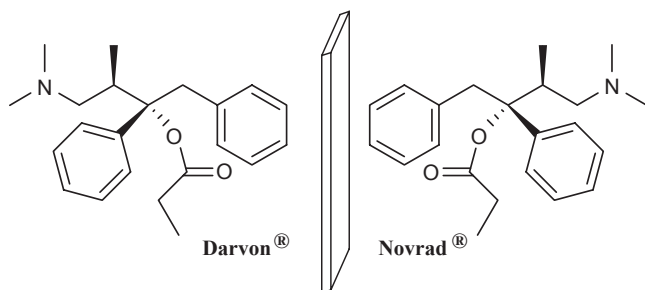


attached to the central carbon atom in one of two arrangements, which are non-superimposable mirror images of each other. The two separate isomers are referred to as enantiomers or optical isomers, and in the absence of a chiral environment, they are identical in all respects, except for the direction in which they rotate plane polarized light. Biological macromolecules, being chiral, offer an environment that predictably discriminates between enantiomers, leading to dramatic changes in the functional activity between pairs of enantiomers. Darvon<sup>2</sup> and Novrad<sup>2a,3</sup> (Figure 5.6), for example, are identical



**FIGURE 5.6** Darvon<sup>®</sup> and Novrad<sup>®</sup> are identical, save for the nature of the chiral center present in each. The enantiomers have very different properties in a biological setting. Darvon<sup>®</sup> is an analgesic that activates the  $\mu$ -opioid receptor, while Novrad<sup>®</sup> is an antitussive agent with minimal efficacy as an analgesic. Unlike its enantiomer, Novrad<sup>®</sup> has little affinity for the  $\mu$ -opioid receptor.

except for the difference in chirality, and this leads to substantially different biological activity. The former is a potent analgesic that acts as a  $\mu$ -opioid receptor agonist,<sup>4</sup> while the latter is an antitussive with minimal potency at the  $\mu$ -opioid receptor.<sup>5</sup> This underscores the importance of how a deceptively simple change in molecular structure, the inversion of a chiral center, can have a significant influence on therapeutic action. In fact, a single change at a chiral center is a drastic change in three-dimensional space and is certainly not viewed as a subtle change to a medicinal chemist. From the perspective of a drug discovery scientist, there is also the underlying question of how one could employ knowledge of the impact of chiral inversions in order to design better candidate compounds. In other words, what is the relationship between structural changes induced by chiral inversion and biological activity?

An understanding of the impact of chiral inversion on biological activity, and thus understanding the role of chirality in structure–activity relationships, is best accomplished through the examination of a practical example. Consider, for example, Tamiflu<sup>®</sup> (oseltamivir), an influenza neuraminidase inhibitor pro-drug useful for the treatment of the common flu.<sup>6</sup> X-ray crystallographic studies of this compound in the binding site of influenza