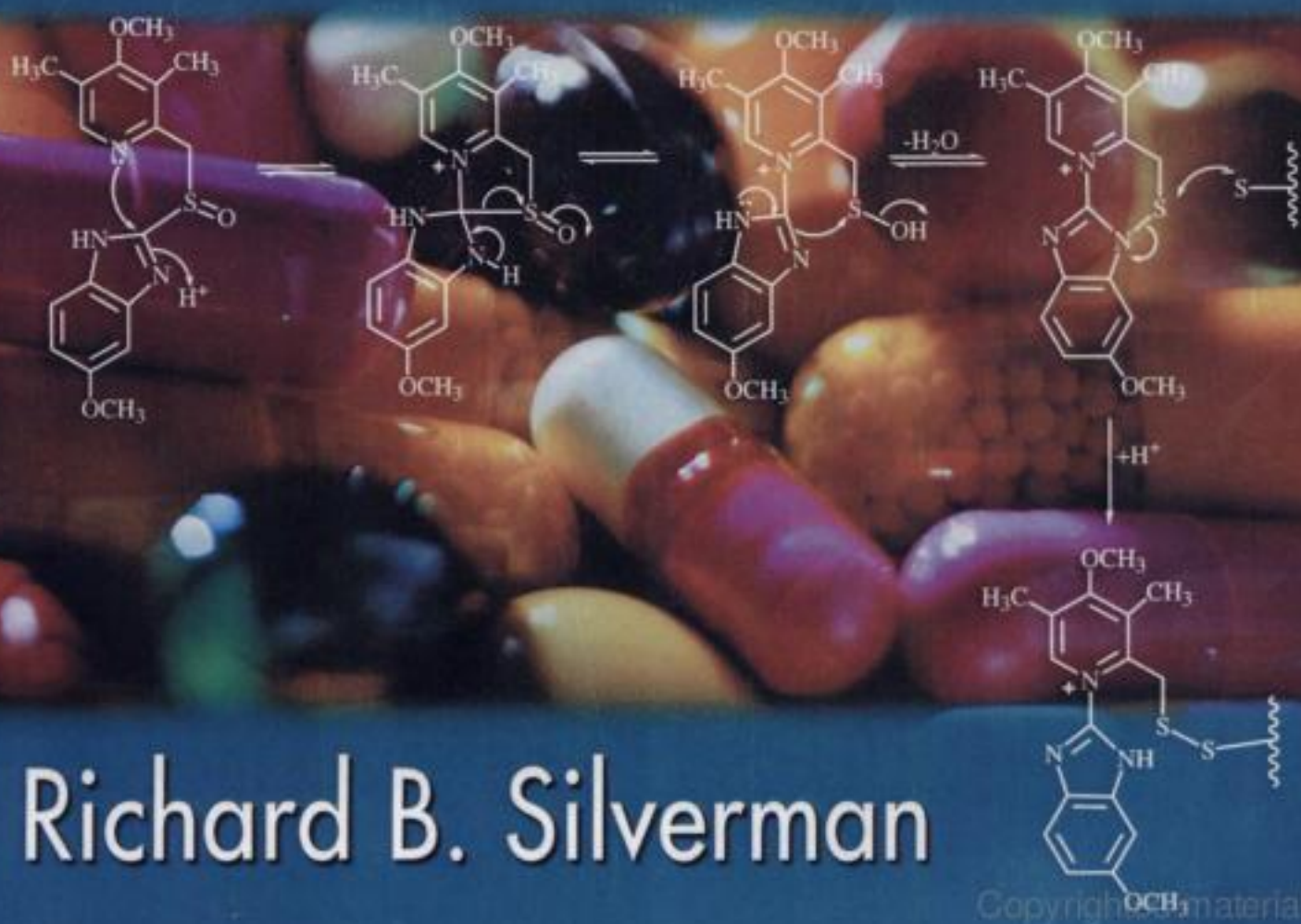




The ORGANIC CHEMISTRY of DRUG DESIGN and DRUG ACTION

Second Edition



Richard B. Silverman

TABLE 2.2 ► Classical Isosteres

1. Univalent atoms and groups				
a.	CH ₃	NH ₂	OH	F Cl
b.	Cl	PH ₂	SH	
c.	Br	<i>i</i> -Pr		
d.	I	<i>t</i> -Bu		
2. Bivalent atoms and groups				
a.	—CH ₂ —	—NH—	—O—	—S— —Se—
b.	—COCH ₂ R	—CONHR	—CO ₂ R	—COSR
3. Trivalent atoms and groups				
a.	—CH≡	—N≡		
b.	—P≡	—As≡		
4. Tetravalent atoms				
a.	$\begin{array}{c} \\ -C- \\ \end{array}$	$\begin{array}{c} \\ -Si- \\ \end{array}$		
b.	≡C≡	≡N ⁺ ≡	≡P ⁺ ≡	
5. Ring equivalent				
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)

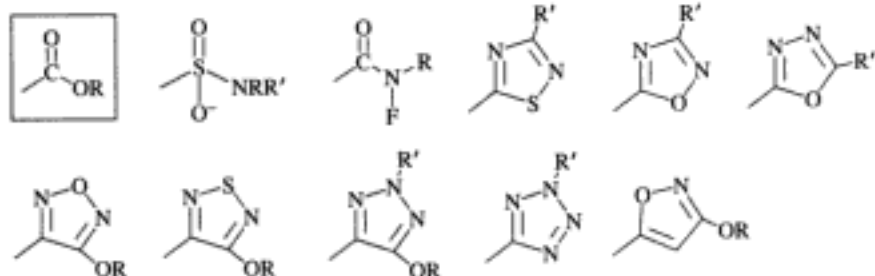
and vomiting) activity is greatly enhanced. In this case, however, an additional methylamino group is also added, which may have an effect in changing the activity.

E.4 Bioisosterism

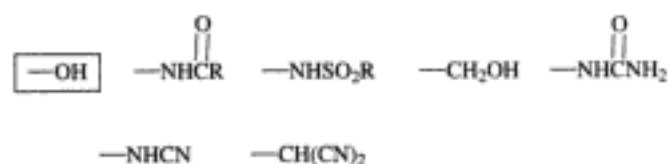
