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SIRT6 is an NAD(+)-dependent deacetylase with a role in the transcriptional control of metabolism and aging but also in genome stability and inflammation. Broad therapeutic applications are foreseen for SIRT6 inhibitors, including uses in diabetes, immune-mediated disorders, and cancer. Here we report on the identification of the first selective SIRT6 inhibitors by in silico screening. The most promising leads show micromolar IC50s, have significant selectivity for SIRT6 versus SIRT1 and SIRT2, and are active in cells, as shown by increased acetylation at SIRT6 target lysines on histone 3, reduced TNF-α secretion, GLUT-1 upregulation, and increased glucose uptake. Taken together, these results show the value of these compounds as starting leads for the development of new SIRT6-targeting therapeutic agents.