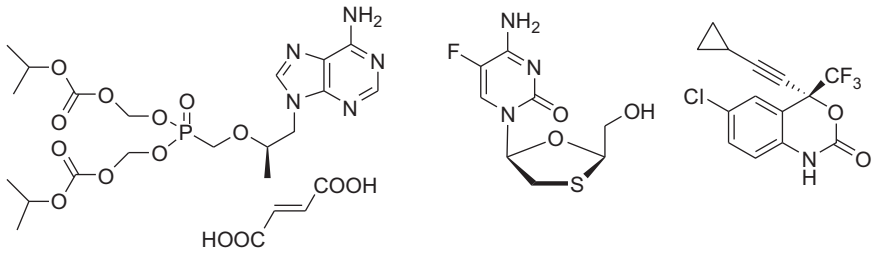

1 tenofovir disoproxil fumarate **2** emtricitavine **3** efavirenz

Figure 13.3 Structures of components of Atripla®.

non-nucleoside inhibitor, a ritonavir-boosted protease inhibitor or an integrase inhibitor. HAART has been responsible for delaying disease progression and a dramatic decline in HIV-related morbidity and mortality,[11] transforming HIV infection from a terminal condition into a chronic and manageable disease in little over a decade. Adherence, driven by a low pill burden, convenient dosing schedules and an improved tolerability and safety profile, plays a critical role in achieving long-term efficacy of HAART and preventing the emergence of drug-resistant variants.[12] Fixed-dose combination (FDC), a combination pill of two or more antiretroviral agents, was also introduced to reduce pill burden and simplify HAART regimens, with the aim of improving adherence to treatment. In 2006, the first single pill containing a complete regimen for treatment-naive individuals was approved. This pill, Atripla® (Figure 13.3), contains the NRTIs tenofovir disoproxil fumarate (**1**) and emtricitabine (**2**) in addition to the NNRTI efavirenz (**3**).

13.3 Ritonavir as a Pharmacoenhancer for HIV Therapy

The introduction of HIV-1 PIs in the mid-1990s marked the beginning of the era of HAART. HIV-1 protease inhibitors remain a mainstay of the antiretroviral arsenal for all stages of HIV-1 infection.[13] However, poor compliance with a PI-containing antiretroviral therapy increases both the risk of incomplete viral suppression and the emergence of drug resistance.

As a class, all PIs are metabolized primarily by cytochromes P450 of the CYP3A subfamily (primarily CYP3A4 and CYP3A5) in the liver and intestine. Since they are substrates, PIs can inhibit the enzymes in a competitive manner; however, studies have shown that other mechanisms of inhibition may also play a role.[14–16] Many PIs also induce CYP3A enzymes. In addition, some HIV-1 PIs are substrates for several transport proteins, such as P-glycoprotein (P-gp) and multidrug-resistance protein 1 and 2 (MRP1 and MRP2).[14] Several PIs, including ritonavir and saquinavir, are known to inhibit P-gp activity. Most PIs have an unfavorable PK profile, including poor and/or variable oral bioavailability and rapid metabolic degradation with relatively short plasma elimination half-lives. They also have high degrees of protein binding and are