Bioisosterism: A Rational Approach in Drug Design

George A. Patani and Edmond J. LaVoie*

Department of Pharmaceutical Chemistry, College of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08855-0789

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Contents

George Patani graduated with a B.Pharm. in 1992 from the College of Pharmaceutical Sciences, Mangalore University at Manipal, India. In 1996, he received his M.S. in Pharmaceutical Science at Rutgers University under the direction of Professor Edmond J. LaVoie. He is presently pursuing graduate studies in pharmaceutics. His current research interests are focused on drug design and controlled drug delivery.

Edmond J. LaVoie received his B.S. in Chemistry from Fordham University in 1971 and his Ph.D. in Medicinal Chemistry from S.U.N.Y. at Buffalo under the direction of Dr. Wayne K. Anderson. After postdoctoral study with Dr. S. Morris Kupchan at the University of Virginia, he joined the American Health Foundation in Valhalla, NY. In 1988, he was appointed Professor of Medicinal Chemistry in the College of Pharmacy at Rutgers University. His current research interests are in the design and synthesis of cancer chemotherapeutics and in the elucidation of mechanism(s) of carcinogenesis.

I. Introduction

Years of cumulative research can result in the development of a clinically useful drug, providing either a cure for a particular disease or symptomatic relief from a physiological disorder. A lead compound with a desired pharmacological activity may have associated with it undesirable side effects, characteristics that limit its bioavailability, or structural features which adversely influence its metabolism and excretion from the body. Bioisosterism represents one approach for the rational modification of lead compounds into safer and more clinically effective agents. The concept of bioisosterism is often considered to be qualitative and intuitive.[1]

The prevalence of the use of bioisosteric replacements in drug design need not be emphasized. This topic has been reviewed in previous years.[2−5] The objective of this review is to provide an overview of bioisosteres that incorporates sufficient detail to enable the reader to understand the concepts being delineated. While a few popular examples of the

present review is focused primarily upon specific examples from current literature. The emphasis in this review was to outline bioisosteric replacements which have been used to advance drug development. No attempt was made to be exhaustive or to illustrate all of the specific analogues represented within a single study.

The ability of a group of bioisosteres to elicit similar biological activity has been attributed to common physicochemical properties. In this review an attempt has been made to quantitate, in specific instances, physicochemical effects such as electronegativity, steric size, and lipophilicity and to correlate these values to the observed biological activity. Thus, an additional objective of this review was to demonstrate the opportunities that one has in employing bioisosteres to gain more specific insight into the quantitative structure−activity relationships (QSAR) associated with a specific class of drugs. While in some instances such associations were detailed by the authors of these literature examples, others were developed on the basis of evident correlations. To further explain and rationalize the biological activity observed with nonclassical bioisosteric groups, the observed biological activity has also been correlated with some substituent constants commonly employed in QSAR studies. These observations are consistent with the fact that bioisosteric replacements often provide the foundation for the development of QSAR in drug design.[4,6] Recent advances in molecular biology, such as cloning of the various receptor subtypes, have enabled a clearer definition of the pharmacophoric sites. Bioisosteric replacements of functional groups based on this understanding of the pharmacophore and the physicochemical properties of the bioisosteres have enhanced the potential for the successful development of new clinical agents.

The bioisosteric rationale for the modification of lead compounds is traced back to the observation by Langmuir in 1919 regarding the *similarities of various physicochemical properties* of atoms, groups, radicals, and molecules.[7] Langmuir compared the physical properties of various molecules such as N_2 and CO, N_2O and CO_2, and N_3^- and NCO^- and found them to be similar. On the basis of these similarities he identified 21 groups of *isosteres*. Some of these groups are listed in Table 1. He further deduced from the octet theory that the number and arrangement of electrons in these molecules are the same. Thus, isosteres were initially defined as those compounds or groups of atoms that have the same number and arrangement of electrons. He further defined other relationships in a similar manner. Argon was viewed as an isostere of K^+ ion and methane as an isostere of NH_4^+ ion. He deduced, therefore, that K^+ ions and NH_4^+ ions must be similar because argon and methane are very similar in physical properties. The biological similarity of molecules such as CO_2 and N_2O was later coincidentally acknowledged as both compounds were capable of acting as reversible anesthetics to the slime mold *Physarum polycephalum*.[8]

