resulting compound would be able to form the hydrogen bond indicated, strengthening the interaction between the ligand and the binding pocket. Knowledge of the increased binding energy, as indicated by IC_{50} screening data against the target of interest, would suggest that replacing the propyl amine side chain with a piperidine (c) would provide a compound of similar potency, as both compounds would provide the framework necessary for the formation of a critical hydrogen bond. In contrast, one could predict that relocating the amine hydrogen bond donor ortho to the fluorine atom (d) would position the potential hydrogen bond donor away from the hydrogen bond acceptor (amide). No significant increase in binding strength would be expected in this scenario.

THE ROLE OF CHIRALITY

All of the aforementioned examples describe the relationship between structural changes and biological activity in a two-dimensional framework. In reality, of course, biological activity, cellular function, and life in general occur in three-dimensional space. Macromolecular targets that are the focus of drug discovery and development efforts possess complex three-dimensional structures. This forms the basis of their ability to differentiate between potential ligands, even in cases where a pair of compounds are simply mirror images of each other. As such, a discussion of structure–activity relationships must include an examination of how changes in the three-dimensional structure of a series of compounds impact biological activity.

The concept of chirality is fundamental to understanding structure–activity relationships and was originally postulated by Lord Kelvin more than 100 years ago. He stated "I call any geometrical figure, or group of points, 'chiral', and say that it has chirality if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."[1] Although this statement applies to any arrangements of materials, within the context of drug discovery the most common occurrence of chirality is a tetrahedral carbon atom with four different substituents (Figure 5.5). In this scenario, the substituents can be

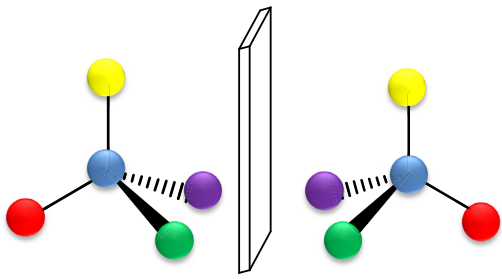

FIGURE 5.5 Chiral compounds cannot be superimposed on their mirror image. The two isomers are referred to as enantiomers (R and S). Chirality often plays a key role in biological activity, as nature is a chiral environment.