bioisosteres that one could consider in a drug discovery program, and a full discussion of this concept is well beyond the scope of this chapter. Fortunately, numerous review articles are available on the subject for those interested in an in-depth analysis of the subject.[44]

STRUCTURE–ACTIVITY RELATIONSHIP, SELECTIVITY AND PHYSICOCHEMICAL PROPERTIES

Although the focus of the previous sections has been on the identification of increasingly more potent compounds through the analysis of structure–activity relationships, potency at a biological target is not the only consideration in a drug discovery program. As noted in Chapter 1, target selectivity is often critical to the identification of clinically relevant compounds, and physicochemical properties such as solubility and metabolic stability are major factors that must be considered. Fortunately, the same principles that have been discussed with respect to optimization of binding interactions at the intended molecular target can be employed to optimize any molecular property, provided there is a means of measuring the impact of structural changes on the property of interest. If, for example, one were targeting Kv1.5, a voltage-gated potassium channel that has clinical relevance in atrial arrhythmia,[45] optimizing this activity would be necessary. It would also be necessary, however, to establish that candidate compounds did not negatively impact the hERG channel, a voltage-gated potassium channel associated with Torsades de pointes and sudden cardiac death.[46] In this instance, a structure–activity relationship could be established for activity at the hERG channel, focusing on minimizing the potency at this channel. Thus, structural changes that *decreased* hERG activity would be maintained, while those that increased hERG activity would be dropped. Successful compounds would be identified by analyzing the SAR of *both* Kv1.5 and hERG in an effort to maximize one while minimizing the other.

In a similar manner, physicochemical properties can be optimized through structure–property relationships. Just as changes in molecular structure will have an impact of the ability of a compound to bind to a biomolecule, changes in molecular structure will also have an impact on physicochemical properties. Quantifying the impact of structural changes on a property of interest provides a means of optimizing that property through manipulation of the molecular structure. Some of these properties, for example, solubility and metabolic stability, require physical assessment. Fortunately, high-throughput screens have been developed to facilitate this process. Other properties, such as lipophilicity and polar surface area, can be calculated using the appropriate software tools. In either case, once knowledge of structural changes is paired with the appropriate data set, patterns can be established and properties can be