Input of Isosteric and Bioisosteric Approach in Drug Design

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Summary: Bioisosterism has unique relevance in the field of pharmaceutical sciences and is conducted to curtail side effects or to alter the biological activity of a lead molecule. In the biomedical field, the aim of exchanging one bioisostere for another is to boost the preferred pharmacological, biological or physical qualities of a substance without making substantial changes in the chemical skeleton. A vital feature of medicinal chemistry has been to ascertain a correlation between chemical skeleton of drugs and their physicochemical properties and in turn such properties modify the pharmacological properties and consequently the therapeutic response of drugs. Drugs with analogous structures often are liable to have comparable pharmacological properties. The present review highlights the vital role of bioisosterism as a special approach of structural modification and optimization process in drug design programme with clear 2D and 3D structural drawings.

Key words: Isosterism; Bioisosterism; SAR; Drug Design; 3D Chemical Structures.

Introduction

Overview on bioisosterism

Isosterism or bioisosterism is one of the approaches most frequently used in the design of new molecules [1]. In a broad sense, bioisosteres may be identified as any two compounds or structures that show similar biological activities and share analogous topology, volume, electronic arrangements or physicochemical properties [2-4]. Bioisosterism is a well established technique in modern drug design, extensively studied for modification of drug target selectivity, bioactivity, efficacy, potency, membrane permeability, biotransformation pathways and toxicity profile [4-6].The isosteric replacement approach is a practical and, possibly, better substitutes to recent lead optimization techniques [7]. This approach is now commonly used in advance drug design to optimize lead compound by rational molecular modification in order to improve its pharmacokinetic i.e. absorption, distribution, metabolism and excretion (ADME) or pharmacodynamic i.e. receptor, enzyme or channel level behavior [8]. Recently we have reported the anti-inflammatory, anti-nociceptive and anti-pyretic activity of bio-isosterically synthesized nitrogen containing derivatives of salicyl alcohol with no propensity of gastric ulceration as compared to aspirin [9-10]. These derivatives include, [4-(2-hydroxybenzyl) morpholin-4-ium chloride]; [1,4-bis (2-hydroxybenzyl) Piperazine-1,4-diium chloride]; [1-(2-hydroxybenzyl)piperidinium chloride] and [4-carbamoyl-1-(2-hydroxybenzyl)piperidinium chloride] (Fig. 35).

Overview on New Drug Development Programme

In a typical new drug development programme, distinct phases are followed in order to develop a new drug of desirable properties. These phases include target identification, target validation, lead identification, lead optimization, pre-clinical and clinical development with high cost [11-12]. For this purpose, several collaborative approaches are used including structure based drug design, mechanism based drug design, molecular or cellular biology, medicinal chemistry, in-vivo pharmacology, toxicology, bioinformatics, genomics, proteomics, high throughput screening (HTS), combinatorial chemistry etc. Structure based designing is the most reliable and established practice for "lead compound" than others and is involved explication of three dimensional (3D) structure of the target protein or macromolecule inside or outside the cell (receptors, enzymes, ion channels, DNA, RNA etc) [13].

Currently most of the pharmaceuticals including drugs in the market are synthetic in origin, produced in bulk with adequate purity. There is a notable difference between the current drugs and those of past with respect to source. A century before, human beings were depended almost utterly on natural products to obtain the organic molecules. In the 1920, synthetic drugs began to emerge at a conspicuously faster rate, mainly due to American chemical industry persuaded by World War 1. The modern era of synthetic pharmaceuticals is considered to be started after arrival of sulfonamide chemotherapeutic drugs in the early 1930.

Structure Activity Relationship, Lead Compound Optimization and Bioisosterism

It is a well recognized position of medicinal chemistry that there can exist a relation between the chemical structure of a compound and its biological activities, characterized as structure activity relationship (SAR) [14-15]. This study of SAR is used in drug design and in turn for new potential drug candidate [16]. A lead compound is a leading drug candidate having potential to be developed as a new drug. Although a lead compound is selected as a leading candidate yet a lead compound may be associated with undesirable behavior in any pharmacokinetic or pharmacodynamic property [17]. Further structural alteration may be conducted to get desirable properties of the lead compound [8]. If a drug exhibits very poor absorption rate after oral administration, chemical modification might be indicated to improve systemic bioavailability. Hence lead optimization is required to produce targeted, clinically safe, effective, potent and commercially attractive new drug.

Why Lead Modification is Necessary?

Lead compound modification is necessary in order to get the answers of the following questions [8, 18].

- How to minimize lead compound toxicity?
- How to modify the existing biological activity of lead compound?
- How to alter biotransformation?
- How to maximize bioavailability?

Currently the concept of bioisosterism is used as a special process of molecular modification to optimize the lead molecule.

A number of articles have been published but there is no 3D chemical structures illustration. In the current review, a chronological order study of bioisosterism and crucial role of isosterism or bioisostreism has been investigated with clear 2D and 3D chemical structures illustration of drugs of therapeutic importance.

Chronology of Bioisosterism

Allen (1918)----------Molecular number

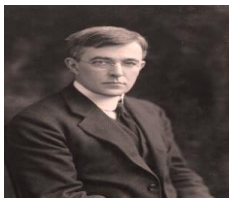
Allen concept of molecular number of compound was based on atomic number [19] as depicted in Table-1 with example. Two compounds having same molecular numbers exhibit some similarities with respect to physical properties.

Table-1: Allen concept of molecular number.

	$N= aN_1+bN_{2+}$ zNi	
Where; N	**Molecular number of compounds**	
N_1+N_2…… Ni	**Respective atomic number of each element of compound**	
a, b, c, ------z	**Number of atoms of each element in a compound**	
	Sodium and ammonium cations comparison as example	
	Sodium ion (Na^+)	**Ammonium ion (NH_4^+)**
Atomic number	**11**	**7+ (4x1) =11**
Molecular number (N)	**11**	**11**

Molecular number of ammonium ion can be calculated as 11 which is same as that of sodium cation.

Irving Langmuir (1919)-------- Concept of isosterism



Irving Langmuir

The term "isosteres" was defined for the first time (1919) by Langmuir in terms of isoelectronic or isosteric concept [6, 20] and thus emerged the concept of isosterism . According to this concept, isosteres are those atoms or groups of atoms or molecules or compounds (organic or inorganic) that have the same arrangement and/or number of electrons that is isoelectronic or isosteric. Irving Langmuir studied comparatively different molecules like N_3^- and NCO^- or CO and N_2 and found that these compounds have analogous physical properties and thus characterized as different groups of isosteres as shown in Table-2. This concept was deduced from the octet theory to explain the number and arrangement of electrons in atoms, ions or molecules and then their correlation with physicochemical

properties. At that time this concept was used to portray the resemblance of ions or molecules like O^{-2} x F^- in terms of the same number of valance electrons and same number of atoms and prediction of similar physicochemical properties for isosteres having same net charge. This concept of atoms, ions or molecules similarities with respect to physical or chemical properties was mainly focused on

- Same arrangement and/or number of electrons i.e. same satiric effect
- Same number of atoms
  e.g. CO_2 and N_2O have been reported as reversible anaesthetics to the slime mould (*physarum polycephalum*).

Table-2: Examples of Langmuir isosteric groups.

S.No (Group)	Langmuir Isosteres
1	He, H^-, Li^+
2.	F^-, O^{2-}, Ne, Na^+, Al^{3+}, Mg^{2+}
3.	S^{2-}, Cl-, Ar, K^+, Ca^{2+}
4.	Zn^{2+}, Cu^{2-}
↓	↓
8.	CO, CN^-, N_2,
9.	NH_4^+, CH_4
10.	CO_2, N_2O, $^-N{=}N{=}N/(N^{3-})$, $N{=}C{=}O^-/(CNO^-)$
20.	CrO_4^{2-}, MnO^-_4
21.	SeO_4^{2-}, AsO_4^{3-}

Grimm's Hydride Displacement Law (1925-29)------- Isoelectronic pseudoatom concept

Grimm formulated an empirical rule to describe isoelectronic pseudoatom concept [4, 21]. According to this law "Atoms any where up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in such a manner that the resulting combinations behave like pseudo atoms, which are similar to elements in the groups one to four places respectively, to their right." According to this, addition of hydride (Hydrogen atom with a pair of electron) gives cumulative properties of the atom of subsequently highest atomic number. This addition exhibiting that any atom in the periodic table groups of 4A, 5A, 6A, and 7A becomes an isoelectronic pseudoatom after addition of hydride as depicted in Table-3. According to Grimm concept, an isoelectronic correlation can exist in each vertical column of Table-3, would signify a group of isosteres.

Table-3: Grimm's hydride displacement law.

Groups					
4A	5A	6A	7A	8A	
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^+

Erlenmeyer H (1932)-- Isosterism Concept Extension

Erlenmeyer further extended the concept of isosterism [22] and reintroduced the term isosteres as atoms/elements, ions or molecules which exhibit similarity with respect to peripheral layers of electrons that is same number of electrons at the valance or peripheral level. This concept can be extended to

- Complete elements of any group of periodic table as shown in Table-4.
- Pseudoatoms (e.g. SCN, CN, Cl)
- Rings electronically equivalent e.g. –S– and –CH=CH– as in thiophene and benzene. Same is the case with furan and thiophene and further pyridine and benzene (Fig.1). These ring equivalents have been shown to possess similarity in important physicochemical properties.

Table-4: Erlenmeyer Isosteres based on number of valance (peripheral) electrons.

Number of peripheral/valance electrons				
4	5	6	7	8
C	P	S	Cl	Ne
Si	As	O	Br	Ar
N+	Sb	Se	I	ClH
P+	N	Te	SH	BrH
S+	CH	PH	PH	IH
As+	SiH	NH	SH	SH_2
Sb+		CH_2	NH_2	PH_3

Friedman H. L. (1951)----Concept of Bioisosterism

After characterization of a lead compound which possesses promising therapeutic activity yet in many cases, it has been founded to be associated with certain undesirable physicochemical or biological activities. In these situations, medicinal chemist logically modify the structure of lead compound to get genially related compounds (structural analogues) of desirable properties. Bioisosterism is one of the techniques to modify the structure to optimize the lead compound. The pervasive applications of isosterism to biological system in search of therapeutically useful drugs raised the concept of bioisosterism. In 1951 Friedman coined the term of bioisosterism [23] and identified bioisosteres as those compounds or molecules or atoms which fulfill the criterion of isosterism, in most cases structural analogues and further possess identical biological properties which may interact to activate (agonism) or inhibit (antagonism) a particular molecule (receptor) in the biological system that depicts a regulatory function. This concept comprised agonist (activator) or antagonist (inhibitor) actions.

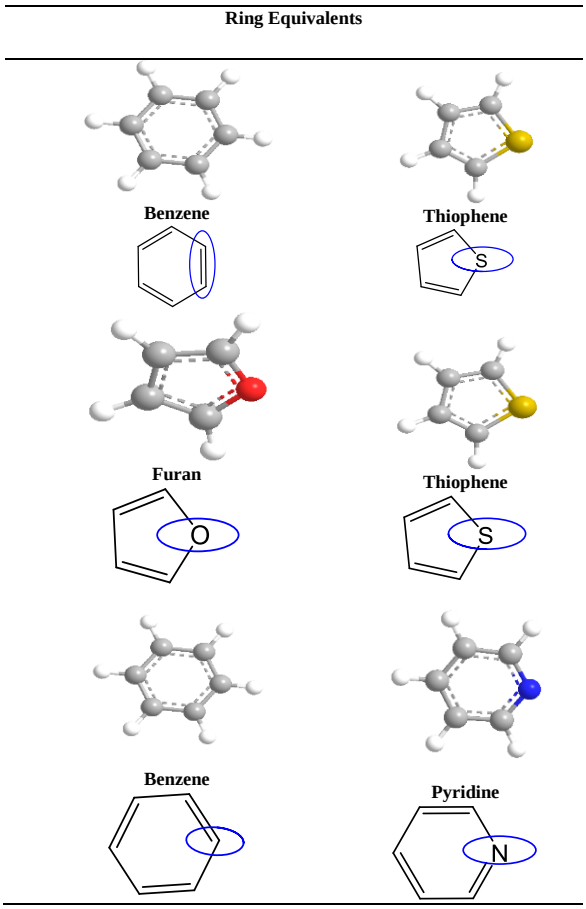


Fig. 1: Illustration of ring equivalents.

