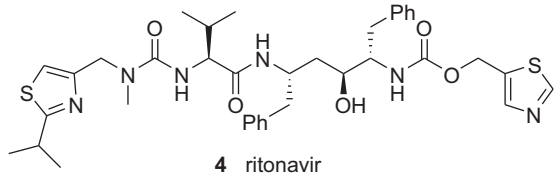

4 ritonavir

HIV EC_{50}: 15 nM

CYP3A (TFD) EC_{50}: 380 nM

Figure 13.4 Structure and activity of ritonavir. Inhibition of terfenadine hydroxylase (CYP3A) activity in human liver microsomes.

subject to efflux by P-gp. As a result, the early PI-containing regimens were typically complex and required frequent dosing, high pill burdens and strict meal and fluid requirements and were associated with significant side effects and undesirable toxicities. These effects presented adherence challenges for both clinicians and patients and, even with complete adherence to these complex regimens, substantial interpatient variability existed. Consequently, the enthusiasm for the use of regimens containing PIs began to wane. However, this changed rapidly with the discovery of the PK-enhancing effect of ritonavir (**4**, Figure 13.4) in the clinic.

CYP3A4 is the most abundant CYP enzyme in the liver, playing key roles in both the detoxification of xenobiotics and the metabolism of endobiotic signaling molecules.[17] Like most other PIs, the metabolism of ritonavir is mediated predominantly by CYP3A4, with a minor contribution from CYP2D6.[18] Additionally, *in vitro* metabolism studies confirmed that ritonavir is a potent inhibitor of CYP3A4, inhibiting the human liver microsomal metabolism of saquinavir (**5**) and indinavir (**6**, Figure 13.5) at low concentrations.[18,19] Subsequently, it was recognized that co-administration of ritonavir with PIs improved the PK of the latter significantly in humans, resulting in higher bioavailabilities and prolonged elimination half-lives. When co-administered with ritonavir in healthy volunteers, the plasma level of saquinavir was greatly increased, leading to a more than 50-fold increase in area under the curve (AUC) and a 22-fold increase in the maximum plasma concentration (C_{max}).[20] More importantly, the $C_{12\,h}$ level of saquinavir (400 mg) increased from undetectable when dosed alone to more than 1 μM when co-dosed with ritonavir (600 mg). In addition, ritonavir reduced intersubject variability of the saquinavir AUC from 60 to 28%.[20] A substantial increase in plasma drug levels of indinavir was also observed when co administered with ritonavir.[21]

Clinical studies with combined PI therapy were first conducted in HIV-infected patients using ritonavir and saquinavir (400 mg each bid).[22] This combination, with both PIs in a therapeutic dose, proved to be safe and effective. The dramatic effect of ritonavir on the PK profile of saquinavir is consistent with a large reduction in the first-pass metabolism and post-absorption clearance of saquinavir. In addition, the GI side effects related to