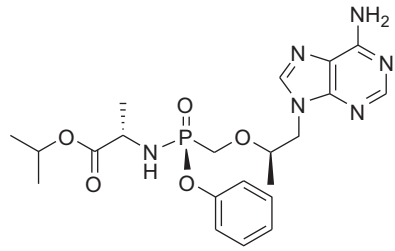

21 GS-7340

Figure 13.13 Structure of GS-7340.

generate a single-tablet regimen containing a PI. It is currently co-formulated with emtricitabine (200 mg), the PI darunavir (800 mg) and the investigational drug GS-7340 (**21**, Figure 13.13) as a single-tablet regimen. This is the first once-daily, PI-based, single-tablet regimen and is currently in clinical Phase 2 studies.

With the discovery of cobicistat as a novel and easily formulated pharmacoenhancer without antiviral activity, alternative single-tablet regimens with new drug classes or mechanisms of action that provide sustained efficacy with favorable tolerability and safety profiles for patients with HIV infection can now be realized.

13.7 Future Perspectives

13.7.1 Pharmacoenhancers in Antiviral Therapies

As mechanism-based inhibitors of CYP3A4, cobicistat and ritonavir can be expected to enhance the clinical PK of many therapeutic drugs that are CYP3A4 substrates. In addition to affecting the PK of HIV PIs and integrase inhibitors,[61] ritonavir has been shown in clinical studies to enhance the PK profile of important antiviral drugs which are CYP3A substrates, including the CCR5 antagonists aplaviroc and maraviroc[62–64] used in HIV therapy and the HCV protease inhibitors narlaprevir[65] and danoprevir.[66]

Aplaviroc is primarily metabolized by CYP3A4. Co-administration of aplaviroc with lopinavir/ritonavir (400/100 mg) increased exposure of aplaviroc by 7.7-, 6.2- and 7.1-fold for its AUC, C_{max} and C_{min} at steady state.[67] Similarly to aplaviroc, the exposure of maraviroc was increased in the presence of ritonavir in both healthy volunteers[63] and patients.[64] Maraviroc was approved in 2006 for use in treatment-experienced patients infected with CCR5-tropic HIV-1, but the development of aplaviroc has been discontinued owing to hepatotoxicity. The dosage of maraviroc requires adjustment when used in combination with PIs, with the exception of tipranavir–ritonavir combinations.[68]

Clinical studies in healthy volunteers have shown that AUC, C_{max} and $C_{12\,h}$ of a single dose of danoprevir (100 mg) before and after administration of ritonavir 100 mg bid for 10 days were increased around 5.5, 3.2 and 26.9,