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Thiazolidine derivatives as promising prostate cancer agents: Design, synthesis, in vitro evaluation, DFT, ADME, POM, docking, and toxicity studies

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ABSTRACT

Prostate cancer remains a leading cause of cancer-related mortality in men, necessitating the development of novel and potent therapeutic agents. In this study, a series of 3-acetyl-2-aryl thiazolidine-4-carbohydrazide derivatives (**AM$_{1-8}$**) were synthesized and systematically evaluated for their anticancer potential. Comprehensive spectroscopic characterization, including FT-IR, NMR, and mass spectrometry, confirmed the molecular structures of the synthesized compounds. The in vitro cytotoxicity against human prostate cancer (PC3) cells was assessed using the MTT assay, revealing that halogenated derivatives **AM$_4$** (4-Cl) and **AM$_5$** (4-Br) exhibited superior anticancer activity, with IC$_{50}$ values of 46.78 μg/mL and 30.52 μg/mL, respectively, outperforming clinically used standards Darolutamide and R-Bicalutamide. Density Functional Theory (DFT) calculations, ADME, molecular docking, and POM analysis were conducted to understand their electronic/structural properties and the structure–activity relationship (SAR) contributing to bioactivity. ADME results indicated favorable pharmacokinetics for **AM$_4$** and **AM$_5$**, including high gastrointestinal absorption, compliance with Lipinski's rule, and no blood-brain barrier penetration. POM analysis revealed key antitumor pharmacophore sites, while Osiris toxicity predictions indicated no mutagenic, tumorigenic, irritant, or reproductive toxicity risks. Molecular docking studies were conducted against two key cancer-related targets: Thymidylate Synthase (PDB: 6QXG) and the anti-apoptotic protein Bcl-2 (PDB: 8HLM) to get better understanding of **AM$_{1-8}$** binding affinities to both targets. Overall, SAR analysis revealed that halogen-substituted thiazolidine derivatives enhance cytotoxicity by modulating electronic properties and improving receptor binding affinity. These findings position **AM$_4$** and **AM$_5$** as promising lead candidates for prostate cancer therapy, warranting further in vivo and clinical investigations for potential drug development.

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