Thronber C.W. (1979)----------Bioiosterism concept further expansion

The concept of bioiosterism further expanded by Thronber [24] and characterized bioisosteres as those molecules or subunits or groups which possess broadly similar biological activities and identified by identical physical or chemical properties e.g diclofenac sodim and diclofenac potassium salts.

Burger A. (1991) -----Bioiosterism further extension

Alfred Burger

Although similarities in molecules with respect to shape (molecular topology), electronic arrangement, isoelectronic or non-isoelectronic (electroforms) are still debatable issues of bioisosterism in medicinal chemistry yet it has been reported that such molecules play a vital role in the target (receptor, channel or enzyme) identification and subsequent binding to the target molecule to produce a pharmacological action either through agonistic or antagonistic mechanisms. Currently Alfred Burger further broadened the biosiosterism concept of Friedman and defined bioisosteres as "Compounds or groups that possess near equal molecular shapes and volumes, approximately the same distribution of electrons and which exhibits similar properties" i.e. the concept of molecular topology and electroforms.

How and why isosteric or bioisosteric replacements----------Criteria

It has been reported that a number of substances, both of synthetic and natural origins, exhibit bioisosteric relationship [5] including essential amino acids, nitrogenous bases (purines, pyrimidines), xanthine derivatives, neueurotransmitters, salicylic and anthranilic acid etc. The major dilemma in the notion of bioisosterism is the recognition of bioisosteric replacement fragments. Some bioisosteric conventions have been traditionally recognized since long ago. The different parameters which are to be considered in bioisosteric replacements include size, shape (hybridization, bond angles, bond length), electronic arrangement (inductive effect, mesomeric effect, polarizability, charge, dipole), nature of atoms and number of atoms, liphophilicity, hydrophilicity, PKa, inter or intramolecular hydrogen bonding and chemical reactivity (biotransformation etc). All these factors affect the ligand-receptor interactions which in turn affect the desired pharmacological response in terms of variation in pharmacokinetic and pharmacodynamic properties of ligand [4,25]. Bioisosteric replacement is one of the strategies frequently used in drug design which influence more or less the above mentioned parameters of lead molecules. Presently this approach is utilized as a special process of molecular modification to optimize the lead molecule.

Classification of Bioisosteres or Bioisosterism

Bioisosteres have been classified by Alfred Burger into two main classes that is classical and non-classical, based on steric and electronic considerations [26]. Each of these major classes has been further categorized as shown in Fig. 2.

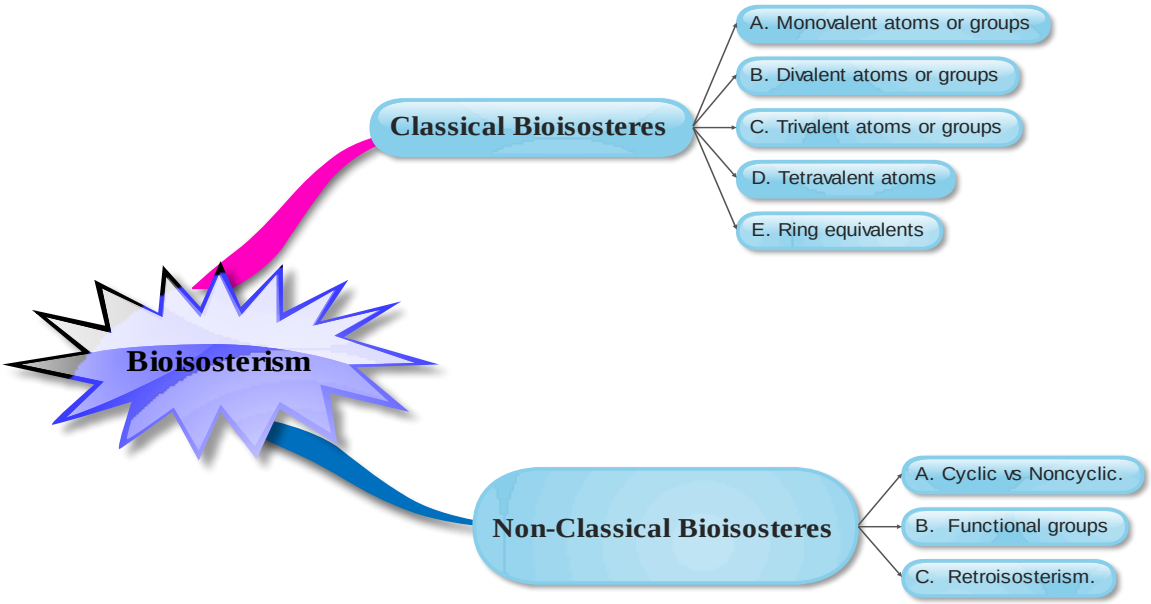


Fig. 2: Classification of bioisosterism.

Classical bioisosteres:

Two classical isostere definitions i.e. Grimm's Hydride Displacement Law and Erlenmeyer concepts regarding isosteres, delineate a wide number of groups or atoms displacements, generally identified as classical bioisosteres. These bioisosteres have been further conventionally categorized as depicted in Fig. 2 and Fig. 3. A number of lead compounds and drugs have been developed based on the concept of classical bioisosterism (Fig. 4-35).

Non-classical bioisosteres

Such bioisosters do not fulfill the criterion of electronic or steric rules. In general, they don't have identical number of atoms as the moiety or group for which they are utilized as bioisosteric replacements but most commonly possess similar biological or pharmacological activities including agonistic and antagonistic. Such bioisosteres may exhibit retention of pharmacological properties by virtue of analogy existing in their conformational or spatial arrangement, electronic arrangement or any other physicochemical property. These are also further divided into different groups as shown in Fig. 2. The concept of non-classical bioisosterism have also been reported for a number of compounds and drugs of therapeutic importance including anticancer, antibacterial, antipsychotic, analgesic and anti-inflammatory etc (Fig. 4-35).

Input of Isosterism or bioisosterism in pharmaceutical field

In the current study, we have created 2D and 3D models for well known bioisosterically developed, therapeutically important drugs and presented their pharmacophores and other atoms of ligands that are considered vital for interaction with the biological system to produce a pharmacological response (Fig.4-35). The 3D approach is very demanding computationally. Molecular frameworks which are able of providing useful ligands for more than one type of receptor or enzyme target can be designed by judicious structural modifications. Classical as well as non-classiacl bioisosterism finds wide spread applications in different areas of pharmaceutical sciences [27] especially pharmacotherapy including cytotoxic drugs, anti-inflammatory, analgesic, anesthetic, anti-gout, antihypertensive, anti-asthmatics and antiulcer etc (Fig. 4-35) [5,28]. Bioisosterism is believed a module of the scale of quantitative structure activity relationship (QSAR). It is the strategy how the physicochemical properties of a series of compounds affect their biological activity. Quantitative values are measured or calculated for the physiochemical properties and then these are linked to biological or pharmacological activities using a mathematical equation.

Pharmacological activity = *f* (physiochemical properties and / or structural properties)

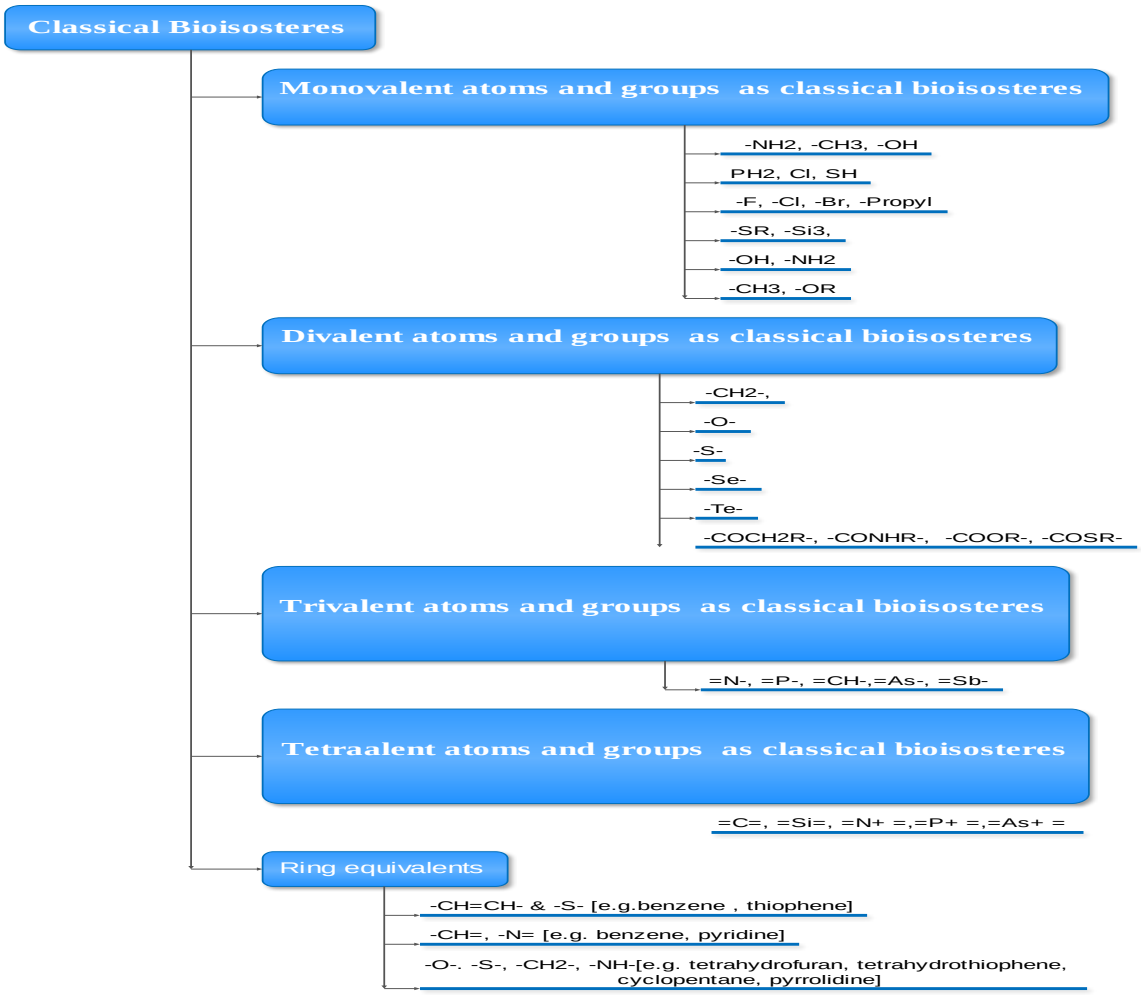


Fig. 3: Classification of classical bioisosteres.

