Research Article

New Approach for Targeting Small Molecule Candidates for Intrinsically Disordered Proteins

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Intrinsically disordered proteins (IDPs), like the Alzheimer's associated tau protein, pose challenges for conventional drug discovery. This study applied the Informational Spectrum Method for Small Molecules (ISM-SM), a computational technique utilising electron-ion interaction potentials (EIIP), to identify potential tau modulators. Characteristic interaction frequencies derived from known ligands and conserved mammalian tau sequences were used to screen DrugBank and the COCONUT natural product database. The screening identified approved drugs previously reported to indirectly influence tau pathology or Alzheimer's disease pathways, alongside natural products like Bryostatin-14, known to modulate kinases involved in tau phosphorylation. These findings suggest ISM-SM can serve as an in silico tool to identify candidate small molecules, including repurposed drugs and natural products, with potential relevance to tau function and pathology, complementing other IDP drug discovery strategies.

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1. Introduction

Intrinsically disordered proteins (IDPs) have essential roles in a variety of biological processes and have been associated with numerous diseases, including neurodegenerative disorders and viral infections[1][2]. In contrast to structured proteins, which contain stable binding pockets, IDPS exist as dynamic conformational ensembles and represent particularly challenging targets in small-molecule drug discovery. Several small molecules have been identified as IDP ligands, usually by binding to transient interaction sites or as modulators of their dynamic conformational states. Notable examples include

epigallocatechin gallate (EGCG) for α-synuclein[3], Phenothiazine for tau[4], and different compounds targeting viral nucleocapsid proteins[5]. IDPs' inherent flexibility leads to specialised experimental and computational methods to identify their ligands.

Conventional structure-based drug development methods are not as successful with IDPs because the binding sites are poorly defined. Similarly, high-throughput virtual screening methods struggle with IDP dynamic and heterogeneous nature. They may call for alternate techniques like ensemble docking[6][7][8][9][10][11], molecular dynamics (MD) simulations[12][13][14][15][16][17][18][19][20], and machine learning models trained using IDP-ligand interactions[16][21][22][23][24][25]. Experimental methods, including nuclear magnetic resonance (NMR) spectroscopy, surface plasmon resonance (SPR), and fluorescence-based assays, can also help demonstrate weak, transient interactions[26]. Therefore, computational and biophysical methods are crucial for discovering and optimising small-molecule ligands.

The standard new drug development process typically involves hit identification, lead optimisation, preclinical testing, and clinical trials. The cost of bringing a drug to market follows the industry standard, averaging $1.39-2.87 billion over 10-15 years, with high attrition rates due to the complexity of validating functional effects and ensuring specificity.[27] Due to the additional perplexity of IDPs-ligand interactions, this process is more challenging, and the introduction of various in silico methods is required.

The ISM-SM (Informational Spectrum Method for Small Molecules) method offers a distinct approach compared to traditional High-Throughput Screening (HTPS) methods for finding small-molecule candidates for disordered proteins, particularly by analysing long-range interaction potentials rather than relying solely on structure [28]. ISM-SM can put molecular structures into a frequency spectrum, enabling it to identify the compatible interaction frequencies for small molecules and target proteins, predicting biological activity. Our previous ISM-SM studies have successfully identified biologically active ligands for specific protein binding sites[29][30]. ISM-SM has also been utilised to discover binders towards proteins associated with emerging viral threats, such as SARS-Cov-2. An example is the determination of the interaction frequencies between small molecules that have been shown to have benefit against viral proteins, predicting drugs that could be repurposed for COVID-19, and significantly accelerating the drug discovery process in response to a pressing public health emergency. [31][32][33]. This work explores the application of ISM-SM for identifying potential therapeutic candidates against

selected disease targets. We will here focus on human tau protein candidates, one of the two hallmark proteins of Alzheimer's disease (AD).[34]

2. Materials and Methods

2.1. Databases

The sequence of Human microtubule-associated protein tau (P10636) was taken from the UniProt database (www.uniprot.org)[35]. Tau proteins from other mammals were also downloaded:

- O02828 Capra hircus
- P10637 Mus musculus
- P19332 Rattus norvegicus
- P29172 Bos taurus
- P57786 Macaca mulatta
- Q5S6V2 Pongo pygmaeus
- Q5YCV9 Hylobates lar
- Q5YCW0 Gorilla gorilla gorilla
- Q5YCW1 Pan troglodytes
- Q6TS35 Spermophilus citellus
- Q9MYX8 Papio hamadryas

For screening of drugs for repurposing to select candidates for Microtubule-associated protein tau, 2627 approved small molecule drugs from DrugBank[36] (http://www.drugbank.ca) were screened. The criteria for candidate selection were five reported tau protein binding drugs: DB00637 Astemizole, DB01248 Docetaxel, DB14914 Flortaucipir F-18, DB00448 Lansoprazole, and DB01229 Paclitaxel.

