ION CHANNELS

Although living organisms are often viewed as complex machines run by chemical reactions, there are many critical functions in living organisms that cannot be accomplished solely by chemical means. In many cases, the generation of an electrical impulse or voltage gradient is required. Ion channels, transmembrane protein assemblies that regulate the flow of ions across biological barriers, play a major role in this process. Nerve impulse transmission,[48] muscle contraction,[49] and cardiovascular function, especially heart rate and rhythm,[50] all depend on the exquisitely balanced flow of ions created by a network of ion channels opening and closing in a coordinated fashion. T-cell activation in an immune response,[51] hormonal secretions (e.g., insulin), cellular proliferation (e.g., lymphocytes, cancer cells[52]), and even cell volume regulation[53] are all impacted by various ion channels. These proteins also play a major role in preventing cellular depolarization by counter balancing the impact of Na^+-coupled transporters (e.g., glucose transporter, amino acid transporters) and Ca^+-signaling events.[54] Modulation of ion channel activity has provided a number of important drugs and lethal toxins (Figure 3.28). Improper ion channel function has

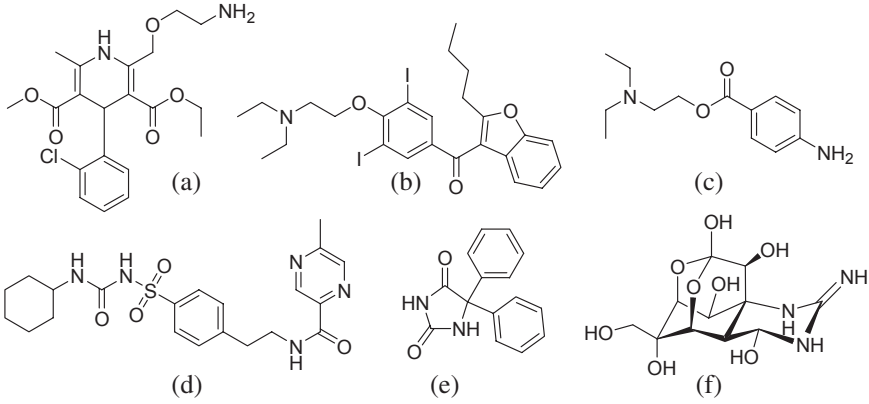

FIGURE 3.28 (a) Norvasc® (Amlodipine), an antihypertensive agent that blocks calcium channels. (b) Amiodarone, an antiarrhythmic agent that blocks potassium channels. (c) Novocaine, a local anesthetic that blocks sodium channels. (d) Glipizide, an antidiabetic that blocks potassium channels in the pancreatic β-cells. (e) Phenytoin, an antiepileptic that blocks sodium channels. (f) Tetrodotoxin, a pufferfish toxin that blocks sodium channels, that is 100 times more lethal than cyanide.

been implicated in a number of important disease states (channelopathies, Table 3.1) such as cystic fibrosis,[55] epilepsy,[56] and long QT syndrome.

Modern efforts to understand the function of ion channels and the role of electrical currents in biological processes predate the age of modern drug discovery. The concept of "bioelectricity" was, in fact, explored as