Design, synthesis, and biological evaluation of novel amide and hydrazide based thioether analogs targeting Histone deacteylase (HDAC) enzymes

Hebatollah Atef Saad ,Ayman B. Farag, Mahmoud Salama Ahmed

Abstract

Development of HDAC inhibitors have become an ultimate need targeting different types of cancer. In silico virtual screening was applied to screen novel scaffolds via scaffold hopping strategy to develop different acrylamide and aryl/heteroaryl hydrazide based analogs merged with thioether moiety. The acrylamide based analogs showed significant hydrophobic interaction within binding pocket in addition to co-ordination with Zn+2 via carbonyl group, however the aryl/heteroaryl hydrazide based analogs showed binding towards Zn+2 via thiol moiety. Two classes (acrylamide and aryl/heteroaryl hydrazide based analogs) were synthesized to be screened along with 60 cancer cell lines panel to reveal that both of AHM-4 and AHM-5 showed significant inhibitory growth against HL-60 (Leukemia cell lines) at GI50 2.87 μM and 3.20 μM, respectively and MDA-MB-435 (Melanoma cell lines) cell lines at GI50 of 0.37 μM and 0.42 μM, respectively. AHM-4 and AHM-5 showed general inhibitory profile against class I HDAC enzymes with differential inhibitory activity towards HDAC 2 at IC50 32 nM and 20 nM, respectively via ELISA enzymatic assay, in addition to inhibiting activity for the expression of class I HDAC enzymes via real time PCR with differential selective inhibition against HDAC 2 up to 10 folds, compared to control. AHM4 and AHM5 showed cell cycle arrest action at G2/M phase along with induction of apoptosis via assessment of apoptotic parameters such as Caspase 3, 9, and ɔ- H2AX. The synthesized analogs offer novel scaffold to be further optimized for development of HDAC inhibitors.

European Journal of Medicinal Chemistry 2018, March