

1.4.3.1 Bioisosteres

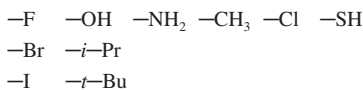
Bioisosteric replacement, also named molecular mimicry, is one of the most widely used principles for optimization of drug molecules. Bioisosteres are molecules in which atoms or functional groups are modified in order to obtain new molecules with a biological activity related to the parent molecule. The purpose is to obtain drug molecules with improved biological properties. Bioisosteric replacement can change a number of physicochemical properties of the resulting molecules compared to the parent molecule: size, shape, electronic distribution, solubility, pK_a , and chemical reactivity. These changes may lead to changes in the pharmacodynamics as well as pharmacokinetic properties, e.g., changes in potency, selectivity, bioavailability, and metabolism.

Bioisosteres have been classified as either classical or nonclassical. In classical bioisosterism, similarities in certain physicochemical properties have enabled investigators to successfully exploit several monovalent isosteres. These can be divided into the following groups: (1) fluorine versus hydrogen replacements; (2) amino-hydroxyl interchanges; (3) thiol-hydroxyl interchanges; and (4) fluorine, hydroxyl, amino, and methyl group interchanges (Grimm's hydride displacement law, referring to the different number of hydrogen atoms in the isosteric groups to compensate for valence differences). The nonclassical bioisosteres include all those replacements that are not defined by the classical definition of bioisosteres. These isosteres are capable of maintaining similar biological activity by mimicking the spatial arrangement, electronic properties, or some other physicochemical properties of the molecule or functional group that are of critical importance. A number of classical and nonclassical bioisosteres are shown in Table 1.1 representing only a selection of more commonly used bioisosteres. The concept of nonclassical bioisosterism, in particular,

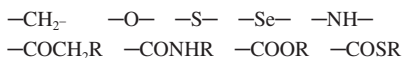
TABLE 1.1
Examples of Bioisosteric Replacements

Classical

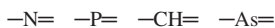
Monovalent
atoms and groups



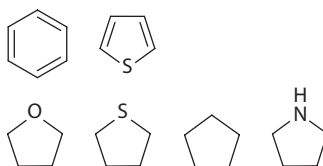
Bivalent
atoms and groups



Trivalent
atoms and groups



Ring equivalents



Nonclassical

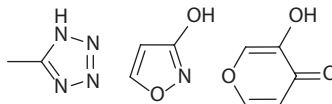
Hydroxyl group



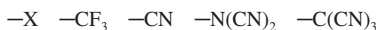
Carbonyl group



Carboxylic acid



Halogen



Spacer group

