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Peer Review

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

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This study introduces a novel and thoughtful computational pipeline to address the critical challenge of ligand discovery for intrinsically disordered proteins - a largely underexplored domain. It addresses an important problem in drug discovery: targeting intrinsically disordered proteins, which are implicated in many diseases and challenging to target with traditional methods. The Informational Spectrum Method for Small Molecules (ISM-SM) is presented as a promising *in silico* tool for identifying potential tau modulators. Here, the use of consensus interaction features across multiple conformations represents a meaningful advancement over traditional single-structure approaches. While experimental validation is lacking, the framework is methodologically sound and offers a solid foundation for future *in vitro/in vivo* studies.

- The introduction might be strengthened by providing more background on the ISM-SM method and its underlying principles, giving the reader a better understanding of its potential advantages and limitations.
- The explanation of the ISM-SM method is relatively concise. Consider expanding this section to include more details about the mathematical principles behind the EIIP calculation, Fourier transformation, and cross-spectrum analysis.
- The rationale for the Drug Score (dS) calculation and its integration with the ISM S/N values should be clearly explained.
- The identification of potential tau modulators from the DrugBank and COCONUT databases is interesting. The authors should discuss the biological significance of the identified frequencies and their potential implications for tau-ligand interactions. Include a more detailed analysis of the identified potential tau modulators, including their potential binding sites and mechanisms of action.

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- Consider including additional validation experiments, such as *in vitro* binding assays or molecular dynamics simulations, to support the *in-silico* findings.

Overall, this study presents a promising application of the ISM-SM method for identifying potential tau modulators. With some revisions, this manuscript could make a valuable contribution to the field of IDP-targeted drug discovery.

Declarations

Potential competing interests: No potential competing interests to declare.