A number of drugs have been designed based on bioisosterism concept, as a special process of structure activity relationship and still currently this concept is successfully exploited in drug development programme [18]. Some of the notable examples with comments are given from Fig. 4 to 35. In the category of non-classical bioisosteric replacements (cyclic versus non-cyclic) includes bioisosteric replacements in which cyclic vs non cyclic transformations occur and analogy have been observed either sterically or electronically between cyclic and non-cyclic moiety. This category has been reported for a number of drugs. A classical example of non-classic ring opening is that of designing of trans-diethylstilbestrol [29].The strategy of noncyclic vs cyclic have also been reported for the development of lidocaine, a useful anesthetic, from mepivacaine. The applications of non-classical bioisosterism have also been reported in a number of areas of pharmacology including adrenergic and anti adrenergic drugs [28, 30-31] , several NSAID classes like aryl acetic acid derivatives [32], cetroplac, tolmetin, indomethacin, etodolac [5], antibacterial drugs [33] , antidepressant of morpholine class [34] , neuropeptide substance P antagonists (NK1 antagonists) [35], cholinergic (muscarinic type) agonists [36], GABA modulators like muscimol, thiomuscimol, isomuscimol as agonists [37-38], peptidomimetics [39], diuretics like ethacrinic acid [5] and 5-hyderoxy tryptamine (5-HT1A;1D) agonists like naratryptan and sumatryptan for acute attack of migraine [40].

From Fig.4-35 depicts comments on different bioisosteres with 2D and 3D structures of lead compounds and drugs having clinical utility. The milestone of the detection of the significance of the bioisosterism of functional groups is the finding of sulfanilamide, an active metabolite of prontosil dye, transfigured antibacterial therapy during 1934. Sulfanilamide is the structural analogue of para

amino benzoic acid (PABA) with respect to electronic, conformational and physiscochemical properties (PKa and log P). This analogy depicts that there exists a valid bioisosteric relationship between SO_2, NH_2 and COOH moieties [5]. The replacement of –COOH in GABA by tetrazole group, resulting a tetrazole bioisostere of GABA, a potent antiepileptic agent [5]. Another example of –COOH replacement by tetrazole group in lead compound i.e. EXP 7711 resulting in losartan, an important antihypertensive ARB (angiotensin receptor blocker) [41]. Bioisosteric relationship between –COOH and several other functionality have been reported as depicted in Table-7. A number of non-classical bioisosteric replacements have been reported for the hydroxyl group (Table-7). A well known example is that of bronchodilator isoprenaline (isoproterenol) in which 3-OH group replacement with other bioisosteric group like 3-CH_2OH, resulting salbutamol (albuterol), selective β-2 agonist, a well known antiasthamatic drug, by 3-$NHSO_2CH_3$, resulting soterenol and by 3-$NHCONH_2$, resulting carbuterol [42-43]. Amide group kind of bioisosterism have also been noticed specially in heterocyclic N containing compounds [28] as depicted in (Table -7).

Table-5: Halo methyl androstane-17beta-carbothionates anti-inflammatory activity.

*Anti-inflammatory activity(topical)	Compound	X	Y	Z
42	**a**	**H**	**F**	**=CH_2**
108	**b**	**F**	**F**	**=CH_2**
27	**c**	**H**	**H**	**β-CH_3**
41	**d**	**H**	**F**	**β-CH_3**

*Topical anti-inflammatory activity measurement in mice in croton oil assay with modifications.
Flucinolone acetonide= positive control; assigned a relative potency index of 100.

Comments on selected bioisosterically developed drugs and certain lead compounds

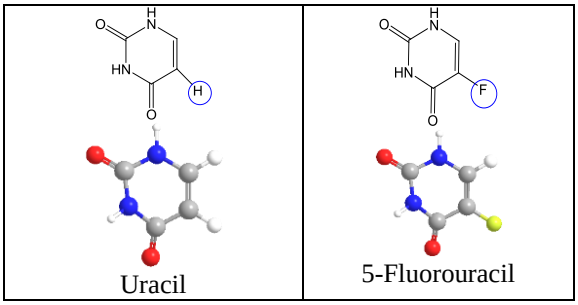


Fig. 4: H vs. F monovalent isosteric replacement.

Bioisosteric replacement of H in uracil by F gives 5-fluorouracil (anti-cancer drug) [4,44]. Replacement of hydrogen with fluorine is one of the most common monovalent isosteric replacements. Sterically H and F are quite similar with their vander walls radii being 1.2 and 1.35A^o respectively. F is most electronegative. H replacement with F alter the biological activity as fluorine exerts strong field and inductive effects. The strong inductive effect of F results in covalent linkage with thymidylate synthetase, an enzyme involved in DNA synthesis.

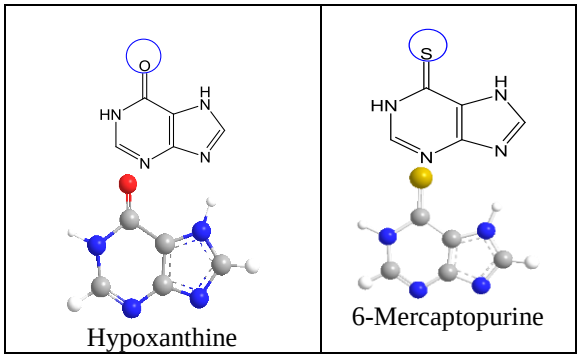


Fig. 5: Carbonyl O vs. S divalent isosteric replacement.

Bioisosteric replacement of carbonyl oxygen in hypoxanthine by S gives 6-mercaptopurine, a potent anticancer antimetabolite [4, 45].

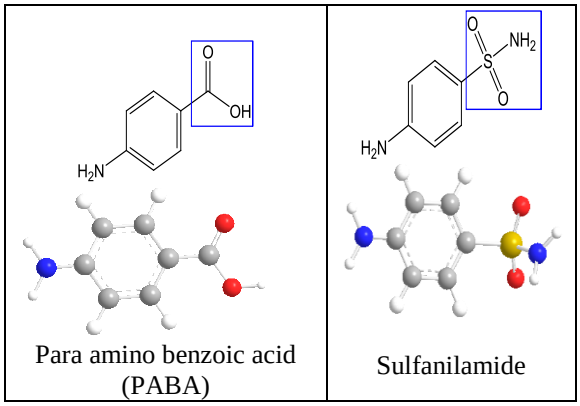


Fig. 6: Bioisosteric relationship between -COOH group and –NH_2.

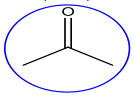
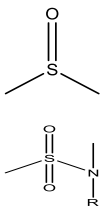
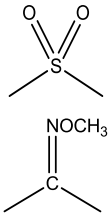
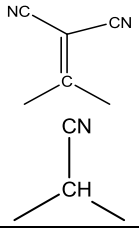
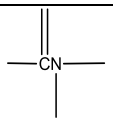
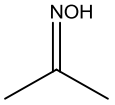
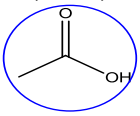
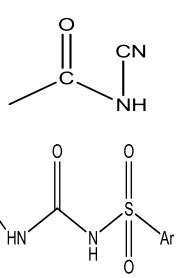
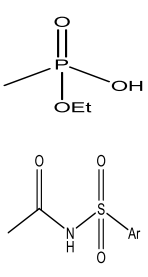
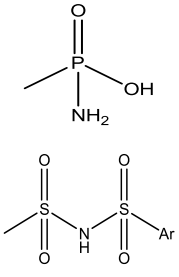
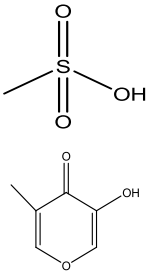
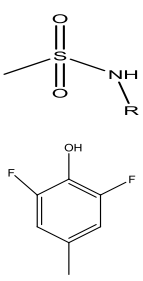
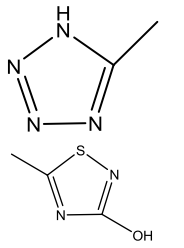
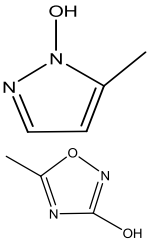
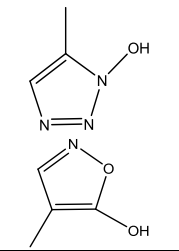
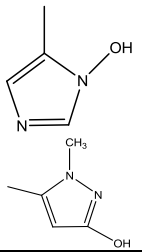
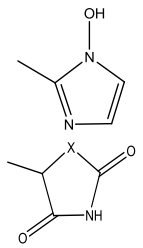
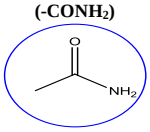
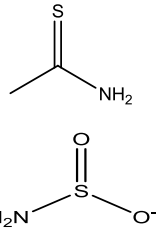
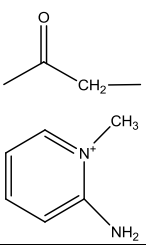
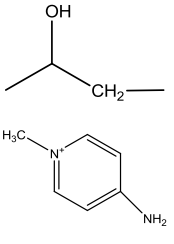
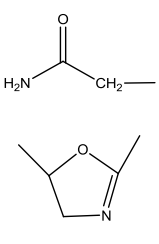
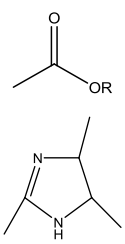
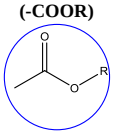
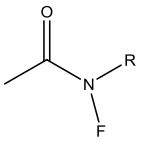
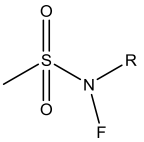
Replacement of-COOH group in para amino benzoic acid (PABA) by –SO_2NH_2 gives sulfonamide (important class of antibacterial drugs), is a typical example of non-classical bioisosterism [46].

Bioisosteric replacement of carbonyl oxygen in guanine (pyridine-imidazole ring system), a nitrogenous base by S gives 6-thioguanine (potent anti-cancer antimetabolite). This is an example of amide and thiamide groups interchange [5, 47].

Table-6: 1,4-dihydrophyridines derivatives.

Compound	Isosteric replacement group (X)	IC_{50} (nm)	Vandar waal's radii (A^o)	Potency	Comment
a	-OH	140	1.40	-OH substitution with – NH_2 resulting an analogue with equal potency	Size of the substituent, H bonding and steric factors are involved
b	$-NH_2$	160	1.50	Equal potency	
c	-SH	117	17	More potent	

Table-7: Isosteric or bioisosteric relationship among different functionalities.

