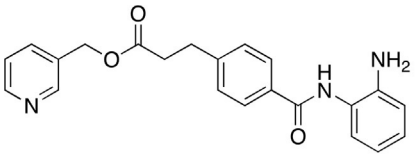
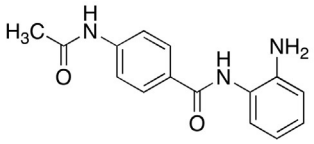
3.4 BENZAMIDES

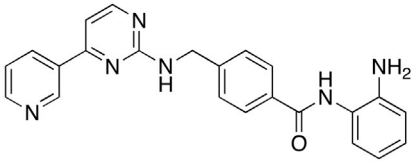
The synthetic benzamides entinostat (MS-275),[65] tacedinaline (CI-994),[66] and mocetinostat (MGCD-0103)[67] are being clinically tested in a variety of tumors, alone or in combination with other drugs. Entinostat is in phase II trials for Hodgkin's lymphoma, lung cancer, and breast cancer.[68] A phase II clinical trial in relapsed/refractory follicular lymphoma has been completed for mocetinostat. It has also been tested in multiple phase I and II trials, either as a single agent or in combination with 5-azacitidine (Vidaza®) or gemcitabine (Gemzar®). Mocetinostat received orphan drug designation from the FDA and EMA for the treatment of Hodgkin's lymphoma and AML. In 2014, the FDA also granted orphan drug designation for this compound for the treatment of diffuse large B-cell lymphoma and also for bladder cancer patients with specific genetic alterations. The presence of an *ortho* amino group into the *N*-phenylbenzamide substituent is essential for activity, and therefore it can be assumed to play a key role in the binding to the active site. In the case of entinostat, binding to zinc has been demonstrated.



Entinostat (MS-275)



Tacedinaline (CI-994, *p*-*N*-acetyldinaline)



Mocetinostat (MGCD-0103)

3.5 THIOLS

Since the initial report about its potent HDAC inhibition activity, the previously mentioned marine natural product psammaplin A has been the model for new HDAC inhibitors and for structure–activity relationship (SAR) studies. Psammaplin A is a prodrug that requires reduction of its disulfide functionality to the corresponding thiol, which acts as a zinc-binding group within the active site of the HDAC protein (Figure 8.17).[26] Its oxime unit is important for high potency and selectivity, but it may be replaced by other groups. Psammaplin A also inhibits topoisomerase II and aminopeptidase N, with *in vitro* angiogenesis suppression.[69]

Highly potent heterocyclic *N*-2-(thioethyl)picolinamide HDAC inhibitors, such as **8.18**, have been discovered by using computational modeling based on the psammaplin A pharmacophore.[70] However, probably because a thiol group is not an ideal functional feature due to potential off-target effects and low metabolic stability *in vivo*, thioester derivatives have been studied as possible prodrugs. Surprisingly, the thioester **8.19** is a potent HDAC inhibitor, despite the fact that previous SAR studies suggested that modification of the thiol functionality should detrimentally affect HDAC potency.[71]