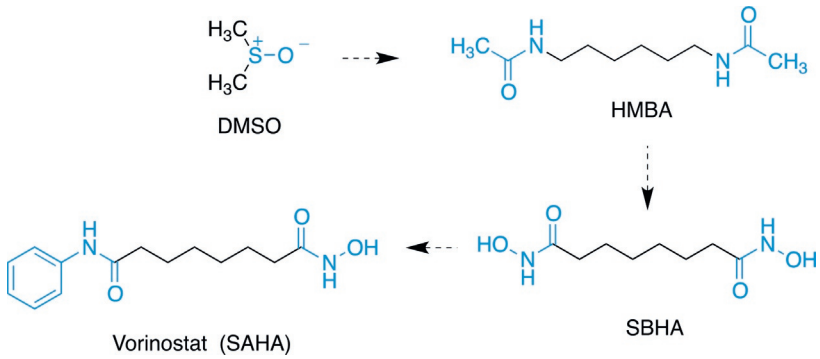

FIGURE 8.14

Stages in the design of vorinostat from DMSO.

The similarity of the structure of SAHA to that of trichostatin A suggested that SAHA acted by HDAC inhibition. Finally, when a complex of SAHA with a histone deacetylase-like protein (HDLP) was examined by X-ray crystallography, it was shown that the hydroxamic acid group chelated a zinc atom at the bottom of a cavity and the phenyl group was lying on the hydrophobic surface of the enzyme.[43]

Pyroxamide is a bioisoster of vorinostat that is also under clinical assays in patients with advanced malignancies.[44] Several hydroxamic derivatives of cinnamic acid, such as belinostat (PDX-101, Beleodaq®), panobinostat (LBH-589, Farydak®),[45] and dacinostat (NVP-LAQ-824),[46] are also under clinical evaluation for hematological and solid tumors. Belinostat entered a phase II trial for relapsed ovarian cancer and showed good results for T cell lymphoma. It was approved by the FDA in 2014 for the treatment of relapsed or refractory peripheral T-cell lymphoma. Panobinostat is a pan-DAC inhibitor got accelerated aprroval by the FDA on 2/23/2015 for use in patients with MM who have received at least two previous treatments. In multiple combinations entered phase I–III studies for cutaneous T cell lymphoma, myelodysplastic syndromes, myelofibrosis, and other hematologic malignancies.[47]