

In contrast, compounds that rapidly disassociate from plasma protein (i.e., have fast kinetics) may not be limited by the impact of plasma protein binding. Even in cases where plasma protein binding is high as a percentage, some level of free drug will always be available to move down a concentration gradient through a plasma membrane. Compounds that have a high plasma protein binding and fast dissociation rates, or have low plasma protein binding (irrespective of the rate of dissociation) are referred to as “permissive” compounds. The importance of dissociation rates as it relates to plasma protein binding becomes evident when considering the currently marketed compounds. A 2002 review of 1500 drugs revealed that over 40% of the compounds are >90% protein bound, and that a high number of anti-inflammatory drugs (26%) displayed >99% protein binding. Clearly, some free drug must be available in order for these compounds to exert a therapeutic effect. In these cases, high on/off rates (dissociation rates) offset the impact of high levels of protein binding.<sup>43</sup> Thus, high plasma protein binding can be tolerated under the correct circumstances (Figure 6.23).

Name	Plasma Protein Binding	Use
Diazepam (Valium®)	99%	Antianxiety agent
Ibuprofen (Advil®)	99%	Antiinflammatory
Lorazepam (Ativan®)	92%	Antianxiety agent
Naproxen (Aleve®)	99%	Antiinflammatory
Amlodipine (Norvasc®)	93%	Antihypertensive
Omeprazole (Prilosec®)	95%	Proton pump inhibitor
Doxycycline (Vibramycin®)	90%	Antibiotic
Efavirenz (Sustiva®)	99%	Antiviral

FIGURE 6.23 Protein binding of known drugs.

## ELIMINATION PATHWAYS

The concepts of absorption and distribution describe how a compound enters and moves through the body. At some point, however, compounds that enter the body are removed via one or two basic elimination methods. Molecules can be metabolized to a different compound, effectively removing the original compound from circulation, or they can be excreted unchanged into the urinary tract by the kidney. These pathways are not mutually exclusive, but one pathway may be the dominant mechanism of elimination. The combined action of these mechanisms, however, will ultimately control how long a given compound will reside in the body after a dose is provided. In order to alter the residence time of a compound in the body, it is essential to understand the contribution of these pathways.