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Targeting epigenetics: Synthesis and biological evaluation of difluorinated propanediones as HMTase inhibitors

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Introduction: Pharmaco-epigenomics constitute the hope for a new strategy in cancer treatment owing to epigenetic deregulation, a reversible process, suspected of playing a role in malignancy 30 years prior to the sequencing of the human genome. In this field, several enzymes like HDACs, DNA methyl transferases (DNMTs) and histone methyl transferases (HMTase) have been studied extensively for their capability to be inherited by natural or synthetic compounds. To date, HDAC and DNMT inhibitors are used in cancer therapy are tested in clinical studies. In contrast to this, the search for inhibitors of HMTase is still in its infancy and *in-vivo* data of most of the agents are not available.

Methods: In this research work, we synthesized few difluorinated propanediones and their structures were determined by analytical and spectral (FTIR, ¹H NMR, ¹³C NMR) methods. The newly synthesized compounds were first evaluated for their antiproliferative activity and then for HMTase inhibitory potential in leukemic cell lines. We have also performed cell cycle analysis to study cell growth arrest.

Results: Amongst all the synthesized compounds, PR-4 was found to be most active. In the cytotoxicity assay, it showed cell growth of 42.6 % and 53.4% comparable to that of adriamycin; 44.5% and 53.2% in U937 and JURKAT, respectively. At a concentration of 1 and 10 μ M, it had shown to alter the methylation levels in two leukemic cell lines of histiocytic lymphoma (U937) and acute T-cell leukemia (JURKAT). Cell growth arrest was found in the G0/G1 phase in both the cell lines.

Discussion: The apoptosis pattern suggests that the molecule PR-4 could emerge as a potential anticancer agent by targeting HMTases.

Biography

Kalpana Tilekar has completed her Post-graduation in Pharmaceutical Chemistry, from Bharati Vidyapeeth's College of Pharmacy, Mumbai. She worked as an Assistant Professor at NCRD's Sterling Institute of Pharmacy, Navi Mumbai, India. Currently, she is working as Junior Research Fellow (JRF) on a project funded by DST, India and she is registered for PhD in Pharmaceutical Sciences at Bharati Vidyapeeth's College of Pharmacy, Navi Mumbai, India.

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