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Integrated experimental and computational insights into thiazolidine derivatives with potent cytotoxicity against PC-3 prostate cancer cells

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HIGHLIGHTS

- **A_4** (4-Cl) and **A_5** (4-Br) outperform standards (Darolutamide/R-Bicalutamide) against PC-3 cells, that induce **p53/p21 upregulation** (24-fold) triggering cell cycle arrest/apoptosis.
- **Electron-withdrawing halogens** enhance reactivity and target affinity.
- **Conserved pharmacophores** with optimal H-bond distances (2.06–2.18 Å, POM analysis).
- High GI absorption, zero Lipinski violations, no mutagenicity (ADME/Osiris).
- **A_4/A_5** exhibit superior bioavailability vs. nitro-analogs (**A_3**).

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ABSTRACT

In this study, a new series of 3-Acetyl-2-phenyl-5,5-dimethylthiazolidine-4-carbohydrazide (**$A_{1\text{-}8}$**) was synthesized and comprehensively characterized by FT-IR, $^{1}H/^{13}C$ NMR, and mass spectrometry. The cytotoxic potential of the compounds was evaluated in vitro against PC-3 human prostate cancer cells using the MTT assay. Among the series, compounds A_4 and A_5, bearing 4-chlorophenyl and 4-bromophenyl groups, respectively, exhibited the most potent cytotoxicity with IC_{50} values of 50.65 ± 0.98 μg/mL and 50.03 ± 0.98 μg/mL, closely comparable to standard drugs Darolutamide (55.4 ± 0.9 μg/mL) and R-Bicalutamide (80.34 ± 0.89 μg/mL). In contrast, the least active compound A_6 which incorporate 4-methylphenyl group exhibited an IC_{50} of 120 ± 0.83 μg/mL. Gene expression analysis confirmed that these compounds induced significant upregulation of tumor suppressor genes *p53* and *p21*, indicating a mechanism of cell cycle arrest and apoptosis. Density Functional Theory (DFT),

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