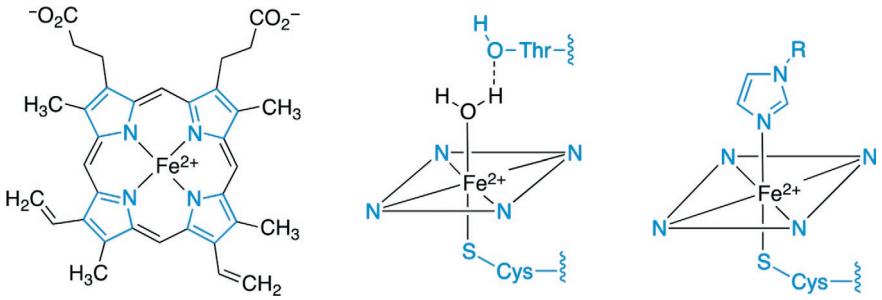


FIGURE 3.29

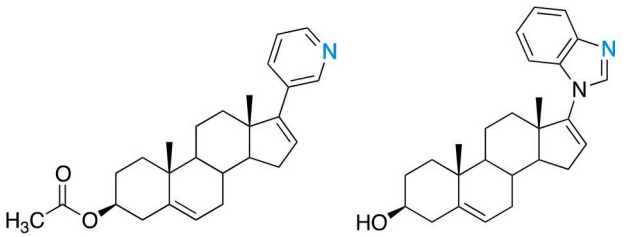
Binding of the imidazole ring of ketoconazole to the hemo group in 14α-demethylase.

The basis for the activity of ketoconazole and related antifungal imidazoles and triazoles is the inhibition of 14α-demethylase, a cytochrome P450 enzyme necessary for the conversion of lanosterol to ergosterol in fungal cells. Because this enzyme is also present in mammalian cells, where it is essential for the transformation of lanosterol into cholesterol, the precursor to all steroidal hormones, high doses of ketoconazole lead to androgen deprivation.[66] Its use for the treatment of metastatic prostate cancers that do not respond to antiandrogens normally involves short treatments due to its toxicity, in association with corticoids to prevent adrenal insufficiency associated with the inhibition of corticosteroid synthesis. Ketoconazole acts by coordination of the unsubstituted imidazole nitrogen atom to the iron atom in the active site of the cytochrome, displacing a coordinated water molecule (Figure 3.29).

6.2.2 Inhibitors of CYP17A1 (17α-hydroxylase and C(17,20)-lyase)

CYP17A1 is a cysteinato-heme enzyme that belongs to the cytochrome P450 superfamily. It contains a heme group, which is covalently linked to the protein through the sulfur atom of a proximal cysteine. The heme is the reactive center to activate molecular oxygen and to oxidize the substrate. This enzyme shows 17α-hydroxylase and C(17,20)-lyase properties and catalyzes the two steps of the transformation of pregnenolone into dehydroepiandrosterone, via 17α-hydroxypregnenolone as an intermediate (Figure 3.30).

The first CYP17A1 inhibitors to be studied clinically were the steroids abiraterone acetate and galeterone. Abiraterone was the first compound acting by this mechanism to be commercialized, under the trade name Zytiga®.



Abiraterone acetate Galeterone