Carbonyl group (-CO-)						
Carboxylic acid group (-COOH)						
						
Amide group ($-CONH_2$)						
Ester group (-COOR)						

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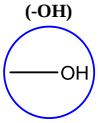
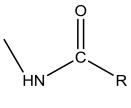
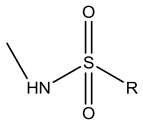
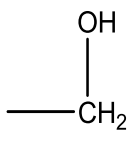
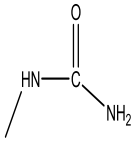
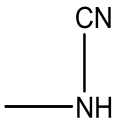
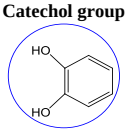
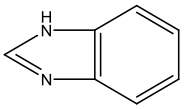
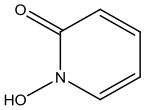
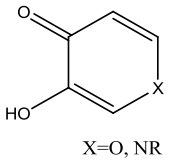
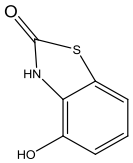
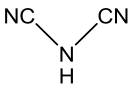
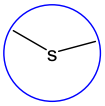
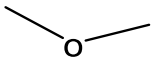
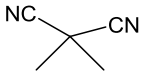
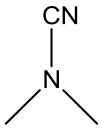
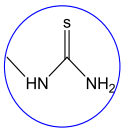
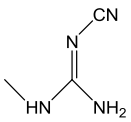
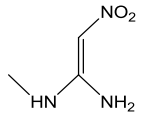
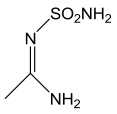
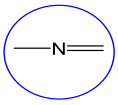
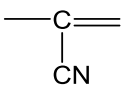
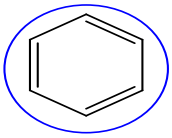
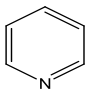
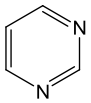
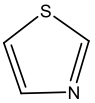
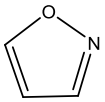
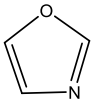
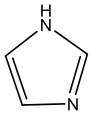
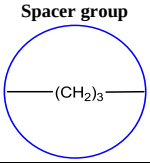
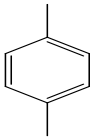
Hydroxal group (-OH)						
Catechol group						
Halogen (-X)		**CF_3**	**CN**			
Thioether						
Thiourea						
Azomethine						
Benzene						
						
Spacer group						

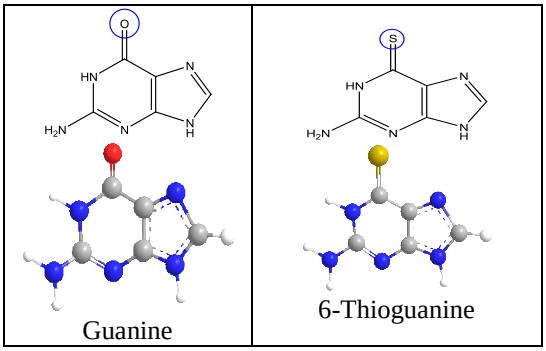


Fig. 7: Bioisosteric relationship between hydroxyl and thiol groups.

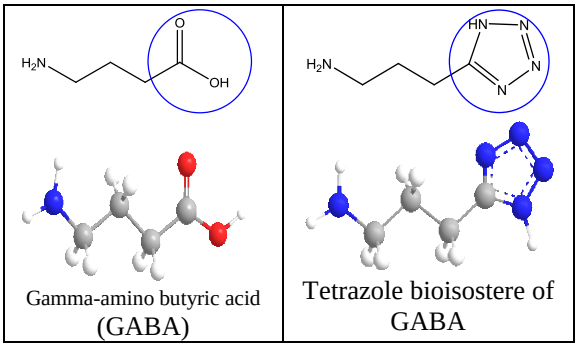


Fig. 8: Bioisosteric relationship between –COOH and tetrazole group.

The replacement of –COOH in gamma-amino butyric acid (GABA) by tetrazole group, resulting a tetrazole bioisostere of GABA, a potent antiepileptic agent [5].

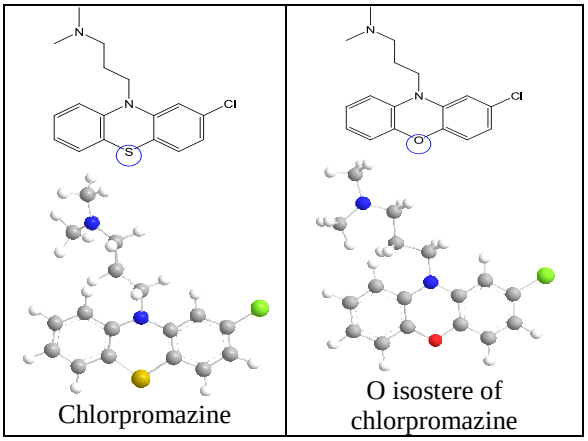


Fig. 9: Oxygen and sulfur bioisosteric replacement.

The bioisosteric replacement of oxygen by sulfur in chlorpromazine to give the oxygen isostere. This compound has 1/10 the soporific activity of the parent molecule [46].

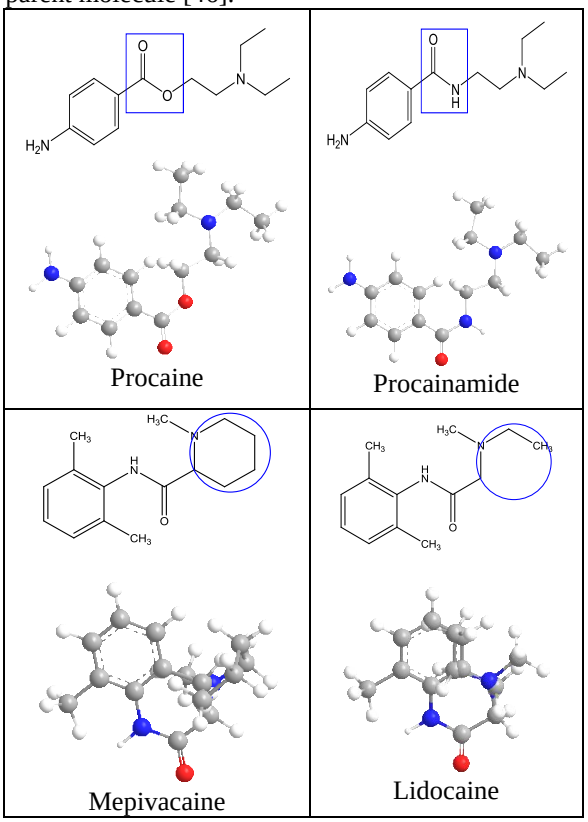


Fig. 10: Bioisosteric replacement of ester and amide functional groups.

Bioisosteric replacement of ester function in procaine (local anesthetic) by amide function gives procainamide (useful anti-arrhythmic drug). An imperative distinction between the two drugs is that the amide function, which allows for similar biological activity, is more stable chemically, can be given orally, and is not affected by the esterases that catalyze the hydrolysis of procaine. Mepivacaine and lidocaine, a well known local anesthetic, is another example [25, 46].

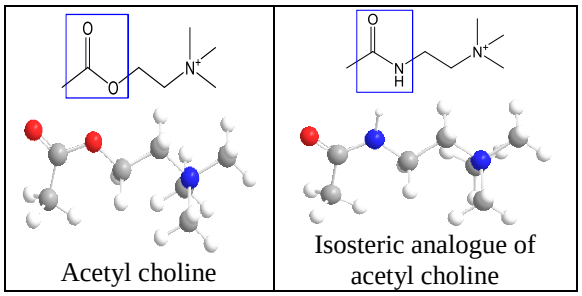


Fig. 11: Bioisosteric replacement of ester and amide functional groups.

As illustrated with bioisosteric replacement of ester function of acetyl cholne by amide function have resulted an isosteric amide analogue having no cholinergic or anticholinergic activity. This revealed that bioisosteric replacement of ester function with amide does not always produce compounds of significant pharmacological activity [46].

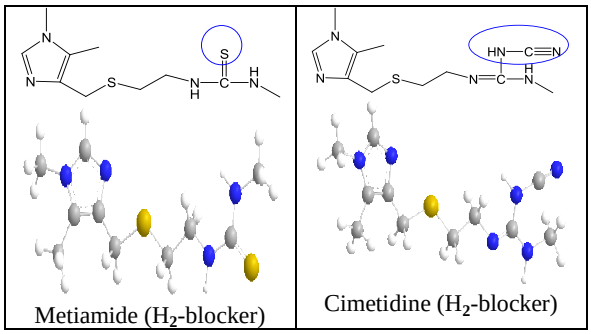


Fig. 12: Bioisosteric replacement of thiourea group with cyanoguanidine group.

Cimetidine (a prototypical H-2 blocker/anti-ulcer), can be obtained from metiamide (H-2 blocker) by bioisosteric replacement of thiourea group with cyanoguanidine group and thus eliminate granulocytopenic toxicity associated with metiamide [46].

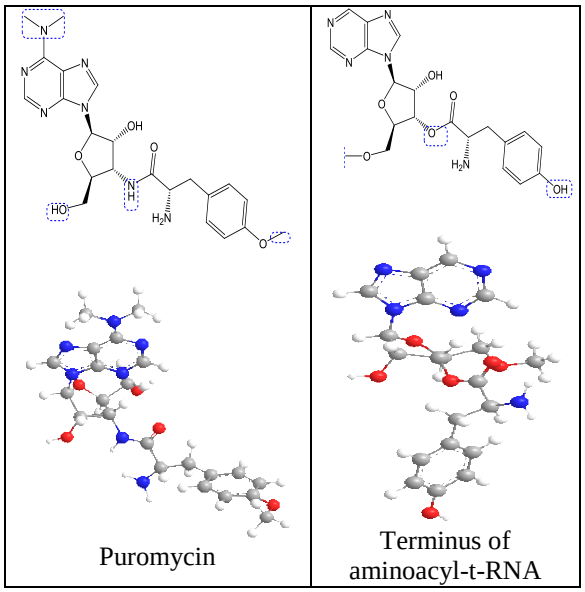


Fig. 13: Bioisosteric relationship between puromycin and aminoacyl-tRNA.

Puromycin (antibacterial/anticancer/ antitrypanosomial) is a protein synthesis inhibitor and bioisosteric analogue of aminoacyl-t-RNA. It interferes with deployment of transfer RNA [46].

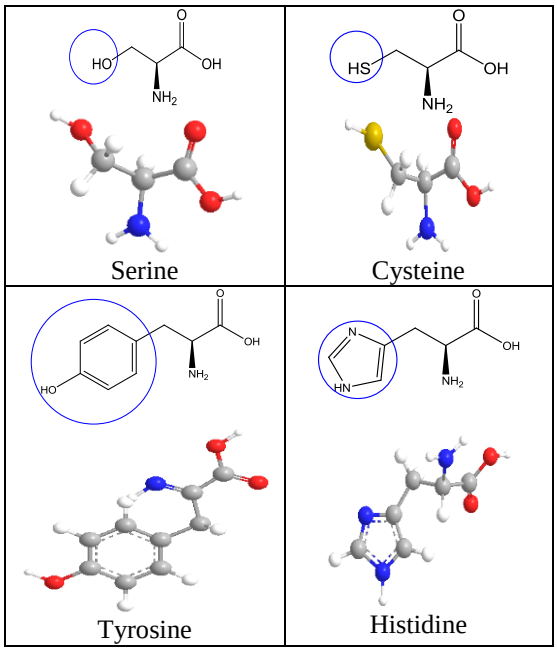


Fig. 14: Classical bioisosterism among essential amino acids.

Essential amino acids like serine and cyteine exhibit classical bioisosterism. Same is the case of tyrosine and histidine [5].

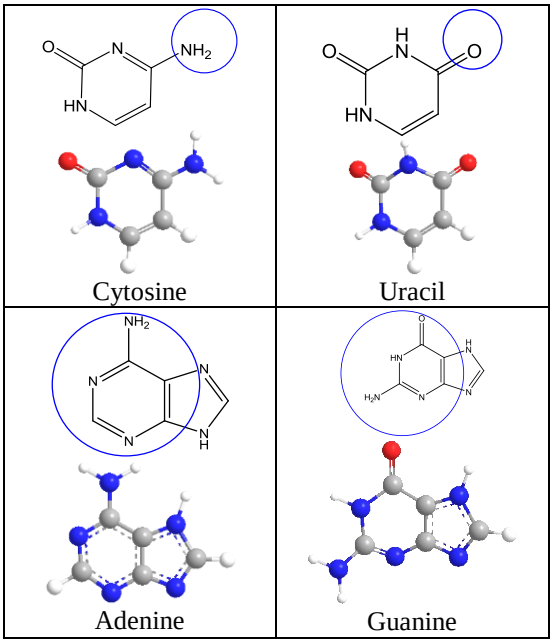


Fig. 15: Classical bioisosterism among nitrogenous bases.

