Table 16.1 Bioisosteric Atoms and Groups

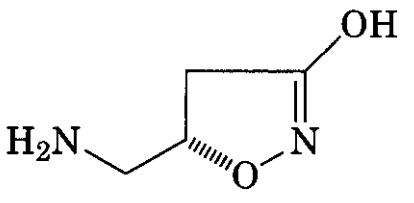
1. Univalent				
–F	–OH	$–NH_2$	$–CH_3$	–Cl
		S H	$–PH_2$	
		–I	$t\text{-}C_4H_9$	
		–Br	$i\text{-}C_3H_7$	
2. Bivalent				
–O–	–S–	–Se–	$–CH_2–$	–NH–
3. Tervalent				
–N=	–CH=			
–P=	–As=			
4. Quadrivalent				
–C–	–Si–			
5. Ring equivalents				
–CH=CH–	–S– (e.g., benzene, thiophene)			
=CH–	=N– (e.g., benzene, pyridine)			
–O–	–S–	$–CH_2–$	–NH–	

diazomethane and ketene both have 22 orbital electrons. Medicinal chemists have expanded and adapted the original concept to the analysis of biological activity. The following definition has been proposed: "Bioisosteres are groups or molecules which have chemical and physical properties producing broadly similar biological properties" (2). This definition might be modified to include the concept that bioisosteres may produce ***opposite*** biological effects, and these effects are frequently a reflection of some action on the same biological process or at the same receptor site. Bioisosteric similarity of molecules is commonly assigned on the basis of the number of valence electrons of an atom or a group of atoms rather than on the total number of orbital electrons, as was originally specified by Langmuir. In a remarkable number of instances, compounds result that have similar (or even diametrically opposite) pharmacological effects compared with those of the parent compound. Categories of classic bioisosteres have been described (2) (Table 16.1).

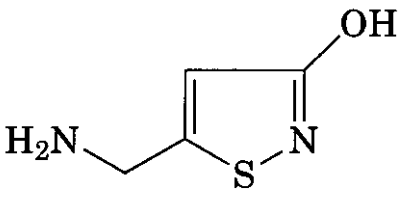
A more recent comprehensive review of bioisosterism appeared in 1996 **(3).** In a short communication, Burger (4) discussed and provided valuable insights into isosterism and bioanalogy in drug design.

Many compounds have been identified that comply with the "biology" aspect of the bioisostere concept but that do not fit the strict chemical (steric and electronic) definition of bioisosteres. Floersheim et al. **(5)** proposed that such compounds be designated as ***nonisosteric bioanalogs,*** replacing the older term, "nonclassical bioisosteres." However, most of the contemporary literature retains the nonclassical bioisostere terminology. Table 16.2 lists representative nonclassical bioisosteres.

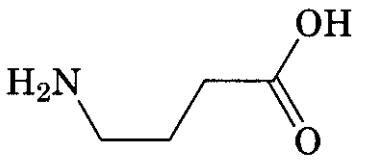
Dihydromuscimol (**1**) and thiomuscimol (**2**) are cyclic analogs of y-aminobutyric acid (GABA) (**3**), in which the C=N moiety of the



(1)



(2)



(3)

heterocyclic ring is considered to be bioisosteric with the of GABA. The –S– moiety of thiomuscimol is bioisosteric with the ring –O– of dihydromuscimol. Both (**1**) and (2) are highly potent agonists at $GABA_A$ receptors, as determined in an electrophoresis-based assay (**6**).

Because of its bioisosteric similarity to the normal physiological substrate L-dopa (**4**), L-mimosine (**5**) inhibits catechol oxidation by the enzyme tyrosinase (7). These compounds exemplify a situation in which bioisosteres display ***opposite*** pharmacologic effects at the same receptor.

The sulfonium bioisostere (6) of *N,N*-dimethyldopamine (7) retains the dopaminergic agonist effect displayed by (7) (**8**). The fact that (6) bears a permanent unit positive charge was invoked in support of the hypoth-