The Coconut database[37] is a freely available collection of over six hundred thousand natural products, some of which may also be commercially available (https://coconut.naturalproducts.net/). The Coconut database was downloaded, and compounds were converted to SMILES notation.

2.2. ISM-SM method

In this work, we analyse the tau protein and its small molecule ligands using the Informational Spectrum Method for Small Molecules (ISM-SM), the extension of the Informational Spectrum Method (ISM).

This bioinformatics approach encompasses three basic steps:

i. the representation of the protein's primary structure as a numerical sequence by assigning to each amino acid the corresponding value of the electron-ion interaction potential (EIIP),
ii. the representation of a small molecule's structure in the SMILES notation as a numerical sequence by assigning to each atomic group the corresponding value of the electron-ion interaction potential (EIIP),
iii. the transformation of the obtained numerical sequences into the informational spectrum (IS), and (iv) the calculation of the cross-spectrum (CS) between interacting protein and small molecules.

These values correspond to the electron–ion interaction potential (EIIP), determining the electronic properties of amino acids/nucleotides, which are essential for their intermolecular interactions. The EIIP descriptors are easily calculated using the following formulas:

The EIIP is the physical parameter determining organic molecules' long-range interactions (distances 5 – 1000 Å[38][39]). The following equation defines this molecular descriptor[40][41]:

$$W = 0.25\frac{Z \times \sin(1.04\pi Z^*)}{2\pi}, \tag{1}$$

Where Z* is the average quasi-valence number (AQVN):

$$Z^* = \frac{1}{N}\sum_{i=1}^{m} n_i Z_i, \tag{2}$$

(2) N is the total number of atoms, ni is the number of atoms of the i-th component, Zi is the valence number of the atomic element in the molecule, and m is the number of components. The EIIP values calculated according to Eq. (1) are given in Rybergs (Ry).

The numerical sequence, representing the primary structure of a protein, is transformed into the informational spectrum by the discrete Fourier transformation:

$$X(n) = \sum_{m=1}^{N} x(m)e^{-i2\pi(m-1)/N}, n = 1, 2, \ldots, N/2 \tag{3}$$

(3) X(m) represents the m-th element of a given numerical series, with N being the total number of points in that series, and X(n) is the coefficient of the discrete Fourier transformation. This transforms the information contained in the sequence of amino acids into a series of frequencies and their corresponding amplitudes. The informational spectrum (IS) frequencies reflect the distribution of structural motifs with specific physicochemical properties, which are crucial in defining a protein's

biological function. The informational spectrum method (ISM) can identify frequency/code pairs specific to their shared biological characteristics or related interactions when comparing proteins with similar biological or biochemical functions. The common spectrum (CS) highlights these shared informational features of the protein sequences:

$$C(j) = \prod_{i=1}^{N} S(i,j) \tag{4}$$

(4) C(j) refers to the j-th element of the common spectrum (CS), while S(i, j) is the j-th element of the i-th informational spectrum (IS). The standard information encoded in the primary structures of the proteins being analysed is captured by the frequencies in the CS. These frequencies correspond to the proteins' typical biological function or shared interactors examined through the ISM analysis. In the CS, the amplitude indicates the strength of the interaction, and the signal-to-noise (S/N) ratio reflects the specificity of the interaction between the two proteins or a protein and a small molecule.

From common frequencies in CS, one can determine whether a protein interacts with other proteins (protein-protein interactions, PPI) or small molecules and identify the corresponding binding region in the protein.

