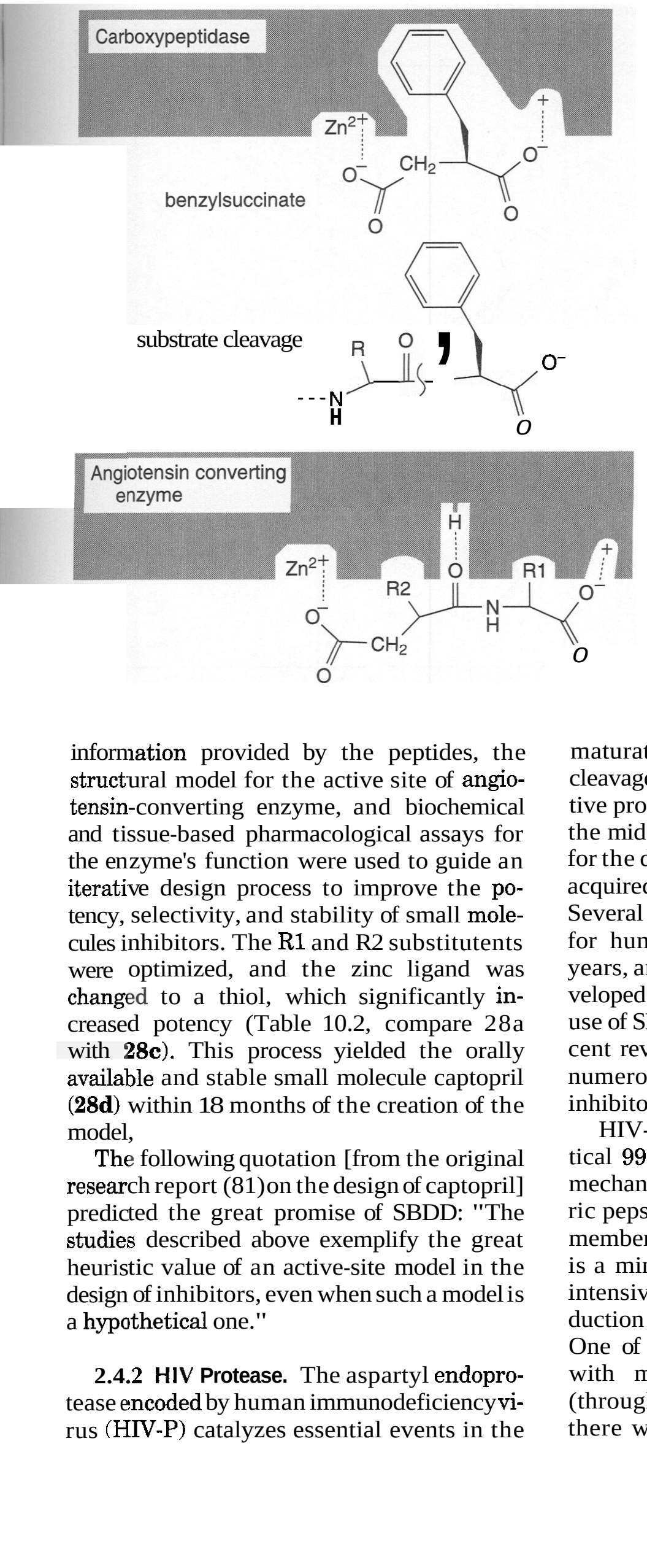

Figure 10.8. Active site models for carboxypeptidase A (top) and angiotensin-converting enzyme (bottom). The design of the dipeptidyl derivative that led to the discovery of captopril is shown bound to the latter enzyme.

information provided by the peptides, the structural model for the active site of angiotensin-converting enzyme, and biochemical and tissue-based pharmacological assays for the enzyme's function were used to guide an iterative design process to improve the potency, selectivity, and stability of small molecules inhibitors. The R1 and R2 substitutents were optimized, and the zinc ligand was changed to a thiol, which significantly increased potency (Table 10.2, compare 28a with **28c**). This process yielded the orally available and stable small molecule captopril (**28d**) within 18 months of the creation of the model,

The following quotation [from the original research report (81) on the design of captopril] predicted the great promise of SBDD: "The studies described above exemplify the great heuristic value of an active-site model in the design of inhibitors, even when such a model is a hypothetical one."

2.4.2 HIV Protease. The aspartyl endoprotease encoded by human immunodeficiency virus (HIV-P) catalyzes essential events in the maturation of infective virus particles, the cleavage of polyprotein precursors to yield active products. After this was demonstrated in the mid to late 1980s, HIV-P became a target for the development of antiviral drugs to treat acquired immunodeficiency syndrome (AIDS). Several HIV-P inhibitors have been approved for human therapeutic use in the past 10 years, and the speed with which they were developed is attributed in part to the successful use of SBDD methods. There are excellent recent reviews of this area (88, 89). There are numerous reviews of the early work on HIV-P inhibitors (8, 9, 90, 91).

HIV-P is a symmetrical homodimer of identical 99 residue monomers, structurally and mechanistically similar to the pseudosymmetric pepsin family of proteases (92–94), whose members include renin. Because the protease is a minor component of the virion particle, intensive structural studies required overproduction through recombinant DNA methods. One of the first structures was determined with material synthesized nonbiologically (through peptide synthesis). As of June 2002, there were over 100 X-ray structures repre-