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Abstract

Design, Synthesis and Biological Evaluation of Novel *1H*-benzo[d]imidazole Derivatives as Fatty Acid Synthase (FASN) Inhibitors for Cancer Treatment †

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Abstract: FASN is a metabolic oncoprotein that is overexpressed in multiple cancers and regulates the fatty acid requirements of proliferating cells. Thus, FASN has been proposed as a promising target for anticancer drug discovery. Herein, we report the *de novo* design and synthesis of small-molecule FASN inhibitors (CTL) that targets breast and colorectal cancer. Our structure–activity relationship studies led to the identification of CTL-1 and CTL-7 as potent, selective FASN inhibitors with IC_{50} values of 2.5 and 3.0 μM respectively. CTL-1 and CTL-7 inhibited the proliferation of colon cancer cells (HCT-116 and CaCO2) in and of breast cancer cells (MCF-7 and MDA-MB-231) at less than 10 μM concentration. However, in the non-cancerous cell line HEK-293, the IC_{50} of CTL-1 and CTL-7 was above 30 μM. Further, cell cycle analysis and apoptosis induction studies of CTL-1 and CTL-7 in HCT-116 cells revealed S-phase arrest along with a prolonged apoptotic effect. Western blot analysis of CTL-1 and CTL-7 established FASN pathway participation in causing cancer cell apoptosis. Molecular dynamics simulation studies of the compounds in KR-domain of the target indicate that CTL-1 and CTL-7 have a high affinity of for the FASN enzyme.

Keywords: fatty acid synthase inhibitor; cancer; apoptosis; cell cycle; enzyme inhibition; MD simulation

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