A Review Report on Newer Advancement in Bioisosteric Replacement in Drug Design

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Abstract

Bioisosteres are major challenge to change a compound with high affinity to a biological lead in to a successful drug. It showes one approach used by the pharmaceutical chemist for the rational modification. The objective of a bioisosteric replacement is to modify a new compound with same biological properties to the original compound and improve the structure activity relationship and purity of the compound also.

Keywords: Bioisosteres, Biological Properties, Structure Activity Relationship

Introduction

The abstraction of bioisosterism has helped considerably over the years in the search for and design of novel drugs. It is a idea which has proved to be useful in the absence of one or more precise knowledge of a chemical structure required to produce some biological effect. The detection of a compound with encouraging medicinal activity leads to a search for other structurally closely related compounds, which have shown modified therapeutic properties and reduced unwanted adverse effects. In the past, medicinal chemists have developed a considerable amount of intuition, in respect to select appropriate structural modifications. Much of the search has been based on bioisosteric relations and has led to fruitful yield new, modified drugs. Medicinal chemist used this approach for the rational modification of lead compound into more safer and essential agent. The concept of bioisosterism is considered to be qualitative and intuitive. Bioisosterism is the term which is widely used to describe the selection of structural components, its steric properties, electronic properties and its solubility characteristics due to which it is interchangeable among the same pharmacological class in the form of drug. Bioisosterism is of vital significance to a medicinal chemist because the biological characteristics of bioisosteres appear to be similar more frequently than their physical or chemical characteristics. Bioisosterism has numerous advantageous applications in resolving biological problems effectively. The stable approach towards more potent biologically active compound has paved the way for research into more specific, essential and structurally close compounds, either possessing it or of contrary activity.

Due to the difference in their physico-chemical properties, bioisosteres regulates biological activity. Systemic association of physico-chemical parameters with observed biological activity has been effective in highlighting the difference between bioisosteric group which increase its biological activity [1]. In QSAR studies, biological activity observed with non classical bioisosteric group can be correlated employed. In drug design, the foundation for the development of QSAR is the bioisosteric replacement [2]. The development of new clinical agents was enhanced by the bioisosteric replacement of functional groups of pharmacophore and physico-chemical parameters of bioisosteres. Langmuir uncovered the bioisosteric rationale for the modification of lead compound according to the observation in 1919 regarding the similarities of various physico-chemical properties, groups and radicals[3]. He measured the physical properties of different molecules such as CO, NO, N3, NCO and found that they are similar. On the basis of these similarities he recognized 21 groups of isosteres. Many groups are listed in **Table I**. He further deduced from the octet theory that the number and arrangement of electrons in these molecules are similar, in this way isosteres were initially defined as those compounds or groups of atoms that have the same number and arrangement of electrons. Molecules such as CO_2 and NO_2 is biologically similar and was later known to be the compound which are capable of acting as reversible anesthetic to the slim mold PHYSARUM POLYCEPHALUM [4].

Table I: Isosteres Group

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+}
5	N2, CO, CN–
6	CH4, NH4
7	CO_2, N_2O, N^{3-}, CNO^{-}

A further extension of this concept of isosteres came about in 1925 with Grimm's Hydride Displacement Law [5]. This law states "a*toms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in the manner that the resulting combinations as a pseudo atom, which are identical to elements in the groups one to four places, to their right*". Every upright column as illustrated in **Table II**, according to Grimm, would represent a group of isosteres.

Table II: Law of Grimm's Hydride Displacement

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

Table III: Isosteres based on the Number of Peripheral Electrons [6]

4	5	6	7	8
$_N+$	P	S	Cl	ClH
$_P+$	As	Se	Br	BrH
$_S+$	Sb	Te	I	IH
As^{+}		PH	SH	SH_2
Sb^{+}			PH_2	PH_3

The widespread application of the idea of isosterism to modify biological activity has been termed-Bioisosterism. It defined by Friedman [7] bioisosteres were to include all atoms and molecules which fail the broadest definition for isosteres and have a identical type biological activity, which may even be antagonistic. This definition has been broadened by Burger as "*compounds or groups that possess near equal molecular shapes and volumes, Generally the equal distribution of electrons, and which exhibit near physical H.L properties"*. Bioisosteres, however, are groups that do not necessarily have the similar size or volume, but are little bit similar in chemical or physical properties, which also show similar biological properties [8].

