growth and increased ROS production and apoptosis in primary chronic lymphocytic leukemia cells and cell lines,[113] adult T-cell leukemia-lymphoma,[114] melanoma cells[115] and NSCLC cells.[116]

Furthermore, SIRT1 expression was upregulated in the androgen refractory PC3 and DU145 human prostate cancer cells and cell growth was dependent on the SIRT1 expression. Treatment of PC3 cells with sirtinol at 50 μM resulted in a significant inhibition of cell growth and also attenuated the chemoresistance that these cells presented against camptothecin and cisplatin by a mechanism that involved inhibition of SIRT1 activity.[117] The exposure of the human prostate cancer cell line LNCaP to sirtinol had a pleiotropic effect leading to G_1/G_0 arrest and the inhibition of cell growth through p53-dependent pathways. Furthermore, the treatment inhibited the expression of markers for both androgen and IGF-1 pathways, which is of great importance since high circulating level of IGF-1 correlated with increased prostate cancer risk.[118] Furthermore, in the BxPC-3 pancreatic cancer xenogeneic mice model a combined treatment of sirtinol and gemcitabine, the standard chemotherapeutic and first line drug for patients suffering from pancreatic cancer, improved the efficacy and survival time compared with either single inhibition of SIRT1 or single gemcitabine therapy,[119] suggesting that high levels of SIRT1 may play an important role in promoting chemoresistance in these cancer cells.

SIRT1 also plays an important role in angiogenesis, modulating the stability of HIF-1α. Although SIRT1 was overexpressed in HCC and many liver cancer cell lines, HIF-1α protein was not detected in cells cultured at 21% O_2 but was stabilized in cells cultured at 1% O_2.[74] In this oxygen tension, there was a dose-dependent repression of HIF-1α transcriptional activity in cells treated with sirtinol, but also a dose-dependent repression of HIF-1α protein accumulation due to a decrease of newly stabilized HIF-1α protein, rather than enhanced degradation of mature HIF-1α.[74]

12.4.4 Cambinol

Cambinol (Figure 12.4), a β-naphthol compound, was discovered in a screening of the National Cancer Institute repository of drugs as an inhibitor of human SIRT1 and SIRT2 activity *in vitro* with IC_{50} values of 56 and 59 μmol L^{-1}, respectively. The substitution of β-naphthol in cambinol with phenol led to loss of inhibitory activity.[120] Cambinol treatment induced apoptosis in Burkitt lymphoma cells by hyperacetylation of p53, even in the absence of any DNA-damaging agent, but was also less toxic to most of the carcinoma and primary cells. Cambinol-induced sirtuin inhibition also increased the acetylation and reduced the activity of BCL6, an oncoprotein that functions as a transcriptional repressor downregulating essential tumor suppressors like p53.[121] In addition, inhibition of SIRT1 and SIRT2 by cambinol was effective, arresting the growth of ER-positive human breast cancer MCF-7 cells. Moreover, inhibiting these sirtuins by treatment with cambinol decreased