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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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1. Executive Summary

This manuscript details the synthesis of two novel β-carboline derivatives (4A and 4B) containing a 1,3,4-oxadiazol-2-amine moiety. The authors employed a Pictet-Spengler condensation followed by oxidative aromatization and N-alkylation to generate the core scaffold. The study further characterizes these compounds using *in silico* methods, specifically molecular docking against the CDK2 protein (PDB: 1aq1) and ADME/Toxicity predictions. The authors report high binding energies (-11.8 and -11.6 kcal/mol) and favorable drug-likeness profiles, suggesting potential as anticancer agents.

2. General Assessment

Strengths:

- **Integrated Approach:** The study successfully combines conventional organic synthesis with computational drug design (CADD) tools, which is a standard and valuable workflow in modern medicinal chemistry.
- **Therapeutic Relevance:** The focus on β-carboline scaffolds is well-justified given their known bioactivity and presence in natural antitumor agents like Eudistomins.
- **Clear Visuals:** The inclusion of 2D interaction diagrams (Figure 2) and ADME "Boiled-Egg" charts (Figure 3) aids in quickly understanding the computational results.

Weaknesses:

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- **Extremely Limited Scope:** The abstract mentions a "series" of compounds, yet the manuscript only reports the synthesis and evaluation of **two** molecules (4A and 4B). This is insufficient to constitute a "series" or to draw meaningful Structure-Activity Relationship (SAR) conclusions.
- **Incomplete Characterization:** While the text claims the use of 1H NMR, 13C NMR, IR, and Mass spectrometry, the Experimental Section only provides 1H NMR data for *one* entry (not clearly distinguished between 4A or 4B) and completely omits the 13C NMR, IR, and Mass spectral data.
- **Language and Phrasing:** The manuscript requires significant copy-editing. Phrasing such as "compounds... are a bit good for ADME" lacks scientific precision.

3. Detailed Comments

A. Novelty and Significance

The modification of the β-carboline scaffold with oxadiazole rings is a valid medicinal chemistry strategy. However, the significance is severely dampened by the small sample size. Without a broader library of derivatives, it is impossible to determine if the specific substitutions in 4A/4B are optimal or if the activity is general to the scaffold.

B. Methodology and Data Validation

- **Synthesis (Scheme 1):** The synthetic route is standard and logical. However, the yield is reported as "40%", but it is unclear if this is an average or specific to one compound.
- **Molecular Docking:** The authors used PDB 1aq1 (CDK2 complexed with Staurosporine).
  - *Critique:* There is no mention of a "redocking" validation step (removing Staurosporine and docking it back to calculate RMSD) to validate the docking protocol before testing new ligands.
  - *Critique:* The binding energies (-11.8 kcal/mol) are very high, which is promising, but without *in vitro* enzymatic assays (e.g., IC50 values), these remain purely theoretical.
- **Toxicity Prediction:** The text states compounds are "active for neurotoxicity... under the 4th category". In many prediction tools (like ProTox), "active" implies toxicity. The authors need to clarify if these compounds are predicted to be neurotoxic or safe, as "active for neurotoxicity" usually implies a negative safety profile.

C. Reporting Standards

- **Missing Spectral Data:** The experimental section lists 1H NMR (400 DMSO d6) but does not specify which compound (4A or 4B) this data belongs to. Furthermore, the 13C NMR data is referenced in the

conclusion but is entirely absent from the text.

- **Inconsistent Terminology:** The title mentions "Inhibitor Anticancer Agents," but the text focuses on "Protein kinase inhibition by the staurosporine". It should be clearly stated that CDK2 is the target.

4. Specific Recommendations for Revision

1. **Expand the Library:** To justify publication as a research article, the authors should synthesize and characterize at least 5–8 additional derivatives to explore the chemical space around the scaffold.
2. **Complete Characterization:**
    - Provide distinct 1H NMR, 13C NMR, and Mass Spectrometry data for **all** synthesized compounds.
    - Ensure the integration values in the NMR data match the proposed structures.
3. **Clarify Toxicity Results:** Rewrite the toxicity section to clearly state whether the compounds are predicted to be toxic or non-toxic. "Active for carcinoma" sounds like a carcinogen, which would be a failure for a drug candidate, yet the conclusion calls them "best for further research".
4. **Editorial Polish:** Replace informal language ("a bit good") with standard scientific terminology (e.g., "favorable pharmacokinetic profiles").
5. **Data Discrepancy:** The abstract says "series... were designed," but the results only discuss two. Align the abstract with the actual content.

5. Conclusion

The study presents a promising scaffold design and preliminary computational validation. However, the current manuscript resembles a "short communication" or a pilot study rather than a full research article due to the synthesis of only two compounds and missing experimental data. Major revisions are required, specifically the inclusion of full spectral characterization and a clearer interpretation of the toxicity predictions.

Recommendation: Major Revisions

Declarations

Potential competing interests: No potential competing interests to declare.