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The Use of Bioisosterism in Drug Design and Molecular Modification

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ABSTRACT

Bioisosteres are atoms or group of molecules that fit the broadest definition for isosteres. They have chemical and physical similarities thus producing broadly similar biological properties. Many heterocycles, when appropriately substituted exhibits bioisosterism. Bioisosterism represents an approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents. It has significant value in drug design and lead optimization process as it may enhance the desired biological or physical properties of a compound, reduce toxicity and also alter the metabolism of the lead. Bioisosteric replacement is not simple replacement with another isostere but they are firstly analyzed by structural, solubility and electronic parameters to obtain molecules having similar biological activity. Few of the popular examples of the successful use of bioisosteres have been included. The objective of this review is to provide an overview of bioisosteric replacements which can be used for advance drug development.

Keywords: Bioisostere, Isostere, Drug design, Replacement, Pseudoatoms

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INTRODUCTION

Bioisosteres are substituents or groups with similar physical or chemical properties which produce broadly similar biological properties to a chemical compound. In a biologically active molecule the replacement of an atom or a group of atoms by another one presenting the same physicochemical properties is based on the concept of isosterism. The notion of isosterism was introduced in 1919 by Langmuir. The extensive application of isosterism to modify a part of a biologically active molecule to get another one of similar activity, has given rise to the term of bio-isosterism.

In drug design, the purpose of exchanging one bioisostere for another is :

1. To enhance the desired biological or physical properties of a compound without making significant changes in chemical structure.
2. To attenuate toxicity.
3. To modify the activity of the lead compound.
4. To alter the metabolism of the lead.

Depending on the molecule used in the substitution, little change in activity (i.e. either increase or decrease in affinity or efficacy) can occur as it is dependent on factors such as electronegativity, size, pka, solubility which are important for target binding such as electronegativity, size, pka, solubility etc. [1].

1.1. History: Development of the isosterism concept

1. a. Molecular number [2]

Allen, in 1918 defined the molecular number of a compound in a similar way of the atomic number:

$$N = aN_1+bN_2+cN_3+\ldots..+zN_i$$

Where *N* = Molecular number

N_1, N_2, N_3 . . . Ni = Respective atomic numbers of each element of the molecule.

a, b, . . . z = Number of atoms of each element present in the molecule.

Example: Comparison of the ammonium and the sodium cations. The atomic number of nitrogen is 7 and that of hydrogen is 1. Thus the molecular number of the ammonium cation can be calculated and compared to that of the sodium ion **(Table 1).**

Possessing the same molecular number, the ammonium cation should resemble the sodium cation. Two compounds with identical molecular numbers present some similar physical properties (e.g. specific heat).

Table 1: Molecular number of ammonium and sodium cations

	Atomic number	Molecular number
NH_4^+	7 + (4 x1)	11
Na^+	11	11

1.2. Isosterism concept [3]

Langmuir in 1919 defined the concept of isosterism as follows:

Comolecules are isosteric if they contain the same number and arrangement of electrons. The comolecules of isosteres must, therefore contain the same number of atoms. The essential differences between isosteres are confined to the charges on the nuclei of the constituent atoms **(Table 2).**

Table 2: Groups of isosteres [4]

Groups	Isosteres
1	H, He, Li^+
2	O^{2-}, F^-, Ne, Na^+, Mg^{2+}, Al^{3+}
3	S^{2-}, Cl^-, Ar, K^+,Ca^{2+}
4	Cu^{2-}, Zn^{2+}
…	…
…	…
8	N_2, CO, CN^-
9	CH_4, NH_4^+
10	CO_2, N_2O, N_3, CNO^-
…	…
…	…
20	MnO_4^-, CrO_4^{2-}
21	SeO_4^{2-} , AsO_4^{3-}

1.3. Grimm's hydride displacement law [5]

Later on, in 1925, Grimm formulated the "Hydride displacement law" according to which the addition of hydrogen to an atom confers on an aggregate the properties of the atom of next highest atomic number. An isoelectronic relationship exists among such aggregates which were named pseudoatoms. Example, when a proton is "added" to the O^{2-} ion in the nuclear sense, an isotope of fluorine is obtained.

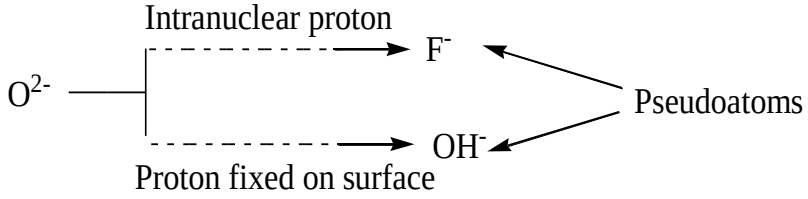


Figure 1: Pseudoatoms.

Here the hydrogen ion has been penetrated into the electronic shell of the oxygen, which is assumed to be masked by the greater atom and exerts only negligible effect toward the outside.

The fluoride anion F^- and the hydroxyl anion OH^- show therefore some analogies. The generalization of the pseudoatom concept represents the "Hydride displacement law" **(Table 3).**

Table 3: Hydride Displacement law [6]

Number of electrons					
6	7	8	9	10	11
—C—	—N—	-O-	-F	Ne	Na^+
	—CH—	-NH-	-OH	FH	
		$-CH_2-$	$-NH_2$	OH_2	
			$-CH_3$	NH_3	OH^{3+}
				CH_4	NH^{4+}

1.4. Erlenmeyer's expansion of the isosterism concept [7]

Erlenmeyer proposed his own definition of isosteres as elements, molecules or ions, in which the peripheral layers of electrons may be considered identical.

Erlenmeyer also proposed three expansions of the isosterism concept:

1. To the whole group of elements present in a given column of the periodic table. Thus silicon becomes isosteric to carbon, sulfur to oxygen, etc.
2. To the pseudoatoms, with the aim of including groups which at a first glance seem totally different, but which in practice, possess rather similar properties. This is the case for the pseudohalogens (e.g. Cl, CN, SCN, etc.)
3. To the ring equivalents: the equivalence between —CH=CH— and -S- explains the well known analogy between benzene and thiophene.

$M_{(-CH=CH-)} = 26$ $M_{(S)} = 32$

Figure 2: Analogy between benzene and thiophene.

1.5. Friedman's and Thornber's definitions

Friedman proposed to call bioisosteres compounds: "which fit the broadest definition of isosteres and have the same type of biological activity [8]." Friedman considered that, isosteres that exhibit opposite properties (antagonists) have also to be considered as bioisosteres, as they interact with the same recognition site. eg. Para-amino benzoic acid and Para-amino benzene-sulfonamide [9, 10]. Thornber proposed a loose and flexible definition of the term bioisostere as: "Bioisosteres are groups or molecules which have chemical and physical similarities producing broadly similar biological effects [11]."

2. CLASSIFICATION OF BIOISOSTERISM [4,12]

In 1970, Burger classified and subdivided bioisosteres into two broad categories according to the degree of electronic and steric factors.

