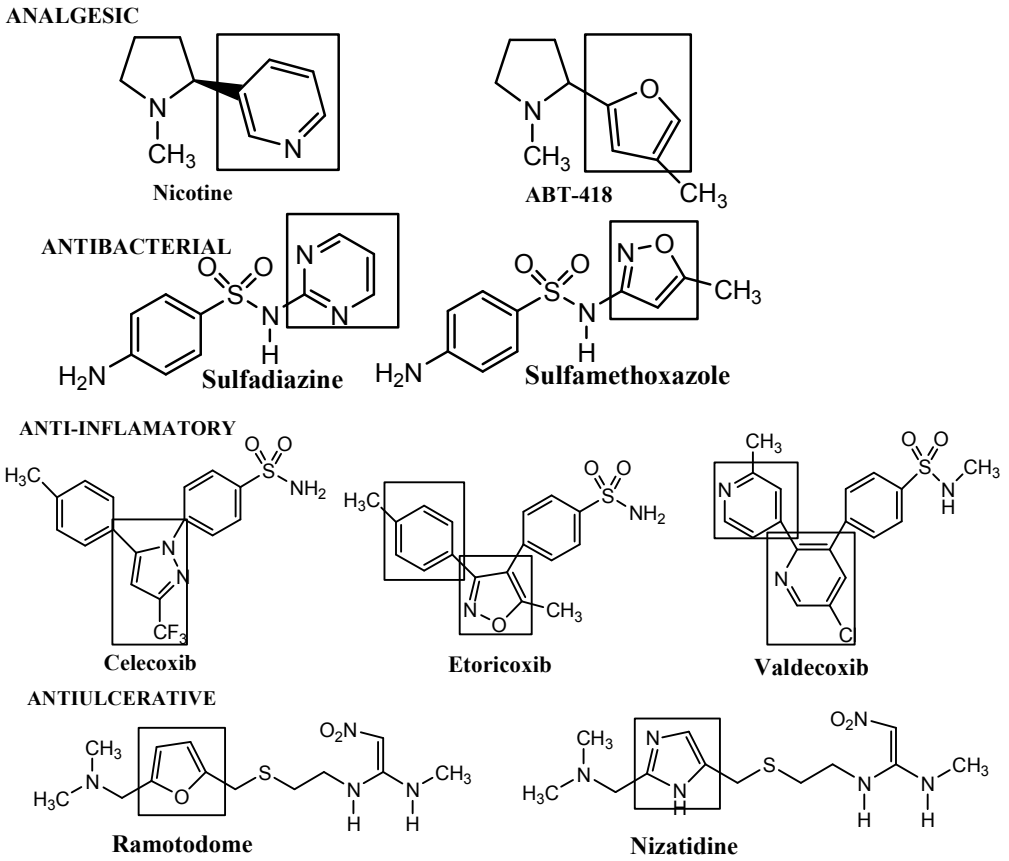
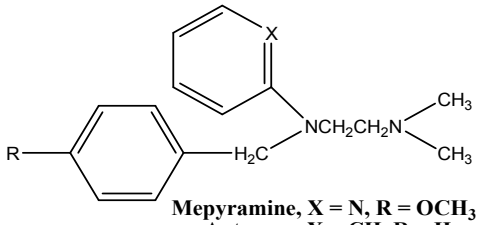


Figure 14: Examples of ring bioisosterism between drugs belonging to different therapeutic classes.

One of the successful uses of this replacement resulted in the potent antihistamine **(22)** mepyramine **(Figure 15)** by the replacement of the phenyl moiety in antegran by a pyridyl group.



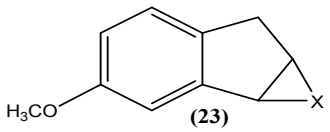
Mepyramine, X = N, R = OCH_3
Antegran, X = CH, R = H
(22)

Figure 15

Bioisosteres will be divided into (a) divalent ring equivalents and (b) trivalent ring equivalents:

(a) Divalent ring equivalents

A copper-containing monooxygenase, dopamine β-hydroxylase, present in mammalian tissues, catalyses the benzylic hydroxylation of dopamine. Since dopamine β-hydroxylase plays an important role in the biosynthesis of noradrenaline, it could be a target for the design of inhibitors as potential therapeutic agents for the modulation of adrenergic activity in vivo. Isosteric divalent ring replacements resulted in retention of activity within a series of indane derivatives **(23) (Figure 16)** evaluated as inhibitors of dopamine β-hydroxylase [34].



