

Peer Review

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

Muhammad Zulfadli Mehat¹

1. Universiti Putra Malaysia, Malaysia

Reviewer Report

Manuscript Title:

New Approach for Targeting Small Molecule Candidates for Intrinsically Disordered Proteins

Author: Milan Sencanski

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General

This manuscript introduces a computational approach—Informational Spectrum Method for Small Molecules (ISM-SM)—to identify potential modulators of intrinsically disordered proteins (IDPs), focusing on tau protein, a key driver in Alzheimer's disease pathology. By applying a frequency-domain analysis based on electron-ion interaction potentials (EIIP), the study avoids reliance on fixed structural conformations, which is a major limitation of conventional docking or MD-based screening for IDPs.

The methodology is innovative, the application is timely, and the manuscript is scientifically well-grounded. That said, a few areas need clarification and revision to strengthen its clarity, presentation, and contextual framing.

Strengths

1. The use of ISM-SM provides a non-structural, scalable strategy to screen for IDP-targeting compounds.
2. Application to DrugBank and the Coconut database produced biologically relevant and literature-supported candidates, including Bryostatin-14 and Everolimus.
3. The mathematical and spectral analysis is clearly explained and technically sound.
4. The study makes a case for ISM-SM as a complement, rather than a competitor, to structure-based screening tools.

Key Points for Revision

1. Scoring and Prioritization

- The chemical-based scoring model (logP, logS, MW, toxicity, etc.) should be explained more clearly.
- Rationale for the weightings and thresholds used in the composite score should be provided or referenced.

2. Visuals and Tables

- Figures 1–4 need higher resolution and full annotation (axes, units, frequency definitions).
- Table 3 (COCONUT compound hits) is referenced but not included in the manuscript or supplement. Please clarify or correct.

3. Method Contextualization

- Add a short section or paragraph comparing ISM-SM with other leading IDP screening techniques, such as ensemble docking, MD with biasing, or ML-based predictors.

4. Language and Style

- Some method and discussion sections use repetitive or overly technical phrasing. Minor editorial revision will improve readability.
- Avoid speculative phrases unless clearly framed as hypotheses, particularly in relation to indirect pathway hits.

5. Workflow Diagram

- A simple pipeline diagram showing the full ISM-SM screening process—from input (e.g., SMILES) to scoring—would help orient readers unfamiliar with spectral methods.

Recommendation

Minor Revision

This is a valuable and forward-looking study that applies a practical and mechanistically distinct approach to an area with high unmet need. With modest revisions to improve clarity, figure quality, and methodological framing, this work would be well suited for publication in a computational pharmacology or translational neuroscience journal.

Declarations

Potential competing interests: No potential competing interests to declare.