2.1. Classic isosteres:

2.1. A. Monovalent atoms or groups

2.1. B. Divalent atoms or groups

2.1. C. Trivalent atoms or groups

2.1. D. Tetravalent atoms

2.1. E. Ring equivalents

2.2. Non-classical isosteres:

2.2. A. Cyclic vs. Non cyclic

2.2. B. Non classic bioisosterism of functional groups

2.2. B.1. Carboxylic group bioisosteres

2.2. B.2 Hydroxyl group bioisosteres

2.2. B.3. Amide group bioisosteres

2.2. B.4. Halogen bioisosteres

2.1. Classic isosteres

They obey steric and electronic definition **(Table 4).**

Table 4: Classic bioisostere atoms and groups

Monovalent	Divalent	Trivalent	Tetravalent
-OH, -NH_2, -CH_3, -OR	-CH_2-	=CH-	=C=
-F, -Cl, -Br, -I, -SH, -PH_2	-O-	=N-	=Si=
-Si_3, -SR	-S-	=P-	=N^+=
	-Se-	=As-	=P^+=
	-Te-	=Sb-	=As=
			=Sb^+=

2.1.A. Monovalent atoms or groups

❖ Hydrogen vs. Fluorine Replacement [13]

Steric parameters for hydrogen and fluorine are similar, their Vander Waal's radii being 1.2 and 1.35 Å respectively. Thus, the difference in the electronic effects (fluorine being the most electronegative element in the periodic table) is often the basis for the major differences in the pharmacological properties of agents. Due to its electronegativity, fluorine exerts strong field and inductive effects on the adjacent carbon atom. However, fluorine can donate a lone pair of electrons by resonance. This is commonly referred to as its mesomeric effect. The opposing resonance and field effects can nearly cancel. The pharmacological differences can be attributed

to the influence of the electron withdrawing effect that the fluorine substitution causes on interaction with a biological receptor or enzyme, as well as its effect on the metabolic fate of the drug.

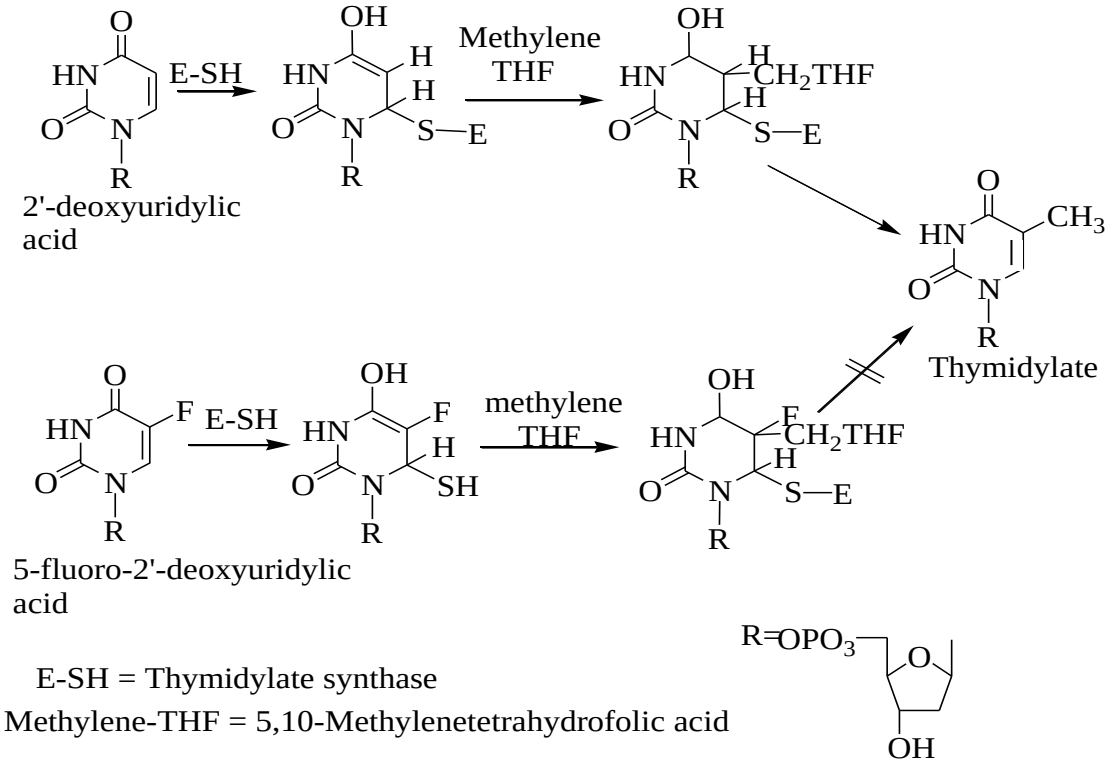


Figure 3: Hydrogen to fluorine replacement.

eg. 1 The biochemically altered form of 5-FU ie. 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. 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.

❖ Interchange of Hydroxyl and Amino Groups

The best known example of classical isosteric substitution of an amino group for a hydroxyl group is illustrated by aminopterin (b) wherein the hydroxyl substituent of folic acid (a) has been substituted by an amino group. This represents a monovalent bioisosteric substitution at a carbon atom adjacent to a heterocyclic nitrogen atom. This bioisosteric replacement has the capability of mimicking even the tautomeric forms of folic acid.

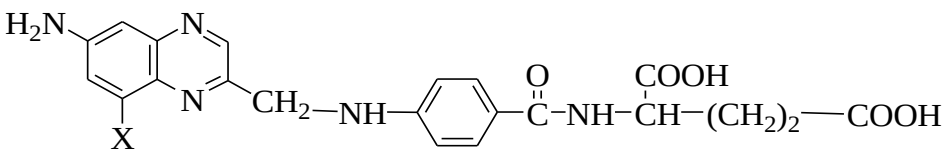


Figure 4: (a) X= OH folic acid, (b) X=NH_2 Aminopterin.

In the presence of electron donating atoms such as nitrogen in heterocyclic systems, it is known that there will be tautomerization where a neighboring C-OH will tautomerize to C=O [14]. In the case of a neighboring carbon containing C-NH_2 the preferred tautomer is the C-NH form [14, 15].

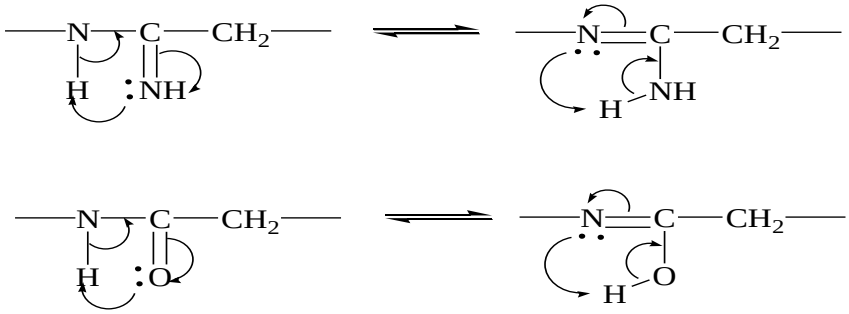


Figure 5: Tautomerization of cyclic nitrogen.

The similarities as well as the capability of the amino group to hydrogen bond and to the enzyme are two important factors that facilitate the binding of aminopterin to the enzyme dihydrofolate reductase [16].

❖ Interchange of Hydroxyl and Thiol Groups

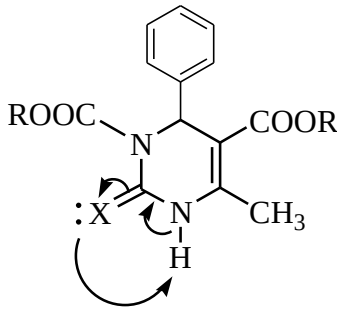


Figure 6: 1, 4-dihydropyrimidine.