Table 1. Groups of Isosteres as Identified by Langmuir

groups	isosteres
1	H^-, He, Li^+
2	O^{2-}, F^-, Ne, Na^+, Mg^{2+}, Al^{3+}
3	S^{2-}, Cl^-, Ar, K^+, Ca^{2+}
4	Cu^{2-}, Zn^{2+}
↓	↓
8	N_2, CO, CN^-
9	CH_4, NH_4^+

A further extension to this concept of isosteres came about in 1925 with Grimm's Hydride Displacement Law.[9,10] This law states: "Atoms 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 such a manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups one to four places respectively, to their right." Each vertical column as illustrated in Table 2, according to Grimm, would represent a group of isosteres.

Table 2. Grimm's Hydride Displacement Law

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^+

Erlenmeyer[11] further broadened Grimm's classification and redefined isosteres as atoms, ions, and molecules in which the peripheral layers of electrons can be considered identical (Table 3).

Table 3. Isosteres Based on the Number of Peripheral Electrons

no. of peripheral electrons				
4	5	6	7	8
N^+	P	S	Cl	ClH
P^+	As	Se	Br	BrH
S^+	Sb	Te	I	IH
As^+		PH	SH	SH_2
Sb^+			PH_2	PH_3

The widespread application of the concept of isosterism to modify biological activity has given rise to the term *bioisosterism*. As initially defined by Friedman,[2] bioisosteres were to include all atoms and molecules which fit the broadest definition for isosteres and have a similar type of biological activity, which may even be antagonistic. More recently this definition has been broadened by Burger as "Compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties...".[5] The critical component for bioisosterism is that bioisosteres affect the same pharmacological target as agonists or antagonists and, thereby, have biological properties which are related to each other.

Bioisosteres have been classified as either classical or nonclassical.[12] Grimm's Hydride Displacement Law and Erlenmeyer's definition of isosteres outline

divalent atoms or groups; (C) trivalent atoms or groups; (D) tetrasubstituted atoms; and (E) ring equivalents.

Nonclassical isosteres do not obey the steric and electronic definition of classical isosteres. A second notable characteristic of nonclassical bioisosteres is that they do not have the same number of atoms as the substituent or moiety for which they are used as a replacement. Nonclassical bioisosteres can be further divided into groups: (A) rings vs noncyclic structures; and (B) exchangeable groups.

This approach to classifying bioisosteres will be used to review literature examples of those bioisosteric replacements that have provided useful information on the structure−activity relationships associated with various pharmacologically active compounds.

II. Classical Bioisosteres

A. Monovalent Atoms or Groups

Similarities in certain physicochemical properties have enabled investigators to successfully exploit several monovalent bioisosteres. These can be divided into the following groups: (1) fluorine vs hydrogen replacements; (2) amino−hydroxyl interchanges; (3) thiol−hydroxyl interchanges; (4) fluorine, hydroxyl, amino, and methyl group interchanges (Grimm's Hydride Displacement Law); (5) chloro, bromo, thiol, and hydroxyl group interchanges (Erlenmeyer's Broadened Classification of Grimm's Displacement Law).

1. Fluorine vs Hydrogen Replacements

The substitution of hydrogen by fluorine is one of the more commonly employed monovalent isosteric replacements. Steric parameters for hydrogen and fluorine are similar, their van der Waal's radii being 1.2 and 1.35 Å, respectively.[13] Thus, the difference in the electronic effects (fluorine being the most electronegative element in the periodic table) is often the basis for the major differences in the pharmacological properties of agents where fluorine has been substituted for hydrogen. Due to its electronegativity, fluorine exerts strong field and inductive effects on the adjacent carbon atom. Fluorine substitution, in general, exerts a diminished electron-withdrawing effect at distal sites. However, fluorine can donate a lone pair of electrons by resonance. This is commonly referred to as its mesomeric effect. The opposing resonance and field effects can nearly cancel. The pharmacological differences can be attributed to the influence of the electron-withdrawing effect that the fluorine substitution causes on interaction with either a biological receptor or enzyme, as well as its effect on the metabolic fate of the drug.