2.3. Drug Score Calculation

Drug Score (dS) values were calculated in DataWarrior.[42] The following descriptors required were calculated (s): druglikeness, logP, logS, Molecular Weight (MW), and four types of drug toxicity (t): primary irritation, mutagenic effects, reproductive effects, and tumorigenic effects. Drug score was calculated according to the following formulas:

$$dS = \Pi \left(\frac{1}{2} + \frac{1}{2} s_i \right) \cdot \Pi t_i, \tag{5}$$

$$s_i = \frac{1}{1 + e^{ap+b}} \tag{6}$$

Where p corresponds to logP, logS, MW and Druglikeness, parameters a and b correspond to values {1, -5}, {1, 5}, {0.012, 6}, {1, 0}, respectively. The ti values are 1.0, 0.8 and 0.6 for no risk, low and high risk, respectively. The Total Score is calculated by multiplying the ISM S/N values and dS from Eq. (5).

3. Results and discussion

3.1. Drugbank candidates

Five reported drugs from the Uniprot database targeting Microtubule-associated protein tau protein (P10636) were extracted with their structures in SMILES format (Figure 1). The structures were converted into explicit hydrogen format, and their CS with the tau protein were calculated (Table 1). Five frequencies, F(0.080), F(0.194), F(0.167), F(0.341) and F(0.435), were identified (Figure 2). The additional frequency, from CS including all five drugs and tau protein, was found at F(0.333) (Figure 3). Interestingly, the same frequency was obtained from the CS spectrum of all mammal tau proteins (Figure 4). This suggests an evolutionarily conserved region in the tau protein.

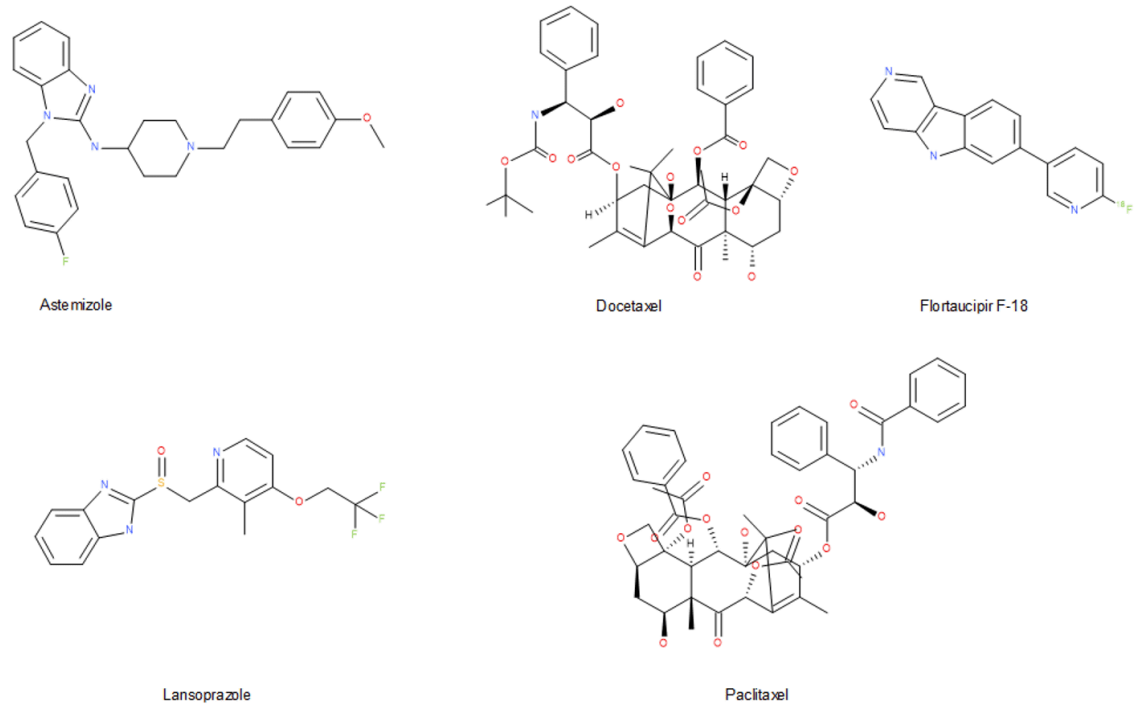

Figure 1. Structures of Drugbank compounds directly binding to the tau protein

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Drugbank compound	Name	CS with taufrequencies	Amplitude	S/N
DB00637	Astemizole	0.341	0.9958	17.353
DB01248	Docetaxel	0.167	1.7847	20.023
DB14914	Flortaucipir F-18	0.080	0.10816	9.0225
DB00448	Lansoprazole	0.435	0.65514	12.299
DB01229	Paclitaxel	0.194	1.1917	14.089

Table 1. Tau-interacting compounds from the Drugbank, with corresponding frequencies from CS spectra with the tau protein.

