the use of certain promoieties can markedly enhance solution stability (Sinkula, 1977). The influence that the prodrug approach has on biopharmaceutical properties has been reviewed (Sinkula, 1975; Sinkula and Yalkowsky, 1975; Sinkula, 1977; Peng et al., 2010; Domião et al., 2014) and will be discussed briefly later.

To take advantage of the prodrug approach, the drug must bear a functional group capable of being derivatized by covalent attachment to the promoiety. The number of functional groups that have proved to be useful in the generation of biologically labile derivatives is now fairly large, and examples of typical functional groups, including esters, thioesters, amides, acetals, and ketals, have been compiled (Charton, 1977, 1985). Of equal importance is that the prodrug must revert to the drug at an appropriate rate and time (Krise et al., 1999c) to deliver the intact parent drug to the site of action. The prodrug to drug conversion can therefore take place before absorption, as in hydrolysis of an ester or peptide linkage in the gastrointestinal tract catalyzed by intestinal enzymes (Simmons et al., 1995); during absorption, as in hydrolysis by esterases found in the skin (Roy and Manoukian, 1994) or in the brush border membrane (Schmidt et al., 1972; Hirano et al., 1977); after absorption, such as taking advantage of phosphomonoesterases in plasma (Melby and St. Cyr, 1961); or even at the site of action, for example, utilization of β-glucuronidase for reconversion at tumor tissues (Watanabe et al., 1981), depending on the goal for which the prodrug was developed (Bundgaard, 1985a). If a prodrug was designed to improve solubility in water to allow the drug to be administered as an injectable solution, it should be converted back to the drug as soon as possible following injection. The rate of conversion must yield a concentration of the parent drug above the minimum effective level at the site of action (Stella, 1975). Any prodrug found in the blood circulation would be considered drug unavailable for pharmacological activity (Bundgaard, 1985a). Ideally, then, the prodrug should possess adequate solubility in the desired dissolution medium, chemical stability to provide an appropriate shelf life for the product, and the ability to convert rapidly *in vivo* to the parent drug. A suitable prodrug and the promoieties themselves must also prove to be nontoxic (Cho et al., 1986).

Although the use of prodrugs has proved to be a convenient way to deal with solubility, some consider this approach to be *an act of desperation* when problems with a drug candidate appear to be insurmountable (Huttunen et al., 2011). One of the key issues hindering the overwhelming adoption of this approach by the pharmaceutical industry is that the Food and Drug Administration (FDA) requires submission of evidence that both the drug and prodrug candidate are safe, efficacious, and well tolerated (Stella et al., 2007; Pevarello 2009; May and Kratochvil, 2010; Sofia 2014). There is an underlying risk regarding the prodrug approach, as in the case of acyclovir S-acylthioethyl esterification, that the prodrugs could have greater toxicity than the parent drug (Hecker and Erion, 2008; Huttunen and Rautio, 2011). Nevertheless, prodrugs with reduced toxicity and equal or improved efficacy have been reported (Nudelman et al., 2001; Huo et al., 2015; Kaul et al., 2015; Phillips et al., 2015). Using a prodrug approach, it should now be possible to appropriately modify physicochemical properties of a drug candidate to obtain desirable absorption, distribution, metabolism, and excretion characteristics (Huttunen et al., 2011). Indeed, it has been recommended that prodrug forms should be considered early in preclinical studies because it is easier to modify the properties of a drug candidate than to search for a new chemical entity with the desired properties (Huttunen et al., 2011).

This chapter focuses on modification approaches that have been adopted to generate prodrugs primarily for the purpose of improved solubility in water, although there are certainly other purposes for which prodrugs are produced. It will be discovered that dramatic changes in the physicochemical properties can be observed upon minor chemical modifications. Successful prodrug design should involve the simplest chemical modification possible that still achieves the desired property modifications (Anderson, 1985). With the advent of molecular modeling in the prediction of solubility and high throughput screening in drug design, it is possible to identify functional groups responsible for poor solubility and to replace them or alter them with functional groups that can increase solubility without adversely affecting the efficacy or toxicity of the parent drug.