Design and evaluation of 3-(benzylthio)benzamide derivatives as potent and selective SIRT2 inhibitors

Abstract
Inhibitors of sirtuin-2 (SIRT2) deacetylase have been shown to be protective in various models of Huntington's disease (HD) by decreasing polyglutamine aggregation, a hallmark of HD pathology. The present study was directed at optimizing the potency of SIRT2 inhibitors containing the 3-(benzylsulfonamido)benzamide scaffold and improving their metabolic stability. Molecular modeling and docking studies revealed an unfavorable role of the sulfonamide moiety for SIRT2 binding. This prompted us to replace the sulfonamide with thioether, sulfoxide, or sulfone groups. The thioether analogues were the most potent SIRT2 inhibitors with a two- to three-fold increase in potency relative to their corresponding sulfonamide analogues. The newly synthesized compounds also demonstrated higher SIRT2 selectivity over SIRT1 and SIRT3. Two thioether-derived compounds (17 and 18) increased α-tubulin acetylation in a dose-dependent manner in at least one neuronal cell line, and 18 was found to inhibit polyglutamine aggregation in PC12 cells.