proceedings

MDPI

Abstract

Computational Exploration of Betulinic Acid Hybrids as Dual BCL-2/BCL-XL Inhibitors †

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† Presented at the International Conference on Interdisciplinary Approaches and Emerging Trends in Pharmaceutical Doctoral Research: Innovation and Integration, Timisoara, Romania, 7–9 July 2025.

Keywords: molecular docking; MD simulation; ADME/T property prediction; betulinic acid hybrids; Bcl-2 inhibitors

Betulinic acid (BA), a lupane-type triterpene widely studied for its selective cytotoxicity against malignancies [1], shows synergistic pro-apoptotic activity when combined with blockade of anti-apoptotic B-cell lymphoma-2 (BCL-2) proteins, key targets of mitochondrial integrity in cancer cells [2]. Guided by this rationale, we assembled a virtual library of BA hybrids by covalently linking the triterpene scaffold to natural molecules with reported antioxidant and anticancer activities. After physicochemical and drug-likeness filtering, the candidates were docked into the BH3-binding groove of BCL-2 (PDB ID: 4LVT), BCL-XL (PDB ID: 2YXJ), and the chimeric receptor BCL2-XL (PDB ID: 2W3L). Two hybrids, BA-Celastrol and BA-Proanthocyanidin B2, emerged with docking scores of −13.0 kcal/mol and −12.5 kcal/mol, respectively, against chimeric BCL2-XL (2W3L); −10.7 and −10.2 kcal/mol, respectively, against BCL-XL (2YXJ); and −9.3 and −8.7 kcal/mol, respectively, on BCL-2 (4LVT), outperforming the parent compound BA in each case. Molecular-mechanics/Poisson–Boltzmann surface area calculations and 100 ns molecular dynamics simulations confirmed stable complexes. In silico Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) profiling predicted favorable profiles for both compounds. Collectively, these findings highlight BA-Celastrol and BA-Proanthocyanidin B2 as a promising dual BCL-2/BCL-XL that can be further synthesized and biologically assessed for experimental validation.

Author Contributions: Conceptualization, M.M. and E.P.A.; methodology, E.P.A.; software, M.M.; validation, M.M., C.Ș. and E.P.A.; formal analysis, M.M.; investigation, E.P.A.; resources, C.Ș.; data curation, E.P.A.; writing—original draft preparation, E.P.A.; writing—review and editing, M.M.; visualization, E.P.A.; supervision, C.Ș.; project administration, M.M.; funding acquisition, M.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in the study are included in the manuscript, further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

Academic Editor: Cristina Adriana Dehelean

Published: 25 September 2025

Citation: Atyim, E.P.; Mioc, M.; Șoica, C. Computational Exploration of Betulinic Acid Hybrids as Dual BCL-2/BCL-XL Inhibitors. *Proceedings* **2025**, *127*, 14. https://doi.org/10.3390/proceedings2025127014

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