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Leveraging the HDAC Inhibitory Pharmacophore to Construct Deoxyvasicinone Based Tractable Anti-Lung Cancer Agent and pH-Responsive Nanocarrier

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Abstract : A tractable anti-lung cancer agent was identified via the installation of a Ring C expanded synthetic analogue of the alkaloid vasicinone [7,8,9,10-tetrahydroazepino[2,1-b] quinazolin-12(6H)-one (TAZQ)] as a surface recognition part in the HDAC inhibitory three-component model. Noteworthy to mention that the candidature of TAZQ was deemed suitable for accommodation in HDAC inhibitory pharmacophore as per the results of the fragment recruitment process conducted by our laboratory. TAZQ was pinpointed through the fragment screening program as a synthetically flexible fragment endowed with some moderate cell growth inhibitory activity against the lung cancer cell lines, and it was anticipated that the use of the aforementioned fragment to generate hydroxamic acid functionality (zinc-binding motif) bearing HDAC inhibitors would boost the antitumor efficacy of TAZQ. Consistent with our aim of applying epigenetic targets to the treatment of lung cancer, a strikingly potent anti-lung cancer scaffold (compound 6) was pinpointed through a series of in-vitro experiments. Notably, the compounds manifested a magnificent activity profile against KRAS and EGFR mutant lung cancer cell lines (IC50 = 0.80 - 0.96 µM), and the effects were found to be mediated through preferential HDAC6 inhibition (IC50 = 12.9 nM). In addition to HDAC6 inhibition, the compounds also elicited HDAC1 and HDAC3 inhibitory activity with an IC50 value of 49.9 nM and 68.5 nM, respectively. The HDAC inhibitory ability of compound 6 was also confirmed from the results of the western blot experiment that revealed its potential to decrease the expression levels of HDAC isoforms (HDAC1, HDAC3, and HDAC6). Noteworthy to mention that complete downregulation of the HDAC6 isoform was exerted by compound 6 at 0.5 and 1 µM. Moreover, in another western blot experiment, treatment with hydroxamic acid 6 led to upregulation of H3 acK9 and α-Tubulin acK40 levels, ascertaining its inhibitory activity toward both the class I HDACs and Class II B HDACs. The results of other assays were also encouraging as treatment with compound 6 led to the suppression of the colony formation ability of A549 cells, induction of apoptosis, and increase in autophagic flux. In silico studies led us to rationalize the results of the experimental assay, and some key interactions of compound 6 with the amino acid residues of HDAC isoforms were identified. In light of the impressive activity spectrum of compound 6, a pH-responsive nanocarrier (hyaluronic acid-compound 6 nanoparticles) was prepared. The dialysis bag approach was used for the assessment of the nanoparticles under both normal and acidic circumstances, and the pH-sensitive nature of hyaluronic acid-compound 6 nanoparticles was confirmed. Delightfully, the nanoformulation was devoid of cytotoxicity against the L929 mouse fibroblast cells (normal settings) and exhibited selective cytotoxicity towards the A549 lung cancer cell lines. In a nutshell, compound 6 appears to be a promising adduct, and a detailed investigation of this compound might yield a therapeutic for the treatment of lung cancer.

Keywords : HDAC inhibitors, lung cancer, scaffold, hyaluronic acid, nanoparticles
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