simply a matter of designing compounds that are no longer substrates for the various metabolizing enzymes. This can be accomplished through the same type of structure–activity analysis designed to optimize biological activity at the target of interest, but with the opposite goal, minimized enzymatic activity. Of course, this has to be accomplished without eliminating the desired biological activity, as a metabolically stable compound with no biological activity is not very useful as a therapeutic agent.

There are essentially three methods of addressing metabolic instability through structural modifications of candidate compounds, remove, replace, and restrict. If a functional group on a compound is a metabolic weak point (site of metabolism), it may be possible to remove the offending functionality in order to increase metabolic stability. Metabolically labile sections of a candidate compound can also be replaced with groups that are less vulnerable to metabolic degradation. Bioisosteric replacement of labile functionality is a common theme in drug discovery. Restricting access to sites of metabolism, either by physically blocking access via steric crowding, conformational restrictions, or changes in the electronic character of an aromatic ring, has all been successfully employed to slow the metabolism of biologically interesting compounds.

Unfortunately, given the wide range of metabolic enzymes and the disparate nature of chemical space and compound classes that have potential utility as drugs, there is no one specific course of action that can be taken to alleviate problems associated with poor metabolic stability while maintaining activity at the intended biological target (not to mention target selectivity, solubility, permeability, and every other property that must be maintained in a successful candidate compound). Each class of compounds must be examined independently with an eye towards balancing the structure–activity relationships that maintain the desired properties, while using structure activity relationships that suppress metabolism to enhance stability. It is, however, worthwhile to consider some examples of how structural changes impact metabolic stability.

Removing functionality that is not necessary for biological activity can be an effective method of improving metabolic stability. In an effort to identify novel heat shock protein 90 (HSP90) inhibitors, Zehnder et al. identified a series of pyrrolodinopyrimidines. Although a phenethyl side chain (Figure 6.33(a)) was tolerated within the context of HSP90 inhibition, its presence was a liability with respect to metabolic stability. Removal of the phenyl ring (Figure 6.33(b)) greatly improved metabolic stability with minimal impact on HSP90 inhibition.[57] In a similar manner, the aromatic character of the pyridine ring of a series of Rho-associated protein kinase-2 (ROCK-2) inhibitors proved to be a metabolic liability that could be removed by simply eliminating the aromatic character of the ring. Replacing the pyridine ring with the corresponding piperidine ring provided a significant boost in metabolic stability