improvement over previously reported SIRT inhibitors. Furthermore, EX-527 showed a higher degree of selectivity for SIRT1 over two other sirtuins: SIRT2 and SIRT3. This compound entered into the cells and inhibited the deacetylation of p53 at a concentration of 1 μM.[129]

Deacetylation of cortactin is associated with high levels of SIRT1 and tumorigenesis. EX-527 inhibition of SIRT1 induced greater amounts of acetylated cortactin in C13 and A2780cp cells.[94] SIRT1 is involved in tumorigenesis and drug resistance. Gemcitabine, which is used as a first-line therapy in pancreatic cancer patients, induced SIRT1 expression and potentially SIRT1-mediated pathways in the PANC-1 cell line. In this cell line, EX-527 inhibited or reduced proliferation PANC-1 cells *in vitro* and enhanced their sensitivity to gemcitabine treatment through increased apoptosis and the augmentation of caspase 3/7 activity, but had no effect on EMT.[130] Moreover, SIRT1 was upregulated in gastric cancer and ESCC with SIRT1 being required for the ATF4-induced multidrug resistance (MDR) effect in these cancers.[41,131] The inhibition of SIRT1 with EX-527 could partly reverse the gastric cancer MDR phenotype mediated by ATF4 in a dose–response manner.[41] Furthermore, the growth of endometrial carcinoma cells was also mediated by SIRT1. This sirtuin was significantly higher in endometrial carcinoma than in normal endometria and its overexpression was associated with a shorter survival and significantly enhanced the resistance for cisplatin and paclitaxel. EX-527 significantly suppressed the proliferation and cisplatin resistance of three endometrial carcinoma cell lines and also markedly inhibited tumor growth in a mouse xenograft model of endometrial carcinoma cell lines, regardless of the p53 mutational status.[132]

A significant increase, not only in SIRT1 expression, but also in SIRT2 and SIRT7, was noted during different stages of cervical cancer progression. Similar to ovarian cancer, SIRT1 expression was noted in both the cytoplasm and nucleus of the preneoplastic lesions. The treatment of cancer cell lines with EX-527 and AGK2, which specifically inhibit SIRT1 and SIRT2, respectively, also inhibited cell growth.[133] Furthermore, it has recently been reported that EX-527, like sirtinol, impaired cell growth and increased ROS production and apoptosis in primary chronic lymphocytic leukemia cells.[113]

The first Phase I pharmacokinetics studies has been carried out in seven cohorts of eight subjects that received a single dose of EX-527 (selisistat) at levels of 5, 25, 75, 150, 300 and 600 mg, and four cohorts of eight subjects that were administered 100, 200 and 300 mg once daily for 7 days. EX-527 was rapidly absorbed in proportion to the dose in the 5–300 mg range and a plateau in plasma was achieved within 4 days of repeated dosing. No serious adverse events were reported and EX-527 was considered safe and well tolerated by healthy male and female subjects after single doses up to 600 mg and multiple doses up to 300 mg per day.[134]

12.4.7 Tenovin

Using a cell-based screen for small molecules able to activate p53 and decrease tumor growth, Lain *et al.* (2008) found two SIRT1 inhibitors, tenovin-1 and its more water-soluble analog tenovin-6 (Figure 12.8), which