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SYNTHESIS, MOLECULAR MODELLING AND BIOLOGICAL CHARACTERIZATION OF NOVEL ANTIMIGRATORY AND ANTIINVASIVE 1-BENZHYDRYL PIPERAZINE DERIVATIVES

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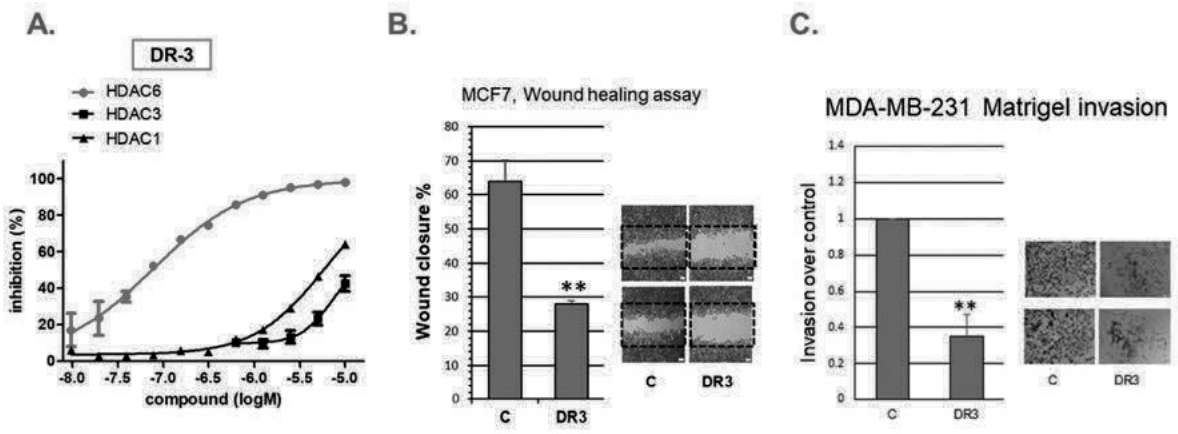
Human epigenetic metalloenzymes that modulate the acetylation status of histones, alter cancer cell morphology and cell survival are histone deacetylases (HDACs). Of particular importance, histone deacetylase 6 is studied as a cytoplasmic isoform implicated in the microtubule dynamics in cancer [1]. Still, more efforts need to be undertaken to make these inhibitors reach to global oncology market [2]. In this study, we probed the 1-benzhydryl piperazine as the capping (CAP) group to selectively target the HDAC6 isoform and alter the migration and invasiveness of the breast cancer cell lines. Nine different 1-benzhydryl piperazine derivatives were synthesized and the structure-activity relationship study was postulated with combined ligand-based (3D-QSAR) and structure-based (molecular docking) *in silico* approaches [3,4]. We performed wound healing, matrigel invasion and transwell migration assays to search for the inhibitor that shows antimigratory and antiinvasive properties of the breast cancer cell lines (MDA-MB-231 and MCF-7). Most of the synthesized compounds induce apoptosis in high concentrations (> 60 μM) in cell viability assay, whereas the antimigratory and antiinvasive effects were significantly pronounced at subapoptotic concentrations (5 μM). One of the nine synthesized inhibitors showed excellent non-cytotoxic, antimigratory and antiinvasive profile in breast cancer cell lines, which is in agreement with the proposed cellular roles of HDAC6 in cancer.



The work presented in this study integrates *in silico* modelling, synthesis and *in vitro* biological profiling to discover selective HDAC6 inhibitor. Identification of potent HDAC6 inhibitor that alters migration and invasiveness of breast cancer cell lines opens up new horizons to treat metastatic diseases.

References

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