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Peer Review

Review of: "Synthesis, ADME, Toxicity, and in Silico Molecular Docking Study of Novel β-Carboline Derivatives as Potential Inhibitor Anticancer Agents"

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This study introduces the synthesis and in silico evaluation of novel 5-(9-benzyl-1-methyl-9H-pyrido\[3,4-b]indol-3-yl)-1,3,4-oxadiazol-2-amine derivatives (4A and 4B) as potential anticancer agents. A major strength of the manuscript lies in its clear rationale for molecular design, rooted in the β-carboline scaffold known for its broad spectrum of bioactivities. The incorporation of the 1,3,4-oxadiazole moiety adds further medicinal value, often associated with anticancer and antimicrobial properties. The contextualization of cancer as a global burden and the limitations of current chemotherapies, including drug resistance, strengthens the relevance of the work and justifies the pursuit of novel scaffolds.

The synthetic pathway is well-organized and supported by classical organic reactions. The stepwise conversion from L-tryptophan ester to the final oxadiazole-bearing compound is methodically executed, and yields are appropriately reported. A commendable aspect is the thorough characterization of intermediates and final compounds using NMR spectroscopy. However, it would improve transparency and reproducibility if all spectral data were included in the supplementary material or summarized in tabulated form within the article for ease of reference.

The molecular docking study provides valuable insights into the potential mechanism of action, targeting the CDK2 kinase, a well-established player in cancer progression. The use of AutoDock Vina and the PDB:1aq1 complex is appropriate. Binding energies of -11.8675 and -11.6600 kcal/mol for 4A and 4B, respectively, suggest favorable interactions, with key hydrogen bonds identified in the active site. While informative, the docking study would benefit from additional validation, such as RMSD analysis of binding poses or molecular dynamics simulations to account for receptor flexibility.

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The ADME profile prediction using SwissADME offers an essential preliminary pharmacokinetic assessment. High gastrointestinal absorption and CYP450 inhibition are promising features. However, the inability of both compounds to cross the blood-brain barrier (BBB) may limit their application in treating brain cancers unless modified. Additionally, the compounds' Log Kp values suggest modest skin permeability, potentially relevant for topical formulations. Including comparisons with existing anticancer drugs would provide perspective on how these properties align with clinical candidates.

Toxicity assessments via ProTox 3.0 indicate a relatively safe profile with an LD50 of 1000 mg/kg, classifying both compounds as toxicity class IV. Notably, predictions of neurotoxicity and respiratory toxicity merit careful consideration. These predictions underscore the necessity of future in vitro and in vivo toxicological studies to validate these findings. Furthermore, more information on predicted mutagenicity or cardiotoxicity (e.g., hERG inhibition) would be valuable.

One of the manuscript's limitations is the absence of biological validation beyond in silico docking. While computational modeling is an efficient screening tool, confirming cytotoxic effects through in vitro assays (e.g., MTT or cell viability in cancer cell lines) would strengthen the claims. Even preliminary IC50 values against a representative panel of cancer cell lines would significantly elevate the impact and credibility of the study.

The graphical elements, including 2D docking interactions and ADME visualizations, enhance the manuscript's clarity. However, some figures (e.g., toxicity radar, network charts) are referred to but not adequately explained or contextualized within the text. Their interpretation should be expanded upon for a more cohesive presentation. A comprehensive table summarizing docking scores, ADME parameters, and toxicity for both compounds would consolidate key findings for readers.

From a writing perspective, the manuscript is mostly well-structured, yet some language editing would enhance fluency. Occasional grammatical inconsistencies and long, complex sentences could be streamlined. Clarifying the novelty of this scaffold compared to existing β-carboline derivatives in the literature would also reinforce the originality of the work. Additionally, the introduction could benefit from more discussion on the role of CDK2 in oncogenesis, linking the biological target more explicitly to the synthesized compounds.

Ethically, the manuscript is transparent, with declarations of data availability and methodology. However, no information is provided regarding ethical approval for any in vivo studies, though none were conducted. If future research is anticipated to include biological testing, the authors should preemptively mention adherence to institutional and international ethical standards.

In conclusion, this manuscript presents a promising early-stage investigation into novel β-carboline–oxadiazole hybrids with potential anticancer activity. The study is scientifically sound in its synthetic and in silico methodology and provides a solid foundation for further biological testing. To enhance the translational value, future research should incorporate in vitro efficacy data, mechanism-of-action studies, and expanded toxicity profiling. The manuscript is a commendable contribution to the field of medicinal chemistry and provides momentum for continued exploration of heterocyclic scaffolds in cancer drug discovery.

Declarations

Potential competing interests: No potential competing interests to declare.