the melanoma cell line to doxorubicin, and also impaired the migration of MDA-MB-435S melanoma cells.[148]

A novel benzimidazole derivative that showed SIRT1/SIRT2 inhibition activity with micromolar $IC_{50}$ values has been described. This compound was able to inhibit MCF-7 breast cancer, as well as the triple-negative breast cancer cells (MDA-MB-468), although target therapies currently do not exist.[149]

SIRT3 was overexpressed in 3 cell lines of oral squamous cell carcinomas that have a poor 5 year survival rate.[48] A novel SIRT3-specific inhibitor, named LC-0296 (Figure 12.10), showed 10-fold greater inhibition towards SIRT3 enzymatic activity in comparison with SIRT1 and SIRT2. LC-0296 inhibited cell growth and proliferation and promoted apoptosis of HNSCC cells, in part by increasing ROS levels, and enhanced the sensitivity of these cells to both radiation and chemotherapeutic drugs without affecting normal human oral keratinocytes at any of the inhibitor doses.[150]

Finally, a number of compounds have been reported to inhibit SIRT1 expression instead of affecting its enzymatic activity. Divalproex sodium, a drug used in the treatment of epilepsy, downregulated SIRT1 expression in K562 cells enhancing the antileukemic effects of imatinib.[151] In addition, alisertib, an Aurora kinase A inhibitor, suppressed the expression of Sirt1 in human pancreatic cancer cells and exerted a potent cell growth inhibitory effect on two human pancreatic cancer cell lines.[152]

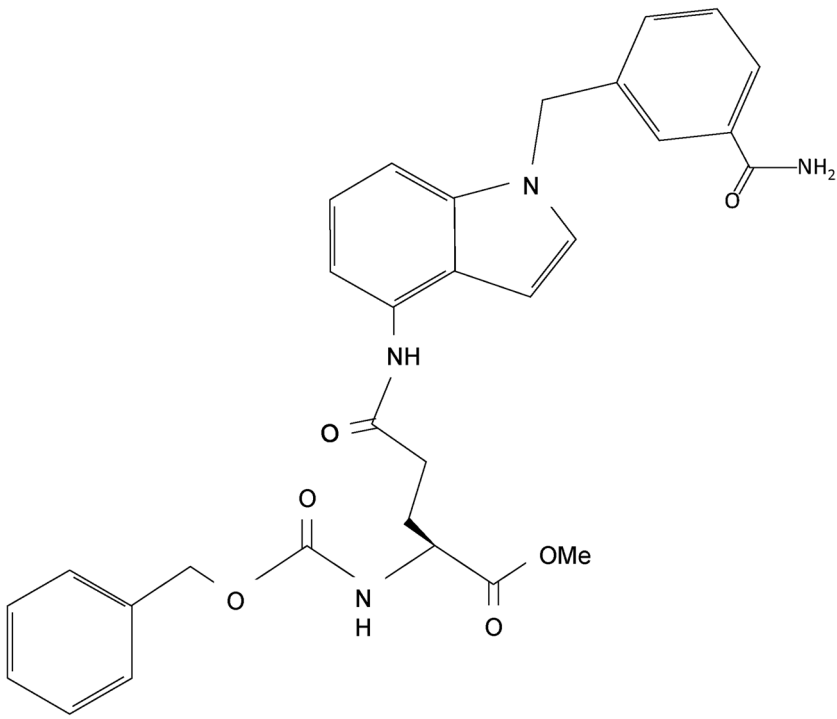


**Figure 12.10** LC-0296.