12.4.3 Sirtinol

Sirtinol (2-[(2-hydroxy-naphthalen-1-ylmethylene)-amino]-*N*-(1-phenyl-ethyl)-benzamide) (Figure 12.3) was found to be an efficient inhibitor of yeast Sir2 and human SIRT2 in a screening of more than 1500 compounds from two chemical libraries, with an IC_{50} of 68 and 38 μM, respectively. The 2-hydroxyl-1-napthol moiety was sufficient for inhibition because it makes important contacts with the enzyme active site.[108]

Sirtinol induced senescence-like growth arrest in human breast cancer MCF-7 cells and lung cancer H1299 cells by impairing activation of mitogen activated protein kinase (MAPK) pathways, but neither expression nor acetylation of p53 were found to be upregulated by sirtinol.[109] However, later studies using MCF-7 cell lines confirmed that p53 is essential for sirtinol-induced apoptosis. Sirtinol was found to be a potent inhibitor of both SIRT1 and SIRT2 and combined targeting of both sirtuins was required to significantly increase the acetylation of p53 and induce cell death.[110,111] MCF-7 is an estrogen receptor (ER)-positive human breast cancer cell line expressing higher levels of SIRT1 than ERα-negative tumors and cancer cell lines. ERα and SIRT1 physically interact, but catalytically active SIRT1 was required for the interaction between ERα and SIRT1, increasing levels of antioxidative enzymes, especially Mn-SOD and glutathione peroxidase, and protecting tumor cells from ROS-induced cell death. In addition, ERα only bound directly to p53 and repressed its transcriptional activity when interacting with SIRT1. A combined treatment with tamoxifen (an antiestrogen) and sirtinol produced a greater magnitude of apoptosis in these cells than the individual treatment, suggesting that interaction at the molecular level could be used for the treatment of breast cancer.[112] Sirtinol also impaired cell

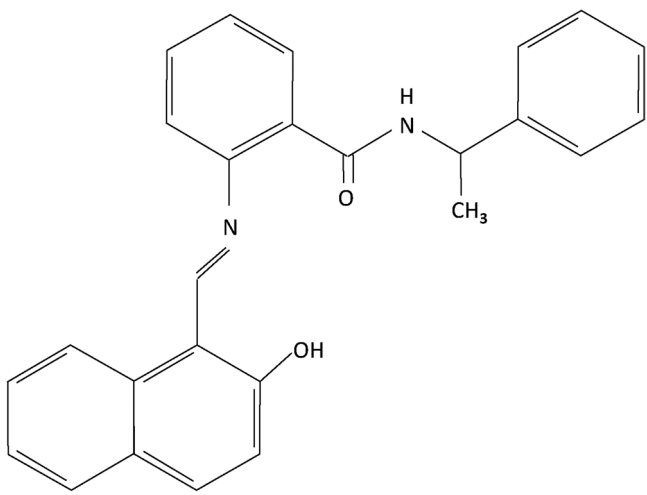

Figure 12.3 Sirtinol.