The antineoplastic agent 5-fluorouracil (5-FU) represents a classical example of how fluorine substitution of a normal enzyme substrate can result in a derivative which can alter select enzymatic processes. form of 5-FU, 5-fluoro-2′-deoxyuridylic acid, is ultimately responsible for the inhibition of thymidylate synthase, an enzyme involved in the conversion of uridylic acid to thymidylic acid and critical for DNA synthesis (Figure 1). The increased reactivity of 5-fluoro-2′-deoxyuridylic acid relative to 2′-deoxyuridylic acid is due to the inductive effect of fluorine which results in its covalent binding to thymidylate synthase.

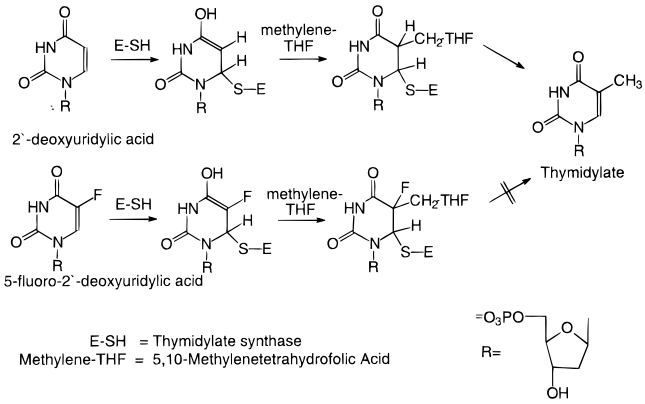

Figure 1.

The application of the monovalent substitution of a fluorine atom for a hydrogen atom can also be seen in a more recent study with naphthyl-fused diazepines, which were employed as agonistic probes of the pharmacophore of benzodiazepine receptors.[14] Replacement of the hydrogen with fluorine at the *ortho* position of the pendent phenyl group of either naphthyl-fused diazepines, as illustrated in Figure 2, resulted in enhanced affinity and efficacy for both naphthyl isomers (Table 4). This greater receptor binding affinity could again be attributed to the inductive effect of the fluorine atom facilitating a stronger interaction with the receptor.

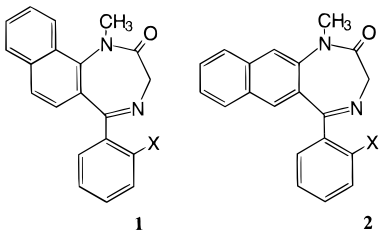

Figure 2.

Table 4. Benzodiazepine Receptor Binding Affinity for Naphthyl-Fused Diazepines

compound	X	IC_{50} (nM)[a]
1a	H	1000
1b	F	260
2a	H	1000
2b	F	55

[a] *In vitro* potency of the compound to displace [^{3}H]flunitrazepam from the benzodiazepine receptor.

Another good illustration of this monovalent bioisosteric replacement is observed in a recent series of anti-inflammatory corticosteroid analogues (**3**, Figure 3).[15] In this study, the topical anti-inflammatory

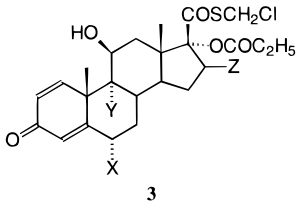

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Figure 3.

Table 5. Biological Activities of Halomethyl Androstane-17β-carbothionates

compound	X	Y	Z	topical anti-inflammatory activity[a]
3a	H	F	$=CH_2$	42
3b	F	F	$=CH_2$	108
3c	H	H	β-CH_3	27
3d	H	F	β-CH_3	41

[a] Topical anti-inflammatory activity was measured in mice by modifications of the croton oil ear assay.[16] Fluocinolone acetonide served as a positive control and is assigned a relative potency index of 100.

