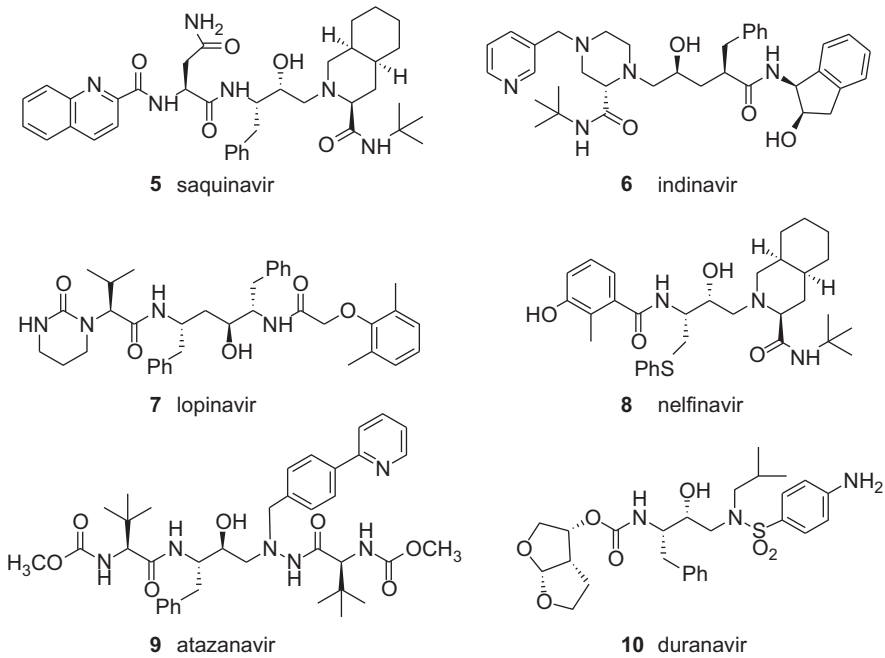

Figure 13.5 Structures of HIV-1 PIs.

dosing with ritonavir at 400 mg bid were reduced compared with those seen with ritonavir at 600 mg bid, although they remained a concern. Consequently, to improve tolerability, lower doses of ritonavir co administered with a PI were then investigated in the clinic. This clearly demonstrated that the low dose (100 or 200 mg daily) of ritonavir was sufficient to inhibit CYP3A4 metabolism and greatly enhance the PK of the co administered PIs to allow for once- or twice-daily dosing. Ritonavir-boosted PIs thus provide simplified regimens, reducing the pill burden, improving PK and treatment response, diminishing interpatient variability and obviating food restrictions, thereby enhancing adherence to therapy and slowing the emergence of resistance. As a result, co-administration of a PI with a low dose of ritonavir, often called 'a boosted PI,' has been adopted as standard practice. All currently prescribed PIs, apart from nelfinavir[23] (**8**, Figure 13.5), are typically boosted with a low dose of ritonavir;[24] whereas lopinavir (**7**) is coformulated with a low dose of ritonavir in the products Kaletra and Aluvia. Ritonavir-boosted atazanavir (**9**) or darunavir (**10**) are the preferred PIs as the third agents on treatment guidelines from the DHHS[1] and also IAS.[10]

Although boosting doses of ritonavir (100 to 200 mg once to twice daily) are better tolerated, even these lower doses are associated with safety and tolerability issues in some patients. Recent studies in healthy volunteers showed that 100 mg bid of ritonavir is still associated with adverse effects on the serum lipid profile, characterized by an increase in the concentration of total cholesterol,