to procainamide versus procaine is critical to its utility as an oral antiarrhythmic agent.[41]

Non-classic bioisosteres represent a much broader range of structural diversity, as this category is defined as anything that does not fit the definition of a classic bioisostere. It should come as no surprise that the vast majority of examples of bioisosterism fall into this category and that a full characterization of this area of drug discovery is beyond the scope of this chapter. The concepts involved, however, can be described in a few examples. Replacing carboxylic acids in candidate compounds, for example, has been widely studied, as this functional group can create undesirable physicochemical properties. Compounds containing carboxylic acids tend to have low permeability through biological membranes, are poorly absorbed when dosed orally, and are rapidly cleared by the body. Their ability to cross the blood–brain barrier is also often limited at best. In other words, if a compound with a high degree of potency at a biological target of interest contains this functional group, moving the compound down the drug discovery and development pathway may prove challenging. Replacing this functionality with a suitable bioisostere may alleviate these issues, and some examples are shown

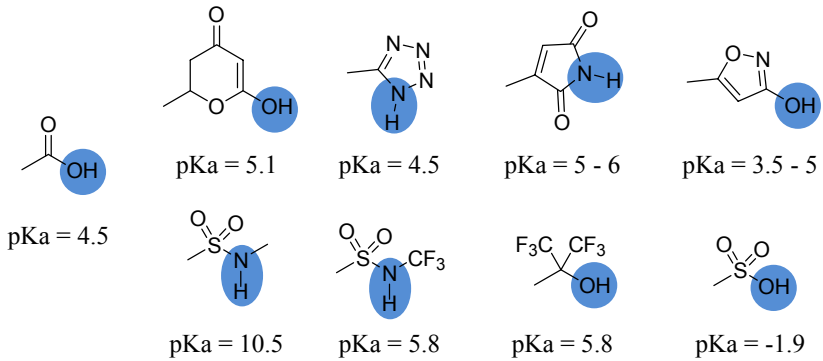

FIGURE 5.25 There are many potential non-classic bioisosteric replacements for a carboxylic acid, but they are by no means equivalent. Structural diversity is readily apparent, but an examination of the pKa values of each (highlighted in blue) provides an alternative view of the differences between the various possible carboxylic acid mimetics.

in Figure 5.25. In each instance, the dissociable proton of the carboxylic acid is maintained, but the remainder of the functionality is replaced with a collection of atoms capable of mimicking the original structure in a biological setting. The successful application of any one of these carboxylic acid bioisosteres is dependent upon the nature of the interaction between the candidate compound and the macromolecular target. In one successful example, one of the two carboxylic acids of Carbenicillin was