Bioisosteres are substituents or groups that have chemical or physical similarities, and which produce broadly similar biological properties.^[54] Bioisosterism is an important lead modification approach that has been shown to be useful to attenuate toxicity or to modify the activity of a lead, and may have a significant role in the alteration of pharmacokinetics of a lead. There are classical isosteres^[55,56] and nonclassical isosteres.^[57] In 1925 Grimm^[58] 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^[59] 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 bioisosteres* do not have the same number of atoms and do not fit the steric and electronic rules of the classical isosteres, but do produce similar 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;^[60] some examples are shown in Table 2.4.

TABLE 2.3 ► Continued

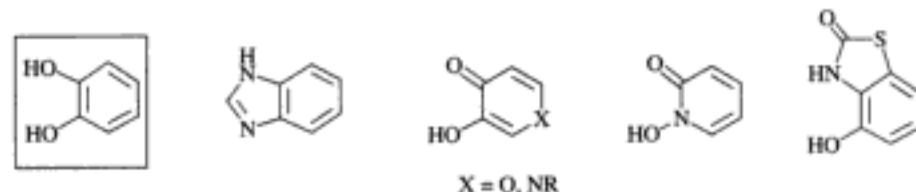
Ester group



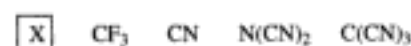
Hydroxyl group



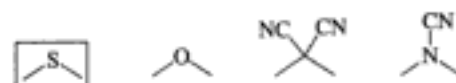
Catechol



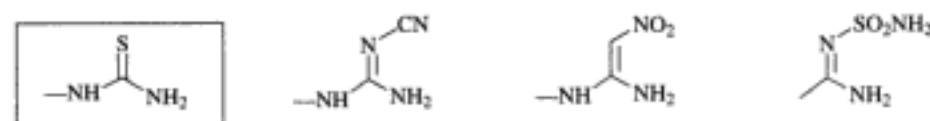
Halogen



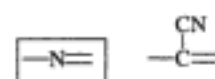
Thioether



Thiourea



Azomethine



Continued