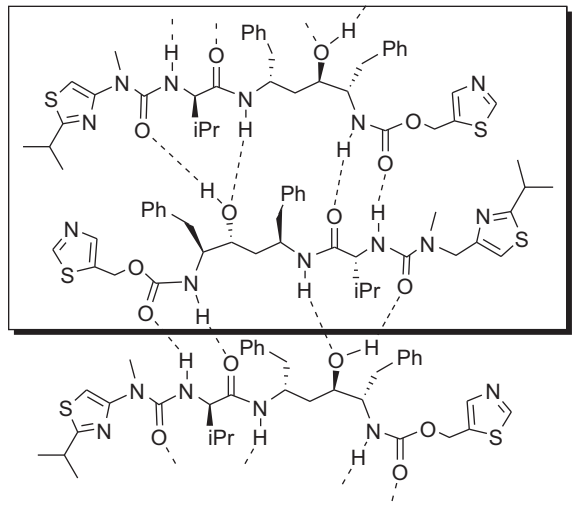

Figure 13.6 Hydrogen bonding network for ritonavir polymorph form II.

13.4 Mechanism of CYP3A Inhibition of Ritonavir

There have been many studies on the mechanism of action (MOA) of ritonavir as a CYP3A inhibitor, but no definite conclusions have been reached. The available data are inconsistent and suggest that ritonavir acts as a competitive, mixed competitive–non-competitive, quasi-irreversible or mechanism-based CYP3A inhibitor. Through kinetic and equilibrium analysis, the most recent studies[33] on the MOA of ritonavir concluded that ritonavir is an irreversible type II (Figure 13.7) inhibitor that inhibits CYP3A4 turnover both by replacing substrates in the active site and binding irreversibly to the heme iron and also through changes in the protein redox potential which preclude reduction by cytochrome P450 reductase (CPR). From the crystal structure of ritonavir and the CYP3A4 enzyme complex (Figure 13.8), it is evident that ritonavir fits perfectly into the active-site cavity with extensive hydrophobic enclosure by the enzyme and the nitrogen of the unsubstituted thiazole ligates to the heme iron.

The conclusion that ritonavir exerts its PK-enhancing effect *via* a type II binding with CYP3A through the 5-thiazolyl group is consistent with the first reported mechanism study by Kempf *et al.*[19] They also examined the structural features of ritonavir responsible for CYP binding and inhibition, showing the important contribution of the two terminal thiazoles to inhibiting the oxidizing capability of the enzyme (Table 13.1). Although compounds **4** and **11**–**14** potently bind to CYP3A, only ritonavir (**1**) inhibits the CYP3A-mediated oxidation of terfenadine. Compounds **11** and **12** differ from ritonavir only in a change of the terminal 5-thiazolyl to 4-thiazolyl and pyridinyl, respectively, but the inhibitory capacity was significantly reduced. Compound **13** incorporated a pyridyl carbonate instead of the isopropyl-4-thiazolylurea of ritonavir and compound **5** truncated the left portion; both lost their potency as