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**A novel SIRT1 inhibitor, 4bb induces apoptosis in HCT116 human colon carcinoma cells partially by activating p53**

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**Abstract**

The NAD<sup>+</sup>-dependent protein deacetylase SIRT1 has emerged as an important target for epigenetic therapeutics of colon cancer as its increased expression is associated with cancer progression. Additionally, SIRT1 represses p53 function via deacetylation, promoting tumor growth. Therefore, inhibition of SIRT1 is of great therapeutic interest for the treatment of colon cancer. Here, we report discovery of a novel quinoxaline based small molecule inhibitor of human SIRT1, 4bb, investigated its effect on viability of colon cancer cells and molecular mechanism of action. *In vitro*, 4bb is a significantly more potent SIRT1 inhibitor, compared to  $\beta$ -naphthols such as sirtinol, cambinol. Increasing concentration of 4bb decrease viability of colon cancer cells but, does not affect the viability of normal dermal fibroblasts depicting cancer cell specificity. Further, 4bb treatment increased p53 acetylation, Bax expression and induced caspase 3 cleavage suggesting that the death of HCT116 colon cancer cells occur through intrinsic pathway of apoptosis. Overall, our results presents 4bb as a new class of human SIRT1 inhibitor and suggest that inhibition of SIRT1 by 4bb induces apoptosis of colon cancer cells at least in part via activating p53 by preventing p53 deacetylation, increasing Bax expression and inducing caspases. Therefore, this molecule

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