In order to enhance the calcium channel blocking capacity of certain dihydropyrimidine agents, a number of isosteric analogues with the general structure were synthesized [17]. Substitution of the hydroxyl with an amino resulted in analogues with similar potency. However, substitution with the thiol resulted in enhanced potency. This is due to the size of the substituent, described here as the Vander Waal's radii and the hydrogen bonding ability. Therefore, replacement with the amino group, which has a similar size, resulted in similar potency and replacement with the sterically optimal thiol resulted in an analogue which was more potent **(Table 5)[18].**

Table 5: Calcium channel blocking activity of 1, 4-Dihydropyrimidines

Compound	X	Vander Waal's radius (A°)	IC_{50}(nM)
15a	=O	1.40	140
15b	=NH	1.50	160
15c	=S	1.85	17

❖ Replacement of chlorine with methyl [19]

The chlorine atom is often viewed to be isosteric and isolipophilic with the methyl group it is very often selected as a bioisosteric replacement because of its ability to alter the metabolism. Replacement of a chloro atom with a methyl substituent can facilitate metabolism of a xenobiotic. Lipid-soluble chemicals tend to be distributed into adipose tissue where, unless they are metabolized, they tend to accumulate for long periods of time, e.g. DDT. The replacement of the trichloromethyl moiety with a tert-butyl group results in diminished persistence of this pesticide. The methyl substituent provide a site which is susceptible to metabolic degradation.

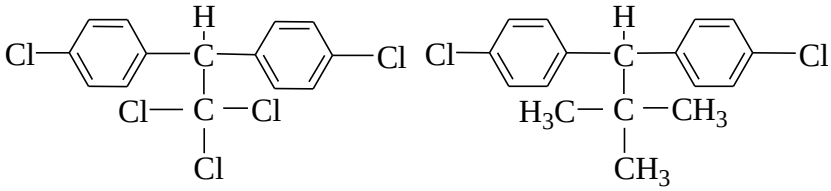


Figure 7: Replacement of chlorine with methyl in DDT.

2.3. B. Divalent atoms and groups

➢ Divalent replacements involving double bonds [20]

This subclass includes replacements of groups such as C=S, C=O, C=NH and C=C.

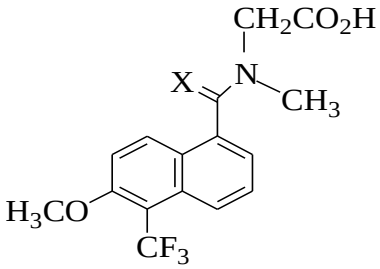


Figure 8: (a) X= S Tolrestat, (b) X= O Oxotolrestat.

The replacement of C=S with C=O in Tolrestat (a) an aldose reductase inhibitor, currently under study in human subjects for the treatment of diabetic neuropathy, resulted in oxo-Tolrestat (b) which retained activity both *in vitro* and *in vivo* (Table 6).

Table 6: Aldose Reductase inhibitory activity of Tolrestat and Oxo-Tolrestat

Compound	X	Aldose reductase inhibition	
		In vitro	***In vivo***
A	S	94	53
B	O	86	56

➢ Divalent Replacements Involving Two Single Bonds [21]

The second major class of divalent bioisosteres represents those atoms or groups which are attached to different substituent. The bond angle or the conformation associated with the use of

these divalent bioisosteres may be an important factor associated with retention of biological activity (**Table 7).**

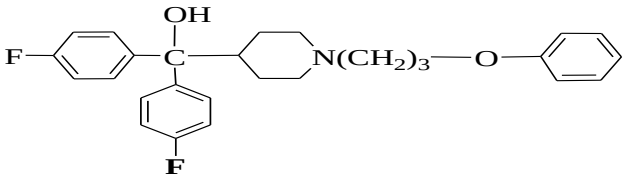


Figure 9: Divalent replacement involving two single bonds.

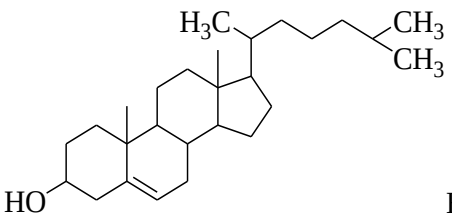
Table 7: Oral antiallegy activity in the passive foot anaphylaxis assay of analogues containing varied heteroatoms

Compound	X	Electronegativity	Bond angle(deg)	Passive foot anaphylaxis assay (10mg/kg)
a	-O-	3.51	108.0	+++
b	-S-	2.32	112.0	+
c	-CH2-	2.27	111.5	+
d	-NH-	2.61	111.0	+

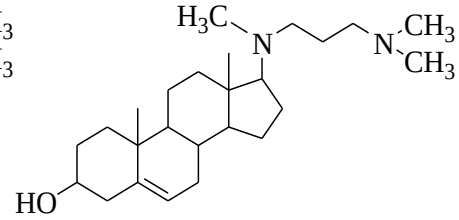
2.1. C. Trivalent atoms and groups

A classical trivalent bioisosteric replacement is –CH= with –N=

I. This replacement when applied to cholesterol resulted in 20, 25-diazacholesterol which is a potent inhibitor of cholesterol biosynthesis. The greater electronegativity of the nitrogen atom could be responsible for the biological activity of this bioisostere [22].



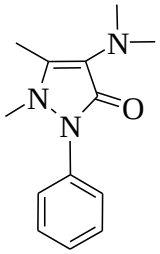
Cholesterol



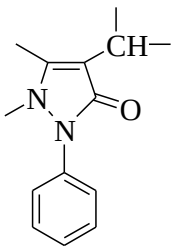
20,25 Diazacholesterol

Figure 10: Trivalent bioisosteric replacement.

II. The 4-dimethylamino-antipyrine and its carba-isostere are about equally active as antipyretics [23].



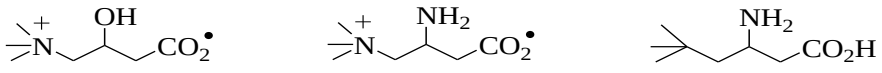
4-Dimethylamino-antipyrine



4-Isopropyl -antipyrine

Figure 11: Antipyretics.

2.1. D. Tetra substituted Atoms [24]



(1) (2) (3)

Figure 12: Replacement of tetravalent trimethyl ammonium group with tert-butyl group.

Certain simple acyl carnitine analogues are potent carnitine acyltransferase (CAT) inhibitors (Table 8). Structure-activity studies in this series have included the bioisosteric replacement of the hydroxyl group of carnitine **Figure 12** (1) with an amino **Figure 12** (2) and replacement of the tetravalent trimethylammonium group with a tertiary butyl group **Figure 12** (3).

Table 8: Rate constants for carnitine and synthetic analogues with Pigeon breast carnitine acyltranceferase

X	Ki (mM)
1	4.0
2	2.6

2.1. E. Ring equivalents

1. In sulphonamide antibacterials phenyl group may be replaced by heterocyclic group to give active compound eg. sulfadiazine and sulfamethoxazole etc. In this case no essential activity difference is found between the original drug and its isostere [25].

Sulfadiazine Sulfamethoxazole

Figure 13: Sulfonamide antibacterial.

