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Novel 1-benzhydryl piperazine derivative inhibits the migration and invasiveness of breast cancer cells: Synthesis, molecular modelling and biological characterization

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Introduction

The most studied epigenetic metalloenzymes which regulate acetylation status, cell phenotype and cell survival are histone deacetylases (HDACs). In the last few years, histone deacetylase 6 became an interesting cellular target of particular interest to study the microtubule dynamics in cancer, due to its predominant cytoplasmic localization[1]. Today, there have been developed many potent chemical probes acting as selective HDAC6 inhibitors and none of them has reached the market[2]. In this study, we examined the usefulness of the 1-benzhydryl piperazine as the surface recognition (CAP) group to selectively target the HDAC6 isoform and alter the migration and invasiveness of the breast cancer cell lines.

Material and Methods

The synthesis of nine 1-benzhydryl piperazine derivatives is presented along with their in silico modelled binding poses in the HDAC1 and HDAC6 crystal structures. To screen for the most potent inhibitor that reduces the migration and invasiveness of the breast cancer cell lines (MDA-MB-231 and MCF-7), we performed wound healing, matrigel invasion and transwell migration assays.

Results and Discussions

The synthesis of designed 1-benzhydryl piperazine derivatives was performed in good yields. Most of the synthesized compounds induce apoptosis in high concentrations (> 60 μM), whereas the anti-migratory and anti-invasive effects were significantly pronounced at subapoptotic concentrations (5 μM). One of the nine synthesized inhibitors showed excellent non-cytotoxic, anti-migratory and anti-invasive profile in breast cancer cell lines, which is in agreement with the proposed cellular roles of HDAC6 in cancer.

Conclusion

The work presented in this study connects in silico, synthetic and in vitro biological techniques to identify potent HDAC6 inhibitor. Disclosure of new potent HDAC6 inhibitor in this study may open new doors for selective HDAC6 inhibitors in the management of the metastatic malignant disease.