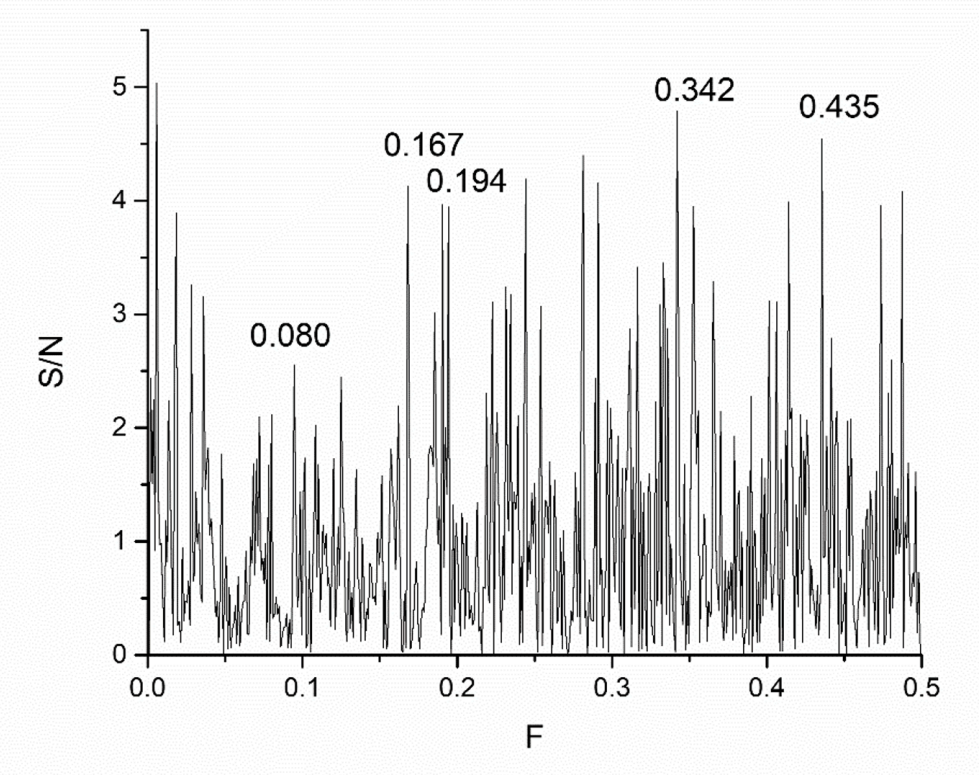

Figure 2. ISM spectrum of the tau protein

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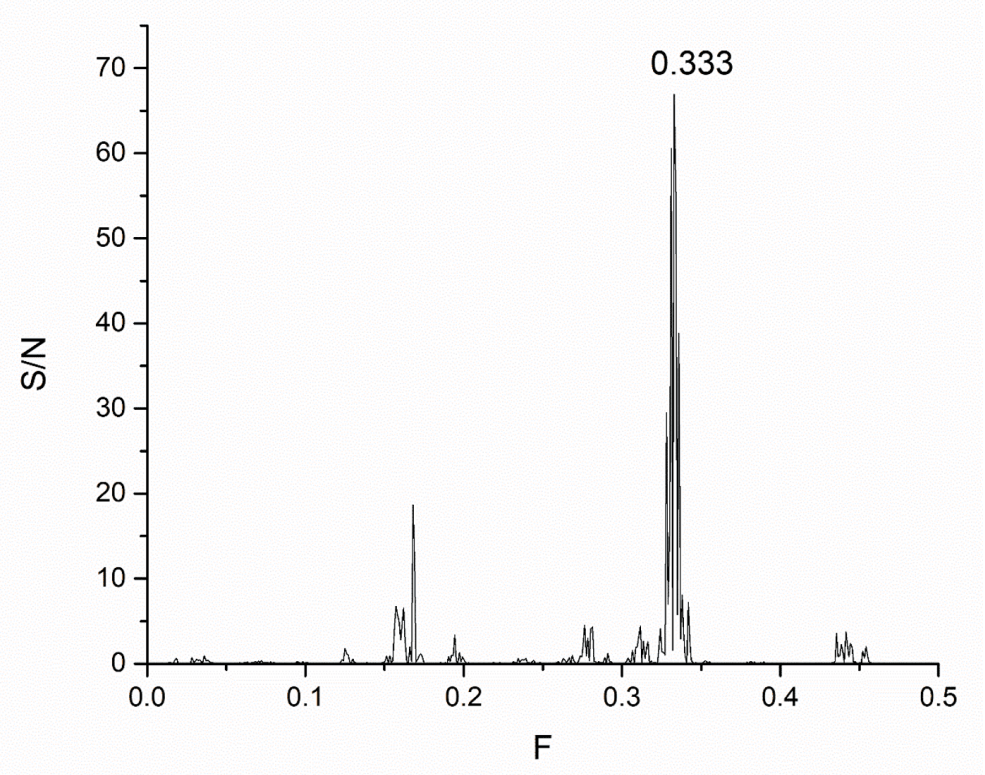