(23)

Figure 16

The search for novel cardio-tonic agents resulted in the successful development of two clinically useful agents, amrinone [35] **(24)** and milrinone [36] **(25) (Figure 17)**. Positive vasodilatory actions of amrinone and milrinone are related to the inhibition of adenosine 3', 5'-cyclic phosphate phosphodiesterase III (c AMP PDE III). During SAR studies on amrinone, it was found that a free amino group was not necessary for in vitro c AMP PDE III activity [37]. This prompted the design and synthesis of analogues with general structure [38] **(26)**. Divalent isosteric ring substitutions of the pyrazino[2,1-a][2]benzazepine system **(Figure 18)** resulted in derivatives **(27)** containing different heterocyclic systems. All these bioisosteres exhibited anthelmintic activity [38]. Replacement of the methylene with a sulfur or oxygen atom resulted in analogues with decreased potency relative to the carbocyclic analogue.

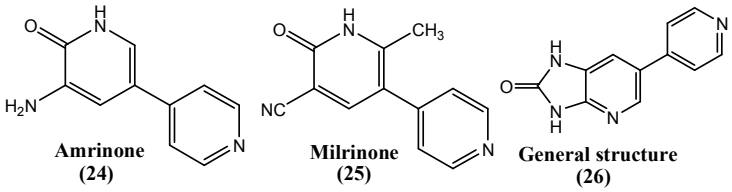


Figure 17

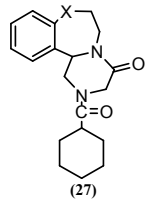


Figure 18

(b) Trivalent Ring Equivalents

The trivalent substitution of -CH= with -N= is commonly used in modern drug design. Pilocarpine **(28)**, employed as a topical miotic has short duration of action is mainly due to the hydrolytic cleavage of the lactone ring, resulting in the formation of pilocarpic acid and rapid elimination and/or epimerization to form isopilocarpine [40]. Replacement of the carbon atom on the oxazolidinone ring with nitrogen resulted in the carbamate analogue [41] **(29) (Figure 19)** which was equipotent with pilocarpine. This analogue bypasses the problem associated with epimerization as seen with pilocarpine.

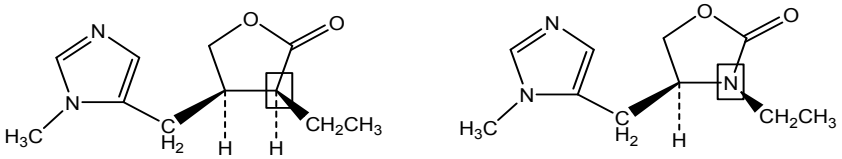


Figure 19

Replacement of phenyl ring of the indolic nucleus, present in the structure of lead compound, N,N-dimethyltryptamine **(30)** by the thiophene ring produce isomeric systems thieno[3,2-b] pyrrole **(31)**, thieno[2,3-b]pyrrole **(32)**, thieno[4,3-b]pyrrole **(33) (Figure 20)** [42]. Bioisosteres of the indole ring, presenting affinity and selectivity by the serotonin receptors similar to lead compound. Regioisomeres formation occurs in this replacement.

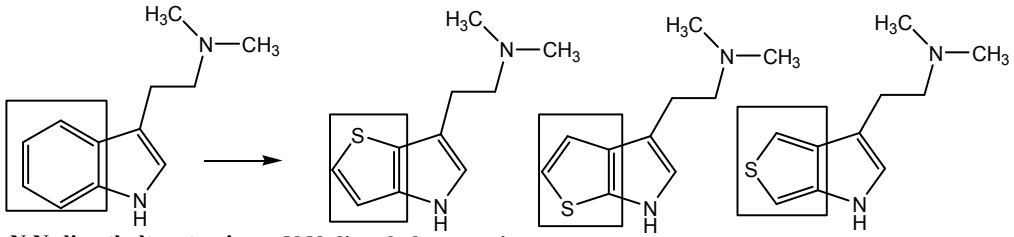


Figure 20

Taking Piroxican **(34)** as lead compound in developing new non-steroid anti-inflammatory agents of the oxican group [43], tenoxican **(35)**, the newest member of the class of arylthiazine-1, 1-dioxides **(Figure 21)** was synthesized where the benzothiazinic nucleus of Piroxican was replaced by the thienothiazinic moiety [44], discovered by Lombardino and collaborators [45], at Pfizer Laboratories in England. Both derivatives act by the same mechanism of action, at the same receptor level, i.e. cyclooxygenase, an enzyme involved in arachidonic acid metabolism. Pharmacological activity profile of tenoxican proved to be comparable to that of piroxican [46].