Bioisosteres may produce opposite biological effects and these effects are frequently a reflection of some action on the same physiological process or at the same receptor site. Bioisosteric similarity of molecules is commonly assigned on the basis of number of valence electrons of an atom or groups of atoms or a group of atoms rather than on the number of total orbital electrons. Thus, significant concept is that the bioisosteres are affecting in same fashion, at the same receptor site or by the same pharmacological mechanisms.

It is therefore unlikely that bioisosterism will produce marked increased in potency; however significant changes in selectivity, toxicity, and metabolic stability could be expected. Traditionally, bioisostereres have been categorized into two groups, classical Bioisosteres and non-classical Bioisosteres [9].

Compounds may be altered by bioisosteric replacements of groups, in order to develop analogs with selected biological effects, or to act as antagonists to normal metabolites.

Classification of Bioisosteres [10]

I. Classical Isosteric Replacement

Classical isosteric replacement is like-for-like in terms of number of atoms, valency, degree of unsaturation, and only becomes and bioisosteric replacement if biological activity is retained.

1. Univalent atoms and groups
   - (A) $–CH_3$, $–NH_2$, –OH, –F, –Cl:
   - (B) –Cl, $–PH_2$, –SH
   - (C) –Br
   - (D) –I, -t-Bu
2. Bivalent atoms and groups
   - (A) $–CH_2$, –NH, –O, –S, –Se–
   - (B) $-COCH_2-$, CONH-, -COO-, -COS-.
3. Trivalent atoms and groups
   - (A) –CH=, –N=
   - (B) -P=, -As=
4. Tetravalent atoms and groups
   - (A) >C<, >Si< and
   - (C) =C=, $=N^+=$, $=P^+=$
5. Ring Equivalents
   - (A) -CH=CH-, -S- (e.g. benzene, thiophene)
   - (B) -CH=, -N= (e.g. benzene, pyridine)
   - (C) -O-, -S-, $-CH_2-$, -NH- (e.g. tetrahydrofuran, tetrahydrothiophene, cyclopentane, pyrrolidine)

II. Non-Classical Isosteric Replacement

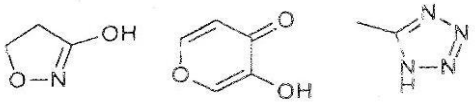
Non-classical isosteric replacement retains activity by the retention of other properties such as pKa, electrostatic potentials, HOMOs and LUMOs etc. for which modern computational analysis methodology can aid in rationalization.

Carbonyl group

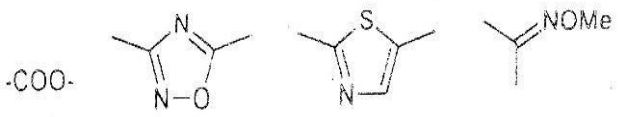
A. Cyclic vs Noncyclic Bioisosteric Replacement

B. Noncyclic Bioisosteric Replacement of Functional Groups

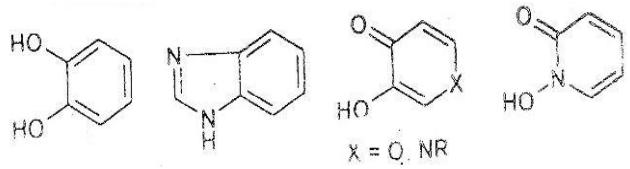
1. Carbonyl group
2. Carboxylic Acid group
   COOH, SO_2NHR, SO_3H, CONHCN, CONHON, PO(OH) OEt, $PO(OH)NH_2$



3. Carboxylic Ester group



4. Carboxylic Amide group (in Peptides)
   -CONH-, CONMe-, -CSNH-, CH2NH-, -NHCO-, >C=C<, $-CH_2S-$
5. Hydroxy group
   -OH, -NHCOR, $-NHSO_2R$, $-CH_2OH$, $-NHCONH_2$, -NHCN, $-CH(CN)_2$
6. Catechol