Figure 3. Cross-spectrum of all five tau protein targeting drugs from Drugbank

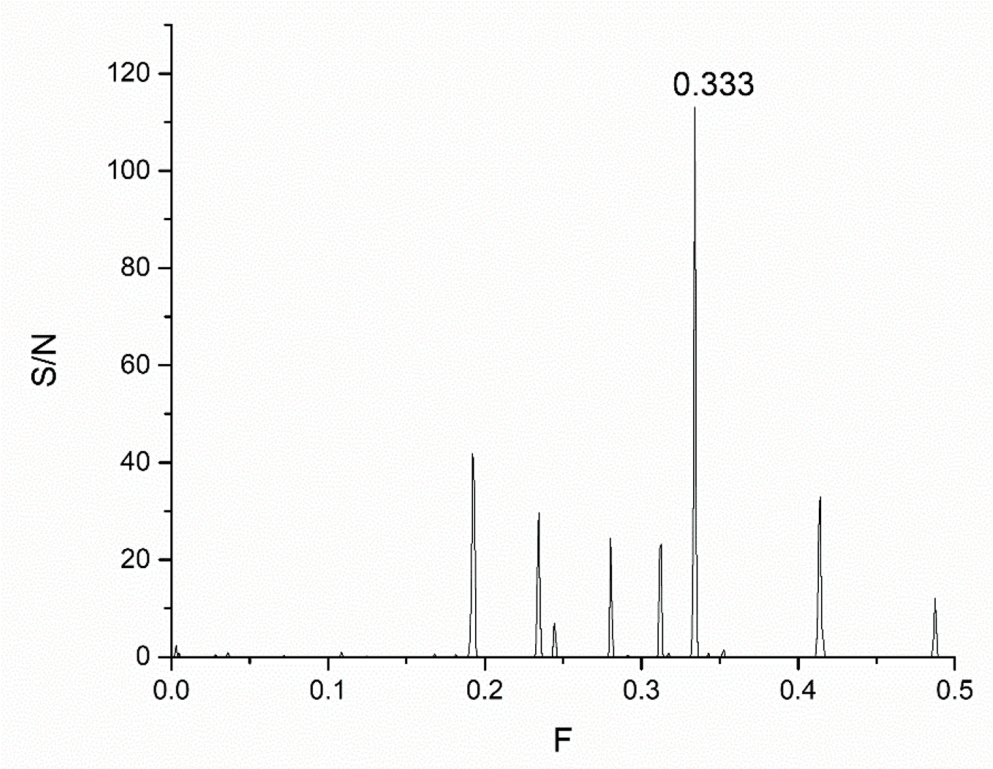


Figure 4. Cross-spectrum of all mammal tau proteins

The 2506 approved Drugbank candidates' structures were subjected to the same format conversion as literature compounds and were further CS scanned at all six frequencies. From the obtained candidates (Supplementary material), 25 were already reported to affect the Tau protein or AD progression indirectly. (Table 2).