2. In class of arylthiazine-1, 1-dioxides the newest member was found where the benzothiazinic nucleus was replaced by the thienothiazinic moiety. This example represents the bioisosteric relationship existing between aromatic heterocyclic rings and the phenyl group. The profile of pharmacotherapeutic activity proved to be comparable 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 [26].

Piroxicam Tenoxicam

Figure 14: Ring equivalents.

(i) Bioisosteres of pyridine [27-29]

The pyridine ring of nicotine can be replaced by different other rings like methyl-isoxazole or methylisothiazole. The bioisosteric replacement of the isoxazole ring in the (3-methyl-5-isoxazolyl) methylene-azacyclic compound with pyridine, pyrazine, oxadiazole or an acyl group resulted in ligands with moderate to high affinity for the central nicotinic cholinergic receptors.

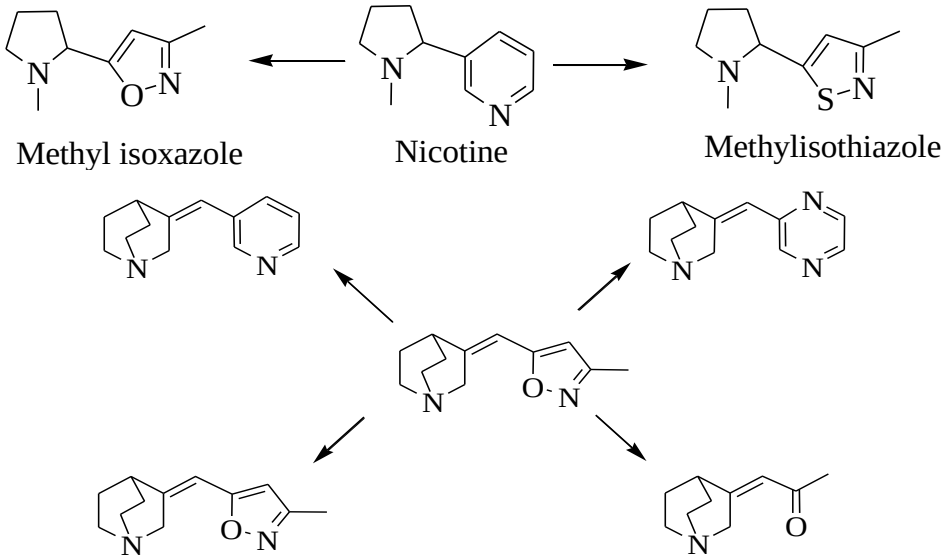


Figure 15: Non classical bioisosteres of pyridine ring.

(ii) Bioisosteres of other heterocycles [26]

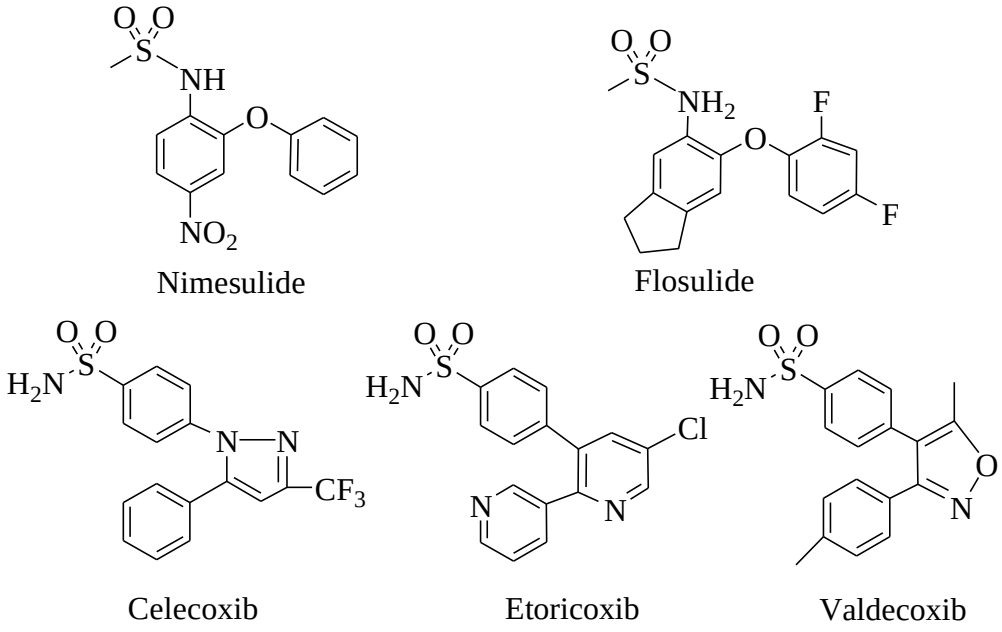
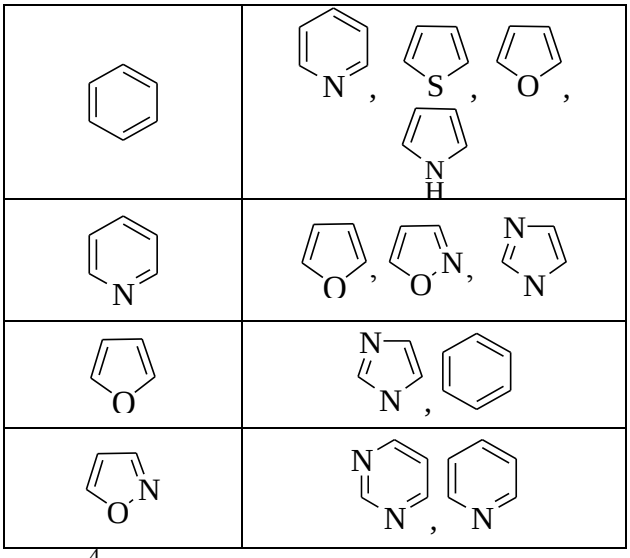


Figure 16: COX-2 inhibitors.

Selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) is a nice example of bioisosters of heterocycles. The comparison of the most potent selective COX-2 inhibitors suggests that

isoxazoles, pyridines and pyrazoles are good bioisosteres of each other as well as nitrophenol and indanones **(Table 9).**

Table 9: Ring replacements



2.2. Non classic bioisosteres [4]

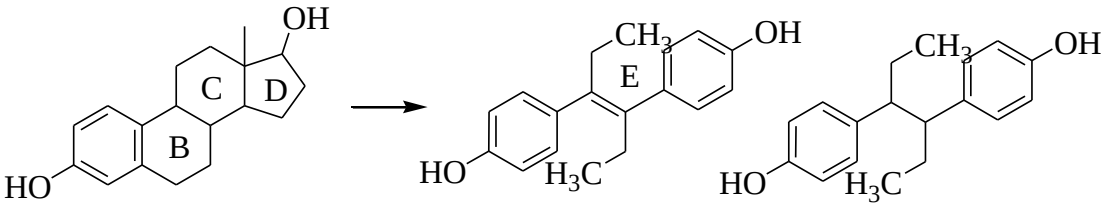
- They do not obey the steric and electronic definition of classical isosteres.
- They do not have the same number of atoms as the substituent or moiety for which they are used as a replacement **(Table 10).**

