However, the antiproliferative effect of tenovin-6 in different gastric cancer cell lines was p53-independent because a similar inhibitory effect was achieved with cell lines containing wild-type p53 and with cells endowed with mutant-type or null versions of p53 protein.[146] The inhibitory effect of tenovin-6 was linked to upregulation of the death receptor 5, a member of the tumor necrosis factor receptor family. Tenovin-6 showed a slight to moderate synergistic effect in treatment with chemotherapeutic agents, including docetaxel, SN-38, cisplatin, and 5-FU, in gastric cancer cell lines.[146]

In synovial sarcoma tumors and soft tissue sarcoma cell lines, SIRT1 expression was higher than in normal mesenchymal cells, but this difference was not statistically significant. Tenovin-6 treatment inhibited cell proliferation and induced p21 in all sarcoma cell lines tested independently of p53 status, without affecting the viability of primary mesenchymal stem cells, and antitumor growth effect of tenovin-6 was enhanced in starving nutrient-deprived conditions. Furthermore, treatment with tenovin-6 had an inhibitory effect on the growth of rhabdomyosarcoma xenografts.[38] Similarly to chronic lymphocytic leukemia,[137,138] tenovin-6 induced a time-dependent accumulation of LC3-II in all cell lines.[38]

12.4.8 Other Inhibitors of Human Sirtuins

Recently, new inhibitors for SIRT1, SIRT2 and SIRT3 have been designed and their ability as anticancer drugs tested in cell culture. An SIRT2 inhibitor, named AC-93253 (Figure 12.9), was identified by Zhang *et al.* in 2009 and exhibited selective inhibition of SIRT2 with an IC_{50} value of 6.0 μM, compared with related sirtuins for SIRT1 and SIRT3 for which IC_{50} values of 45.3 μM and 24.6 μM, respectively, were reported.[147] AC-93253 arrested cell growth in four different cancer cell lines derived from the prostate (DU145), pancreas (MiaPaCa2), and lung (A549 and NCI-H460), but was dramatically less active against non-transformed cell lines. AC-93253 toxicity was mediated by a significant induction of apoptotic cell death with few necrotic cells being observed.[147] In addition, AC-93253 exerted a negative effect on the expression of a set of genes involved in the progression and chemoresistance in melanoma and HeLa cells. The compound decreased expression of ABC transporters that mediate doxorubicin resistance in melanomas, sensitizing

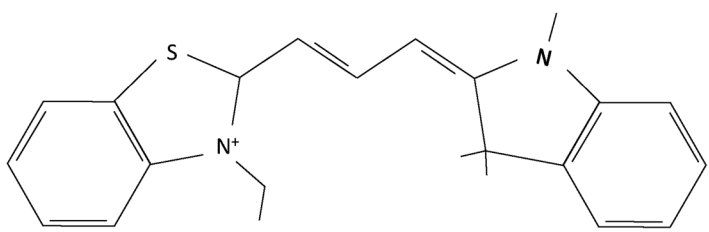

Figure 12.9 AC-93253.