- Chemical modification must be reversible and allow the parent drug to be released by an in vivo chemical and/or enzymatic reaction at the rate that is greater than the elimination rate of the prodrug or parent drug.
- The promoiety should ideally be safe and rapidly excreted from the body. The selection of promoiety should be considered with respect to the disease, the dose, and the duration of therapy.
- The absorption, distribution, metabolism, and excretion (ADME) properties of both the parent drug and prodrug need to be comprehensively understood.
- Can bioavailability in humans be predicted, with a high degree of certainty, using preclinical animal models?
- Is the final prodrug formulation sufficiently chemically and physically stable with a reasonable shelf life?

Some of the most common functional groups on parent drugs that are amenable to chemical modification to form prodrugs include hydroxyl (—OH), carboxyl (—COOH), as well as basic and acidic NH-groups. Prodrugs typically produced via the modification of these groups include esters, carbonates, carbamates, amides, phosphates, as well as various *N*-acyl derivatives and *N*-Mannich bases. Also phosphate ($—OPO(OH)_2$) and phosphonate ($—C—PO(OH)_2$) groups present in various nucleoside analogs have been very popular targets in prodrug design resulting in many different types of experimental and clinically approved phosphate and phosphonate nucleoside prodrugs. Figure 10.4 illustrates prodrug structures for the most common functional groups of parent drugs. Not surprising that the most common prodrugs are those requiring a hydrolytic bioconversion in vivo by ubiquitous hydrolases. Less frequently prodrugs are designed to be bioconverted by oxidative or reductive processes mediated by enzymes such as cytochrome P450, monoamine oxidase, nitroreductase, or azoreductase. The use of these enzymes is often sought out for liver or cancer targeting prodrug approaches, and some of the examples are represented in more detail in Section 10.5.

Besides utilization of enzymes to carry out necessary bioconversion of prodrugs to their respective active drugs, a wide variety of different prodrug bonds are designed to undergo a spontaneous nonenzymatic reaction. For example, lower pH in tumor environment has prompted the exploitation of acid-sensitive prodrug bonds such as acetals, ketals, hydrazones, and imines. *Cyclo*SAL phosphate and phosphonate prodrugs have recently been extensively studied to deliver nucleoside analog monophosphates. These prodrugs are stable in acidic media but undergo a chemical hydrolysis to generate nucleoside analog monophosphates and salicyl alcohol under basic conditions. Hydroxyalkyl and especially hydroxymethyl prodrugs of carboxylic acids and NH-acidic groups are known to undergo rapid spontaneous conversion at pH 7.4 resulting in the formation of an aldehyde (e.g., formaldehyde from hydroxymethyl derivative) and a respective parent drug. While the hydroxymethyl esters of carboxylic acids are highly unstable, the pK_a value of NH-acid influences on the rate of conversion of *N*-hydroxymethyl prodrugs with the more acidic parent drugs giving the fastest conversion. For *N*-hydroxymethyl prodrugs, a conversion half-life is less than 1 hour for NH-acids having the pK_a less than 13. While hydroxymethyl prodrug approach offers very little design flexibility, its practical utility can be extended to double prodrug approach where a terminal hydroxyl group is further phosphorylated or acetylated. These phosphoryloxy or acyloxyalkyl prodrugs undergo a two-step cleavage mechanism where the first rate-determining step is the enzymatic hydrolysis of the terminal acyl group with a subsequent spontaneous chemical reaction releasing the active drug. As a representative example (Figure 10.5), after cleavage of the phosphate group, dehydroxymethylation has been shown to be very rapid (less than 2 seconds at pH 7.4 and 37°C) for a relatively strong NH-acid, phenytoin. In comparison, a conversion half-life of *N*-hydroxymethyl intermediate of a weaker NH-acid, aripiprazole, should be in hours.