doi.org/10.32388/5DGYBH

No	ID	Name	Amplitude	S/N	Frequency	Effect on tau protein/AD
1	DB01012	Cinacalcet	0.40481	13.45278	0.080	Indirect on tau phosphorylation
2	DB01393	Bezafibrate	0.32723	9.6733	0.080	Reduces Aβ and tau pathology
3	DB06287	Temsirolimus	1.14833	28.35191	0.167	Reducing tau hyperphosphorylation
4	DB01590	Everolimus	3.23776	20.74836	0.167	Reducing tau hyperphosphorylation
5	DB00035	Desmopressin	2.30313	20.55908	0.167	Could influence Aβ/tau cross-interactions
6	DB01130	Prednicarbate	1.34609	18.58936	0.167	Potential tau aggregation modulator
7	DB01656	Roflumilast	17.85085	0.05962	0.167	Ameliorates cognitive deficits in tauopathy models
8	DB00166	Lipoic acid	17.1443	0.04087	0.167	Reduces tauopathy
9	DB01420	Testosterone Propionate	1.00595	22.21979	0.194	Hyperphosphorylation of tau
10	DB06772	Cabazitaxel	2.47515	22.12693	0.194	Microtubules stabilisation
11	DB01599	Probucol	0.50271	19.55832	0.194	Reduce amyloid deposition
12	DB08866	Estradiol valerate/Dienogest	0.91072	19.02854	0.194	Prevents tau hyperphosphorylation
14	DB00850	Perphenazine	0.71948	14.65717	0.333	Lower the levels of insoluble tau.
15	DB06699	Degarelix	2.05541	13.78509	0.333	Hormone modulation may influence neurodegeneration.
20	DB00883	Isosorbide Dinitrate	0.87453	22.00889	0.341	Nitric oxide modulation (could influence neurodegeneration)
21	DB00243	Ranolazine	1.48002	23.2534	0.435	Reduces oxidative stress, lacks tau-specific evidence.e
22	DB00423	Methocarbamol	0.80441	21.58701	0.435	Promoting tau clearance
23	DB01136	Carvedilol	1.07707	21.14359	0.435	May reduce Aβ and tau toxicity
25	DB00206	Reserpine	2.15401	19.96937	0.435	Reduces Aβ toxicity

Table 2. The list of identified Drugbank compounds from the tau protein ISM spectrum

Cinacalcet was reported to play a significant role in AD. As a calcimimetic agent used for hyperparathyroidism, it modulates calcium-sensing receptors, which may influence amyloid-beta (Aβ) pathology and neuronal calcium dysregulation, both implicated in AD. It may indirectly influence tau phosphorylation by regulating calcium signalling, but direct evidence is lacking.[43] Bezafibrate is a PPAR-alpha agonist used for lipid disorders. It has been shown that bezafibrate treatment could attenuate the severity of tau pathology in the streptozotocin-intracerebroventricular-induced sporadic AD rat model.[44] Temsirolimus[45][46] and Everolimus[47][48] were reported to demonstrate neuroprotective effects in AD models by reducing tau hyperphosphorylation and promoting autophagic clearance of amyloid-β (Aβ) and tau aggregates, improving cognitive function. Desmopressin[49], a neurohypophyseal hormone analogue, has been suggested to modulate amyloid aggregation, though its direct role in tau pathology remains less explored. Prednicarbate[50] (a topical corticosteroid) was identified in a drug screening study as one of the prescription drugs that may influence hyperphosphorylated tau aggregation and cytotoxicity. Roflumilast[51] ameliorates cognitive deficits in AD mice by reducing Aβ and tau pathology, potentially via nitric oxide signalling and upregulating Aβ transporters like ABCB1. Lipoic acid[52][53][54][55][56][57][58][59][60][61] shows potent antioxidant and anti-inflammatory properties, mitigating tau hyperphosphorylation, oxidative stress, and behavioural deficits in tauopathy models, while enhancing mitochondrial function. Testosterone Propionate is a synthetic androgen, and androgens are found to regulate tau phosphorylation.[62] Cabazitaxel is a chemotherapy agent. While not directly linked to AD, its ability to stabilise microtubules has prompted interest in its potential to address tau pathology, a hallmark of AD.[63] Probucol is a lipid-lowering drug with antioxidant properties. It may reduce oxidative stress and amyloid deposition, which are implicated in AD.[64] Estradiol valerate and Dienogest are hormonal agents. Estrogen has been studied for its neuroprotective effects, preventing neural tau hyperphosphorylation, particularly in postmenopausal women, who are at higher risk for AD. [65] Perphenazine is an antipsychotic, found, among some others, to lower the levels of insoluble Tau. [66] Degarelix is a GnRH antagonist. Hormonal modulation has been explored in AD, particularly regarding sex hormones and their impact on cognitive function.[67] Isosorbide Dinitrate is a vasodilator. Improving cerebral blood flow may have neuroprotective effects in AD.[68] Ranolazine is an antianginal