Table 10: Non-Classic bioisosteres

-CO-	-COOH	$-SO_2NH_2$	-H	-CONH-	-COOR	$-CONH_2$
$-CO_2-$	$-SO_3H$	$-PO(OH)NH_2$	-F	-NHCO-	-ROCO-	$-CSNH_2$
$-SO_2-$	-tetrazole					
$-SO_2NR-$	$-SO_2NHR$		-OH $-CH_2OH$		-catechol	
-CON-	$-SO_2NH_2$				-benzimidazole	
-CH(CN)-	-3-hydroxy isoxazole		$-NHCONH_2$			C_4H_4S
R-S-R	-2-hydroxy chromones		$-NH-CS-NH_2$			$-C_5H_4N$
(R-O-R')						$-C_6H_5$
R-N(CN)-	=N-		$-NH-C(=CHNO_2)-NH_2-NH-C(=CHCN)-NH_2$			$-C_4H_4NH$
-halide	C(CN)=R' $-CF_3$ -CN $-N(CN)_2$ $-C(CN)_3$					

2.4.A. Cyclic vs. Non cyclic [30]

The molecular design of Hexestrol was carried out from the opening of rings B and C of the steroidal skeleton of estradiol. However, in analogy to what was observed for estradiol, the activity of Hexestrol 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 that is compound Diethylstilbestrol.

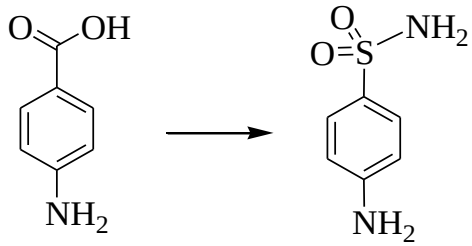


Estradiol Diethylstilbestrol Hexestrol

Figure 17: Ring opening bioisosterism.

2.2. B. Non classic bioisosterism of functional groups

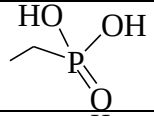
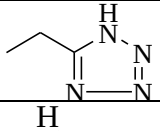
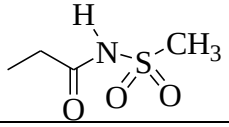
2.2. B.1. Carboxylic group bioisosteres [31]



Paraamino benzoic acid Sulfanilamide

Figure 18: Carboxylic group bioisosteres.

Table 11: Carboxylic group bioisosteres

-COOH	$-SO_2NH_2$
	-CONHOH
	
	
	
	$-SO_2OH$
	-CONHCN

Evidence of the similarity between sulfanilamide and paraminobenzoic acid was found during elucidation of its mechanism of molecular action. This similarity was based on electronic and conformational aspects as well as the physicochemical properties such as pKa and log P. This denotes an authentic bioisosteric relationship between the sulfonamide (SO_2NH_2) and carboxylic acid functionalities (CO_2H) **(Table 11).**

2.2. B.2. Hydroxyl group bioisosteres

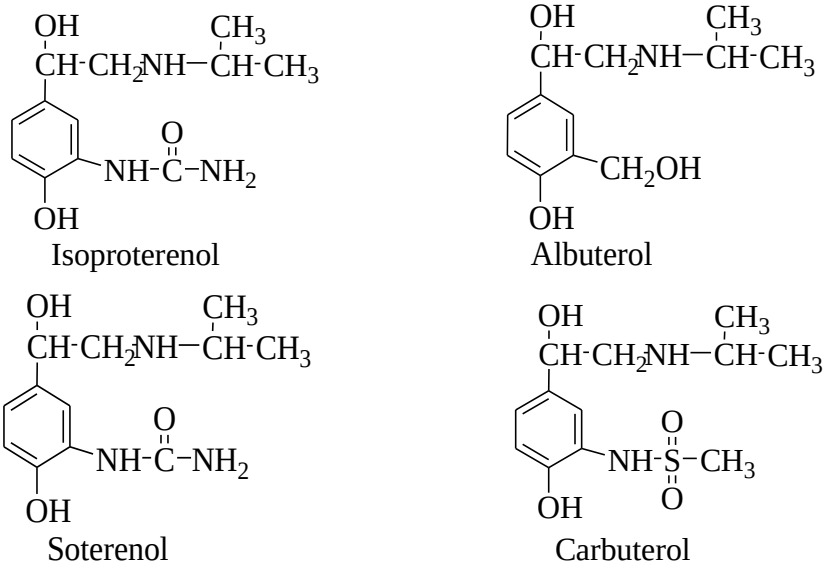


Figure 19: *β*-adrenoceptor agonists.

Notable example of *β*-adrenoceptor agonists that is isoproterenol, is widely used clinically as a bronchodilator; in which a 3-hydroxyl group has been replaced with bioisosteric groups which include albuterol 3-CH_2OH, soterenol 3-$NHSO_2CH_3$[32] and carbuterol 3-$NHCONH_2$[33]. This results in agents with potent and selective activities **(Table 12).**

Table 12: Hydroxyl group bioisosteres

-OH	-CH_2OH
	-$NHCONH_2$
	-$NHCOCH_3$
	-$NHSO_2CH_3$
	-NHCN

2.2. B.3. Amide group bioisosteres [34]

Bioisosteric replacements for the amide are done because of its implications in peptide chemistry and the development of peptide mimetic. Peptide bonds and peptide fragments have been replaced with a wide variety of structural moieties in attempts to convert peptides into chemically stable and orally available molecules.

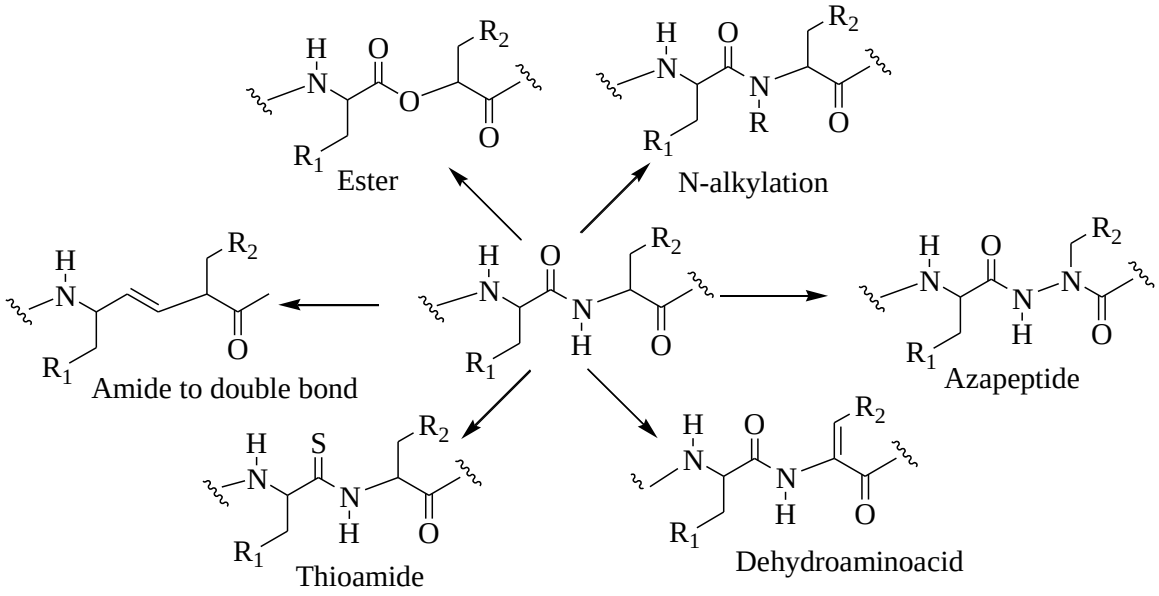


Figure 20: Amide group bioisosteres.

