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Assessment of Isatin as Surface Recognition Group: Design, Synthesis and Anticancer Evaluation of Hydroxamates as Novel Histone Deacetylase Inhibitors

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Abstract : Histone deacetylase (HDAC) are promising target for cancer treatment. The panobinostat (Farydak; Novartis; approved by USFDA in 2015) and chidamide (Epidaza; Chipscreen Biosciences; approved by China FDA in 2014) are the novel HDAC inhibitors ratified for the treatment of patients with multiple myeloma and peripheral T cell lymphoma, respectively. On the other hand, two other HDAC inhibitors, Vorinostat (SAHA; approved by USFDA in 2006) and Romidepsin (FK228; approved by USFDA in 2009) are already in market for the treatment of cutaneous T-cell lymphoma. Several hydroxamic acid based HDAC inhibitors i.e., belinostat, givinostat, PCI24781 and JNJ26481585 are in clinical trials. HDAC inhibitors consist of three pharmacophoric features - an aromatic cap group, zinc binding group (ZBG) and a linker chain connecting cap group to ZBG. Herein, we report synthesis, characterization and biological evaluation of HDAC inhibitors possessing substituted isatin moiety as cap group which recognize the surface of active enzyme pocket and thiosemicarbazide moiety incorporated as linker group responsible for connecting cap group to ZBG (hydroxamic acid). Several analogues were found to inhibit HDAC and cellular proliferation of Hela cervical cancer cells with GI50 values in the micro molar range. Some of the compounds exhibited promising results in vitro antiproliferative studies. Attempts were also made to establish the structure activity relationship among synthesized HDAC inhibitors.

Keywords : HDAC inhibitors, hydroxamic acid derivatives, isatin derivatives, antiproliferative activity, docking
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