selected to serve as a preliminary assessment of risk. If, for example, a program were targeting the 5-HT_{1a} serotonin receptor, a selectivity panel designed to assess compounds for off-target side effects would most likely include the remaining serotonin receptors (5-HT_2 through 5-HT_7), as they have a high degree of homology with the target of interest. This type of assessment often occurs early in the *in vitro* screening process and can be used to prioritize candidate compounds. Ultimately, however, a candidate compound must be assessed across a wide range of targets in order to assess its propensity for side effects, safety, and toxicity issues. Even the largest of pharmaceutical companies do not have the capacity to establish *in vitro* screens for the multitude of possible targets that could produce untoward effects. There are, however, a number of organizations that specialize in this particular aspect of the drug discovery and development process. These institutions (e.g., EMD Millipore,[7] Perkin Elmer,[8] Cerep,[9] National Institute of Mental Health's Psychoactive Drug Screening Program,[10] etc.) maintain a diverse set of *in vitro* assays covering important enzymes, ion channels, GPCRs, and other biomolecules that can provide additional insight into potential side effects.

In some cases, safety and toxicology problems associated with a candidate compound are not directly associated with the compound itself. When compounds enter the body, they are subject to the metabolic processes designed to remove them from the circulation. Modification of the candidate compound by metabolic enzyme will produce new compounds that have properties different from the original. If these new compounds are, in turn, capable of binding to biomolecules associated with negative effects, then safety and toxicity issue may arise. Consider, for example, a candidate compound that has negligible binding to the hERG channel, but is metabolized into a compound with strong hERG binding (Figure 8.3). Even though

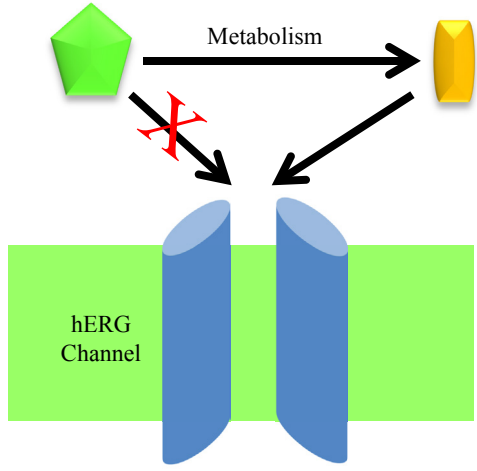

FIGURE 8.3 The drug (green) does not interact with the hERG channel. It is converted to a metabolite (yellow) that blocks the hERG channel.