catalyzed structural conversion within the active site of an enzyme. Substrate, cofactor, and product mimicry, however, is not the only method for the design of high-affinity, selective enzyme inhibitors. Advances in transition state theory during the past four decades have helped to establish an alternative approach for mechanism-based design: intermediate state-based design (sometimes also referred to as transition state-based design). In this latter approach, inhibitors that mimic the steric and electronic features of high-energy reaction intermediate states are designed to capitalize on the specific interactions of active site residues with the reaction intermediate. In the next two sections, cases for substrate structure-based design and intermediate state-based design will be discussed to exemplify inhibitor design strategies that have led to successfully marketed products or clinical candidates.

11.4.1 Substrate Structure-Based Design

11.4.1.1 Nucleoside and Nucleotide Inhibitors of HIV Reverse Transcriptase

HIV reverse transcriptase (RT) is one of two main targets for anti-acquired immunodeficiency syndrome (AIDS) therapy (the second target being the HIV protease; *vide infra*). The RT enzyme catalyzes the synthesis of double-stranded proviral DNA from single-stranded genomic HIV RNA. Drugs targeting HIV RT can be divided into two categories: (1) nucleoside and nucleotide RT inhibitors (NRTIs) which are competitive with respect to the natural deoxynucleotide triphosphates (dNTPs) and serve as alternative substrates for catalysis (resulting in chain termination) and (2) non-nucleoside RT inhibitors (NNRTIs) which are allosteric, noncompetitive inhibitors that bind at a site distal to the RT active site. NRTIs were the first class of chemotherapeutic agents to be utilized in the clinic to treat AIDS patients and offer excellent examples of inhibitor design based on substrate mimicry. The first NRTI, Zidovudine (AZT) was approved by the FDA in 1987 (Figure 11.3).

AZT is a thymidine analog with an azido group in place of the hydroxyl group at the 3′ position of the ribose. Since the advent of AZT-based therapy, a number of NRTIs have joined the anti-AIDS treatment armamentarium. Most of these are nucleoside analogs with the exception of tenofovir

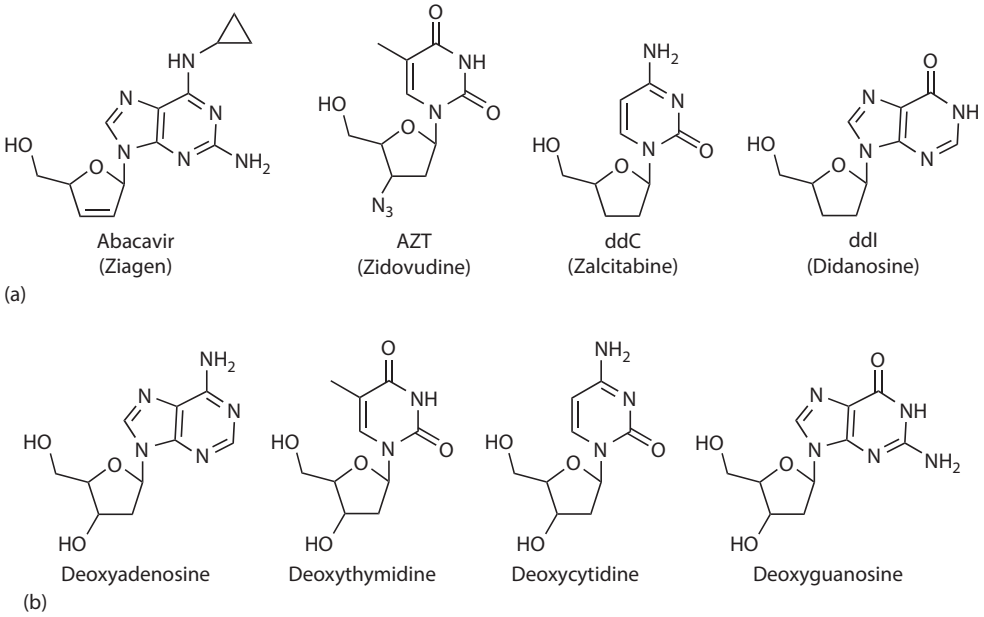

FIGURE 11.3 Representative FDA-approved nucleoside/nucleotide reverse transcriptase inhibitors (a) that closely mimic the natural deoxynucleotides (b).