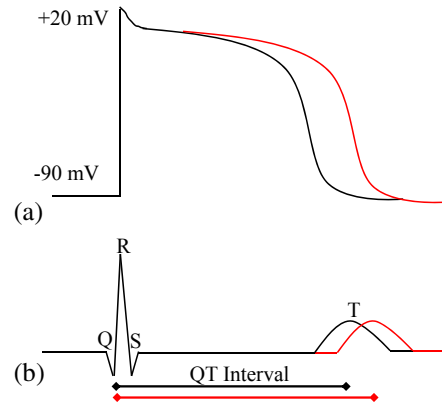
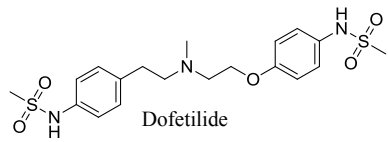


FIGURE 8.17 Compounds that block the hERG channel increase the QT interval of the heart and raise the risk of ventricular arrhythmia, Torsades de pointes, and sudden cardiac death. (a) Cellular level electronic signaling. (b) Electrocardiogram view of electrical signaling. The black line represents normal electrical activity, while the red line represents electrical activity in the presence of a hERG channel blocker.

interval (Figure 8.17) are linked to increased risk for ventricular arrhythmia, Torsades de pointes (ventricular tachycardia), and sudden cardiac death. These dangerous events have, in turn, been linked blockade of the hERG channel. Decreased hERG activity as a result of channel blockade increases the duration of the action potential, lengthens the time required for repolarization, and increases the likelihood of dangerous side effects.[36]

Given the significant risk associated with hERG channel, it is clear that monitoring candidate compounds for activity at this "anti-target" is very important. At the *in vitro* level, it is possible to assess compounds for hERG activity in competitive binding assays (Figure 8.18). In these assays, a potent, radiolabeled hERG channel binder such as



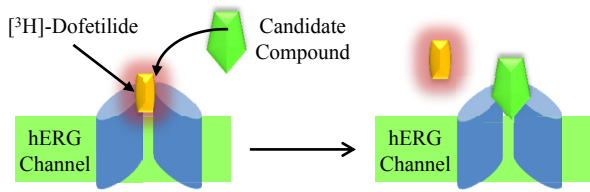


FIGURE 8.18 Displacement of [^{3}H]-dofetilide from it binding site on the hERG channel by candidate compounds can be used to assess the level of hERG risk associated with candidate compounds. This method will only identify compounds that bind to the dofetilide binding site, but there are other binding sites on the hERG channel. Additional assessments using other methods are often performed as a candidate compound advances in the drug discovery process.