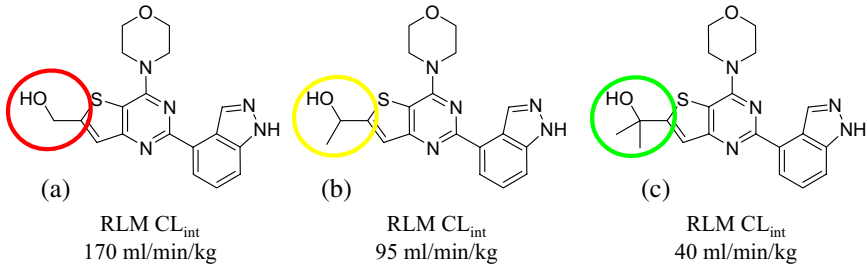

FIGURE 6.39 Adding steric bulk next to the alcohol of (a) decreased metabolism by rat liver microsomes (RLM) as indicated by the change in RLM intrinsic clearance upon incorporation of a first (b) and second (c) methyl group on the alkyl chain.

metabolic substrate, thereby increasing metabolic stability as compared to the unsubstituted analog.[63]

There are, of course, cases in which a metabolically labile site plays a role in the overall structure of a pharmacophore, but does not participate directly in binding with the macromolecular target of interest. In these cases, removing the metabolically labile group would be detrimental to the biological activity of the compound class, as the substituent or functionality plays a role in maintaining the molecule in the proper configuration for biological activity. In these instances, it may be possible to replace the metabolically labile section of the molecule with an alternate group of atoms that can serve the same purpose but that are also more stable to metabolism. Bioisosteric replacements of this type are a common method of suppressing undesired metabolic activity. In the development of CB2 agonists, for example, the metabolically labile piperidine was readily replaced with the corresponding morpholine ring (Figure 6.40). This

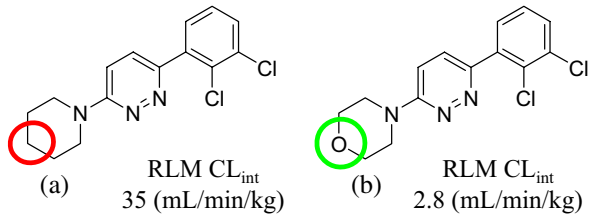

FIGURE 6.40 A carbon/oxygen isosteric exchange to convert a piperidine analog (a) into a morpholine analog (b) increases metabolic stability in rat liver microsomes (RLM).

exchange represents a carbon/oxygen isosteric replacement that produced a greater than 10 fold increase in metabolic stability.[64] Biological activity was not significantly impacted, as crucial binding interaction with the target of interest were not changed as a result of this exchange of atoms.

In some situations, it may be possible to replace large portion of a compound in order to solve metabolic issues. As long as the replacement group can serve as a suitable bioisosteric replacement, metabolic stability can be