Design, Synthesis and Bioevaluation of Novel Hydroxamic Acids Incorporating 2-Oxoindoline Moiety as Histone Deacetylase Inhibitors and Anticancer Agents

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Nowadays due to the urgent needs of cancer medication, the molecular, targetbased drug discovery has become the most effective method of drug development with promising targets such as HDACs. In this work, a novel series of hydroxamic acids incorporating 2-oxoindoline moiety (compound series 5a-g, 6a-g) were designed based on the structure of SAHA (a compound that has been approved by FDA as an HDAC inhibitor) and the combination of the replacement of the benzene ring with the isatin ring and the addition of the triazole ring to the lipophilic linker. The synthesis was achieved using three basic organic chemistry reactions – alkylation, Click reaction, and substitution reaction. The synthesized compounds' structures were confirmed by using IR, HRMS, 1H-NMR, and 13C-NMR spectroscopy. The HDAC inhibition and cytotoxicity against three human cancer cell lines (colon cancer, prostate cancer and pancreatic cancer) were evaluated using the HDAC Fluorogenic assay kit and the Sulforhodamine B Assay. The results demonstrated that these hydroxamic acids exhibited strong HDAC inhibition and cytotoxic effects. Especially compound N-hydroxy-4-(4-((3-(hydroxy-l4azanylidene)-5-methyl-2-oxoindolin-1-yl) methyl)-1H-1,2,3-triazol-1-yl)butanamide (5e) is 5-8 fold more cytotoxic than SAHA, as indicated by the IC50 value ranging from 0.49 to 0.76 μM, meanwhile this value for SAHA is between 3.20 and 3.75 μM. Further bioactivity evaluation of these compounds against other HDACs and isoforms is undergoing for in vivo testing. The replacement of the 1,2,3-triazole ring with other isostrerics and/or the alteration of the functional groups on the 3-hydroxylmino-2oxoindoline moiety are being considered in order to design more promising derivatives.

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