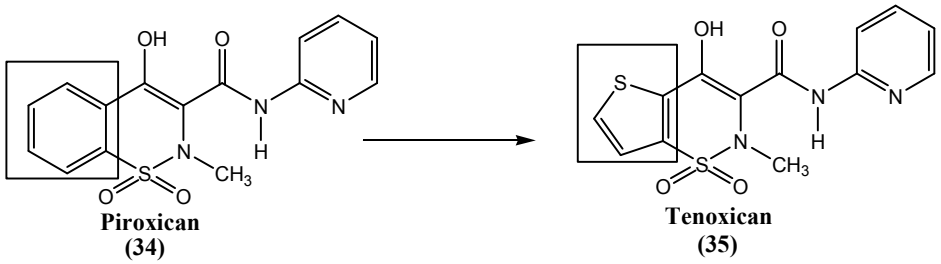


Figure 21

(B) Non-classical Bioisosterism

This major class of isosteres includes all those replacements that are not defined by the classical definitions of bioisosteres.

1. Cyclic vs Non-Cyclic

Trans-diethylstilbestrol [47] having an estrogenic properties, illustrating the application of non-classic ring opening bioisosterism. Molecular design of **37** could be carried out from the opening of rings B and C of the steroidal skeleton of estradiol **(36) (Figure 22)**. Central bond of diethylstilbestrol is important for the correct orientation of the phenolic and ethyl groups for binding to the estrogenic receptor [48]. Cis isomer is only 1/14 as active as the trans isomer [49]. The activity of **37** 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. Structurally or conformationally rigid analogues are equipotent as estradiol. Nonrigid analogues have little or no estrogenic activity [50, 51].

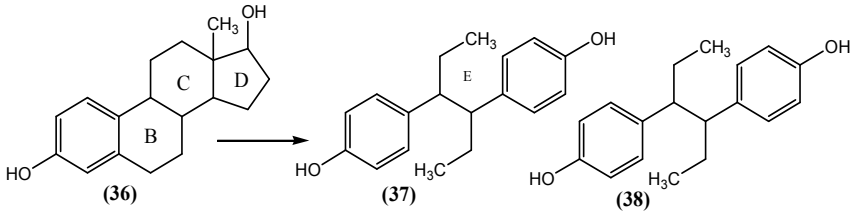


Figure 22

Another example of the application of non-classic bioisosterism is shown by lidocaine **(40)** from mepivacaine **(39) (Figure 23)**, contributing to the design of the important anesthetic agent with predominant antiarrhythmic properties.

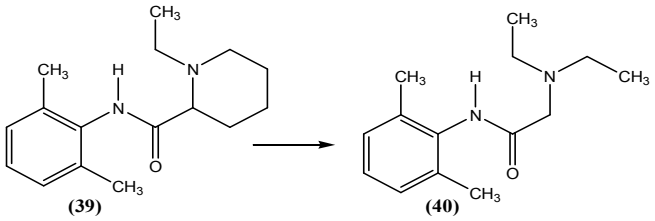


Figure 23

2. Non-Classic Bioisosterism of Functional Groups

Bioisosteric relationships exist between sulfonamide (SO_2NH_2) and carboxylic acid (COOH) [52] **(Figure 24)**. P-aminosulfanilamide [53] (42), an active metabolite of Prontosil [54, 55] which was able to provide cures of streptococcal infections in mice revolutionized chemotherapy and on later elucidation of its mechanism of action shows similarity of its structure with p-aminobenzoic acid (PABA, 41). These similarities based on electronic and conformational aspects as well as the physicochemical properties such as p Ka and log P. Sulfonamides act as competitive inhibitors of the incorporation of p-aminobenzoic acid associated with the formation of dihydropteroic acid, thereby, ultimately inhibiting the biosynthesis of dihydrofolic acid [56].

