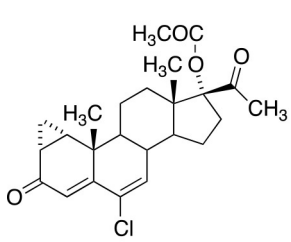
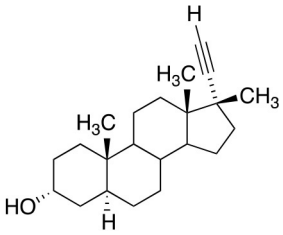


Cyproterone acetate

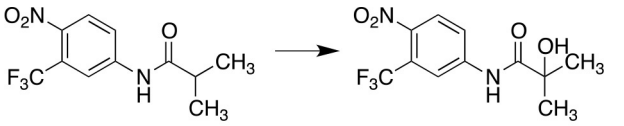


Apoptone (HE 3235)

The crystal structure of the ciproterone acetate–androgen receptor complex shows that the steric bulk from the drug 17α-acetate group displaces the Leu-701 side chain, resulting in the expansion of the receptor binding cavity by generation of an additional hydrophobic pocket surrounded by the Leu-701, Leu-704, Ser-778, Met-780, Phe-876, and Leu-880 residues (Figure 3.26a). As a consequence, the H11 and H12 helices are displaced. Hydrogen bonds with Arg-752, Gln-711, and Asn-705 also contribute to the complex stabilization (Figure 3.26b).

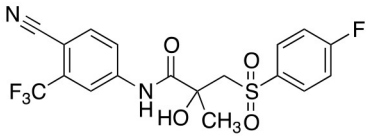
6.1.2 Nonsteroidal Antiandrogens

Flutamide (Eulexin® and Drogenil®) was the first nonsteroidal antiandrogen to be developed. It is a prodrug whose active metabolite (hydroxyflutamide) acts by inhibiting the binding of testosterone and 5α-dihydrotestosterone (DHT) to the androgen receptor. Molecular modeling studies have attributed the greater affinity of this metabolite to its dominant conformation, induced by intramolecular hydrogen bonding (see later). Another related antiandrogen that is in clinical use for the treatment of prostate cancer is bicalutamide (Casodex®), whose structure allows similar hydrogen bonding.



Flutamide

Hydroxyflutamide
(flutamide active metabolite)



Bicalutamide

In all these compounds, binding to the receptor is similar to that of testosterone. Thus, the aromatic ring on nitrogen occupies the same region of the receptor as the testosterone A ring, via hydrogen bonding of the nitro or cyano groups with Gln-711 and Arg-752 and stacking interactions with Phe-778. The hydroxy group interacts by hydrogen bonding with the same region of the receptor as the testosterone C17-OH, albeit less efficiently due to the loss of one hydrogen bond because of its involvement in intramolecular hydrogen bonding. The R substituent protrudes from a pseudocyclic structure generated by intramolecular hydrogen bonding and blocks the rotation of the H12 chain of the receptor, being thus responsible for the antagonistic effect (Figure 3.27).[61]