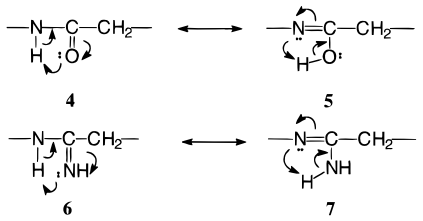
5 shows that, in the case of the pair of compounds possessing a 16-methylene substituent, the presence of an additional fluorine atom at the 6α position results in a derivative with greater activity than **3a** or fluocinolone acetonide. With the pair of corticosteroids with a 16-methyl substituent (Z = CH_3), replacement of hydrogen with fluorine at the 9α position, **3d**, also increased anti-inflammatory activity relative to **3c**.

Thus, the ability of fluorine to replace hydrogen is an effective method of exploring the affinity of an agent to the target site (receptor or enzyme) by virtue of its greater electronegativity while other parameters such as steric size and lipophilicity[17] are maintained.

2. *Interchange of Hydroxyl and Amino Groups*

The monovalent interchange of amino and hydroxyl groups is well known and has been successfully employed in the development of various pharmacological agents. The similar steric size (Table 7), spatial arrangement, and the ability of these functional groups to act as either *hydrogen bond acceptors or donors* is likely responsible for their successful use as bioisosteres.

Several medicinal agents under investigation as potential clinical agents carry heteroaromatic moieties. Many of these heteroaromatic compounds are capable of tautomerization. The prototropic tautomerism of heteroaromatic compounds includes all agents wherein a mobile proton can move from one site to another within the heteroaromatic molecule. Figure 4 illustrates one of the more common types of tautomerization involving the movement of a proton between a cyclic nitrogen atom and a substituent on the neighboring carbon atom within the ring. Tautomerism in heterocyclic molecules has been extensively studied.[18] In the presence of electron-

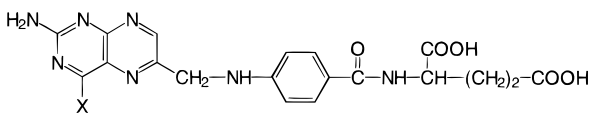


4 5 6 7

Figure 4.

carbon containing C—NH_2 (**7**, Figure 4), the preferred tautomer is the C—NH_2 form.

Perhaps the best known example of classical isosteric substitution of an amino for a hydroxyl group is illustrated by aminopterin (**8b**) wherein the hydroxyl substituent of folic acid (**8a**) has been substituted by an amino group (Figure 5). As previously noted, this represents a monovalent bioisosteric substitution at a carbon atom adjacent to a heterocyclic nitrogen atom. Thus, this bioisosteric replacement has the capability of mimicking even the tautomeric forms of folic acid. The similarity as well as the capability of the amino group to hydrogen bond to the enzyme are two important factors that facilitate the binding of aminopterin to the enzyme dihydrofolate reductase.



8a X = OH Folic Acid
8b X = NH_2 Aminopterin

Figure 5.

Interchange of an amino group with a hydroxyl moiety in the case of 6,9-disubstituted purines (Table 6) has been shown to result in the development of agents with similar benzodiazepine receptor binding activity.[20] This example further substantiates the ability of the amino group to mimic the hydroxyl group at the receptor site. In this study a series of 6,9-disubstituted purines were tested for their ability to bind to the benzodiazepine receptor in rat brain tissue. The relative activity of the 9-(3-aminophenyl)-methyl derivative (**9a**) was compared to the 9-(3-hydroxyphenyl)methyl analogue (**9b**) (Figure 6). In contrast to aminopterin where a dramatic difference in binding affinity was observed relative to the normal substrate, these bioisosteric 6,9-disubstituted

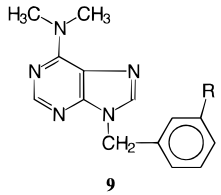


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Figure 6.

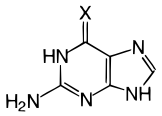
Table 6. Benzodiazepine Receptor Binding Activity of Substituted 6-(Dimethylamino)-9-benzyl-9*H*-purines

compound	R	IC_{50} (μM)[a]
9a	NH	0.9

purines exhibited similar activity with regard to their affinity for the benzodiazepine receptor. In this example of bioisosteric replacement, pharmacological activity was retained. It is important to note that retention of biological activity based on *in vitro* data can be critical in those instances where differences between bioisosteric analogues exist with regard to *in vivo* parameters which may include absorption, distribution, metabolism, or elimination. While one may only observe retention of activity associated with interaction of drug with the pharmacophore, bioisosteres may differ dramatically in their *in vivo* efficacy. Additional examples of this bioisosteric replacement will be discussed in the next section on monovalent replacement of hydroxyl and thiol groups.