Classical bioisosterism can exists among pyrimidine nitrogenous bases (single ring structure) like cytosine and uracil. Same is the case in purine nitrogenous bases (double ring structure) like adenine and guanine. [5].

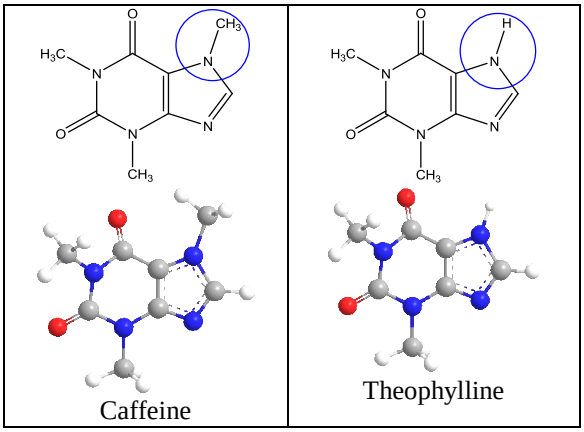


Fig. 16: Classical bioisosterism among xanthine derivatives.

Classic bioisosteric relationship have also been observed among xanthine derivatives like caffeine and theophylline [5].

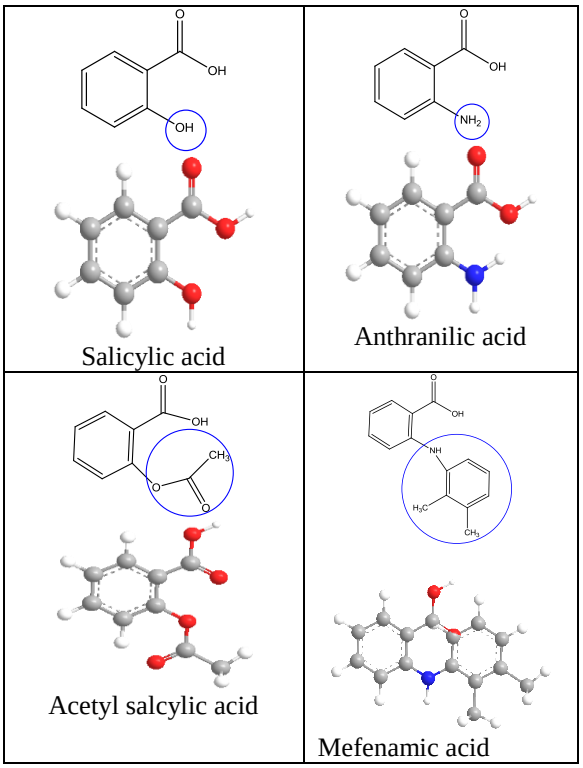


Fig. 17: Classical bioisosterism among NSAIDs.

The classical bioisosteric relationship between salicylic acid and anthranilic acid has been resulted in the generation of two important classes of non-steroidal anti-inflammatory drugs (NSAIDs) that is salicylate (acetyl salicylic acid) and mefenamic acid [5].

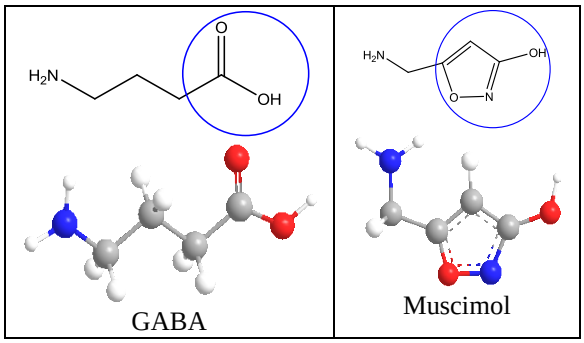


Fig. 18: Non-classic bioisosteric relationship between γ-aminobutyric acid (GABA) and muscimol.

Examples of clinically useful non-classic bioisosteric relationship has been reported between γ-aminobutyric acid (GABA) and muscimol [28].

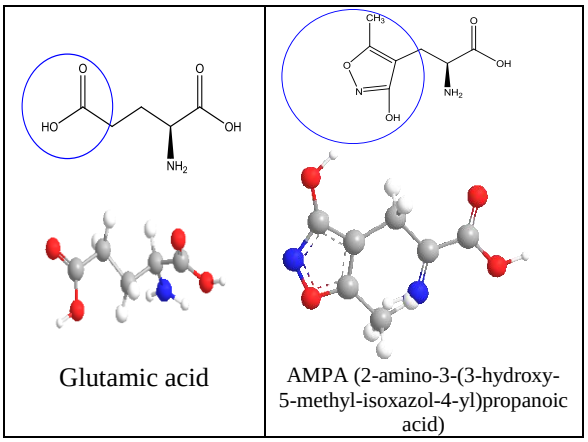


Fig. 19: Non-classic bioisosteric relationship between glutamate and AMPA.

Non-classic bioisosteric relationship can also exist in neurotransmitters like glutamate and AMPA (2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid) [5].

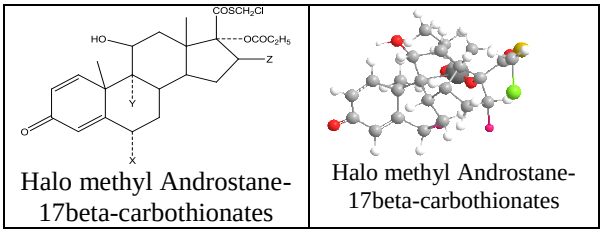


Fig. 20: Bioisosteric relationship of H and F in halo methyl androstane-17beta-carbothionates for anti-inflammatory activity.

As depicted in Table-5, replacement of H by more electronegative F, resulted in enhanced topical anti-inflammatory activity of compound **b** as tested in croton oil assay with modifications. This table shows halo methyl androstane-17beta-carbothionates anti-inflammatory activity [28].

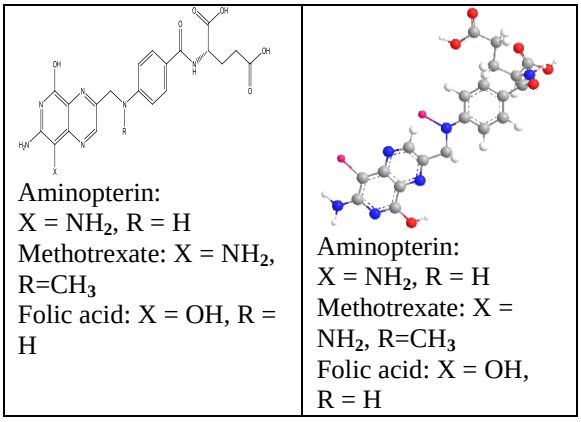


Fig. 21: Isosteric monovalent replacement of hydroxyl group and amino group.

The isosteric univalent replacement of hydroxal group by amino group can be illustrated with 4-amino-4-deoxyderivative (aminopterin), its N10- and its N10-Methyl derivative (methotrexate) and folic acid. In such case, pharmacological activity is changed, as –NH2 and -OH functional groups having similar spatial arrangement, steric size and the capacity to act as either H bond donors or acceptors, probably responsible for their successful use as bioisosteres [47].

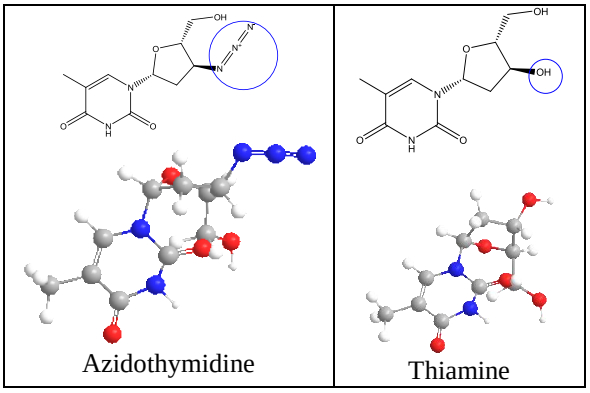


Fig. 22: Bioisosterism for azidothymidine.

Azidothymidine/azidodine (AZT) is a well known anti-HIV drug, obtained by isosteric replacement of –OH in nucleoside thiamine by N3, just like recently reported pyridazinylthioacetamide (anti-HIV) utilizing the bioisosterism strategy [48].

Bioisosteric replacements in which cyclic vs. non cyclic transformations occur and analogy have been observed either sterically or electronically between cyclic and non cyclic moiety. A classical example of non-classic ring opening is that of designing of trans-diethylstilbestrol [29]. This design is based on non-cycling of rings (B and C) of estradiol with special emphasis on configuration that is superior estrogenic activity with diastereoisomer E, less with diastereoisomer Z and furthermore, reduced activity with dihydrogenated compound. The said configuration is mainly depending upon central bond orientation in diethyl stilbesterol.

Schann and coworkers [49] have been conducted a structural modification investigation on a lead compound named rilmenidine [**a**], an analogue of clonidine [**b**] (anti-hypertensive, α-2 agonist). The replacement of O atom in the oxazoline ring of rilmenidin [**a**] by CH2 group resulted in a pyrrolidine derivative [**c**] and subsequent replacement of H at C-4 and C-5 by CH3 group resulting the cis/tans 4, 5-dimethyl derivatives [**d**].The derivative so obtained possesses affinity for imidazoline receptor (I-1R) and α-2 adrenoceptor comparable to rilmenidine (lead compound).

A well known example of non-classical bioisosteric replacement have been reported for the hydroxyl group as shown in case of bronchodilator isoprenaline (isoproterenol) in which 3-OH group replacement with other bioisosteric group like 3-CH_2OH, resulting salbutamol (albuterol), selective beta-2 agonist, a well known anti-asthamatic drug, by 3-$NHSO_2CH_3$, resulting soterenol and by 3-$NHCONH_2$, resulting carbuterol [42-43].

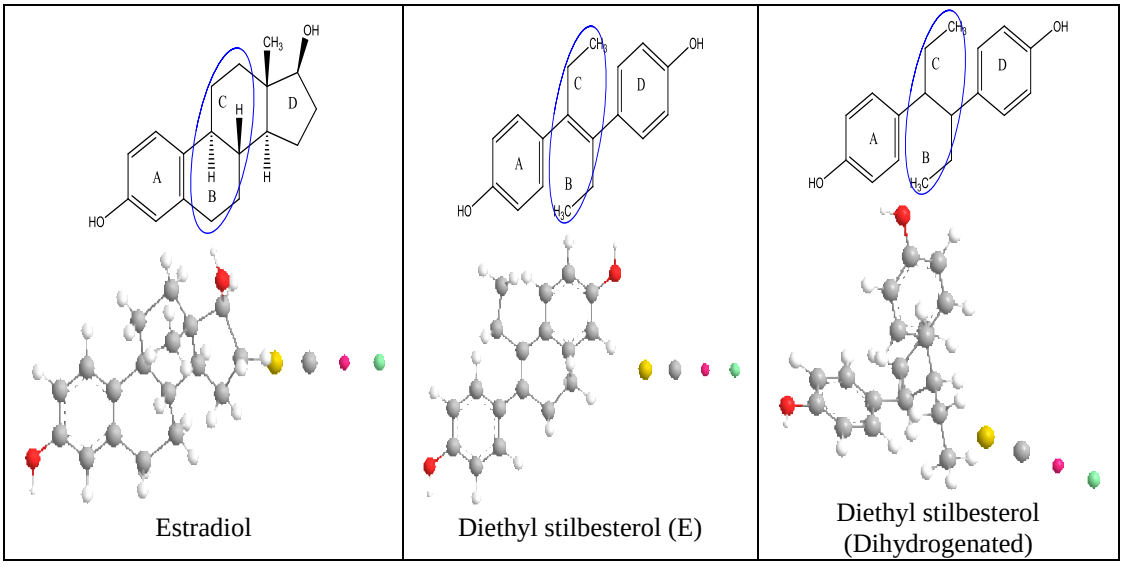


Fig. 23: Non-classical bioisosteric cyclic vs. non cyclic transformations in sterol.

