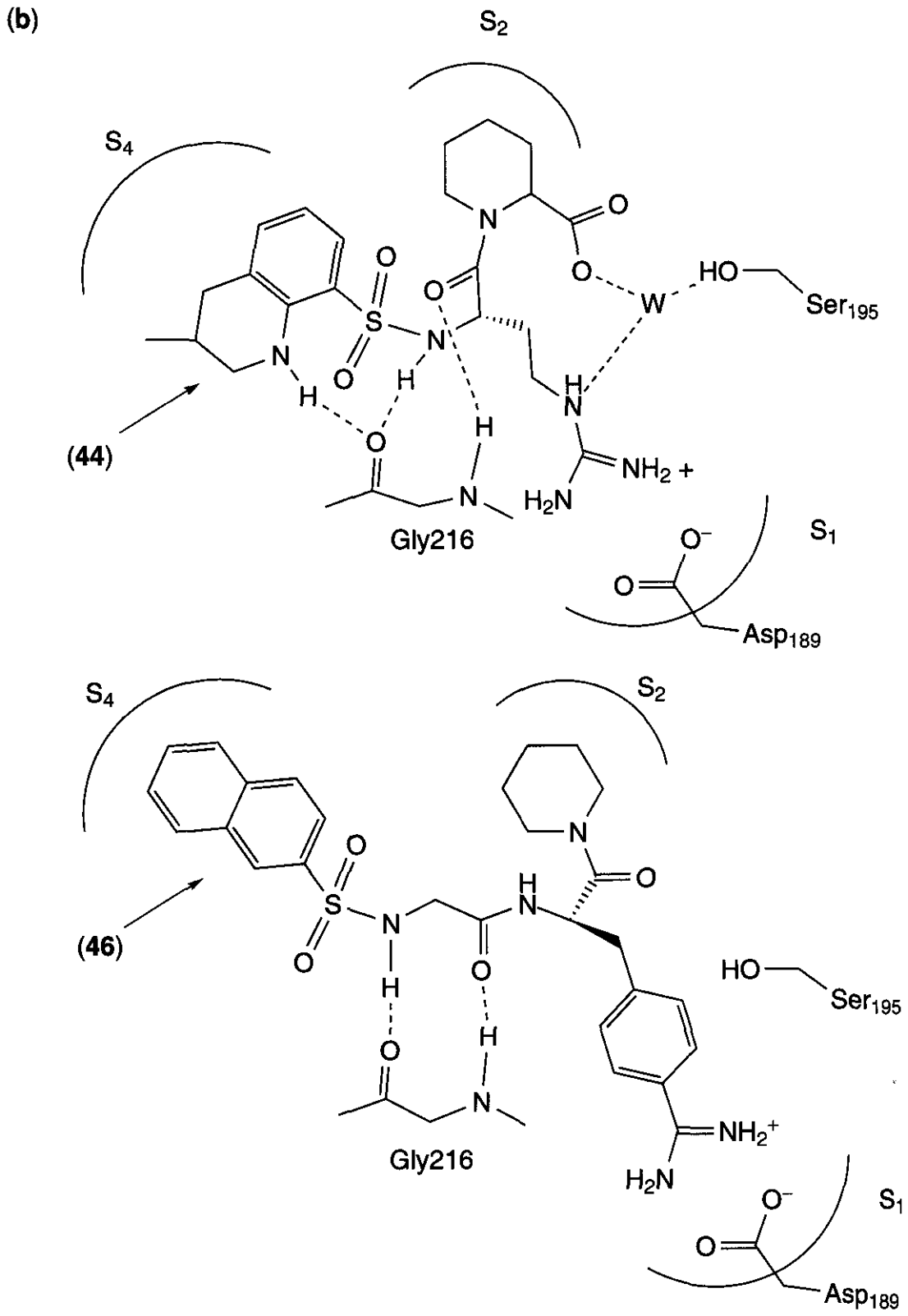

Figure 10.14. (b) Schematic comparison of the binding interactions for (**44**) and (**46**) in X-ray structural models of crystalline thrombin.

2.4.4 Caspase-1. Caspase-1 (interleukin 1-β converting enzyme, or ICE) is a member of a family of cysteine proteases that catalyze the cleavage of key signaling proteins in such processes as inflammatory response and apoptosis. Genetic methods have provided evidence supporting a role for caspase-1 in diseases such as stroke (118) and inflammatory bowel disease (119). The X-ray structure of crystalline human caspase-1 was solved in 1994 by several groups (120, 121), and has been a valuable tool in intensive efforts to design potent and bioavailable inhibitors of the enzyme.

Compound (**52**) (pralnacasan, VX-740) was developed as a caspase-1 inhibitory therapeutic agent through use of SBDD in a collaboration between Vertex and Aventis. Although the details of the discovery process have not been published, (52) probably functions as a prodrug. The cleavage of the lactone of (52) would yield a hemiacetal that could hydrolyze to release ethanol and the aldehyde form of the drug, which then can form a covalent thioacetal with the active site thiol of caspase-1, leading to pseudoirreversible inhibition. Clinical trials of compound (52) as an anti-inflammatory agent for treatment of rheumatoid arthritis began in 1999 (122). In April 2002, the