7. Halogen
   Halogen, $-CF_3$, -CN, $-NCN_2$, $-C(CN)_3$
8. Thiourea
   -NHC (=S) NH_2, $-NHC(=NCN)NH_2$, $-NHC(=CHNO_2)\ NH_2$

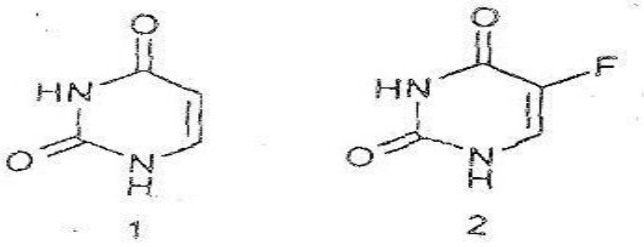
Classical Bioisosteres

1. Univalent Atoms or Groups

Fluorine vs Hydrogen Replacement

The substitution of hydrogen by fluorine is one of the more commonly employed monovalent. The steric properties of hydrogen and fluorine are similar and their van der Waal's radii is 1.2 and 3.5 A^0 respectively [11]where fluorine has been substituted for hydrogen is the difference in the electronic effect.

A classical example showing how fluorine substitution of a normal enzyme substrate can result in a derivative, which can change prime enzymatic processes, is anticancer agent 5-fluorouracil (2). In this case 5-FU is biochemically transformed in-vivo into 5-fluoro-2 deoxyuridylic acid which is similar to uracil (1) and allow this fluoro derivatives to be a successful mimetic.

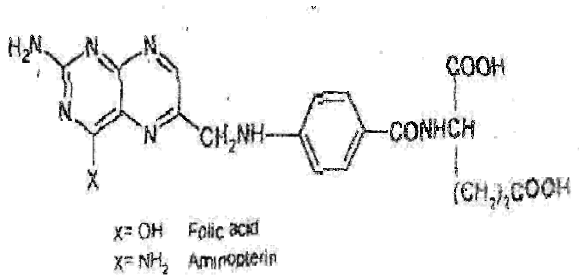


Interchange of Hydroxyl and Amino Groups

The monovalent interchange of hydroxyl groups are well known today and it has been successfully employed in the development of lead compound. For the success of spatial arrangement and the ability of functional groups to act as either hydrogen bond acceptors or donors are important. Aminopterin in which the dydroxyl group of folic acid has been substituted by amino groups is well known example of classical isosteric

substitution of an amino for hydroxyl group [12]. This sample exihibits monovalent bioisosteric substitution at carbon atom which is adjacent to a heterocyclic nitrogen atom.

The similarities and capability of the amino group in comparison to hydrogen bond of the enzyme are two important factors which facilitate the binding of aminopterin to the enzyme dcihydrofolate reductase.



Interchange of Hydroxyl and Thiol groups

An extension of the amino hydroxyl replacement is the interchange of thiol for hydroxyl has been used extensively in medicinal chemistry. The replacement is based on potency of both groups to be hydrogen acceptor or donors. The antagonistic activity develops when the 6-OH of inosine and guanine is replaced by –SH to give the anticancer drugs, 6-mercaptopurine and 6-thioguanine [13].

B. Divalent Isosteres

Divalent isosteres can be classified into two subgroups:

(1) Those divalent Bioisosteres which involve the interchange of atoms that are involved in a double bond, such as in the series; C=C, C=N, C=O, and C=S.

(2) Those divalent isosteres where substitution of a different atom results in the alteration of two single bonds such as in the series; C–C–C, C–NH–C, C–O–C, and C–S–C. In the study of the structure activity relationships of various pharmacologically active agents

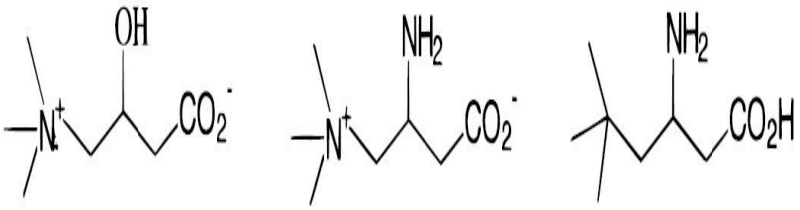
.both type of bioisosteric substitutions have been used [14].

