A novel prodrug type was developed for drugs bearing a hydroxyl or an NH-acidic group (Bundgaard et al., 1989, 1991). For the cases involving an NH-acidic group, the drug must first be converted to the *N*-hydroxymethyl derivative to provide the alcohol group available for further derivatization. In the promoiety, an ionizable amine is separated by a benzene ring from the carboxylic acid group to be employed in ester derivatization. To achieve an amine pK_a value greater than 6, the amino group was separated from the benzene ring by a methylene group, yielding, in the simplest case, an aminomethylbenzoic acid. It was noted that 4-(aminomethyl)benzoic acid has been used as an antifibrinolytic agent, suggesting that this particular cleaved promoiety is not pharmacologically inactive. Other alkylated amines were investigated because *N*-substituted 4-(aminomethyl)benzoic acids, such as 4-(*N,N*-dimethylaminomethyl)benzoic acid, do not possess the antifibrinolytic or trypsin-inhibiting effect. Prodrugs with the aminomethyl or another amino group at the 3- or 4-position of the benzene ring show promise of being useful prodrugs since they are able to improve drug solubility and stability in aqueous media. Maximal stability occurred in the pH 3–5 range where shelf lives of up to 14 years were achieved. In pH 7.4 phosphate buffer at 37°C, half-lives in excess of 200 h were obtained. In the presence of 80% human plasma at 37°C, the prodrugs were readily hydrolyzed to quantitatively yield the parent drug.

Some studies have shown that a correlation might not always exist between solubility and the hydrophilicity of the promoiety. For example, the incorporation of polar, hydrogen-bonding substituents in a series of prostaglandin derivatives resulted in an increase in both crystalline interaction energies and hydration energies, and therefore the solubility in water did not increase (Anderson and Conradi, 1980). Predicting an increase in solubility as a result of an increase in the hydrophilicity of a promoiety is considered unreliable (Anderson and Conradi, 1987).

Promoieties employing ionizable acid or base functional groups to accomplish an enhanced solubility in water yield prodrugs where a pH effect on the solubility profile will be evident. Thirteen derivatives of the semisynthetic surfactant 24,25-dihydrofusidic acid have been synthesized and their solubility characterized (Lee et al., 1992). The derivatives were prepared using promoieties employing carboxylic acids, phosphates, sulfates, and primary, tertiary, and quaternary amines. As expected, the carboxylic acids and phosphates contributed to the solubilizing effect when the pH was increased; the amines, with the exception of the quaternary amines, improved solubility when the pH was lowered. Sulfates and the quaternary amines were ionized over the pH ranges studied, and no solubility enhancement due to pH modification was observed.

MODIFICATIONS EMPLOYING AMINO ACIDS

Amino acid esters have been recommended as potentially useful progroups (Kovach et al., 1975; Amidon et al., 1977) in that they provide the carboxylic acid group for reaction with an alcohol or phenol to form an ester prodrug, an ionizable amine as a side group, and the potential for another ionizable side group in certain amino acids. In general, esters employing amino acids, or related short-chain aliphatic amino acids, are rapidly hydrolyzed by plasma enzymes (Bundgaard et al., 1984b), and offer the potential advantage of enhanced absorption from the small intestine due to the presence of amino acid and peptide transporters in the brush border membrane (Majumdar et al., 2004; Dobson and Kell, 2008). Unfortunately, some amino acid prodrugs exhibit poor stability in aqueous solutions, as evidenced by acetaminophen (Kovach et al., 1975), hydrocortisone (Johnson et al., 1985; Fleisher et al., 1986), metronidazole (Bundgaard et al., 1984a), and Taxol (Deutsch et al., 1989) esters. One reason offered for the instability of these esters in aqueous media is the strongly electron-withdrawing effect of the protonated α-amine that makes the ester linkage susceptible to nucleophilic attack (Bundgaard et al., 1989; Zhao et al., 1991). This was supported by the improved stability of the 2′-β-alanyl taxol derivative (Zhao et al., 1991) that, although structurally similar to the 2′-glycyl derivative (Magri, 1985), minimized the effect of the protonated amine by shifting its position one carbon further away. Improved solubility and stability was also observed with the β-alanyl prodrug of bromhexine (Aggarwal and Gupta, 2012). The γ-aminobutyryl taxol