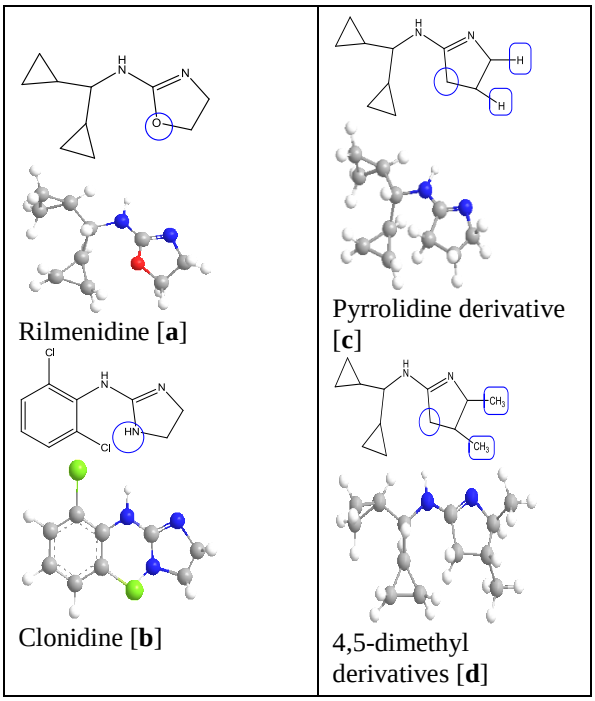


Fig. 24: Bioisosteric transformations in antihypertensive α-2-agonists.

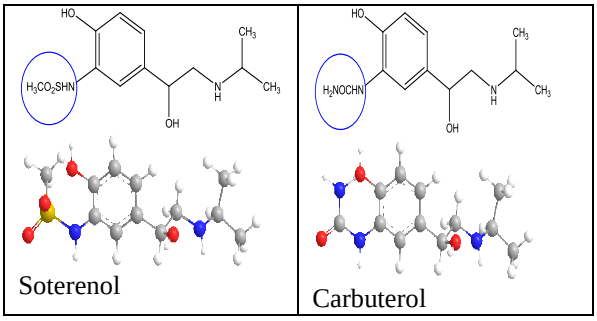


Fig. 25: Non-classical bioisosteric replacement in β-2-agonists.

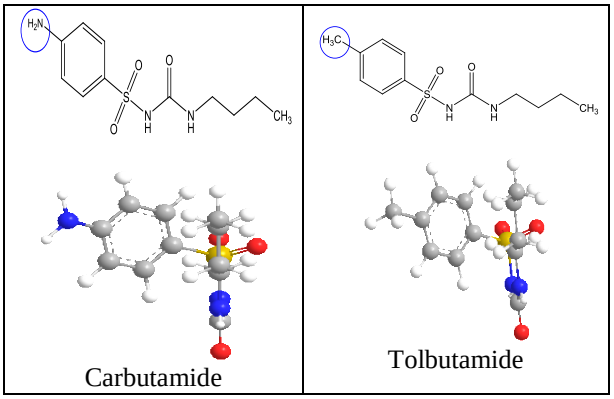


Fig. 26: Bioisosteric relationship between oral antidiabetics.

Tolbutamide can be obtained by the isosteric replacement of NH_2 by CH_3 group in carbutamide. Both are oral antidiabetic drugs but tolbutamide has got desirable half life and attenuated toxicity [50] .

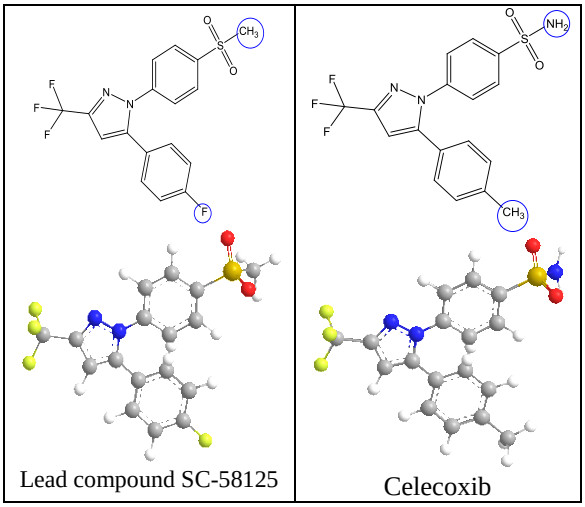


Fig. 27: Two monovalent isosteric substitutions in lead compound SC-58125 for celecoxib.

The two desirable properties identified in lead compound SC-58125, were, high selectivity rate for PGHS-2 (Prostagladin-H Synthase-2) i.e SI> 1000 and desirable inhibitory potential but very long half life and less susceptibility for cytochrome P-450 as undesirable properties, so these problems were solved by two univalent isosteric substitutions (CH_3 by NH_2 and F by CH_3) in lead compound SC-58125 and the optimized bioisostere thus obtaine is known as celecoxib (NSAID) [5], a well known selective COX-2 inhibitor.

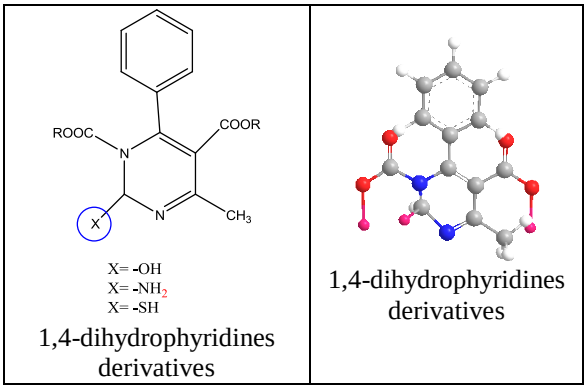
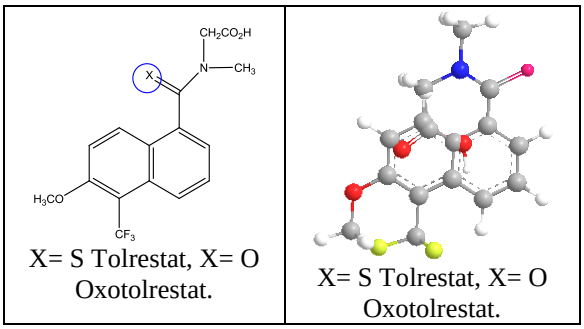


Fig. 28: Bioisosteric replacements in 1,4-dihydrophyridines derivatives.

As depicted Table-6, there is a potency wise difference among 1,4-dihydrophyridines derivatives as calcium channel blockers, due to bioisosteric replacement groups with general structure shown (Fig. 28) [51].

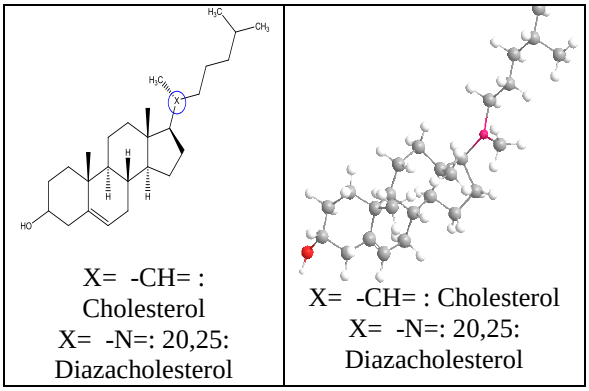


X= S Tolrestat, X= O Oxotolrestat.

X= S Tolrestat, X= O Oxotolrestat.

Fig. 29: Divalent isosteric replacement of C=S by C=O in tolrestate.

As an example of bivalent isosteric replacement of C=S by C=O in tolrestate (aldose reductase inhibitor), presently under clinical study for diabetic neuropathy, resulting a bioisosteric ananlogue i.e Oxotolrestat that retained both in-vitro and in-vivo activities [52].

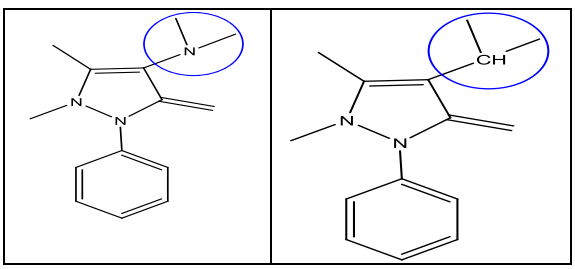


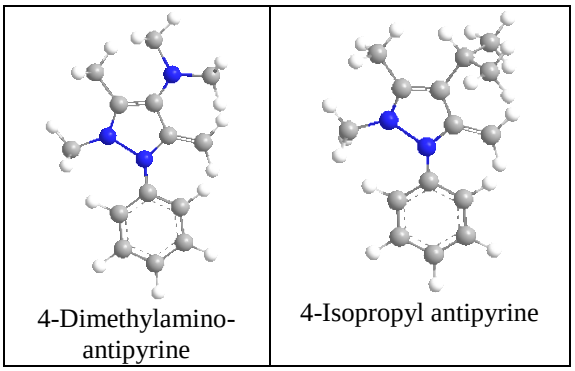
X= -CH= : Cholesterol
X= -N=: 20,25: Diazacholesterol

X= -CH= : Cholesterol
X= -N=: 20,25: Diazacholesterol

Fig. 30: Trivalent bioisosteric replacement in cholesterol.

The isosteric replacement of -CH= in cholesterol by -N= resulting in a potent cholesterol biosynthesis inhibitor named as 20,25-diazacholesterol as a standard trivalent bioisosteric replacement [53].





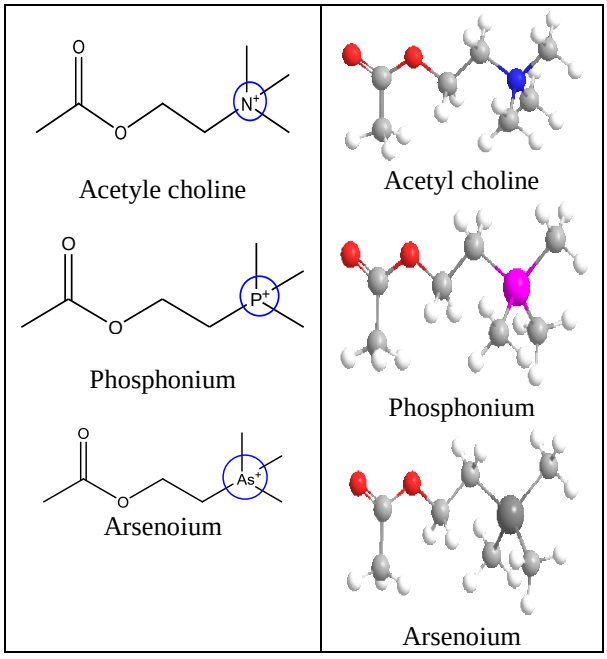
4-Dimethylamino-antipyrine

4-Isopropyl antipyrine

Fig. 31: Trivalent isosteric replacements in anti-pyretic agents.

