exposure, and half-life. Higher rates of metabolism lead to decreases in each of these properties, and as such, compound metabolism is often a critical concern in drug discovery programs.

Compound metabolism can be divided into two sets of processes that are referred to as phase 1 and phase 2 metabolism.[44] In general, phase 1 metabolism reactions modify the molecular structure of a compound via processes such as oxidation or dealkylation, often leading to the production of material that possess a "handle" that can be utilized as an attachment point for a polar group that facilitate excretion by the kidneys. Phase 2 metabolism takes advantage of the presence of potential points of attachment, such as hydroxyl groups, by adding polar groups to molecules, such as glucuronic acid or glutathione. These reactions are referred to as conjugation reactions, and although phase 1 metabolism can prepare a compound for conjugation, phase 1 metabolism is not necessarily a prerequisite for phase 2 metabolism. Compounds containing functional groups capable of undergoing conjugation reactions can bypass phase 1 metabolism and act as substrates for the enzymes responsible for phase 2 metabolism.

Chemical modifications that occur in phase 1 metabolism include oxidations, reductions, and dealkylation. While there are a wide range of enzymes that take part in these processes, *monooxygenases* are the most prominent players in these processes. As the name implies, these enzymes generally add an oxygen atom to their substrate (Scheme 6.1). This process requires the consumption of molecular oxygen and converts NADPH to NADP+ (dihydronicotinamide-adenine dinucleotide phosphate to nicotinamide adenine dinucleotide phosphate).

$$\mathrm{R{-}H + O_2 + NADPH + H^+ \longrightarrow R{-}OH + O_2 + NADP^+ + H_2O}$$

SCHEME 6.1 General process of monooxygenase metabolism.

Monooxygenases are classified based on the cofactors that are required for activity. The cytochrome P450 (CYP450) family of enzymes is the largest family in this class. Functional activity requires the presence of both a heme molecule and an iron atom (Figure 6.25).[45] It is estimated

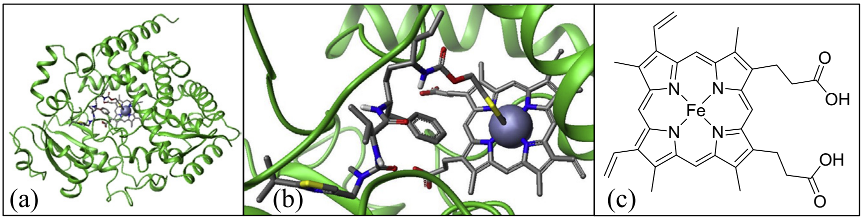

FIGURE 6.25 (a) Crystal structure of CYP3A4 bound to desoxyritonavir analog (RCSB 4K9W). (b) Close up of binding site (RCSB 4K9W). (c) Structure of heme molecule from CYP3A4.