improved while biological activity is maintained. The metabolic stability of a series of 1,4-diazepames CB2 agonists, for example, was significantly enhanced when a thiazole ring was replaced with a similarly substituted isoxazole ring (Figure 6.41). Bioisosteric replacement is a common tactic employed in an effort to improve the metabolic profile of potential lead compounds.[65]

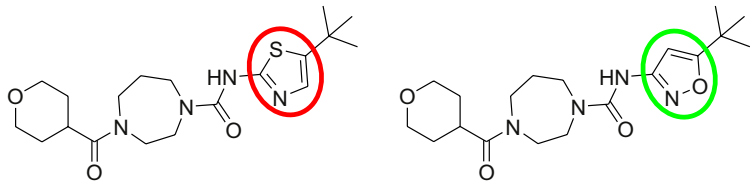


**FIGURE 6.41** Human liver microsomal stability in a series of 1,4-diazepames is increased when a thiazole ring (a) is replaced with an isoxazole ring (b) as indicated by the increase in half-life ($t_{½}$). HLM, human liver microsome.

There are many additional methods that can be employed to improve the metabolic stability of candidate compounds. Cyclization to form a ring system, changing the size of a ring, inversion of a chiral center, or altering lipophilicity may have a positive impact on the metabolic profile within a given series of compounds. Metabolism itself is an enzymatic process, and as such, all of the methods one might employ to modulate active site binding through structure activity relationships are available for the purposes of modulating metabolism. There are many reviews on the topic that those with a deeper interest in the area are encouraged to read.[66a,b,c,d]

## Excretion

Although metabolic processes can be an effective mechanism for the elimination of xenobiotics from the systemic circulation, they are not the only method available for clearing materials from the body. The rate of elimination of compounds from the body is also impacted by their rate of excretion. Metabolic by-products are also cleared from the body by excretion, which serves to prevent the build up of undesired metabolites. In general, compounds, both unchanged drugs and their metabolites, can be excreted into urine, sweat, bile, breast milk, or even into expired air as it leaves the lungs (e.g., anesthetic gases). The two most important methods are excretion into the urine by the kidneys and deposition into bile fluids by the liver.

In order to understand the mechanism of renal excretion, also referred to as renal elimination, it is important to have a basic understanding of the functional units of the kidney that carries out this process. The working unit of the kidney that functions to regulate the concentration of soluble material