C. Trivalent atoms or groups

In drug discovery process a classical trivalent bioisosteric has been widely used .It has been further discussed among the ring equivalent class of classical Bioisosteres. When this replacement is related to cholesterol, it will result in 20,25-diazacholesterol which is a potent inhibitor of cholesterol biosynthesis [15]. For the biological activity of this Bioisosteres, greater electronegativity of the nitrogen atom is responsible.

D. Tetra substituted Atoms

Interchange of a quaternary charged nitrogen atom with a tertiary carbon atom is mostly used tetravalent replacement. In the presence of carnitine acyltransferases C2-C20 acyl groups are reversibly transferred to the β-hydroxyl group of (R)-carnitine. Inhibition of single carnitine acyltransferases is useful in the therapy of diabetes and cardiac disease. The determination of respective substrate specificity and specific inhibitors for individual carnitine acyltransferases is of highly interest because of its possible therapeutic implications. The potent carnitine acyltransferase (CAT) inhibitors is acylcarnitine analogues[16]. In studying Structure-activity studies of this series the bioisosteric replacement of the hydroxyl group of carnitine (c) is done with an amino (c) and replacement of the tetravalent trimethylammonium group with a tertiary butyl group.



E. Ring Equivalents

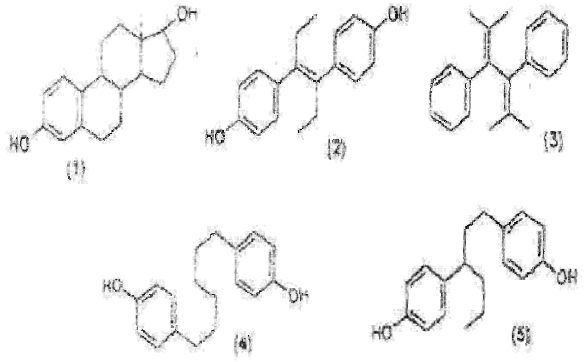
Ring equivalent bioisosteres represent the final subclass of classical bioisosteres that will be studied. Classical isosteric substitutions when applied within ring systems result in different heterocyclic analogues which can be effective bioisosteres. The role of the classical Bioisosteres benzene, thiophene, and pyridine developed in analogues with retention of biological activity within different series of pharmacological agents.

Non classical Bioisosteres

These types are undefined by the classical definition of bioisosteres but by mimicking spatial arrangement, electronic properties, or physicochemical characteristics of the molecule of functional group it maintain similar biological activity.

A. Cyclic vs Noncyclic Nonclassical Bioisosteric Replacements

In this a noncyclic functional moiety mimics and cyclic group sterically or electronically resulting in retention of biological activity. This phenomenon is explained by comparing different analogues structure of estradiol. The structure of estradiol has ability to hold the critical functionality in a particular spatial configuration is important for its biological activity. It is known that central bond of diethylstilbestrol (2) is essential for correct orientation of the phenolic and ethyl groups and for the binding to the estrogenic receptor [17] which was evidence the cis isomer of DES is only 1/14 as active as the trans isomer [18]. When Structurally or conformationally rigid analogues are injected (compounds 2, 3) then it is equipotent as estradiol. No rigid analogues (compounds 4, 5), however, were found to have little or no estrogenic activity [19].



B. Nonclassical Bioisosteric Replacement of Functional Groups

It is not necessarily result in a compound with comparable biological activity to the template drug. In some aspects where such replacements have resulted in retention of biological activity, the examples as outlined in this section may encourage the use of these bioisosteres in future structure activity studies.

