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Note to subscribers. *We regret the delays in publication of the 1979 issues of CS Reviews. The main causes were the long-term effects of shortages in submitted articles and production difficulties during earlier years. Steps have been taken to rectify this distressing situation, and the intention is to revert to the usual quarterly publication dates by the end of 1980 or the beginning of 1981.*

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Isosterism and Molecular Modification in Drug Design

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1 Introduction

The idea of isosterism goes back to Langmuir[1] in 1919. At that time the word isosterism was used to describe the similarity of molecules or ions which have the same number of atoms and valence electrons *e.g.* O^{2-}, F^-, Ne. Clearly only those isosteres with the same nett charge show similar chemical and physical properties. Grimm[2] enunciated his hydride displacement law to describe the similarity between groups which have the same number of valence electrons but different numbers of atoms. For example some similarities are present in the sequence: CH_3, NH_2, OH, Hal.

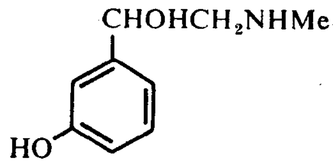
Grimm's hydride displacement law points out some similarities of size in groupings based on elements in the same row of the periodic table. Other similarities to be found in the periodic table are within the groups, where chemical reactivities are similar but with electronegativity decreasing as atomic weight increases and lipophilicity and polarizability increasing with the size of the atom. Other relationships exist in diagonal lines across the periodic table where atoms of similar electronegativity such as nitrogen and sulphur, oxygen and chlorine are found.

In trying to relate biological properties to the physical and chemical properties of atoms, groups, or molecules, many physical and chemical parameters may be involved and the simple relationships mentioned above are clearly inadequate for this purpose. Friedman[3] introduced the term 'bioisosterism' to describe the phenomenon in which compounds which are related in structure have similar or antagonistic properties. The use of the word isosterism has clearly outgrown its original meaning when used in medicinal chemistry and a loose flexible definition could be adopted such as: 'Bioisosteres are groups or molecules which have chemical and physical similarities producing broadly similar biological properties'.

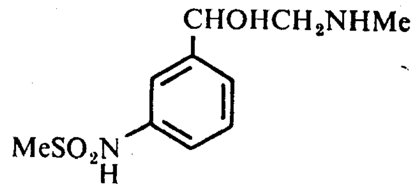
The term non-classical isosterism is also used interchangeably with bioisosterism, particularly in connection with isosteres which do not have the same number of atoms but do produce a similarity in some key parameter of importance in

[1] I. Langmuir, *J. Amer. Chem. Soc.*, 1919, **41**, 868, 1543.
[2] H. G. Grimm, *Z. Elektrochem.*, 1925, **31**, 474; 1928, **34**, 430; 1934, **47**, 53, 594.
[3] H. L. Friedman, 'Influence of Isosteric Replacements upon Biological Activity', National Academy of Sciences—National Research Council Publication No. 206. Washington D.C., 1951, p. 295.

that series. For example[4] the two β-adrenergic stimulants compounds (1) and (2) have similar activity.



(1) pK_a 9.6



(2) pK_a 9.1

The concept of bioisosterism has been described in reviews by Burger,[5a] Schatz,[5b] Foye,[6] Korolkovas,[7] Ariens,[8] and Hansch.[9] This present review collates and extends the earlier observations with more recent reports from the literature and suggests new techniques for exploiting the concept.

The 'classical' isosteres as defined by Burger[5] and Korolkovas[7] are given in Table 1.

Table 1

1) *Univalent atoms and groups*

F	OH	NH_2	Me	Cl
	SH	PH_2		
	I	Bu^t		
	Br	Pr^i		

2) *Bivalent atoms and groups*

O	S	Se	CH_2	—NH—
CO_2R	COSR	$COCH_2R$	CONHR	

3) *Tervalent atoms and groups*

—N=	—CH=
—P=	—As=

4) *Quadrivalent atoms*

>C<	>Si<

5) *Ring equivalents*

—CH=CH—	S	*e.g.* benzene: thiophen
=CH—	=N—	*e.g.* benzene: pyridine

—O— —S— —CH_2— —NH—

[4] A. A. Larson and P. M. Lish, *Nature*, 1964, **203**, 1283.

[5a] A. Burger in 'Medicinal Chemistry' 3rd Edn., ed. A. Burger, Wiley-Interscience, New York, 1970.

[5b] V. B. Schatz in 'Medicinal Chemistry' 2nd Edn., ed. A. Burger, Wiley-Interscience, New York, 1960.

[6] W. O. Foye, 'Principles of Medicinal Chemistry', Lea and Febiger, Philadelphia, 1970.

[7] A. Korolkovas, 'Essentials of Molecular Pharmacology: Background for Drug Design', Wiley, 1970.

[8] E. J. Ariens in 'Drug Design', ed. E. J. Ariens, Academic Press, New York, 1971, Vol. 1.

[9] C. Hansch, *Intra-Science Chem. Rep.*, 1974, **8**, 17.

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