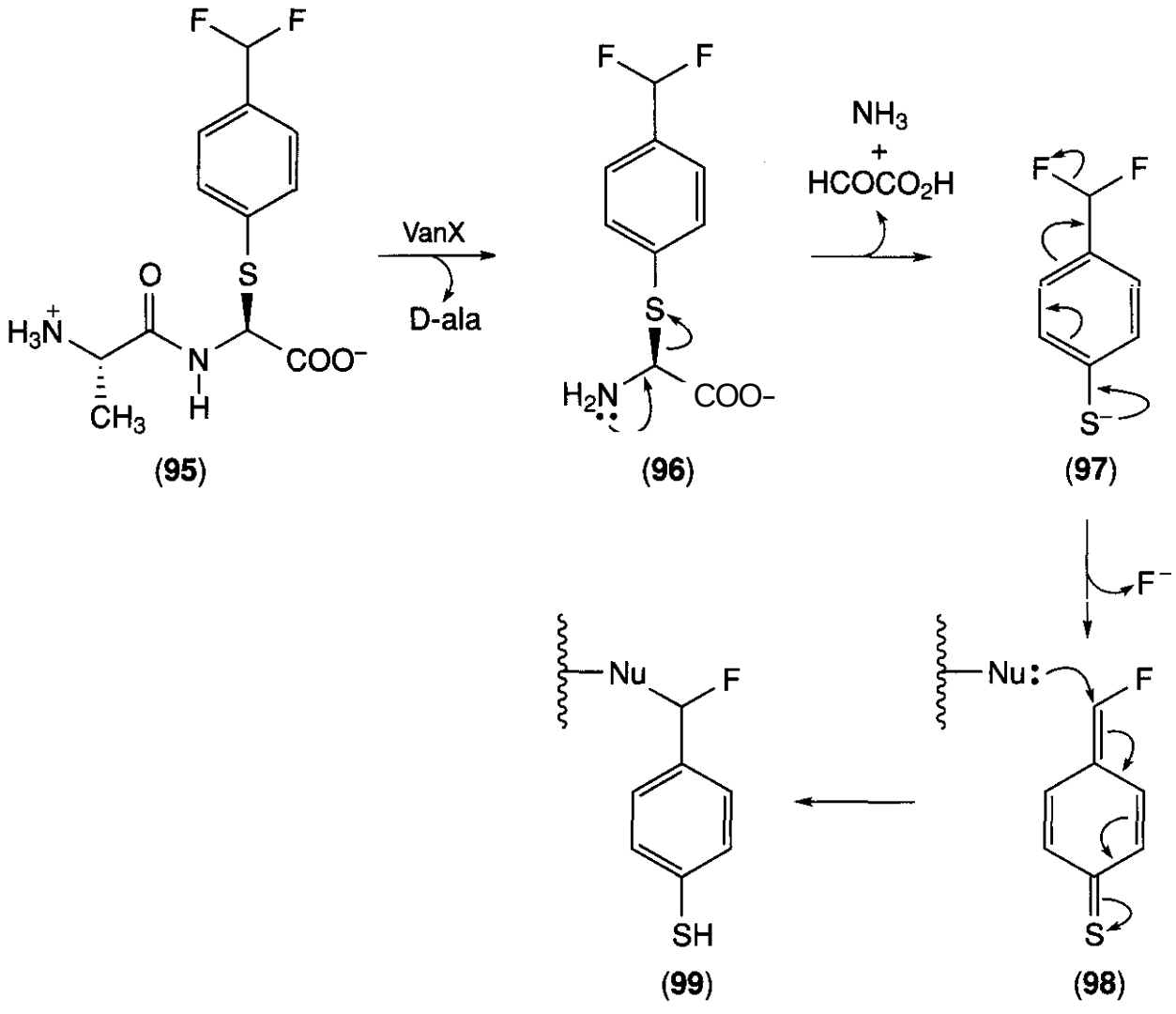


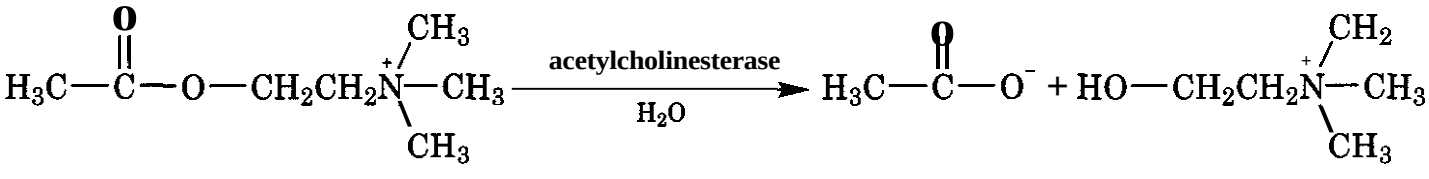
Figure 17.37. Mechanism-based inhibition of VanX.

ible inhibitor will be determined by a combination of the rate of formation of the covalent enzyme inhibitor adduct and the half-life for reactivation.

As may be expected, criteria for the study of pseudoirreversible inhibitors are very similar to those for both affinity labels and mechanism-based inhibitors. However, because of the inherent reversibility of pseudoirreversible inhibitors, it may be more difficult to obtain structural evidence for the covalent enzyme inhibitor adduct. Further, determination of the rate of reactivation and characterization of the products of the recovery process will also be of major importance in designating an inhibitor as pseudoirreversible.

Pseudoirreversible inhibitors can be broken into two classes, depending on how the active enzyme is regenerated. In the first class, exemplified by inhibitors of acetylcholinesterase, the enzyme is regenerated as the covalent E-I' bond is hydrolyzed (i.e., $k_3 \gg k_{-2}$). As shown in Equation 17.58 , acetylcholinesterase catalyzes the hydrolysis of acetylcholine, yielding choline and acetate.

Acetylcholine is a neurotransmitter that relays nerve impulses across the neuromuscular junction. Acetylcholinesterase (AcChE) rapidly breaks down acetylcholine, thereby lowering its concentration in the synaptic cleft and ensuring that nerve impulses are of a finite length. As shown in Fig. 17.38, a nucleophilic serine residue reacts with the substrate to form an acetyl-serine intermediate (100) with concomitant release of choline. This intermediate is then rapidly hydrolyzed by wa-



(17.58)

acetylcholine **acetate** **choline**