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The NAD(+)-dependent sirtuin SIRT6 is highly expressed in human breast, prostate, and skin cancer where it mediates resistance to cytotoxic agents and prevents differentiation. Thus, SIRT6 is an attractive target for the development of new anticancer agents to be used alone or in combination with chemo- or radiotherapy. Here we report on the identification of novel quinazolinedione compounds with inhibitory activity on SIRT6. As predicted based on SIRT6's biological functions, the identified new SIRT6 inhibitors increase histone H3 lysine 9 acetylation, reduce TNF-α production and increase glucose uptake in cultured cells. In addition, these compounds exacerbate DNA damage and cell death in response to the PARP inhibitor olaparib in BRCA2-deficient Capan-1 cells and cooperate with gemcitabine to the killing of pancreatic cancer cells. In conclusion, new SIRT6 inhibitors with a quinazolinedione-based structure have been identified which are active in cells and could potentially find applications in cancer treatment.