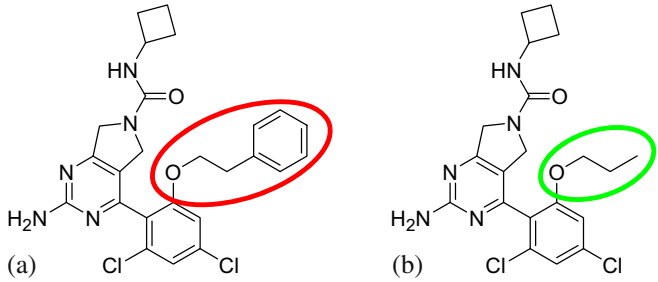

FIGURE 6.33 Removal of a benzene ring that is not required for biological activity increases metabolic stability as indicated by the drop in human liver microsome intrinsic clearance (HLM Clint CL_{int}) from (a) to (b).

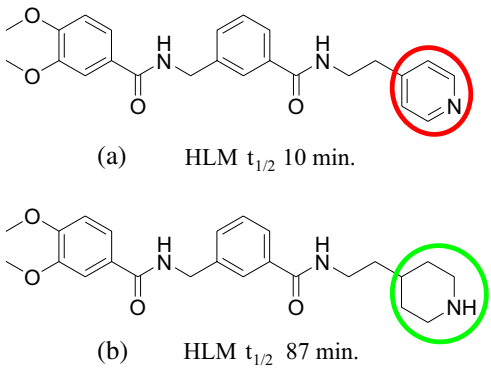

FIGURE 6.34 A significant boost in metabolic stability is observed when a pyridine ring (a) is replaced with a piperidine ring (b), as indicated by the increase in human liver microsome half-life ($t_{½}$). HLM, human liver microsome.

(Figure 6.34).[58] In both of these cases, removal of a metabolically labile feature of a compound provided a path forward for a drug discovery program.

In some situations, it is not possible to remove metabolically labile groups, as they are required for biological activity. It may, however, be possible to modify a vulnerable site within the labile group so that it is no longer subject to metabolism. This can often be accomplished by replacing hydrogen atoms with fluorine atoms. While hydrogen atoms on an alkyl chain can be metabolically replaced with an alcohol, fluorine atoms cannot. This strategy was successfully employed to increase the metabolic stability of urea transporter B inhibitors. A compound that was substantially metabolized after a 30-min incubation with rat liver microsomes (<5% remaining, Figure 6.35(a)) could be modified to a compound that was minimally metabolized under the same conditions (96% remaining after 30 min) by simply replacing two hydrogen atoms