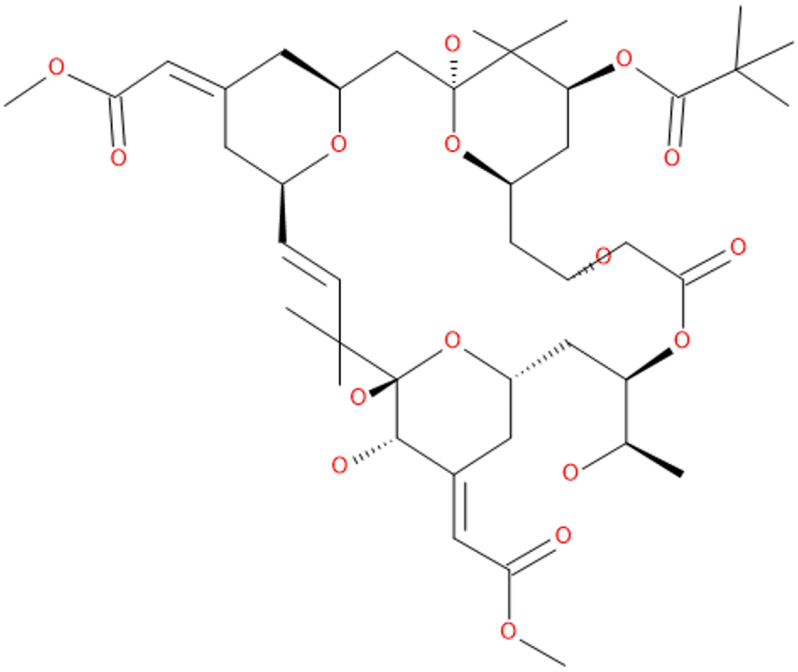
drug. It modulates cellular metabolism and has been explored for its potential to enhance neuronal energy deficits in AD.[69] Methocarbamol[70], a carbonic anhydrase inhibitor, has been shown to reduce tau toxicity by promoting its clearance. Studies in tauopathy models, including zebrafish and transgenic mice, have demonstrated that methocarbamol can rescue neuronal degeneration, improve cognitive function, and reduce phosphorylated tau levels. Carvedilol is a beta-blocker with antioxidant properties. It may reduce oxidative stress and inflammation, both implicated in AD.[71] Reserpine is an antihypertensive with neuroprotective potential. Reserpine[72][73], in particular, has been studied for its ability to modulate neurotransmitter systems involved in AD. The complete list of the Drugbank candidates is given in the Supplementary Material.

Although not directly involved in interaction with tau protein, the identified drugs affect processes in AD via other targets in the tau signalling pathway, such as phosphorylation. This is possible due to the PPI interactions in the signalling pathways, occurring at the standard ISM frequency. The ISM-SM analysis identified compounds that have indirect effects on the tau pathway. This suggests the method might capture broader signalling relationships, potentially reflecting in vivo activity, although the mechanism for this requires further investigation and validation.

An important future direction would be integrating AI tools, particularly machine learning and deep learning models, to automate and refine the identification of druggable motifs within IDPs. AI could be employed to predict binding hotspots and rank compound libraries based on learned bioactivity patterns, potentially reducing the need for extensive experimental validation. Fusing traditional structure-based modelling and AI-assisted screening might offer a more robust platform for targeting IDPs.

3.2. Coconut database candidates

Compounds from the Coconut database were also screened on all frequencies, as were the Drugbank compounds. However, in the case of small organic molecules, contrary to the proteins, mere calculation of A and S/N values cannot be considered the final step. Further insight into the candidate's structure and properties is required. Therefore, the dS values of the candidates were also calculated. Those values were integrated into the final Total Score descriptor as their product, and the candidates were finally sorted accordingly. The top compounds at all frequencies are presented in Table 3.



Bryostatin 14

Figure 5. Structure of Bryostatin 14.

