World Academy of Science, Engineering and Technology
International Journal of Pharmacological and Pharmaceutical Sciences
Vol:19, No:01, 2025

Rationally Designed Dual PARP-HDAC Inhibitor Elicits Striking Anti-leukemic Effects

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Abstract : The transfer of ADP-ribose residues onto target substrates from nicotinamide adenine dinucleotide (NAD) (PARylation) is catalyzed by Poly (ADP-ribose) polymerases (PARPs). Amongst the PARP family members, the DNA damage response in cancer is majorly regulated by PARP1 and PARP2. The blockade of DNA repair by PARP inhibitors leads to the progression of DNA single-strand breaks (induced by some triggering factors) to double-strand breaks. Notably, PARP inhibitors are remarkably effective in cancers with defective homologous recombination repair (HRR). In particular, cancer cells with BRCA mutations are responsive to therapy with PARP inhibitors. The aforementioned requirement for PARP inhibitors to be effective confers a narrow activity spectrum to PARP inhibitors, which hinders their clinical applicability. Thus, the quest to expand the application horizons of PARP inhibitors beyond BRCA mutations is the need of the hour. Literature precedents reveal that HDAC inhibition induces BRCAness in cancer cells and can broaden the therapeutic scope of PARP inhibitors. Driven by such disclosures, dual inhibitors targeting both PARP and HDAC enzymes were designed by our research group to extend the efficacy of PARP inhibitors beyond BRCA-mutated cancers to cancers with induced BRCAness. The design strategy involved the installation of Veliparib, an investigational PARP inhibitor, as a surface recognition part in the HDAC inhibitor pharmacophore model. The chemical architecture of veliparib was deemed appropriate as a starting point for the generation of dual inhibitors by virtue of its size and structural flexibility. A validatory docking study was conducted at the outset to predict the binding mode of the designed dual modulatory chemical architectures. Subsequently, the designed chemical architectures were synthesized via a multistep synthetic route and evaluated for antitumor efficacy. Delightfully, one compound manifested impressive anti-leukemic effects (HL-60 cell lines) mediated via dual inhibition of PARP and class I HDACs. The outcome of the western blot analysis revealed that the compound could downregulate the expression levels of PARP1 and PARP2 and the HDAC isoforms (HDAC1, 2, and 3). Also, the dual PARP-HDAC inhibitor upregulated the protein expression of the acetyl histone H3, confirming its abrogation potential for class I HDACs. In addition, the dual modulator could arrest the cell cycle at the G0/G1 phase and induce autophagy. Further, polymer-based nanoformulation of the dual inhibitor was furnished to afford targeted delivery of the dual inhibitor at the cancer site. Transmission electron microscopy (TEM) results indicate that the nanoparticles were monodispersed and spherical. Moreover, the polymeric nanoformulation exhibited an appropriate particle size. Delightfully, pH-sensitive behavior was manifested by the polymeric nanoformulation that led to selective antitumor effects towards the HL-60 cell lines. In light of the magnificent anti-leukemic profile of the identified dual PARP-HDAC inhibitor, in-vivo studies (pharmacokinetics and pharmacodynamics) are currently being conducted. Notably, the optimistic findings of the aforementioned study have spurred our research group to initiate several medicinal chemistry campaigns to create bifunctional small molecule inhibitors addressing PARP as the primary target.

Keywords : PARP inhibitors, HDAC inhibitors, BRCA mutations, leukemia
Conference Title : ICPP 2025 : International Conference on Pharmacy and Pharmacokinetics
Conference Location : New York, United States
Conference Dates : January 30-31, 2025