Oral Presentation

Direct and Indirect DNA Targeting by Arylidene Hydrazinyl Thiazole Hybrids

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KEYWORDS: Thiazoles, DNA, Cytotoxicity, Molecular modelling.

ABSTRACT: In light of searching for new breast cancer therapies, DNA-targeted small molecules were rationally designed to simultaneously bind DNA and inhibit human dihydrofolate reductase (hDHFR). Fourteen new arylidene-hydrazinyl-1,3-thiazoles were synthesized and their dual DNA groove binding potential and in vitro hDHFR inhibition were performed. Two compounds proved their dual efficacy. Molecular docking and molecular dynamics simulations were performed for those active derivatives to explore their mode of binding and stability of interactions inside DHFR active site. Anti-breast cancer activity was assessed on MCF-7 cells using MTX as reference. IC50 measurements revealed that both compounds were more potent and selective than MTX. Cytotoxicity was examined against normal skin fibroblasts to examine safety and selectivity. Moreover, mechanistic studies including apoptosis induction and wound healing were performed. Further in silico ADMET assessment was conducted to determine their eligibility as drug leads suitable for future optimization and development.

Alexandria Journal of Science and Technology, 2025**, 3**(2), 126–126
Online ISSN: 2974-3273

DOI: 10.21608/AJST.2025.452260