We identified a highly ranking compound, bryostatin-14, at F(0.167) (Figure 5). Bryostatins are macrocyclic lactones from marine bryozoans. They are increasingly being considered for therapeutic development in AD because of their ability to modulate protein kinase C (PKC) activity and ultimately mitigate pathological features of AD, such as tau hyperphosphorylation and amyloid-β (Aβ) aggregation. Several preclinical studies have demonstrated that bryostatin-1 enhanced synaptic plasticity and cognitive behaviour through the activation of PKCε, which inactivated glycogen synthase kinase-3β (GSK-3β), a critical kinase driving tau hyperphosphorylation[74][75]. The inhibition of GSK-3β reduces pathological aggregation of tau, which improves neurons' survival in transgenic tauopathy models[74]. Although their binding to tau protein is not well characterised, their modulation of tau phosphorylation through PKC/GSK-3β signalling makes them an unusual therapeutic approach to targeting tauopathies such as AD.

3.3. Limitations of the method

This study primarily utilises the ISM-SM method, an in silico approach based on electron-ion interaction potentials, to identify potential tau modulators. A key limitation is that ISM-SM predicts potential interactions based on calculated spectral compatibility rather than direct structural binding or dynamics. The underlying biophysical mechanism linking EIIP frequencies to specific long-range interactions and biological activity warrants further theoretical and experimental investigation, especially for dynamic IDPs like tau. The validation here relies heavily on identifying known drugs or compounds with literature support for indirect effects on tau pathology or AD, rather than primary experimental validation of direct binding or modulation of tau by the novel candidates identified (e.g., from the Coconut database). Furthermore, the study does not directly compare ISM-SM's performance against other established computational methods for IDP ligand discovery, such as enhanced sampling MD simulations or ensemble docking approaches. While interesting, the potential of ISM-SM to identify compounds acting indirectly through pathway interactions also introduces challenges in confirming the mechanism of action and requires careful interpretation. Future work should incorporate experimental validation (e.g., binding assays, cellular assays) and comparative computational studies to more rigorously assess the predictive power and applicability of ISM-SM for IDP drug discovery.

4. Conclusion

Intrinsically disordered proteins (IDPs) remain the most problematic targets for drug discovery because of their high dynamics and poorly defined binding pockets. Conventional structure-based approaches are generally ineffective in finding effective small-molecule modulators of such proteins. The Informational Spectrum Method for Small Molecules (ISM-SM) is another method that uses long-range interactions to predict functional ligand interactions by the electron-ion interaction potential (EIIP). We depicted our study to demonstrate that ISM-SM is able to accurately identify small molecules that potentially have activity against tau protein, which is an essential contributor to Alzheimer's pathology. Based on their spectral compatibility, the drug candidates identified by this study were considered likely direct/indirect modulators of tau. In fact, because of PPI, ISM-SM can also identify drugs that indirectly impact the target through other signalling pathways, such as a singular in vivo activity on a similar disease related to the target. This is a disadvantage to the target itself, although it can be considered an advantage from a potential in vivo activity standpoint. Combining ISM-SM with molecular dynamics simulation and

experimental validation could further improve the efficiency and precision of IDP-targeted drug discovery.

Integrating ISM-SM with molecular dynamics simulations and experimental validation could significantly enhance the efficiency and accuracy of IDP-targeted drug discovery. This approach accelerates the identification of novel candidates and reduces the high costs associated with traditional high-throughput screening methods. Given its success in other areas of drug repurposing, ISM-SM stands as a valuable tool for advancing therapeutic development, not only speeding up the identification of novel candidates but also aiding in identifying IDPs implicated in neurodegenerative disorders and other complex diseases. Future work should focus on refining ISM-SM-based predictions through experimental validation and exploring its applications for broader IDP-related disease targets.

AI methods could significantly enhance the framework provided, expediting the process of identifying small-molecule modulators of IDPs with higher accuracy. This would have a transformative effect on the drug discovery pipelines for this challenging class of proteins.

Supplementary Materials

Table S1 contains the lists of Drugbank and Coconut database candidates at all ISM frequencies, along with the amino acid and atomic group EIIP parameters used in the calculations.

Statements and Declarations

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Data Availability

This article and the Supplementary Material include the original contributions presented in this study. Further inquiries can be directed to the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

Statement on AI Use

Artificial intelligence tools were used solely to improve the clarity and language of the manuscript. All scientific content, analysis, and conclusions are the author's original work.

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