disoproxil fumarate (TDF) which is a nucleotide analog of adenosine phosphate. The NRTIs are administered as unphosphorylated prodrugs. Upon entering the host cell, these prodrugs are recognized by cellular kinases and further converted to the tri-phosphorylated form. The tri-phosphorylated NRTIs then bind to the active site of RT and are catalytically incorporated into the growing DNA chain. The incorporated NRTIs block the further extension of the chain since the NRTIs lack the 3′ hydroxyl group on their ribose or pseudo-ribose moiety and thus cannot form the 3′–5′ phosphodiester bond needed for DNA extension. NRTIs are one of the major classes of inhibitors used in all combination therapies for the treatment of HIV-infected patients. However, the clinical successes of these agents are limited by viral resistances to NRTIs, arising through mutations in the coding region of RT. These mutations confer viral resistances through improved discrimination of a nucleotide analog relative to the natural substrate, or by increased phosphorolytic cleavage of an analog-blocked primer. To overcome these acquired resistances, the design of the next generation of NRTIs has been mainly focused on two fronts: (1) nucleoside analogs possessing a 3′ hydroxyl group that can induce delayed polymerization arrest and (2) nucleotide analogs that are designed to be incorporated into the viral genome during replication. These nucleotide analogs can introduce mutations into the HIV genome through mispairing and blockade of the replication process.

11.4.1.2 Human Steroid 5α-Reductase Inhibitors

The human enzyme steroid 5α-reductase is responsible for the conversion of testosterone (T) to the more potent androgen, dihydrotestosterone (DHT). It has been shown that abnormally high 5α-reductase activity in humans leads to excessively high DHT levels in peripheral tissues. Inhibition of 5α-reductase thus offers a potential treatment for DHT-associated diseases, such as benign prostate hyperplasia, prostate cancer, acne, and androgenic alopecia. In humans, there are two types of steroid 5α-reductase: type I and type II. The type I 5α-reductase is mainly expressed in the sebaceous glands of skin and the liver, while the type II enzyme is most abundant in the prostate, seminal vesicles, liver, and epididymis. The first 5α-reductase inhibitor approved for clinical application in the United States was finasteride; it is currently employed in the treatment of benign prostatic hyperplasia (BPH) in men. This compound is approximately 100-fold more potent toward the type II than the type I isozyme of 5α-reductase. In humans, finasteride decreases prostatic DHT levels by 70%–90%, resulting in reduced prostate size. The detailed biochemical characterization of finasteride inhibition suggested that finasteride is a mechanism-based inhibitor. It is proposed that by closely mimicking the substrate (testosterone), finasteride is accepted as an alternate substrate and forms an NADP-dihydrofinasteride adduct at the enzyme active site (Figure 11.4). This covalent NADP-dihydrofinasteride adduct represents a bisubstrate analog with extremely high affinity ($K_i \leq 1 \times 10^{-13}$ M) to the type II 5α-reductase. Interestingly, finasteride is also a mechanism-based inhibitor of the human type I 5α-reductase. However, the NADP-dihydrofinasteride adduct formation rate at the type I 5α-reductase active site is reduced by more than 100-fold compared to that for the type II isozyme. This difference in NADP-dihydrofinasteride adduct formation rate accounts for the isozyme selectivity of finasteride both in vitro and in vivo. Knowledge of the mechanism of inhibition of 5α-reductase by 4-azasteroids (represented by finasteride) and of the SAR for dual 5α-reductase inhibition led to the discovery of a potent, dual inhibitor of 5α-reductase, known as dutasteride. Dutasteride is equipotent versus type I and type II 5α-reductase and demonstrates exceptional in vivo potency. This compound has also been approved for clinical use in the treatment of BPH.

11.4.2 Intermediate State-Based Design

11.4.2.1 Inhibitors of Hydroxymethylglutaryl-CoA Reductase (HMG-CoA Reductase)

The biosynthetic pathway for cholesterol involves more than 25 different enzymes. The enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase catalyzes the conversion from HMG-CoA to mevalonate, the rate-limiting step of the entire pathway. Inhibition of HMG-CoA reductase provides a very attractive opportunity to inhibit cholesterol biosynthesis because no