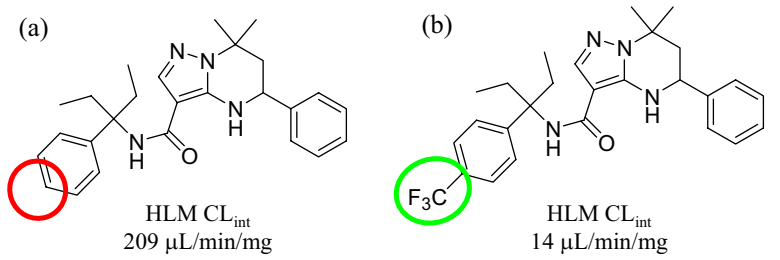

FIGURE 6.37 Adding a CF_3 group to the four position of (a) provides a compound that is significantly more stable to human liver microsomes (b) as indicated by the change in intrinsic clearance. HLM CLint, human liver microsome intrinsic clearance.

density of the aromatic ring as a whole. This change in electronic character further decreases the susceptibility of the benzene ring to metabolic oxidation processes.[61] In a similar manner, the metabolic stability of a series of indole-2-carboxamide antituberculosis agents was substantially improved with the incorporation of a second chlorine atom. Once again, in this case a halogen is used to replace a vulnerable hydrogen atom and decrease the overall electronic character of the benzene ring (Figure 6.38).[62]

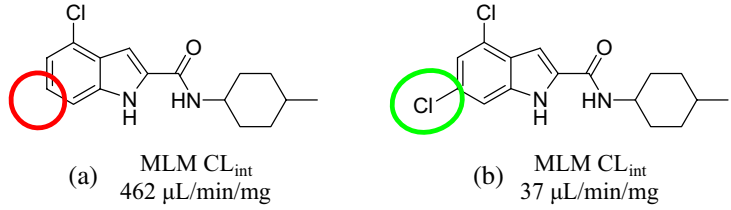

FIGURE 6.38 Metabolism of (a) in mouse liver microsomes (MLM) was suppressed by chlorination of the indole ring (b) as indicated by the change in intrinsic clearance.

In some instances, it is not possible to directly block a metabolically labile site while still preserving the desired biological activity. An alcohol or amine in biologically relevant compound could participate in a key hydrogen-bonding interaction with the target of interest, while also serving as a target for metabolic enzymes. Replacing the offending functionality could be explored, but it may also be possible to restrict metabolic activity at this site by increasing the steric encumbrance around the site. Adding sequential methyl groups to the alcohol side chain of a series of PI3-kinase inhibitors, for example, demonstrated a step-wise increase in metabolic stability as each methyl group was added to the overall framework (Figure 6.39). Each additional methyl group increases the steric hindrance around the alcohol, limiting its ability to act as a