with α-methoxypolyethylene glycol (mPEG)-thiopropionic acid amide of 20,000 molecular weight, α, ω-*bis*-thiopropionic acid amide polyethylene glycol of 20,000 molecular weight, or α-*tert*-butoxy-polyethylene glycol-thiopropionic acid amide of 70,000 molecular weight. The thiol group adds to the double bond of the maleimide group in a rapid and selective manner to form a stable thioether bond (Rodrigues et al., 1999). The derivative involving the 70,000 molecular weight PEG was found to possess good chemical stability in pH 7.4 buffer, with less than 10% drug released after 48 h in the medium, but more rapid release at pH 5.0, indicating an acid-sensitive degradation.

Because of its poor solubility in water, tacrolimus, a potent immunosuppressant, was derivatized with mPEG by initially acylating the drug at the 24-, 32-, or 24,32-positions using iodoacetic acid in the presence of dicyclohexylcarbodiimide as a coupling reagent with dimethylaminopyridine as a base (Chung and Cho, 2004). After separation of the three types of iodoacetate esters, reaction of this intermediate ester with the thiol of 5 kDa mPEG-SH, in the presence of sodium bicarbonate as a base, yielded the desired prodrugs. These derivatives proved to be soluble in water and could be converted into tacrolimus using liver homogenates. The half-lives are approximately 10 min in the homogenate, indicating their potential as prodrugs for the immunosuppressant. The half-life in pH 7.4 phosphate buffer at 37°C was 20 h, indicating sufficient chemical stability that solutions of these products could be reconstituted by simple dissolution in water without concern for chemical degradation.

N-hydroxymethylphenytoin, a prodrug in its own right as described earlier, was linked to mono- and polyfunctional polyethylene glycols bearing ionizable and nonionizable end groups (Dal Pozzo and Acquasaliente, 1992). In each of the six derivatives, *N*-hydroxymethylphenytoin was linked to the terminal hydroxyl group of the PEG using a succinic acid spacer. At the opposite end of the PEG chain was a hydroxy, a methoxy, a sodium succinate, or the disodium salt of a more complex dicarboxylate group. Each of the prodrugs, with the exception of the derivative involving a methoxy-capped PEG of only three monomeric units, was freely and rapidly soluble in water in all proportions and demonstrated stability in water for 1 month at room temperature. In undiluted plasma, hydrolysis was too rapid to be characterized. The half-life in 10% diluted plasma exhibited pseudo-first-order kinetics with a half-life of about 3 h. The half-life in isotonic phosphate buffer was 150 h, indicating that these prodrugs possess the *in vivo*/*in vitro* conversion rate ratio desired of superior prodrugs.

A series of zero generation polyamidoamine dendrimer-based prodrugs were prepared in an attempt to improve the solubility and bioavailability of poorly soluble naproxen (Freeman et al., 2005). Dendrimers are branched molecules with multiple end groups, and typically a drug molecule is covalently bound to an end group of the dendrimer (De Groot et al., 2003). The dendrimer used with naproxen, (G0) PAMAM, was linked through formation of an amide (Figure 16.6). Alternatively, one of two linking chemicals, either lactic acid or diethylene glycol, was attached to the dendrimer, and then naproxen was esterified with the free alcohol group of the linking chemical to form this type of prodrug. In each of the three cases, the water-soluble dendrimer provided a prodrug form that was more hydrophilic than naproxen. Hydrolysis of the prodrug was evaluated at 37°C in pH 1.2 hydrochloric acid buffer, in pH 7.4 phosphate buffer, in pH 8.5 borate buffer, and in 80% human plasma. In the buffer systems, each of the three prodrugs was chemically stable over the

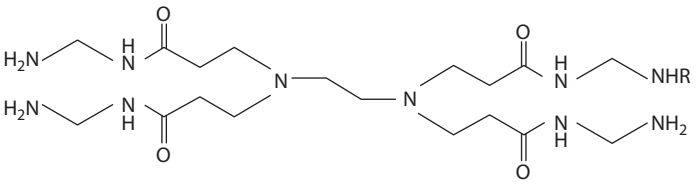

FIGURE 16.6 Dendrimer (G0) PAMAM linked through an amide bond.