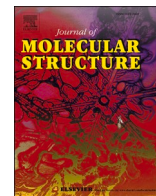




Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

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

Hamsa H. Al-Hujaj^{a,b}, Ahmed A. Majed^{c,*}, Qeaser R. Abdalzahra^d, Dawood S. Abid^c, Noor H. Faisal^c, Huda H. Nameh^e, Naser A. Naser^f, Magdi E.A. Zaki^{*,g}, Sami A. Al-Hussain^g, Sobhi M. Gomha^h, Anas Alfarsiⁱ, Ahmed A. Elhenawy^{i,j}, Islam M. Abdellah^{*,k,l}

^a Department of Pharmaceutical Chemistry, Collage of Pharmacy, Basrah University, Basrah, Iraq

^b Almamoon University College Baghdad, Baghdad, Iraq

^c College of Education for Pure Sciences, Department of Chemistry, Basrah University, Basrah, Iraq

^d College of Oil and Gas Engineering, Department of Oil and Gas Engineering, Basrah University for Oil and Gas, Iraq

^e College of Pharmacy, University of Hilla, Babylon, Iraq

^f College of Pharmacy, AL-Mustaqbal University, Iraq

^g Department of Chemistry, Faculty of Science, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh 11623, Saudi Arabia

^h Chemistry Department, Faculty of Science, Islamic University of Madinah, Madinah, 42351, Saudi Arabia

ⁱ Chemistry Department, Faculty of Science, Al-Baha University, Al-Baha 65731, Saudi Arabia

^j Chemistry Department, Faculty of Science, Al-Azhar University, Cairo 11884, Egypt

^k Department of Chemistry, Faculty of Science, Aswan University, Aswan 81528, Egypt

^l TSCS Department, Wilson College of Textiles, North Carolina State University, Raleigh, NC 27606, USA

ARTICLE INFO

Keywords:

ADME
DFT
Drug discovery
Molecular docking
Prostate cancer
POM analysis
Thiazolidine derivatives

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 IC₅₀ 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.

* Corresponding authors.

E-mail addresses: eduppg.ahmed.majed@uobasrah.edu.iq (A.A. Majed), eduppg.ahmed.majed@uobasrah.edu.iq, mezaki@imamu.edu.sa (M.E.A. Zaki), islamabdellah2@aswu.edu.eg (I.M. Abdellah).

<https://doi.org/10.1016/j.molstruc.2025.142544>

Received 18 March 2025; Received in revised form 26 April 2025; Accepted 29 April 2025

Available online 30 April 2025

0022-2860/Published by Elsevier B.V.