A well known example of trivalent substitution is the equally active anti pyretic agents i.e 4-Dimethylamino antipyrine and 4-Isopropyl antipyrine [54].

A well known tetra substituted atom is the replacement of quaternary ammonium ion in acetyle choline by phosphonium and arsenoium. The bioisosteres so obtained are less potent and enhanced toxicity, hence there is no further encouragement in the synthesis of direct acting parasympathomimetic. As the size of onium ion increased, the pharmacological activity was decreased [55].



Acetyle choline

Acetyl choline

Phosphonium

Phosphonium

Arsenoium

Arsenoium

Fig. 32: Tetra substituted isosteric replacements.

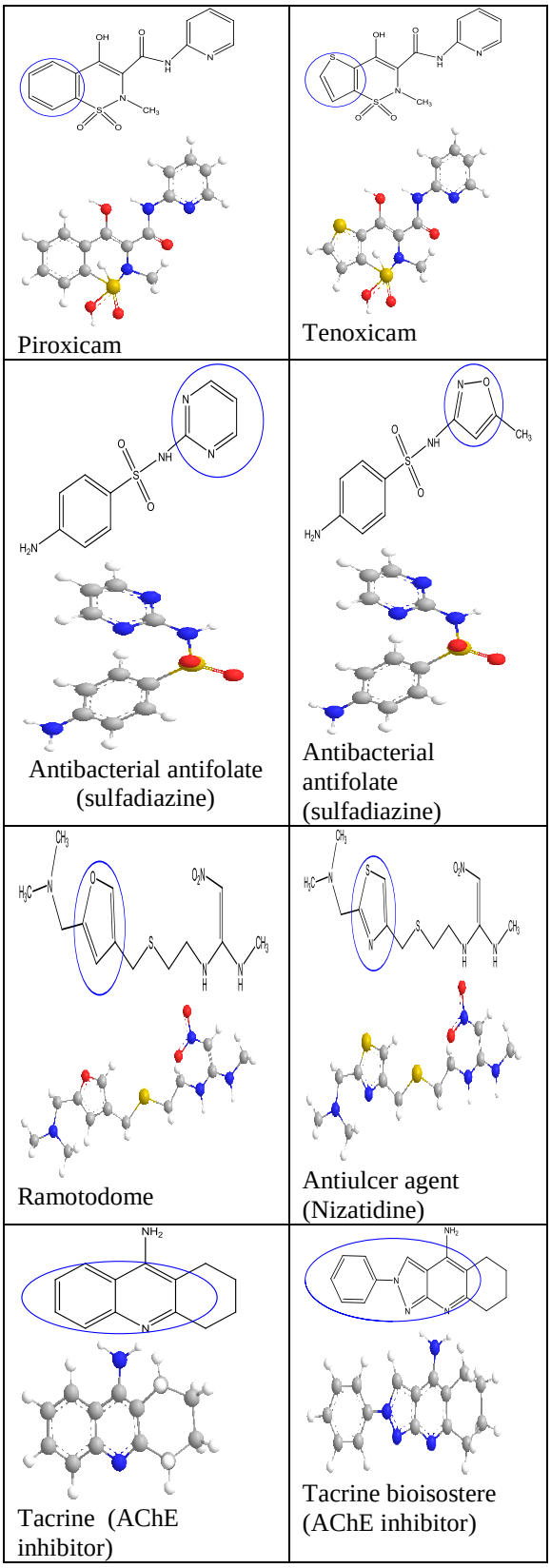


Fig. 33: Ring bioisosterism.

In the field of medicinal chemistry, ring equivalents or ring-to-ring transformations are among the most frequent approach of bioisosteric structural modifications. Most commonly heterocyclic and less commonly carbocyclic and also chain to chain replacement have been noticed and is the focused area of research for scientists [4, 6]. Ring bioisosterism especially aromatic, has been reported to possess wide applications in the field of drug design. A number clinically useful drugs have been developed from different therapeutic classes including NSAIDs, as shown in Fig. 33 [5, 28].

Binder, Lombardino and collaborators extended the concept of ring equivalent to develop new NSAID of the oxicam group [5]. They developed tenoxicam from piroxicam, an important member of 1,1-dioxibenzene-1,2-thiazine [BTA] synthetics, by replacement of benzothiazinic moiety of piroxicam with thienothiazinic nucleus, illustrated

that there exists an isosteric relationship between phenyl group and aromatic heterocyclic rings. Apart from NSAIDs, other areas covered by ring bioisosterism include antibacterial folate antagonists, autonomic (Barreiro and coworkers work on tacrine for new selective acetylcholinesterase (AChE) inhibitors), antipeptic ulcer drugs, antidepressant (work of Watthey and coworkers), sexual erectile dysfunction etc. In general it has been argued that ring bioisosterism is possible among benzene, thiophene, furan, pyrrol, pyridines and pyrazoles etc.

Currently we have reported the anti-inflammatory, anti-nociceptive and anti-pyretic activity of bioisosterically synthesized nitrogen containing derivatives of salicyl alcohol with no propensity of gastric ulceration as compared to aspirin [9-10]. These derivatives include, [4-(2-hydroxybenzyl) morpholin-4-ium chloride]; [1,4-bis (2-hydroxybenzyl) Piperazine-1,4-diium chloride]; [1-(2-hydroxybenzyl)piperidinium chloride] and [4-carbamoyl-1-(2-hydroxybenzyl)piperidinium chloride].

Salicin is chemically interrelated to aspirin and possesses almost comparable pharmacological activities. Salicin on hydrolysis results in liberation of salicyl alcohol. Phenolic hydroxyl group of saligenin is making a β-glucosidic bond with D-glucopyranose in salicin structure. We were interested in the replacement of methylene hydroxyl group with nitrogen containing different nuclei (morpholine, piperazine, piperidine and carbamoyl-piperidine ring) to see desirable pharmacological activities as depicted in Fig. 34 and Fig. 35.

2D structures of nitrogen containing different rings	3D structures of nitrogen containing different rings
Morpholine	Morpholine
Piperazine	Piperazine
Piperidine	Piperidine

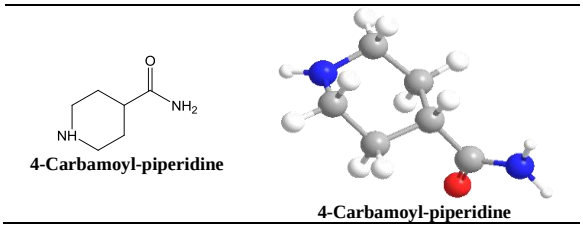
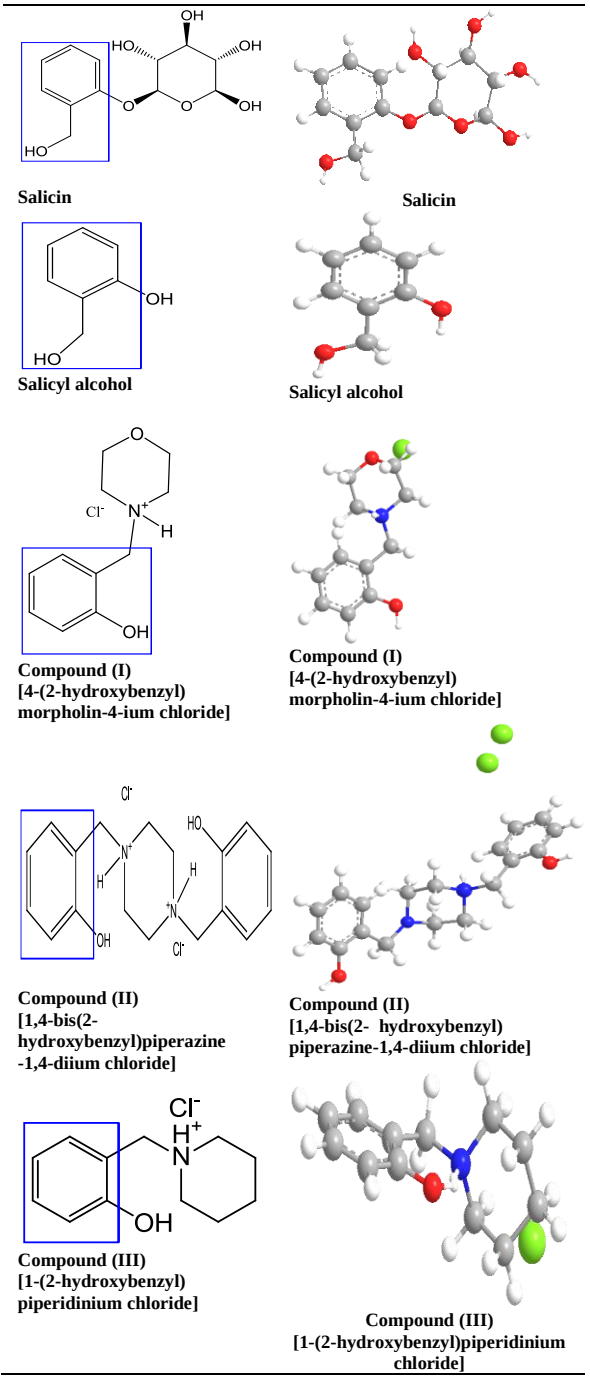


Fig. 34: Morpholin, Piperazine, Piperidine and 4-Carbamoyl-piperidine rings.



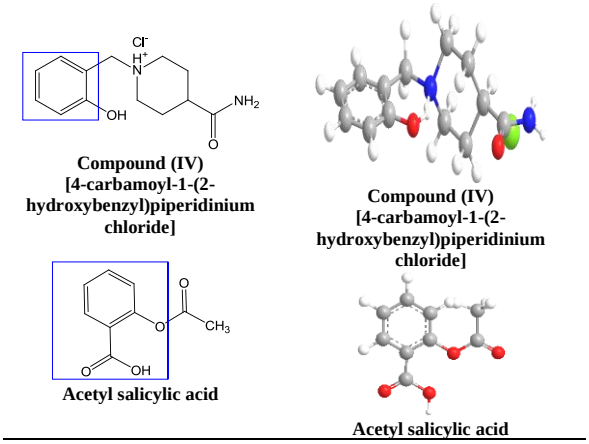


Fig. 35: Bioisosteric nitrogen containing derivatives of salicyl alcohol; compound I [4-(2-hydroxybenzyl) morpholin-4-ium chloride], compound II [1,4-bis(2-hydroxybenzyl) piperazine-1,4-diium chloride], compound III [1-(2-hydroxybenzyl)piperidinium chloride], compound IV [4-carbamoyl-1-(2-hydroxybenzyl)piperidinium chloride], salicin, salicyl alcohol and acetyl salicylic acid.

Conclusion

In the current review, a chronological study of bioisosterism and crucial role of isosterisn and bioisostreism has been investigated with clear illustration of 2D and 3D chemical structures of drugs of therapeutic importance. Drugs of desirable properties can be obtained by judicial monitoring the principles of bioisosterism. The various physicochemical properties which affect the binding of ligand/drug with the target site i.e. receptor, enzyme or channel include steric, electronic interactions and hydrophobicity. Bioisosterism influence all these properties of ligands and biological response of ligands. In summary, bioisosterism is a special process of rational molecular modification in drug design and is one of the key strategies, commonly exploited in pharmaceutical organic chemistry to optimize lead compounds. Summary of this review article in graphical form is depicted in Fig.36.

