BIOISOSTERISM

As discussed above, simple structural changes, such as increasing the length of a side chain (methyl, ethyl, propyl, etc. Figure 5.3), adding functionality to a benzene ring as described in the Topliss Tree (Figure 5.10), or the additions of hydrogen bond acceptors/donors (Figure 5.4) can lead to improvements in biological properties. There are, however, additional avenues that can be explored. The concept of isosterism, originally developed by Langmuir[36] and then broadened by Erlenmeyer,[37] can also be applied to drug discovery. Langmuir (1919) and Erlenmeyer (1932) hypothesized that compounds, functional groups, or atoms with the same arrangement and number of electrons in their outermost electron shells would have similar physical and chemical properties based on their isoelectronic features. The scope of Erlenmeyer's original premise was eventually expanded by Harris L. Friedman in 1951 when he defined compounds as bioisosteric "if they fit the broadest definition for isosteres and have the same type of biological activity."[38] In a similar manner, functional groups and atoms within a more complex molecule that can be interchanged while maintaining the same or similar biological properties are referred to as bioisosteres of each other. Modification of candidate compounds by applying the premise of bioisosterism is commonplace in drug discovery programs, as it is a useful tool for expanding the structural diversity of a lead series to identify novel chemical space and to alter physicochemical properties. These subjects will be addressed in greater detail in Chapters 12 and 6, respectively.

Bioisosteres can be divided into two broad classes: classic and nonclassic bioisosteres, as first proposed by Alfred Burger.[39] According to this system of classification, classic bioisosteres are broadly defined as atoms, molecular fragments, or functional groups that have the same valence and ring equivalents (Table 5.1). Typical examples include exchanging halogen atoms and replacing methylene units with an oxygen or sulfur atom. A practical application of this principle is seen in efforts to develop alternatives to the antihypertensive drug rilmenidine (Albarel). In this instance, replacing the oxygen atom of rilmenidine's 4,5-dihydro-oxazole ring system with a methylene unit provided the 4,5-dihydro-pyrrole analog

TABLE 5.1 Classic Bioisosteres

Monovalent	Divalent	Trivalent	Tetravalent
–OH, $–NH_2$, $–CH_3$, –OR	$–CH_2–$	=CH–	=C=
–F, –Cl, –Br, –I, –SH, $–PH_2$	–O–	=N–	=Si=
$–SiR_3$, –Sr	–S–	=P–	$=N^+=$