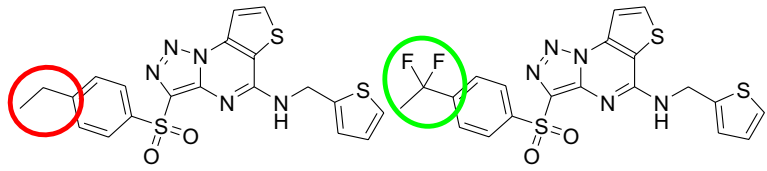

FIGURE 6.35 In the absence of fluorine atoms on the ethyl side chain (a) is highly metabolized by rat liver microsomes (RLM). Adding two fluorine atoms to the ethyl side chain (b) greatly enhances metabolic stability.

with two fluorine atoms (Figure 6.35(b)).[59] In a similar manner, replacing two hydrogen atoms in a metabolically labile cyclohexane ring of a chemokine (C-C motif) receptor 1 (CCR1) antagonist with two fluorine atoms led to the identification of a compound with improved metabolic stability with human liver microsomes (Figure 6.36). Further modification of this same set of compounds by replacing the primary amide with a hydroxamic acid led to additional improvements in metabolic stability, suggesting that the amide is also a key player in the metabolism of this compound class (Figure 6.36(c)).[60]

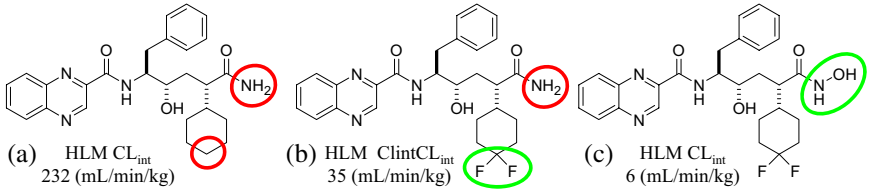

FIGURE 6.36 Human liver microsome (HLM) stability of (a) is low, but incorporation of fluorine atoms in the cyclohexane ring (b) increases metabolic stability. Conversion of the primary amide of (b) into hydroxamic acid (c) further improves microsomal stability in this series of compounds.

Hydroxylation of aromatic ring system is also a common metabolic pathway and is often a problem in the identification of suitable lead compounds. Blocking metabolism by installing aryl substituents in the position that would otherwise be hydroxylated by an enzymatic process has been shown to be an effective means of dealing with issues of metabolic instability. In an effort to identify calcium-sensing receptor antagonists, for example, it was found that replacing an aromatic hydrogen atom with a trifluoromethyl substituent produced a greater than 10 fold increase in stability (Figure 6.37). In this case, the addition of a strongly electron withdrawing group both blocks potential hydroxylation in the 4-position of the benzene ring and significantly decreases the electron