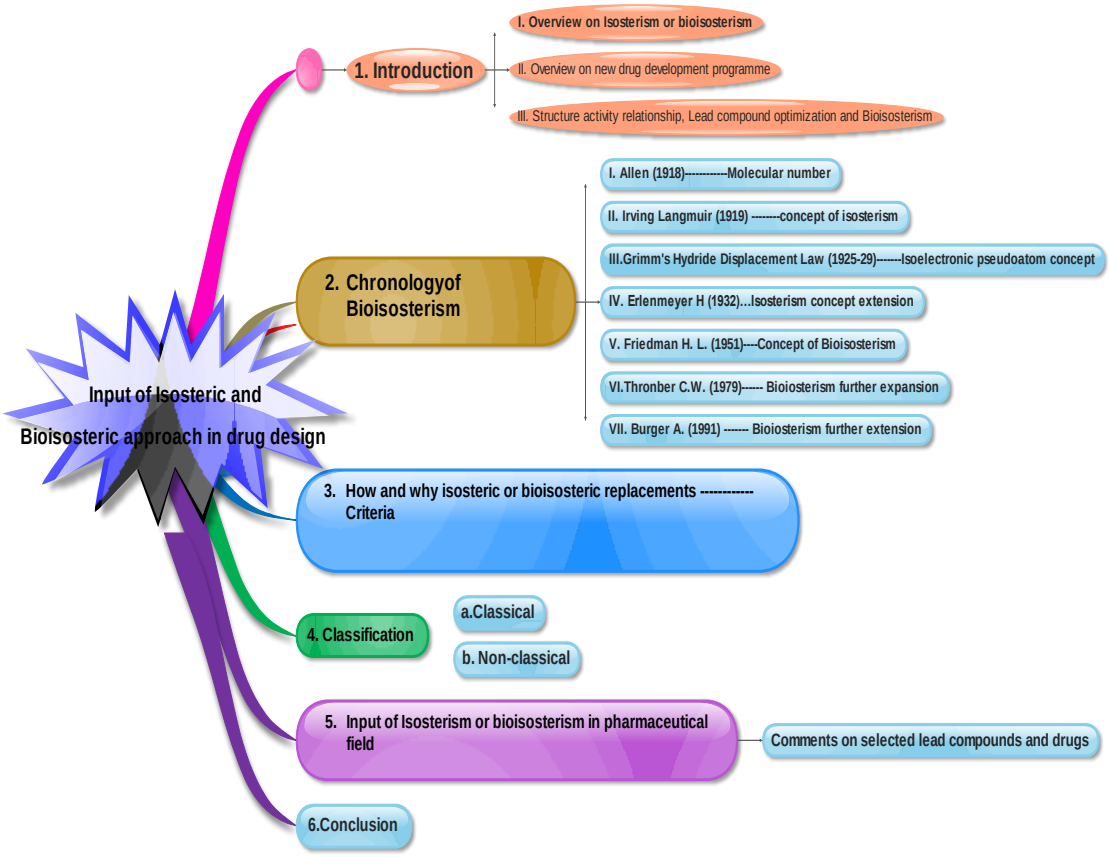


Fig. 36: Summary in graphical form.

Conflict of interest

We declare that we have no conflict of interest.

References

1. C. A. Lipinski, *Annual Reports in Medicinal Chemistry*, **21**, 283 (1986).
2. C. A. Lipinski, E. F. Fiese, and R. J. Korst, *Quantitative Structure-Activity Relationships*, **10**, 109 (2006).
3. G. A. Showell and J. S. Mills, *Drug discovery today*, **8**, 551 (2003).
4. G. A. Patani, E. J. Lavoie, *Chemical reviews*, **96**, 3147 (1996).
5. L. M. Lima and E. J. Barreiro, *Current medicinal chemistry*, **12**, 23 (2005).
6. A. Burger, *Progress in drug research*, **37**, 287 (1991).
7. M. Wagener and J. P. Lommerse, *Journal of Chemical Information and modeling*, **46**, 677 (2006).
8. P. H. Olesen, *Current opinion in drug discovery and development*, **4**, 471 (2001).
9. N. Ullah, N. U. Islam, G. Ali, F. Subhan, and I. Khan, *Medicinal Chemistry Research*, **22,** 10 (2013).
10. G. Ali. F. Subhan, Wadood, A. khan, A. Ullah, N. Islam, N. U. Islam, and I. Khan, *African journal of pharmacy and pharmacology*, **7**, 11 (2013).
11. C. P. Adams, and V. V. Brantner, *Health Affairs*, **25**, 420 (2006).
12. J. A. DiMasi, *Clinical Pharmacology and theraputics-St Louis*- **69**, 297 (2001).
13. S. Tomlinson, R. Malmstrom, and S. Watowich, *Infectious Disorders-Drug Targets*, **9**, 327 (2009).
14. W. Karcher, and J. Devillers, *Practical applications of quantitative structure-activity relationships (QSAR) in environmental chemistry and toxicology*,SpringerP. (1990).
15. A. Burger, and A. P. Parulkar, *Annual Review of Pharmacology*, **6**, 19 (1966).
16. W. J. Geldenhuys, S. F. Malan, J. R. Bloomquist, A. P. Marchand, and C. F. Van der Schyf, *Medicinal research reviews*, **25**, 21 (2004).
17. Y. Cui, and F. Nan, *Chinese Bulletin of Life Sciences*, **18**, 161 (2006).
18. L. B. Kier, and L. H. Hall, *Chemistry and biodiversity*, **1**, 138 (2004).
19. P. L. Gaikwad, P. S. Gandhi, D. M. Jagdale, and V. J. Kadam, *American Journal of PharmTech Research*, **2**, 1 (2012).
20. I. Langmuir, *Journal of the American Chemical Society*, **41**, 1543 (1919).
21. H. Grimm, *Naturwissenschaften*, **17**, 557 (1929).
22. H. Erlenmeyer, and M. Leo, *Helvetica Chimica Acta*, **15**, 1171 (1932).
23. H. L. Friedman, *National Academy of Sciences-National Research Council Publication*, 295 (1951).
24. C. W. Thornber, *Chemical Society Reviews*, **8**, 563 (1979).
25. C. G. Wermuth, and J. de la Fontaine, *The Practice of Medicinal Chemistry*, 189 (2003).
26. A. Burger, *Medicinal chemistry*,Wiley-Interscience, New York P. (1970).
27. Q. Song.MEI, X.-d., and NING, J., *Hebei Journal of Industrial Science and Technology*, **2**, 1 (2009).
28. G. A. Patani, and E. J. LaVoie, *Chemical reviews*, **96**, 3147 (1996).
29. A. Korolkovas, *Essentials of medicinal chemistry*, John Wiley and Sons, NY, USA P. (1988).
30. B. Macchia, A. Balsamo, A. Lapucci, Martinelli, A. Macchia, F. Breschi, M. Fantoni, and E. Martinotti, *Journal of medicinal chemistry*, **28**, 153 (1985).
31. C. Petrongolo, Macchia B, F Macchia, and A. Martinelli, *Journal of medicinal chemistry*, **20**, 1645 (1977).
32. B. Macchia.Balsamo, A. Lapucci, A. Macchia, F. Martinelli, A. Nencetti, S. Orlandini, E. Baldacci, M., and G. Mengozzi, *Journal of medicinal chemistry*, **33**, 1423 (1990).
33. A. Balsamo, G Broccali, A. Lapucci, B. Macchia, F. Macchia, E. Orlandini, and A. Rossello, *Journal of medicinal chemistry*, **32**, 1398 (1989).
34. A. Balsamo, A. Lapucci, M. Macchia, A. Martinelli, S. Nencetti, A. Rossello, and T. Cristina, *ChemInform*, **49**, 77 (1994).
35. A. M. MacLeod, K. J. Merchant, Brookfield, F..Kelleher, F..Stevenson, A. P. Owens C. J. Swain, M. A. Cascieri, and S. Sadowski, *Journal of medicinal chemistry*, ***37***, 1269 (1994).
36. S. Freedman, E. Harley, S. Patel, N. Newberry, M. Gilbert, A. McKnight, J. Tang, J. Maguire, N. Mudunkotuwa, and R. Baker, *British journal of pharmacology*, **101**, 575 (2012).
37. P. Krogsgaard-Larsen.Johnston, G. D. Curtis, C. Game, and R. McCulloch, *Journal of neurochemistry*, **25**, 803 (2006).
38. P. Krogsgaard Larsen, H. Hjeds, D. Curtis, D. Lodge, and G. Johnston, *Journal of neurochemistry*, **32**, 1717 (2006).

39. R. L. Johnson, G. Rajakumar, and R.K. Mishra, *Journal of medicinal chemistry*, **29**, 2100 (1986).
40. P. Tfelt-Hansen, P. De Vries, and P. R. Saxena, *Drugs*, **60**, 1259 (2000).
41. D. J. Carini.Duncia, J. V. Aldrich, P. E. Chiu, A. T. Johnson, A. L. Pierce, M. E. Price, W. A. Santella III, and G. J. Wells, *Journal of medicinal chemistry*, **34**, 2525 (1991).
42. A. Larsen.Gould, W. A. Roth, H. R. Comer, W. T. Uloth, R. H. Dungan, and P. Lish, *Journal of medicinal chemistry*, **10**, 462 (1967).
43. C. Kaiser.Colella, D. F. Schwartz, M. S. Garvey, and J. R. Wardell Jr, *Journal of medicinal chemistry*, **17**, 49 (1974).
44. J. Campos.Saniger, E. Marchal, J. A. Aiello, S. Suarez, I. Boulaiz, H. Aranega, A. Gallo, M. A, and A. Espinosa, *Current medicinal chemistry*, **12**, 1423 (2005).
45. C. Avendaño, and J. C. Menéndez, *Medicinal chemistry of anticancer drugs*, Elsevier ScienceP. (2008).
46. H. Randy, (Ed.) (2005) *Remington:The Science and Practice of Pharmacy*, 21th ed., Lippincott Williams andWilkins, New York.
47. R. Bhatia.Sharma, V..Shrivastava, B., and Singla, R. K., *Pharmacologyonline*, ***1***, 272 (2011).
48. Y. Song.Zhan, P. Kang, D. Li, X. Tian, Y. Li, Z. Xuwang, C. Chen, W. Pannecouque, C. De Clercq, and X. Liu, *Medicanal Chemistry Communation*, DOI: 10.1039/C3MD00028A (2013).
49. S. Schann, V. Bruban, K. Pompermayer, J. Feldman, B. Pfeiffer, P. Renard, E. Scalbert, P. Bousquet, P., and J. D. Ehrhardt, J.-D., *Journal of medicinal chemistry*, **44**, 1588 (2001).
50. U. Argikar, B. Mangold, and S. Harriman, *Current topics in medicinal chemistry*, **11**, 419 (2011).
51. K. S. Atwal, G. Rovnyak, C. Kimball, S. D. Floyd, D. M. Moreland, N. B. Swanson, J. Z. Gougoutas, J. Schwartz, K. M. Smillie, K. M., and M. F. Malley, *Journal of medicinal chemistry*, **33**, 2629 (1990).
52. J. Wrobel.Millen, J. Sredy, J. Dietrich, A. Kelly, J. M. Gorham, and K. Sestanj, *Journal of medicinal chemistry*, **32**, 2493 (1989).
53. R. Counsell.Klimstra, P. Nysted, L. and R. Ranney, *Journal of medicinal chemistry*, **8**, 45 (1965).
54. H. Erlenmeyer, and E. Willi, *Helvetica Chimica Acta*, **18**, 740 (1935).
55. R. Hunt, and R. Renshaw, *Journal of Pharmacology and Experimental Therapeutics*, **25**, 315 (1925).