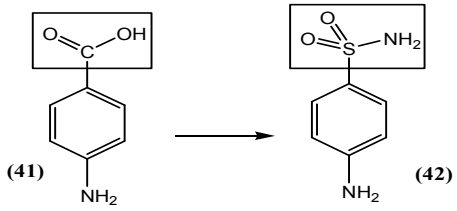


Figure 24

Bioisosteric replacement of –COOH by a tetrazole group resulted in enhanced potency due to the reduced hydrophilicity [57, 58]. Tetrazole act as bioisostere of γ-aminobutyric acid (GABA, 43), an important selective inhibitory properties of GABA-transaminase **(Figure 25)** [59] showing a potential pharmacotherapeutic application as an anticonvulsant agent. The tetrazole group mimics the carboxylate group, principally in terms of its physicochemical properties related to acidity.

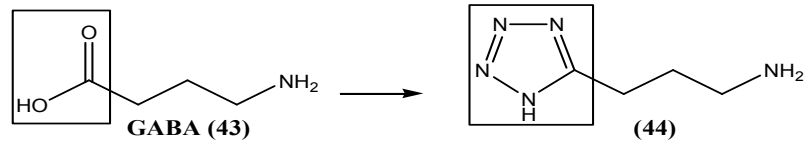


Figure 25

A non-classic bioisosteric relationship exist between the functional groups thioamide (CS-NH-) and amide (CO-NH-) [60, 61]. Oxatolrestat (46) [62], represent a classic bioisostere of tolrestat (45) **(Figure 26)**, a potent aldose reductase inhibitor [63].

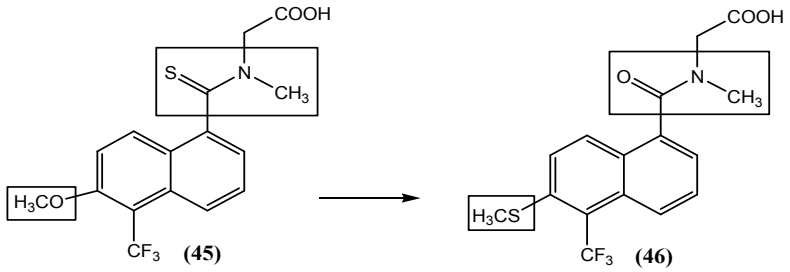


Figure 26

3. 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 **(Figure 27)**. Main aim is 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 metabolic intermediates.

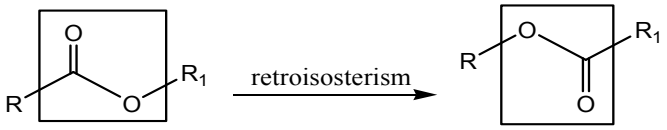


Figure 27

Lages et al described the retroisosteric relationship between the methylsulfonylamine and methylsulfonamide functions **(Figure 28)** present in the structures of new selective COX- 2 inhibitor lead compounds (47) and (48) [64].

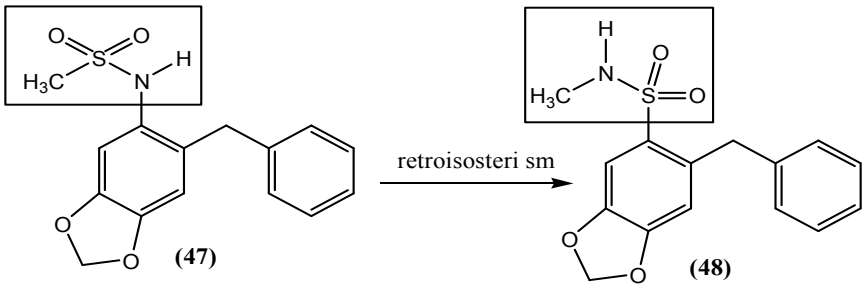


Figure 28

This type of retroisosteric relationship confers metabolic susceptibility and distinct p Ka values between compounds 47 and 48, while the greatest activity found for the methylsulfonamide derivative 47 may be explained considering the profile of interaction of this group with the Arg_{513} and Ser_{353} amino acid residues present at the catalytic site of COX-2, favored in 47 when compared to the 48 retroisostere.

Conclusion

Bioisosterism represents a successful strategy in rational drug design, useful in molecular modification and design of new therapeutically attractive drug substances of different pharmacological classes. The correct use of the strategy of molecular modification also allows the identification of new classes of lead compound with attractive pharmacotherapeutic activity, maximizing the chances for success in discovering medications both more efficient and of safer use, minimizing the efforts of synthetic work.

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