Heterocyclic bioisosteres of the amide bond are as follows **(Table 13).**

Table 13: Bioisosteres of the amide bond

Amide	2-isoxazoline
	Imidazoline
	1,2,4-oxadiazoles
	1,3,4- oxadiazoles
	1,2,4-triazoles

2.2. B.4. Halogen Bioisosteres [32]

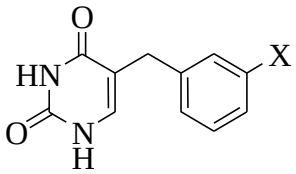


Figure 21: Halogen Bioisosteres.

Replacements of this type were observed in a series of 1-[(2- hydroxyethoxy) methyl]-5-benzyluracils that were tested for inhibition of liver uridine phosphorylase (UrdPase) [35]. Uridine phosphorylase is an enzyme that catalyzes the reversible phosphorolysis of pyrimidine

nucleosides. Uridine phosphorylase is responsible for the degradation of chemotherapeutic agents such as 5-fluoro-2-deoxyuridylic acid [36]. Within the series of 5-benzyluracils, it was suggested that electron-withdrawing groups at the 3-position decreased potency. This hypothesis was supported by the observation that replacement of the chloro atom with stronger electron-withdrawing groups such as the cyano or the trifluromethyl resulted in less potent analogues **(Table 14).**

Table 14: Uridine phosphorylase inhibition of 5-Benzyluracil

Compound	X	IC_{50}
1	Cl	2.5
2	CN	13.2
3	CF3	21.4

3. ANALYSIS OF THE MODIFICATIONS RESULTING FROM ISOSTERISM

In general the isosteric replacement, even though it represents a subtle structural change, results in a modified profile: some properties of the parent molecule will remain unaltered, others will be changed. Isosteric modification can be governed by following parameters:-

- structural parameters
- electronic parameters
- solubility parameters

A. Structural parameters

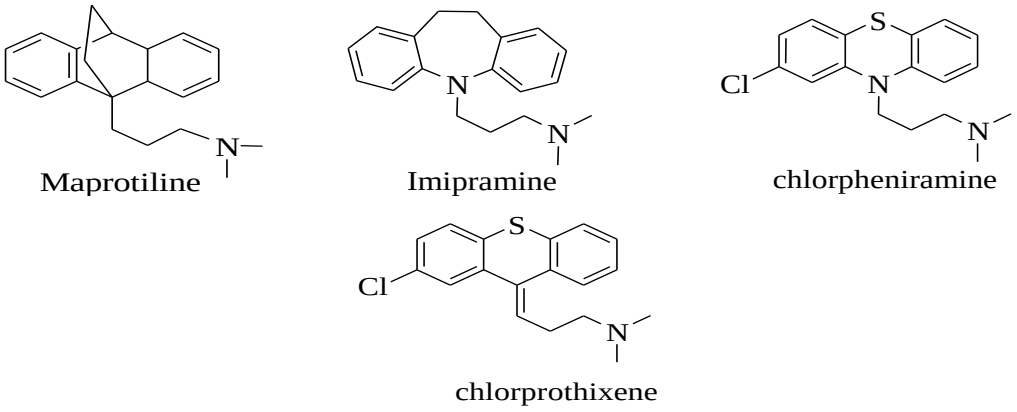


Figure 22: Dihedral angle formed by the two benzo rings dibenzazepine & dibenzocycloheptadiene.

These will be important when the portion of the molecule involved in the isosteric change serves to maintain other functions in a particular geometry. That is the case for tricyclic psychotropic drugs. In the two antidepressants (imipramine and maprotiline) the bioisosterism is geometrical that is the dihedral angle α formed by the two benzo rings is comparable: $\alpha = 65°$ for the dibenzazepine and $\alpha = 55°$ for the dibenzocycloheptadiene [37]. This same angle is only 25° for the

neuroleptic phenothiazines and the thioxanthenes. In these examples the part of the molecule modified by isosterism is not involved in the interaction with the receptor. It serves only to position correctly the other elements of the molecule [38].

B. Electronic parameters [39]

It governs the nature and the quality of ligand–receptor or ligand enzyme interactions. The relevant parameters will be inductive or mesomeric effects, polarizability, p*K*a, capacity to form hydrogen bonds etc. Despite their very different substituents in the meta-position, the two epinephrine analogs exert comparable biological effects: they are both β -adrenergic agonists. In fact the key parameter resides in the very close p*K*a.

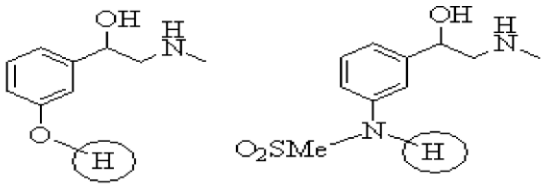
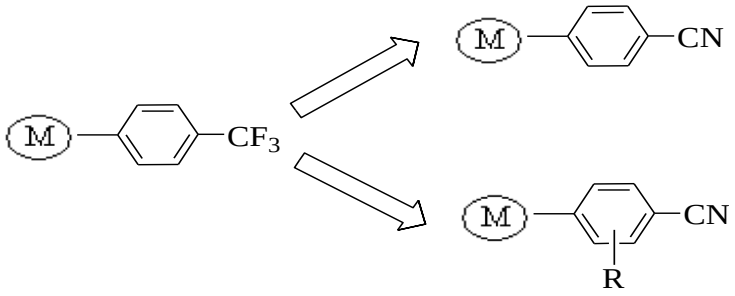


Figure 23: Non-classical isosterism, methyl sulfonamide substituent has comparable acidity to the phenolic hydroxyl group.

C. Solubility parameters [40]

When the functional group involved in the isosteric change plays a role in the absorption, distribution or excretion of the active molecule, the hydrophilic–lipophilic parameters become important.

For example in an active molecule the replacement of -CF_3 (π =+0.88) by -CN (π = -0.57), the electron-attracting effect of the two groups will be comparable, but the molecule with the cyano function will be clearly more hydrophilic. This loss in lipophilicity can then be corrected by attaching elsewhere on the molecule a propyl, isopropyl, or cyclopropyl group.



R = propyl, isopropyl, cyclopropyl

Figure 24: Replacement of CF_3 with CN.

4. MINOR METALLOIDS-TOXIC ISOSTERS

A. Bioisosteres involving selenium

Selenium can be considered the best isoster of sulfur as it is just below it in the periodic table. These two atoms have very similar physical properties: the radius of selenium is only 12.5% bigger than that of sulfur and their electro negativity is rather similar. Selenium and its derivatives are highly toxic, with the exception of ^{75}Se derivatives which serve diagnostic purposes (e.g.^{75}Se-selenomethionine is used as a radioactive imaging agent in pancreatic scanning). Selenium bioisosteres of sulfur compounds are mainly used as research tools (e.g. bis [2-chloroethyl] selenide as selenium bioisostere of the classical sulfur mustards). Selenocysteine is present in the catalytic site of mammalian glutathione-peroxidase and this explains the importance of selenium as an essential trace. The only selenium-containing drug candidate is *ebselen* which owes its antioxidant and anti-inflamatory properties to its interference with the selenoenzyme glutathione-peroxidase [41]. Because of its strongly bound selenium moiety only metabolites of low toxicity are formed [42].