1. Hydroxyl Group Bioisosteres

Nonclassical bioisosteres for phenolic hydroxyl groups generally do not resemble this functional group in terms of size or potential as a strong electron-donating group. Several nonclassical bioisosteres for the phenolic hydroxyl group are- CH_2OH, $NHCONH_2$, $NHCOCH_3$, $NHSO_3CH_3$, NHCN etc. Molar refractivity is an index or relative size. While the hydroxymethyl bioisostere most closely approximates the size of the phenoic hydroxyl group, it remains significantly different. In terms of these nonclassical bioisosteres, only the urea bioisosteres is an electron-donating substituent. Thus, these nonclassical bioisosteres are unlikely to be suitable in those instances where biological activity is adversely affected by increased molecular size or is strongly affected by increased molecular size or is strongly dependent on electronic parameters. These nonclassical bioisosteres tend to be most effective, in those instances where the role of the phenolic hydroxyl group is to act as either a hydrogen bond acceptor or donor. Such bioisosteres are also effective when moderate hydrophilicity is correlated with improved biological activity [20].

2. **Carbonyl Group Bioisosteres**

This type of replacement is used for the aldehyde or ketone moiety e.g. SOCH3, SO2CH3 CH=NOH, CH=NOCH3 etc. In these functional group, difference in the electronegativity between oxygen and carbon results in partial positive charge on the carbon atoms while the oxygen acquires a partial negative charge. When we compare substituent constant associated with isosteres for the carbonyl group which show that these nonclassical bioisosteric replacements are generally electron-withdrawing moieties that are relatively large in size [21]. The sulfoxide and the sulfone moieties is used as nonclassical divalent bioisosteres of the carbonyl group [22].

3. Carboxylate Group Bioisosteres

Nonclassical bioisosteres for the carboxylate group consist of replacement which involves (a) only the hydroxyl portion or (b) both the hydroxyl and carbonyl fragments of this functional group.

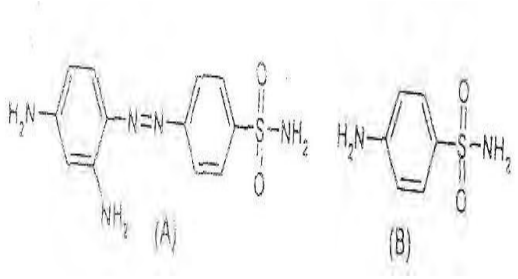
(a) Replacements involving only the Hydroxyl Portion

It is used for the replacement of the hydroxyl group of a particular carboxylic acid are similar to the nonclassical bioisosteres which have been previously outlined for phenolic hydroxyl groups.

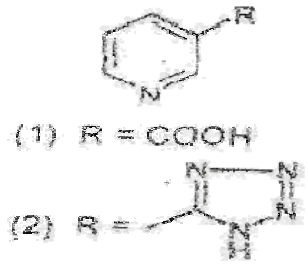
(b) Replacements involving the entire Carboxylate Functional Group

Sulfonamides represent one of the first nonclassical bioisosteres used to replace the carboxyl group

In 1932, it is discovered that Prontosil (A) cures for streptococcal infections in mice. The active form of prontosil is p-amino sulfanilamide. It acts as competitive inhibitors of the incorporation of p-amino benzoic acid which is associated with the formation of dihydropteroic acid and inhibits the biosynthesis of dihydrofolic acid [23]. Thus, one of the earliest synthetic antibiotics developed consisted of an antimetabolite in which nonclassical bioisostere replaced a carboxylic acid moiety.



The well known replacement of carboxylic acid moiety is with tetrazole group and it is used increasingly with different class of medicinal agent. These groups is almost 10 times more lipophilic while have similar acidity, pKa=4.9, to that observed for carboxylic acids (pKa 4.2-4.4). In a search for improved antihyperlipidemic agents the tetrazolyl analogue (2) of nicotinic acid (1) was found to be three times as active in lowering blood cholesterol [24]. While searching improved antihyperlipidemic agents ,it is found that tetrazolyl analogue (2) of nicotinic acid (1) is three times active in lowering blood cholesterol.



Other commonly used isosteres for the carboxylic acid moiety, besides sulfonamides and tetrazoles, include oxadiazole, sulfonate and phosphate. Among these bioisosteic replacements, both the sulfonates and phosphates are more hydrophilic than the carboxylate anion and are 100% ionized at physiological pH.

