The Organic Chemistry of Drug Design and Drug Action

Richard B. Silverman
Department of Chemistry
Northwestern University
Evanston, Illinois

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Different activities can result from a ring–chain transformation as well. For example, if the dimethylamino group of chlorpromazine is substituted by a methylpiperazine ring (**2.34**, X = Cl, R = $CH_2CH_2CH_2N$⟨⟩NCH_3; prochlorperazine), the antiemetic (prevents nausea and vomiting) activity is greatly enhanced. In this case, however, an additional amino group is added.

4. Bioisosterism

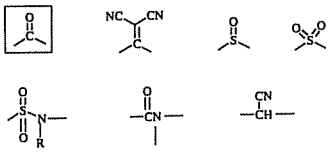
Bioisosteres are substituents or groups that have chemical or physical similarities, and which produce broadly similar biological properties.[23] Bioisosterism is a lead modification approach that has been shown to be useful to attenuate toxicity or to modify the activity of a lead, and it may have a significant role in the alteration of metabolism of a lead. There are classical isosteres[24,25] and nonclassical isosteres.[23,26] In 1925 Grimm[27] formulated the *hydride displacement law* to describe similarities between groups that have the same number of valence electrons but may have a different number of atoms. Erlenmeyer[28] later redefined isosteres as atoms, ions, or molecules in which the peripheral layers of electrons can be considered to be identical. These two definitions describe *classical isosteres*; examples are shown in Table 2.2. *Nonclassical*

Table 2.2 Classical Isosteres[24,25]

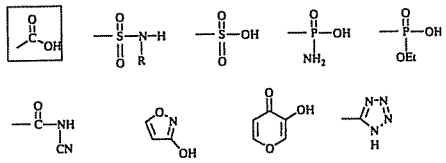
1. Univalent atoms and groups					
a. CH_3	NH_2	OH	F	Cl	
b. Cl	PH_2	SH			
c. Br	*i*-Pr				
d. I	*t*-Bu				
2. Bivalent atoms and groups					
a. $-CH_2-$	—NH—	—O—	—S—	—Se—	
b. $-COCH_2R$	—CONHR	$-CO_2R$	—COSR		
3. Trivalent atoms and groups					
a. —CH═	—N═				
b. —P═	—As═				
4. Tetravalent atoms					
a. $-\overset{|}{\underset{|}{C}}-$	$-\overset{|}{\underset{|}{Si}}-$				
b. ═C═	$=\overset{+}{N}=$	$=\overset{+}{P}=$			
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)	

Table 2.3 Nonclassical Bioisosteres[23]

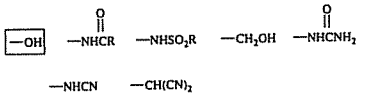
1. **Carbonyl group**



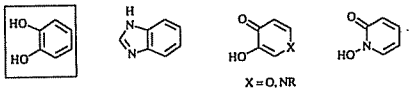
2. **Carboxylic acid group**



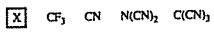
3. **Hydroxy group**



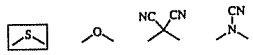
4. **Catechol**



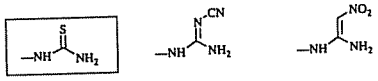
5. **Halogen**



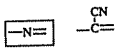
6. **Thioether**



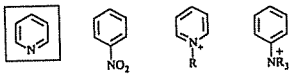
7. **Thiourea**



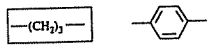
8. **Azomethine**



9. **Pyridine**



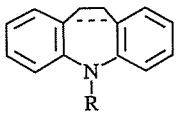
10. **Spacer group**



11. **Hydrogen**

bioisosteres do not have the same number of atoms and do not fit the steric and electronic rules of the classical isosteres, but they do produce a similarity in biological activity. Examples of these are shown in Table 2.3.

Ring–chain transformations also can be considered to be isosteric interchanges. There are hundreds of examples of compounds that differ by a bioisosteric interchange[23,26]; some examples are shown in Table 2.4. Bioisosterism also can lead to changes in activity. If the sulfur atom of the phenothiazine neuroleptic drugs (**2.34**) is replaced by the —CH=CH— or —CH_2CH_2— bioisosteres, then dibenzazepine antidepressant drugs (**2.35**) result.



2.35

It is, actually, quite surprising that bioisosterism should be such a successful approach to lead modification. Perusal of Table 2.2, and especially of Table 2.3, makes it clear that in making a bioisosteric replacement, one or more of the following parameters will change: size, shape, electronic distribution, lipid solubility, water solubility, pK_a, chemical reactivity, and hydrogen bonding. Because a drug must get to the site of action, then interact with it (see Chapter 3), modifications made to a molecule may have one or more of the following effects:

1. Structural. If the moiety that is replaced by a bioisostere has a structural role in holding other functionalities in a particular geometry, then size, shape, and hydrogen bonding will be important.
2. Receptor interactions. If the moiety replaced is involved in a specific interaction with a receptor or enzyme, then all of the parameters except lipid and water solubility will be important.
3. Pharmacokinetics. If the moiety replaced is necessary for absorption, transport, and excretion (collectively, with metabolism, termed *pharmacokinetics*) of the compound, then lipophilicity, hydrophilicity, pK_a, and hydrogen bonding will be important.
4. Metabolism. If the moiety replaced is involved in blocking or aiding metabolism, then the chemical reactivity will be important.

It is because of these subtle changes that bioisosterism is effective. This approach allows the medicinal chemist to tinker with only some of the parameters in order to augment the potency, selectivity, and duration of action and to reduce toxicity. Multiple alterations may be necessary to counterbalance effects. For example, if modification of a functionality involved in binding also decreases the lipophilicity of the molecule, thereby reducing its ability to

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