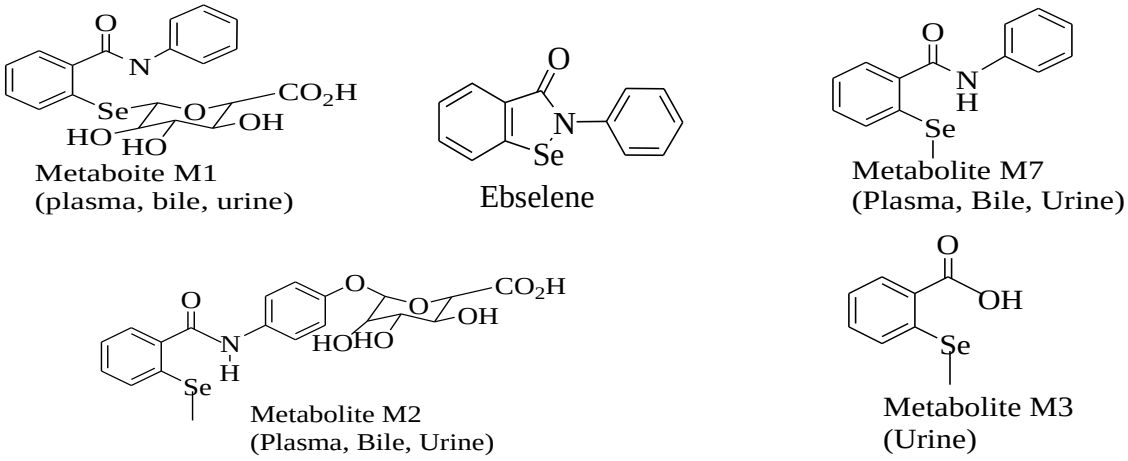
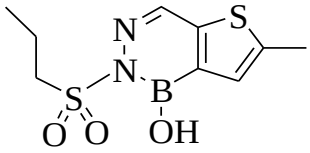


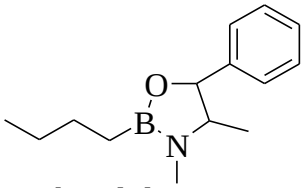
Figure 25: Ebselen and its main metabolites.

B. Carbon–boron isosterism

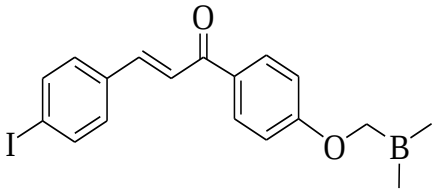
Compounds-containing carboxy boranes have shown anticancer, hypolipidemic and antifungal activity. Diazaborines are active against malaria and oxazaborolidines possess antibacterial activity [43]. Boronic chalcones are reported to be antitumor agents [44]. Organoboron derivatives, even more than organosilicon compounds, are sensitive to hydrolytic degradation that always leads to the final formation of boric acid. But boric acid has teratogenic properties in chickens. It produces the same malformations as those produced by a riboflavine (vitamin B_2) deficiency and the administration of riboflavine prevents these toxic effects. In man the chronic utilization of boron derivatives results in cases of borism (dry skin, cutaneous eruptions, and gastric troubles) tumors by Boron Neutron [45].



Diazaborine
active against malaria



Oxazaborolidine
inhibitor of Streptococcus mutans



Boronic chalcone
antitumour agent

Figure 26: Boron-containing molecules with a biological activity.

A classical illustration of tetra substituted isosteres involves replacement of the quaternary ammonium group in case of cholinergic agonists with the phosphonium and arsonium analogues. In this study, it was observed that such replacements resulted in less potent analogues with greater toxicity. Activity was found to decrease 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 [46].

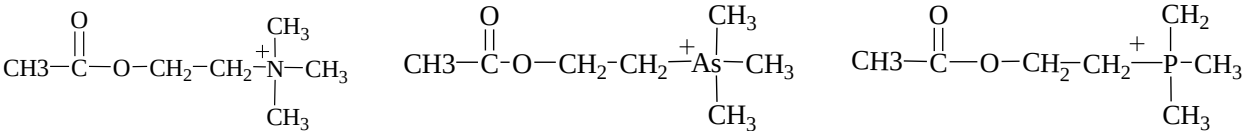


Figure 27: Cholinergic agonists.

CONCLUSION

- The bioisosteric replacements have significant value in lead optimization process. Examples of classical and non classical bioisosteric replacements in the hit to lead optimization process provide building blocks for the synthesis of frequently used bioisosteres.
- In drug design, the purpose of exchanging one bioisostere for another is to enhance the desired biological or physical properties of a compound without making significant changes in chemical structure.
- Bioisosteric replacement is not simple replacement with another isostere but we must analyse them by structural, solubility and electronic parameters to obtain molecules having similar biological activity.

REFERENCES

1. Leon S, Alan H. Comprehensive Pharmacy Review, 6th Ed., Mutnick, 264
2. Allen HS. Molecular Frequency and Molecular Number. London, Vol. parts I–III 1918.
3. Langmuir I. Isomorphism, isosterism and covalence. J Am Chem Soc 1919; 41:1543-59.
4. Grimm HG. Structure and size of the non-metallic hybrids, Z. Electrochem, 1925; 31: 474 – 80.
5. Grim HG. On the systematic arrangement of chemical compounds from the perspective of research on atomic composition; and on some challenges in experimental chemistry, Naturwissen Schaften, 1928; 17:557-64.
6. Erlenmeyer H, Leo M. Pseudoatom, Helv Chim Acta, 1932; 15:1171 – 86.
7. Friedman HL. Influence of isosteric replacements upon biological activity, NASNRS, 1951; 206:295 – 358.
8. Gelmboldt VO, Ennan AA, Ganin EV, Simonov YA, Fonari MS, Botoshansky MM. Synthesis and structure of fluorosilicic acid compounds with 4-aminobenzoic acid and with 4-aminobenzenesulfonamide: the role of H-bonding in crystal structure formation. J Fluorine Chem 2004; 125:1951 – 57.
9. McLeod JW, Mayr-Harting A, Walker N. Observations on the bactericidal and bacteriostatic actions of p–aminobenzenesulfonamide and p-hydroxylamino-benzenesulfonamide, with special reference to their suppression by p -aminobenzoic acid. Br J Exp Pathol 1944; 25:27 – 37.
10. Thornber CW. Isosterism and molecular modification in drug design. Chem Soc Rev 1957; 8:563 – 80.
11. Patani GA, LaVoie EJ. Bioisosterism: a rational approach in drug design. Chem Rev 1996; 96(8):3147 – 76.
12. Chen X, Wang W. Annual Reports in Medicinal Chemistry, 2003; 38:333.
13. Pauling L. In the Nature of the Chemical Bond, 2nd Ed. New York, Cornell University Press, 1940; 189.
14. Elguero J, Marzin C, Katritzky AR, Linda P. Advances in Heterocyclic Chemistry, Katritzky AR. Boulton AJ Eds., New York, Academic Press Inc, 1976;Suppl. 1.
15. Fusco T, Chiavarelli S, Palazzo G, Bovet D. Research on Synthetic Curare. Part II Arylalkyl Derivatives with Two Quaternary Ammonium Functional Groups. Gazz Chim Ital, 1948;78:951.

