



FIGURE 5.3 The Golden Triangle. Compounds with combined good liver microsomal stability and good permeability are typically found within the triangle. The three drugs atorvastatin, linezolid, and escitalopram are indicated in the plot.

5.2.3 MULTIPARAMETER OPTIMIZATION (CNS MPO-SCORE)

Neither the Ro5 nor the Golden Triangle was intended to build “fixed walls” or “forbidden areas” or “uncompromising rules.” However, in reality they are typically applied as strict cutoff filters to, e.g., *in silico* designed compounds or corporate screening collections. When using these kinds of rules of thumb as absolute selection criteria, compounds are discriminated solely qualitatively: either they pass or they fail. All compounds that comply with the rules are considered equal, as are all that breach them. The fact that there are some successful drugs on the market that are not compliant with these rules and the inability of a single descriptor to account for the quality of a small molecule as an oral drug has prompted “moving beyond rules” and paved the way for more sophisticated descriptors of drug-likeness based on scoring schemes. In the following, we will discuss one of these “softer guidelines”: the CNS multi-parameter optimization algorithm (MPO).

Instead of operating with hard cutoff values, the MPO scoring function allows compounds to “go outside” one or more of the optimal property ranges by assigning a gradually decreasing sub-score for that parameter depending on the deviation from the optimal range as illustrated in Figure 5.4. As the name implies, CNS MPO-score was developed for oral CNS drugs, but it is equally applicable to oral peripheral small-molecule therapeutics. The CNS MPO-score for the three drugs discussed so far in this chapter are listed in Table 5.2. From these examples, it is evident that there are significant differences between the three drugs with atorvastatin displaying the lowest score and the other two drugs have near-optimal profiles despite falling short of the ideal for one or more properties. In general, a CNS MPO-score of above 4 is considered good. As we shall see in the next section there is no difference between centrally acting small-molecule drugs and their peripheral counterparts in terms of the MPO-score.

5.2.4 ANALYSIS OF SMALL-MOLECULE ORAL DRUGS

Following the publication of the numerous rules and guidelines for best practices in medicinal chemistry, we performed an analysis of a large set of small-molecule oral drugs to evaluate the validity of some of these mnemonics for a large set of successful drugs. In this study we