3. Interchange of Hydroxyl and Thiol Groups

The interchange of thiol for hydroxyl can be considered as an extension of the amino−hydroxyl replacement and has been used extensively in medicinal chemistry. This replacement is based on the ability of both these functional groups to be *hydrogen bond acceptors or donors*. A classical illustration of this replacement being guanine (**10a**) and 6-thioguanine (**10b**, Figure 7).[21]



10a X = O Guanine

10b X = S 6-Thioguanine

Figure 7.

As discussed in the previous section, when part of a heteroaromatic ring, these functional groups can exist in different tautomeric forms. Figure 8 illustrates the most common example wherein a mobile proton on a nitrogen atom in the aromatic ring can be transferred to the heteroatom attached to the adjacent carbon resulting in the different tautomers.

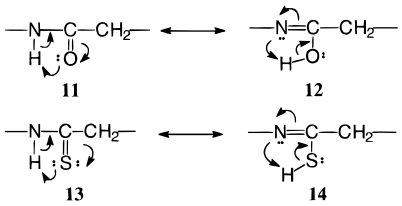


Figure 8.

In the case of 6-thioguanine, the ability of this bioisosteric analogue to be viewed as a substrate by the salvage pathway associated with purine biosynthesis, allows for its transformation into 6-thioguanylic acid by hypoxanthine-guanine phosphoribosyltransferase (HGPRT). However, the significance of this "fraudulent" nucleic acid with respect to its lethality to neoplasms is uncertain.[22] It is as this phosphoriboside that either the *de novo* synthesis of nucleic acids is inhibited or incorporation into deoxyribonucleic acid occurs.

In an attempt to enhance the calcium channel

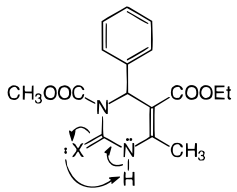


Figure 9.

Table 7. Calcium Channel Blocking Activity of 1,4-Dihydropyrimidines

compound	X	van der Waal's radius[24] (Å)	IC_{50} (nM)[a]
15a	=O	1.40	140
15b	=NH	1.50	160
15c	=S	1.85	17

[a] Concentration that produced 50% inhibition and determined for the vasorelaxant activity with potassium-depolarized rabbit thoracic aorta.

analogues with similar potency. However, substitution with the thiol resulted in enhanced potency (Table 7). This could be explained by the fact that the size of the substituents, described here as the van der Waal's radii, and the ability to hydrogen bond were the important factors influencing retention of activity. Therefore, replacement with the amino group, which has a similar size, resulted in similar potency. However, replacement with the sterically optimal thiol resulted in an analogue which was an order of magnitude more potent.

The use of this replacement in the design of novel anti-inflammatory agents substantiates its utility as a monovalent bioisostere. Long term use of nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of rheumatoid arthritis and other inflammatory diseases has been associated with side effects such as gastrointestinal ulceration, bleeding, and nephrotoxicity.[25,26] With a view to designing new drugs with an improved safety profile, certain thiazoles (**16**, Figure 10 and Table 8) that are dual

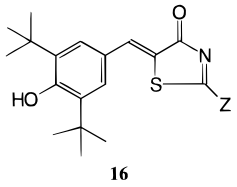


Figure 10.

Table 8. Anti-inflammatory Activity of Benzylidene Derivatives in Intact Rat Basophilic Leukemia (RBL-1) Cells

compound	Z	electronegativity[29]	IC_{50} (μM)[a] 5-LO	IC_{50} (μM)[a] CO
16a	OH	3.51	1.4	0.35
16b	NH_2	2.61	0.77	0.39
16c	SH	2.32	0.38	0.012

[a] Concentration of the test compound causing 50% inhibition of 5-LO or CO formation.

inhibitors of both cyclooxygenase (CO) and 5-lipoxygenase (5-LO) are being studied as potential anti-

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