

Peer Review

Review of: "New Approach for Targeting Small Molecule Candidates for Intrinsically Disordered Proteins"

Yassir Boulaamane¹

1. Université Abdelmalek Essadi, Morocco

The author explored a novel computational approach (the Informational Spectrum Method for Small Molecules, ISM-SM) to identify small-molecule modulators for intrinsically disordered proteins (IDPs), focusing on the tau protein involved in Alzheimer's disease. By calculating electron-ion interaction potential (EIIP)-based spectral compatibility between known tau ligands and the tau protein, they defined key interaction frequencies. These frequencies were used to screen DrugBank (approved drugs) and the COCONUT (natural products) databases. The method recovered drugs with reported relevance to tau or Alzheimer's disease and also identified new candidates such as bryostatin-14. The study highlights ISM-SM as a potential tool for IDP ligand discovery, while discussing its limitations and suggesting integration with experimental validation and AI-based methods in the future.

Comments to Author:

- 1- There is no quantitative or qualitative comparison of ISM-SM's performance with standard computational techniques (e.g., ensemble docking, MD simulations, ML-based screening). Even a small-scale benchmark or expanded discussion would strengthen the manuscript.
- 2- The link between ISM-SM spectral compatibility (EIIP frequencies) and actual molecular interactions with IDPs (like tau) is not fully clarified. Please elaborate on how ISM-SM predictions should be interpreted, especially for proteins lacking stable binding sites.
- 3- The computational pipeline, code, and parameter settings for ISM-SM screening should be provided (as supplementary files or in a public repository) to facilitate reproducibility for other researchers.
- 4- Key results (e.g., top-ranked candidates from the database screens, frequency distributions) should be presented more clearly in the main text, with better integration of supplementary material. Figure and

table legends can be expanded for clarity.

5- The discussion could be strengthened by outlining specific next steps for experimental testing of novel candidates or efforts to integrate ISM-SM with machine learning/AI pipelines.

6- The manuscript is generally well organized but could benefit from minor language editing to improve conciseness and readability.

Declarations

Potential competing interests: No potential competing interests to declare.