clinical observation of the sustained pharmacoenhancing effect of ritonavir, with the duration of effect longer than the persistence of ritonavir in plasma. The 4- and 5-thiazolyl groups of ritonavir are believed to play a key role in this mechanism-based inhibition of CYP3A4.[34a] Modifications of both moieties caused a significant decrease in ritonavir's inhibitory activity.[19]

In the clinic, ritonavir-boosted regimens favorably alter the PK of co administered PIs. Ritonavir inhibits CYP3A4 and exerts most of its effects through two mechanisms: (1) it attenuates first-pass metabolism in the gut and liver and thereby increases the amount of drug reaching the systemic circulation and/or (2) it decreases hepatic metabolism, resulting in a prolonged terminal half-life. In addition, there may be a minor contribution from its inhibition of P-gp. Ritonavir may increase the C_{min}, AUC and C_{max} of co administered PIs; however, the degree to which ritonavir affects these parameters varies with the targeted PI. For PIs that undergo extensive first-pass metabolism, such as saquinavir, ritonavir boosting increases all three parameters in addition to prolonging the elimination half-life. For the PIs indinavir and amprenavir, which have reasonable unboosted bioavailability but a short half-life, ritonavir boosting primarily increases their C_{min} and AUC.

The long-term toxicities associated with chronic inhibition of CYP3A4 are unknown. In general, a major concern for mechanism-based CYP-inhibition is that it may cause hepatotoxicity.[37] However, there is no evidence to support the association of the hepatotoxicity observed with high-dose ritonavir with its CYP inhibition. Low-dose ritonavir-related hepatotoxicity seems uncommon and does not appear to be associated with a significant increase in the risk of hepatotoxicity relative to the other PIs.[35,38] In addition, ritonavir has been marketed and prescribed to millions of patients for more than 15 years and hypersensitivity to ritonavir has not been reported. The mechanism of liver injury observed with PIs, including high doses of ritonavir, is not clear; it is likely that viral hepatitis co-infection may be a risk factor for the observations of increased ALT.[39–41]

13.5 Discovery of the Pharmacoenhancer Cobicistat

Despite advances in antiretroviral therapy, many patients experience suboptimal virologic, immunologic or clinical benefit from currently available treatment options due to development of resistance. New drugs, particular novel drug classes, are needed against highly resistant strains of HIV. Elvitegravir (EVG, **18**, Figure 13.11) is an HIV integrase strand transfer inhibitor with potent antiretroviral activity against wild-type and NRTI, NNRTI and PI-resistant laboratory strains.[42] However, it is extensively metabolized primarily by CYP3A4 in the liver and intestine *in vivo*, excluding its use as a once-daily drug.

In addition to affecting the PK of HIV PI drugs, ritonavir has been shown in clinical studies to enhance the PK of important antiviral drugs that are CYP3A substrates, including elvitegravir.[43] When dosed alone, elvitegravir needs to be administered at 400 mg bid to achieve a plasma trough concentration that is