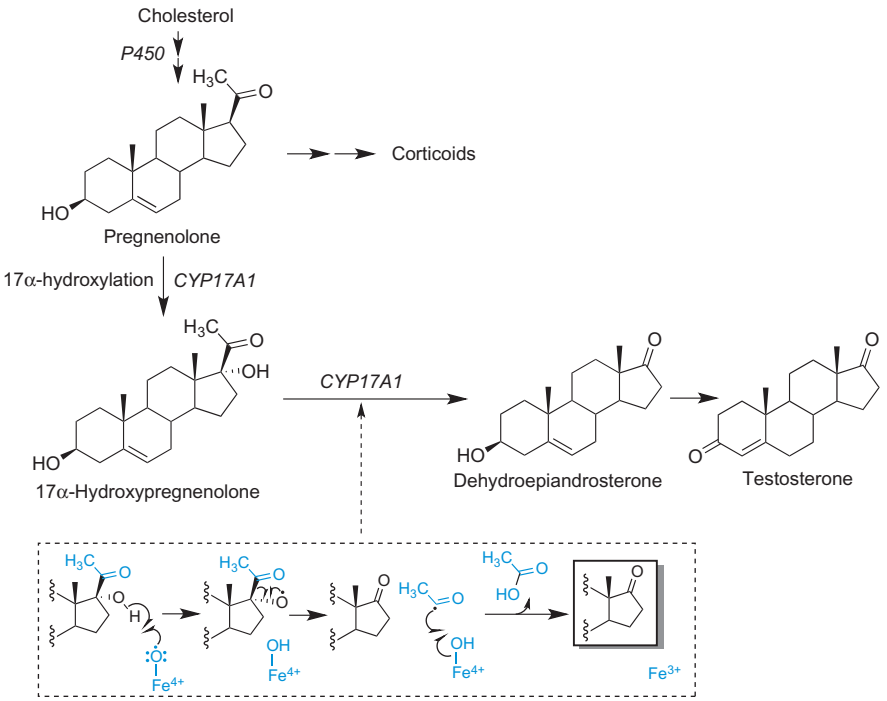

FIGURE 3.30

Reactions catalyzed by CYP17A1 and mechanism of the oxidative deacetylation at C-17.

Abiraterone is an irreversible inhibitor of CYP17A1.[67] Because this is a key enzyme in the production of androgens and estrogens in the adrenal glands and tumor tissues, abiraterone inhibits both adrenal and intratumoral androgen synthesis. A study in humans showed that repeated treatment with abiraterone in men with intact gonadal function can successfully suppress testosterone levels to the castrate range, although this level of suppression may not be sustained in all patients due to compensatory hypersecretion of luteinizing hormone (LH).[68] After several clinical trials to determine its usefulness,[69] abiraterone acetate was tested in patients with CRPC in a phase III trial that demonstrated an overall survival benefit, confirming that CRPC is hormone-driven.[70] These results were the basis of its FDA approval for treatment of prostate cancer in 2011.

Galeterone (TOK-001, VN/124-1) can be regarded as an analog of abiroterone and has a similar binding mode to CYP17, although its benzene moiety occupies an additional hydrophobic pocket. Furthermore, it has a unique, dual mechanism of action involving both androgen receptor antagonism and CYP17A1 inhibition. This compound is being tested in advanced clinical trials for CRPC.[71]

The way in which these inhibitors bind to CYP17A1 is illustrated here for the case of abiraterone. The pyridine nitrogen at the C-17 substituent of this compound binds iron, forming an approximately 60° angle above the heme plane, and simultaneously the 3β-hydroxy substituent interacts with the aspargine-202 residue in the F helix (Figure 3.31).[72]