



FIGURE 3.15 An enzyme binds with a substrate (S), which then binds to a coenzyme that supports the enzymatic process. After the reaction is complete, the product is released, and both the enzyme and coenzyme are recycled. In some cases, the coenzyme must be regenerated before the next reaction cycle.

compounds such as progestins, mineralocorticoids, glucocorticoids, androgens, and estrogens, but it requires the presence of an iron-based heme unit. Redox active compounds such as nicotinamide adenine dinucleotide phosphate (NADP) and flavin adenine dinucleotide (FAD) are critical cofactors in various metabolic processes. Additional important coenzymes include coenzyme A, adenosine-5'-triphosphate (ATP), coenzyme Q, and heme B (Figure 3.16). Recycling of the coenzymes is often achieved through an independent enzymatic pathway.²³

INHIBITION OF ENZYMES

Although there are a large number of enzyme inhibitors, most of them can be categorized in to a relatively small number of distinct classes based on their general mode of actions: competitive inhibitors, irreversible inhibitors, and allosteric inhibitors (Figure 3.17). Compounds that act as competitive inhibitors of an enzyme are capable of occupying the active site of an enzyme (or a portion thereof), thus preventing entry of the natural substrate into the active site. In this case, inhibition is reversible, as no covalent bonds are formed between the enzyme and the inhibitor. The same forces that hold proteins in their native state (e.g., hydrogen bonding, hydrophobic interactions, etc.) allow the inhibitor to associate with the active site. The influenza drug Tamiflu® (Oseltamivir), for example, competitively inhibits influenza neuraminidase, an enzyme that catalyzes cleavage of sialic acid from glycoproteins, by producing transition state mimic (GS-4701) upon metabolism by patients (Figure 3.18). In this case, a series of energetically favorable interactions allow the drug to reversibly occupy the active site of the enzyme, blocking the natural ligand.^{24a,24b}

Selectivity, however, can be an issue with competitive inhibitors. Consider the kinase family of enzymes, for example, which phosphorylate