4. Amide Group Bioisosteres

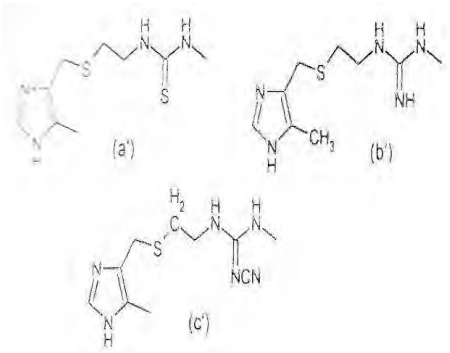
Bioisosteric replacement for the amide is the center of focus due to its implications in peptide chemistry and the development of peptide mimetic. Peptide bonds and peptide fragments have been replaced with a wide variety of structural moieties in attempts to convert peptides into chemically stable and orally available molecules. Bioisosteres of the amide bond are- -CONH- NHSC-, CH_2NHCO-, $-COCH_2$-, - NHCONH-, $-CH_2NH$-, $NHCO_2$- NHCOS- $-CO_2$-, $NHSO_2$-, CH(OH) CH_2-, etc.

Heteroxcylic rings such as 1,2,4-oxadiazoles, 1,3,4-oxadiazoles and trizoles such a the 1,2,4-triazoles, have also been used as replacements for amide or ester bonds.

5. Thiourea Bioisosteres

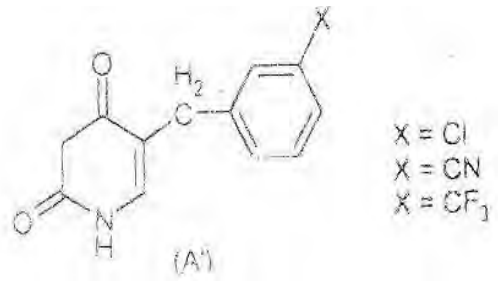
In the development of H2-receptor antagonists, thiourea bioisosteres have been employed successfully. This antagonist is mostly used in the treatment of peptic ulcer. In early clinical studies with the H2-antagonist metamide (a') was attributed to the thiourea moiety and its side effect are agranulocytosis .Due to of its high degree of ionization at physiological pH replacement with a guanidine group (b') resulted in absorption problems

Thus, bioisosteric substitution with the cyanoguanidino derivative with cimetidine (c') was twice active as metiamide which was an inhibitor of gastric acid secretion[25]. The presence of a polar and nonbasic functional group which was attached to the secondary position of an (ethylthio) methyl substituent on an aromatic heterocyclic exists for all of the major H2-antagonists which include cimetidine, famotidine, ranitidine, and nizatidine.



6. Halogen Bioisosteres

Cyano or trifluoromethyl group is an electron withdrawing groups which replaced hydrogen. This type of replacement was observed in a series of 1-[(2-hydroxyethoxy) methyl] -5-benzyluracils (A) and was tested for inhibition of liver uridine phosphorylase. Uridine phosphorylase ,an enzyme which catalyse the reversible phosphorolysis of pyrimidine nucleosides, is responsible for degradation of chemotherapeutic agent like 5-fluoro-2'- deoxyuridylic acid. So, Finally we conclude that agents belonging to this class has been of chemotherapeutic interest. In the series of 5-benzyluracils,when we add electron-withdrawing groups at the 3-position ,its potency decreases[26]. This statement was supported by the observation that when chloro atoms is replaced with stronger electron-withdrawing groups such as the cyano or the trifluromethyl it results in less potent analogues



Conclusion

This review is just an attempt to explain the rationale behind the use of bioisosteric replacements using examples from current literature. Due to the difference between physical properties, bioisosteres regulates biological activity. These biological activity when correlated with these physicochemical parameter, it will show difference within bioisosteric group which increases its activity. The ability of these bioisteric groups is to define some of the essential requirements of the pharmacophore. When the synthesis of a large number of drug candidates for evaluation is not economically feasible than it is important. Due to their inability to demonstrate bioisosterism in more than a single class of agents number of less known replacements have not been reviewed. It is hoped that this systematic approach can be further used in drug discovery and structure activity studies for characterizing drug targets.

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