researchers at Abbott. A 5-thiazolyl moiety was again utilized to achieve potent CYP3A inhibitory activity and the backbone of ritonavir was modified to remove its anti-HIV activity. In preclinical studies, the lead compound demonstrated its boosting effects when co-dosed with lopinavir.[73]

The structures of these potential pharmacoenhancers deviate away from that of ritonavir. It is anticipated their long term safety profiles need to be established during clinical studies and clinical practice.

Pharmacoenhancers have demonstrated their utility in the treatment of HIV and/or HCV infections. It is expected that they will find applications in treating other life-threatening diseases, such as cancer, although close monitoring is necessary in order to avoid unfavorable drug–drug interactions.

13.8 Conclusion

Drug–drug interactions as a result of CYP enzyme inhibition are often regarded as a liability. In the case of cobicistat and ritonavir, however, associated drug–drug interactions have proven to be an asset in the treatment of life-threatening HIV infection. The co-administration of ritonavir, resulting in improvement of the PK properties of concomitant PIs, is a cornerstone of PI-containing regimens; in this respect, ritonavir plays a critical role in the development of HAART regimens and in the chronic management of HIV infection. Without the boosting effect of ritonavir, achieving convenient dosing regimens for the large peptidomimetic PIs would not have been possible. Ritonavir has been used as a pharmacoenhancer for more than 15 years. Thus far, the benefit it brings to patients with HIV infection significantly outweighs the side effects associated with its use. With the exception of predictable drug interactions, there has been no strong evidence to demonstrate significant side effects arising from sustained CYP3A4 inhibition by long-term use of ritonavir as a booster. The second-generation pharmacoenhancer cobicistat, which maintains the CYP3A4-inhibition potency without any antiviral activity and possesses significantly improved physicochemical properties, finds broader use with its improved overall profile. The first integrase inhibitor-based, once-daily single-tablet HAART regimen Quad (Stribild®) has demonstrated promising clinical results. The potent, persistent CYP3A inhibition properties and improved physicochemical properties associated with cobicistat enable elvitegravir to be a once-daily drug; its coformulation with Truvada makes a once-daily, single-tablet, complete regimen possible. Stribild® was approved to for treatment-naive HIV-infected patients and cobicistat is under regulatory review as a general pharmacoenhancer. In addition, a complete single-tablet regimen containing emtricitabine, tenofovir alafenamide fumarate (TAF - a novel prodrug of tenofovir) and cobicistat-boosted daruanavir is currently in Phase 2 studies. Cobicistat potentially makes a once-daily, PI-containing single-tablet regimen possible.

As our knowledge of CYP3A inhibition improves and our experience with pharmacoenhancers increases, it is expected that a clean and safe pharmacoenhancer will also have broad utility against other life-threatening