16. Kelley JL, Mclean EW, Ferris RM, Howard JL, Benzodiazepine Receptor Binding Activity of 6, 9-Disubstituted Purines. J Med Chem 1989; 32:1020-24.
17. Atwal KS, Rovnyak GC, Kimball DS, Floyd DM, Moreland S, Swanson BN et al. Dihydropyrimidine Calcium Channel Blockers 2, 3-Substituted-4-aryl-1, 4 dihydro-6-methyl-5- pyrimidinecarboxylic Acid Esters as Potent Mimics of Dihydropyrimidines. J Med Chem 1990;33:2629-35.
18. Hine J. In Physical Organic Chemistry, J. Hine Ed. New York, Mc Graw Hill Book Co Inc: 1962; 28.
19. Rogers EF, Brown HD, Rasmussen IM, Heal RE. The Structure and Toxicity of DDT Insecticides. J Am Chem Soc 1953; 75:2991-99.
20. Wrobel J, Millen J, Sredy J, Dietrich A, Kelly JM, Gorham BJ et al. Orally Active Aldolase Reductase Inhibitors Derived from Bioisosteric Substitutions on Tolrestat. J Med Chem 1989; 32:2493-2500.
21. Walsh DA, Franzyshen SK, Yanni JM; Synthesis and Antiallergy Activity of 4-(Diarylhydroxymethyl)-1-[3-(aryloxy)propyl] piperidines and Structurally Related Compounds. J Med Chem 1989;32:105-18.
22. Counsell RE, Klimstra PD, Nysted LN, Ranney RE. Hypocholesterolemic Agents V. Isomeric Azacholesterols. J Med Chem, 1965; 8:45-8.
23. Erlenmeyer H, Willi E. Zusammenhange zwischen Konstitution und Wirkung bei Pyrazolon derivaten, Helv Chim Acta, 1935;18:740 – 43.
24. Saeed A, Mcmillen JB, Wolkowicz PE, Brouillette WJ. 3-Amino-5, 5-dimethyl hexenoic Acid synthesis, Resolution and Effects on Carnitine Acyl transferase. J Med Chem, 1994;37:3247-51.
25. Lombaert S. De, Stamford LB, Blanchard L, Tan J, Hoyer D, Diefenbacher CG et al. Potent non-peptidic dual inhibitors of endothelin converting enzyme and neutral endopeptidase 2411. Bioorg Med Chem Lett, 1997;7:1059–64.
26. Biava M, Porretta GC, Cappelli A, Vomero S, Manetti F, Botta M et al. 1, 5- Diarylpyrrole-3-acetic acids and esters as novel classes of potent and highly selective cyclooxygenase-2 inhibitors. J Med Chem 2005;48 (9):3428 – 32 .
27. Garvey DS, Wasicak JT, Decker MW, Brioni JD. Novel isoxazoles which interact with brain cholinergics channel receptors have intrinsic cognitive enhancing and anxiolytic activities. J Med Chem 1994; 37(8):1055-49.

28. Garvey DS, Wasicak JT, Elliott RL, Lebold SA, Hettinger AM. Ligands for brain cholinergics channel receptors: synthesis and in vitro characterization of novel isoxazoles and isothiazoles as bioisosteric replacements for the pyridine ring in nicotine. J Med Chem 1994; 37(26):4455-63.
29. Olesen PH, Tonder JE, Hansen JB, Hansen HC, Rimvall K. Bioisosteric replacement strategy for the synthesis of 1-azacyclic compounds with high affinity for the central nicotinic cholinergic receptors. Bioorg Med Chem, 2000;8(6):1443 – 50.
30. Korolkovas A. Essentials of Medicinal Chemistry, 2nd Ed. NY, EUA, Wiley, 1988; 1015.
31. Korolkovas A. Essentials of Medicinal Chemistry, 2nd Ed. NY, EUA, Wiley, 1988; 80.
32. Shapiro G, Floersheim P, Booelsterli J, Amstutz R, Bolliger G, Gammenthaler H et al. Muscarinic activity of the thiolactone, lactam, lactol and thiolactol analogues of pilocarpine and a hypothetical model for the binding of agonists to the M_1 receptor. J Med Chem 1992;35:15-27.
33. Thompkins L, Lee KH. Comparison of analgesic effects of isosteric variations of salicylic acid and aspirin (acetylsalicylic acid), J Pharm Sci, 1975; 64:760-63.
34. Patani GA, LaVoie EJ. Bioisosterism: A Rational Approach in Drug Design. Chem Rev 1996; 96:3147-76.
35. Orr FG, Musso DL, Boswell GE, Kelley JL, Joyner SS, Davis ST et al. Inhibition of Uridine Phosphorylase: Synthesis and Structure-Activity Relationships of Aryl-Substituted 5-Benzyluracils and 1-[(2-Hydroxyethoxy)- methyl]-5-benzyluracils. J Med Chem 1995;38:3850-56.
36. Kouni MH, Kouni MM, Naguib FMN. Differences in Activities and Substrate Specificity of Human and Murine Pyrimidine Nucleoside Phosphorylases: Implications for Chemotherapy with 5-Fluoropyrimidines. Cancer Res, 1993; 53:3687-93.
37. Wilhelm M. The chemistry of polycyclic psycho-active drugs: serendipity or systematic investigation, Pharm J, 1975; 214:414-6.
38. Yoshimura H, Kikuchi K, Hibi S, Tagami K, Satoh T, Yamauchi T et al. Discovery of novel and potent retinoic acid receptor alpha agonists: Syntheses and evaluation of benzofuranyl-pyrrole and benzothiophenyl- pyrrole. J Med Chem, 2000;43:2929 – 37.
39. Larsen AA, Lish PM. A new bioisostere: alkyl Sulfonamido-phenethonalamines, Nature, 1964; 203:1283-5.
40. Chenoweth MB, McCarthy LP. On the mechanism of the pharmacophoric effect of halogenations. Pharmacol Rev, 1963; 15:673 – 707.

41. Fischer H, Terlinden R, Lohr JP, Romer AA. Novel biologically active seleno organic compound. VIII. Biotransformation of ebselen. Xenobiotica, 1988; 18:1347-59.
42. Parnham MJ, Graf E. Seleno-organic compounds and the therapy of hydroperoxide-linked pathological conditions. Biochem Pharmacol, 1987; 36:3095-102.
43. Jabbour A, Steinberg D, Dembitsky VM, Moussaieff A, Zaks B, Srebnik M. Synthesis and evaluation of oxazaborolidines for antibacterial activity against streptococcus mutans. J Med Chem 2004;47 (10):2409 – 10.
44. Kumar SK, Hager E, Pettit C, Gurulingappa H, Davidson NE, Khan SR. Design, synthesis and evaluation of novel boronicchalcone derivatives as antitumor agents. J Med Chem 2003; 14:2813 – 5.
45. Browning E. Toxicity of industrial metals, 2nd Ed. New York, Appleton-century-Crofts, 1968; 90-97.
46. Hunt R, Renshaw RR. On some effects of Arsonium, stibonium, Phosphonium and Sulphonium compounds on the autonomic nervous system. J Pharmacol Exp Ther 1925; 25:315-55.