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VALPROIC ACID, ARYL AND HYDROAMIC ACID MOITIES TO TARGET HISTONE DEACETYLASES: THEORETICAL, SYNTHESIS AND ANTI-PROLIFERATIVE ASSAYS.

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Valproic acid (VPA) is extensively used as an anticonvulsive agent and as a treatment for other neurological disorders. It has been shown that VPA exerts an anti-proliferative effect on several types of cancer cells by inhibiting the activity of histone deacetylases (HDACs). However, VPA has some disadvantages, among which are poor water solubility and hepatotoxicity. Therefore, the aim of our research was to explore the binding site of VPA on HDAC8 using docking and molecular dynamics simulations; then, a set of VPA derivatives were designed and evaluated computationally to improve its physicochemical properties and anti-proliferative effects; the most promising of them were further synthesized and tested biologically. The results demonstrate that VPA is recognized at HDAC8 hydrophobic channel whereas its derivatives bind on different HDAC8 sites by hydrogen bonds, hydrophobic interactions and $\pi-\pi$ interactions. The IC_{50} values of the VPA derivatives determined using HeLa cells are in mM range whereas on breast cancer is in μM range. This result indicates that VPA derivatives have greater anti-proliferative effects than VPA. Hence, these results suggest that these VPA derivatives may represent a good alternative for anticancer treatment. In addition, we have been designing selective on HDAC8 and HDAC6 and we are developing multi-target compounds.

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