mainly located in the nucleus, SIRT1 can also be found in the cytoplasm, as well as in the nucleus in ovarian cancer specimens. Inhibition of SIRT1 induced greater amounts of acetylated cortactin in nicotinamide-treated C13 and A2780cp cells, and migration was significantly slower than that of vehicle-treated cells.[94]

A clinical trial to determine the maximal tolerated dose and dose-limiting toxicity of vorinostat and nicotinamide in combination enrolled 25 patients with different types of lymphoma. The treatment was well tolerated, and the most significant toxicity was related directly to nicotinamide. The most common toxicities included fatigue (84%), nausea (80%), diarrhea (72%), and anorexia (56%). 24% of patients with relapsed or refractory lymphoma attained a response to vorinostat and nicotinamide, and 57% experienced disease stabilization.[105] Currently, a clinical trial is recruiting patients to determine whether nicotinamide is effective in the treatment of human lung cancer (http://www.ClinicalTrials.gov Identifier: NCT02416739).

12.4.2 Splitomicin and Its Derivatives

In a cell-based screen for inhibitors of the yeast Sir2p, Bedalov *et al.* found that splitomicin (Figure 12.2A) inhibited the deacetylase activity with an IC_{50} of 60 μM.[106] However, splitomicin showed rather weak inhibition on human enzymes and to clarify the spatial orientations that the splitomicins adopt within the SIRT2 binding pocket, a series of splitomicins derivatives was synthesized. Among the different compounds tested, a β-phenylsplitomicin (compound HR73, Figure 12.2B) increased enzyme inhibition and showed antiproliferative properties and tubulin hyperacetylation in MCF-7 breast cancer cells.[107]

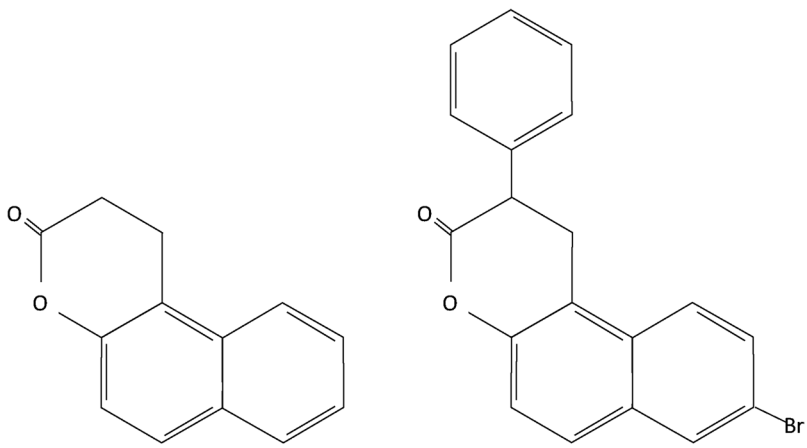

Figure 12.2 (A) Splitomicin and (B) the analogue HR 73.