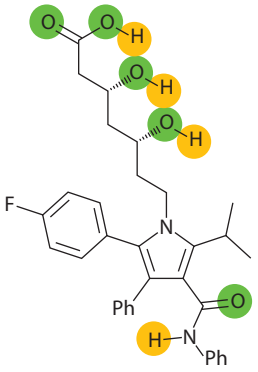
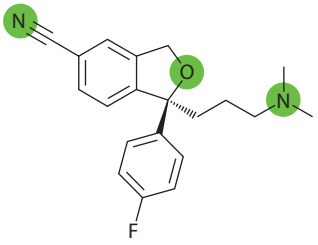
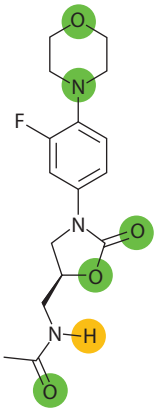
TABLE 5.1
Three Oral Drugs and Their Lipinski Parameters







Lipinski Criteria	Lipitor (Atorvastatin)	Lexapro (Escitalopram)	Zyvox (Linezolid)
MW < 500	559	324	337
Log P < 5	4.46	3.13	0.17
HBD count < 5	4	0	1
HBA count > 10	5	3	5
Number of Ro5 violations	1	0	0

Note: The H-bond donors and acceptors are indicated by the orange and green colors, respectively.

apply to compounds that are subject to active up-take across the gut by transport proteins. Indeed, Pfizer's blockbuster drug Lipitor (atorvastatin) is an example of such a compound. The antidepressant Lexapro (escitalopram) and the antibacterial drug Zyvox (linezolid) are examples of CNS and peripherally acting Ro5-compliant oral drugs, respectively. These compounds and their Lipinski profiles are illustrated in Table 5.1.

5.2.2 The Golden Triangle

Since the publication of the Ro5, a large number of additional analyses have been performed by scientists from many different organizations on a variety of small and large datasets and generally have confirmed the central role of physicochemical properties. One of these analyses led to the so-called Golden Triangle model. This guideline was developed from in vitro ADME data (permeability and metabolic stability) and computational data with the objective of aiding medicinal chemists to identify permeable and metabolically stable compounds. In a plot of MW versus log $D_{7.4}$, the Golden Triangle appears with its apex at MW = 450 and log $D_{7.4}$ = 1.5 and a baseline from log $D_{7.4}$ = −2.0 to log $D_{7.4}$ = 5.0 at MW = 200. Compounds that reside inside the Golden Triangle are more likely to be both metabolically stable and to possess good membrane permeability than those outside. In general, compounds placed in the lower left part of the plot tend to exhibit low permeability and good stability toward hepatic (oxidative) clearance, and they are often excreted unchanged via the urine. Conversely, compounds placed in the upper right part of the plot beyond the Golden Triangle often have poor properties and in order to be useful as oral drugs, special features have to be "build in" to the chemical structure, particularly, problems with metabolic stability are often noticed, so a special attention needs to be paid to secure the compound to be very resistant to liver microsomal clearance (a measure of hepatic clearance). This is illustrated in Figure 5.3.