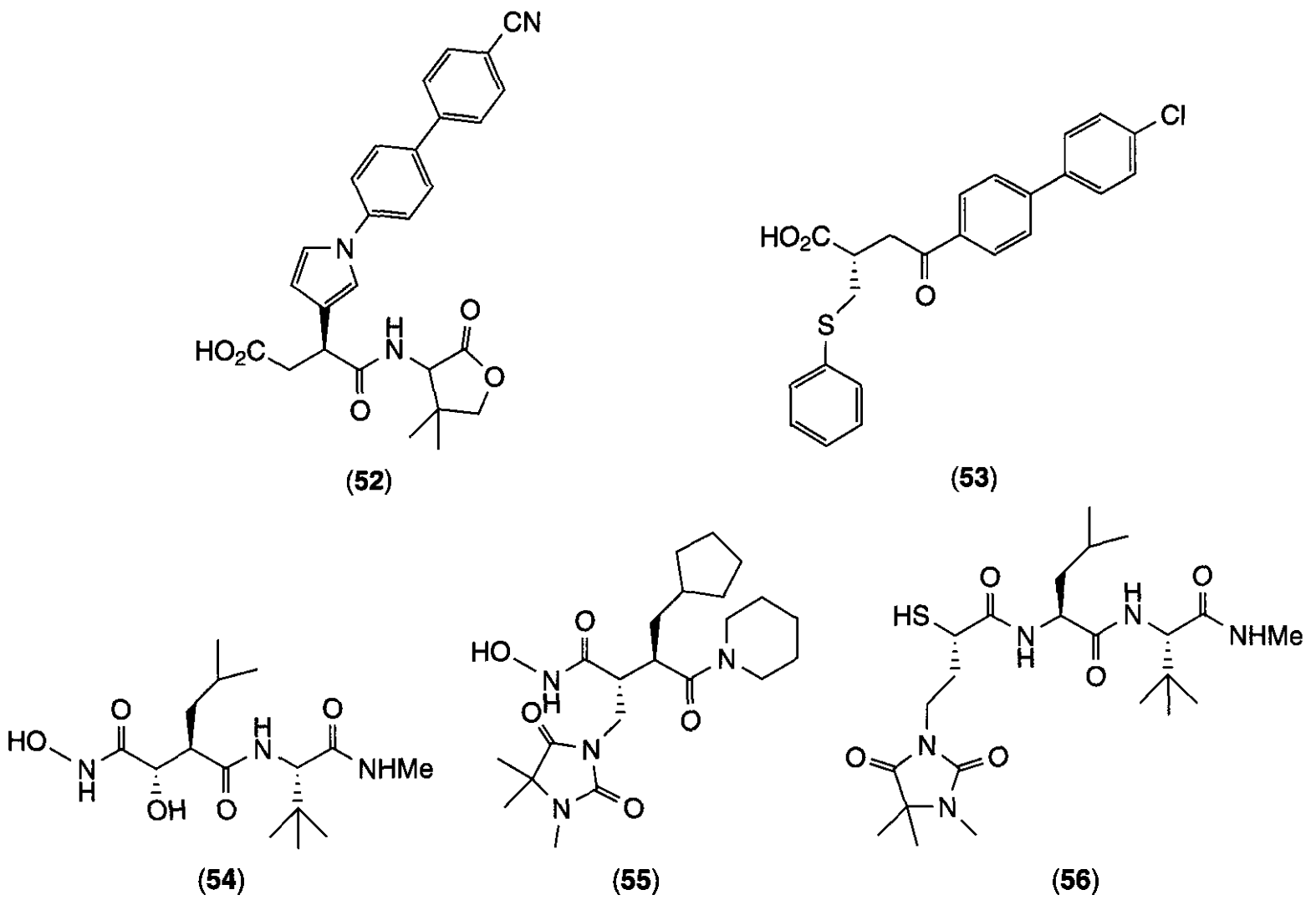

Figure 15.25. Traditional TSA used to inhibit metallopeptidases.

lectivity of this type of compound arises from the specific coordination of the thiirane with the active-site zinc ion, which facilitates thiirane ring opening by nucleophilic attack by neighboring Glu-404. This novel mode of binding was assessed by X-ray absorption studies because of the difficulty to obtain a suitable crystal structure (111,112).

ADAMs are membrane proteins that contain *a* disintegrin and *a* metalloprotease domain. Disintegrins are RGD-containing proteins that inhibit cell/matrix interactions (adhesion) and cell/cell interactions (aggregation) through the integrin receptors. In addition, ADAMs have two other domains that are involved in signaling and transport (113).

There are more than 25 ADAMs proteases identified so far. ADAM 17 has been shown to be TNF-a converting enzyme (TACE) (114). Inhibition of TACE slows the production of TNF-a, a potent cytokine involved in inflammatory responses to infection. Normally TNF-a produces a useful response, but in some cases, too much TNF-a is released and inhibition of TNF-a production would be therapeutically useful. Synthetic analogs have been synthesized that inhibit this enzyme. Clinical candidates like Ro-32,7315 (59) (Fig. 15.27) are starting to emerge, and more are expected in the near future (115,116).

Aminopeptidases, enzymes that cleave off the N-terminal amino acid from a peptide chain, are bismetallo peptidases, a class of metallopeptidase that contain two metals ions in the catalytic site (117, 118). These can be inhibited by compounds related to bestatin (60) (Fig. 15.28), which contains the *N*-terminal α-hydroxy-β-amino acid residue, sometimes referred to as norstatine. In leucine amino peptidase, chelation occurs between both the amide carbonyl group and the adjacent hydroxyl and the hydroxyl and the *N*-terminal amino group (119,120).

6.3 TSA-Derived Cysteine and Serine Peptidase Inhibitors

Classical TSA inhibitors of cysteine and serine proteases differ from the metallo- and aspartic protease inhibitors in that they mimic the tet-