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Targeting Dopamine Transporter (DAT) with *Peronema canescens* Bioactives: A Molecular Docking Study for Stroke-Related Pain and Sedation Management

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ABSTRACT

Pain and drowsiness are common symptoms of stroke recovery, which can be difficult to manage owing to neurochemical abnormalities in the dopamine system. The Dopamine Transporter (DAT) controls dopamine levels, which influences pain perception and neurological recovery. This study examines bioactive chemicals found in *Peronema canescens* leaves and their possible interactions with DAT. AutoDock Vina was used to perform molecular docking simulations to determine the binding affinities of Peronemin derivatives (A2, A3, and B2) to the Dopamine Transporter (DAT). The receptor structure (PDB ID: 4M48) was created by eliminating water molecules, introducing polar hydrogens, and optimizing the structure using AutoDockTools. Ligand structures were translated to the proper format, and docking was conducted using a grid box centered on DAT's active site, with an exhaustiveness value of 10. The Peronemin derivatives A2, A3, and B2 demonstrated binding affinities stronger than nortriptyline, native ligand (−10.6, −10.5, and −10.3 kcal/mol, respectively) and binding similarities ranging from 72.2% to 94.4%. These findings suggest that *Peronema canescens* bioactives may be promising candidates for stroke-related pain and sedative control, warranting further experimental validation.

Keywords: Dopamine Transporter (DAT), Molecular Docking, Neuropharmacology, *Peronema canescens*, Stroke-Related Pain

1. INTRODUCTION

Stroke is a primary cause of long-term impairment globally, and it is typically accompanied by persistent pain and neurological problems that impede rehabilitation [1]. Post-stroke pain is tough to control because of the intricate interaction of neurochemical abnormalities and the limited effectiveness of available treatments [2]. Among the several neurochemical pathways involved, the dopamine system, which governs mood, reward, and motor function, is frequently altered after a stroke. This disruption incorporates uncommon pain processing and sedation-related difficulties, affecting rehabilitation [3].

The Dopamine Transporter (DAT) is a key regulator of dopamine levels, responsible for dopamine reuptake from the synaptic cleft to maintain neurotransmitter homeostasis [4]. DAT dysregulation has been linked to neurological diseases, including stroke, by causing dopamine depletion and consequent neurochemical imbalances [5]. Targeting DAT provides a viable therapeutic method since it improves.

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Dopamine signaling is required for motor and cognitive recovery while also modifying pain perception. However, existing DAT-targeting medicines are frequently accompanied by side effects or low effectiveness, emphasizing the need for new treatment possibilities [6].

Natural products are widely recognized as important sources of bioactive chemicals with therapeutic applications, notably in neuroprotection and pain treatment [7]. *Peronema canescens*, a medicinal herb native to Southeast Asia, has long been used to treat inflammation and pain [8]. Despite its historical usage, *P. canescens* pharmacological potential in regulating neurotransmitter systems, particularly the dopamine pathway, is relatively unknown. Given the growing involvement of DAT in post-stroke pain and sedation, bioactive compounds from *P. canescens* should be investigated further as possible DAT modulators.

Recent breakthroughs in computational biology, particularly molecular docking studies, have made it easier to screen plant-derived compounds for interactions with specific molecular targets, resulting in cost-effective and efficient drug discovery [9]. Molecular docking approaches identify ligands with high binding affinity and specificity for DAT, offering insights into possible treatment options [10]. This work uses molecular docking to assess the interaction of bioactive chemicals from *P. canescens* with DAT to identify novel candidates for stroke-related pain and sedation control. The findings of this study may help not only our understanding of
P. canescens is a source of medicinal chemicals and has also contributed to the development of novel techniques for post-stroke recovery.

2. METHODS

This study was conducted using a computational approach to evaluate the binding interactions of bioactive compounds from *P. canescens* with the Dopamine Transporter (DAT) through molecular docking. The workflow involved compound selection, ligand and protein preparation, docking simulations, and interaction analysis to identify potential DAT modulators.

2.1. Selection of Bioactive Compounds

Based on prior molecular docking studies, seven bioactive compounds from P. canescens were chosen for this investigation. They observed bioactivity, as seen in Table 1 [11], emphasizing their structural diversity and pharmacological relevance. These compounds were selected for their structural diversity and potential pharmacological relevance, as evidenced by studies highlighting *P. canescens* bioactive properties, such as its ability to reduce inflammatory biomarkers and therapeutic applications in various disorders [12-14]. Furthermore, earlier work on comparable plant-based substances, such as the *Spatholobus suberectus* study, which investigated psychostimulant activity via interactions with the Dopamine Transporter (DAT), served as a comparison foundation for this investigation [15]. The structures were optimized using Chembiodraw 14.0 and energy-minimized with Hyperchem Professional to ensure stability before docking [16, 17]. A native ligand DAT inhibitor, nortriptyline, was included to provide comparative docking scores and validate the docking methodology [18].

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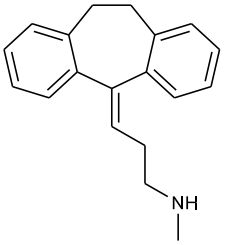
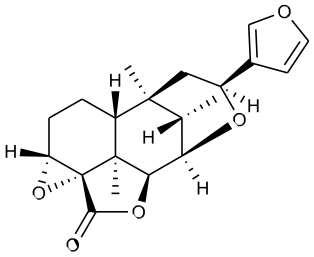
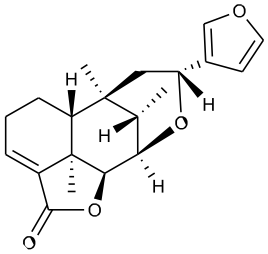
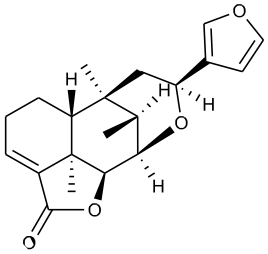
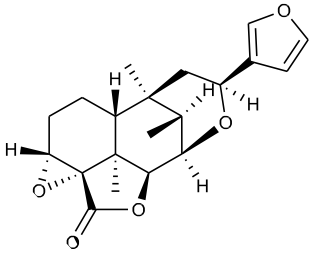
Table 1. Binding Energy of Peronemin Derivatives isolated from *P. canescens*

Compound	Name	Structure	Binding Energy (kcal/mol)
1	**Nortriptyline (native ligand)**		-10.1
2	**Peronemin A2**		-10.6
3	**Peronemin A3**		-10.5
4	**Peronemin B1**		-9.0
5	**Peronemin B2**		-10.3

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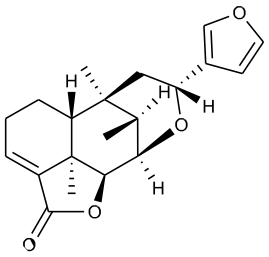
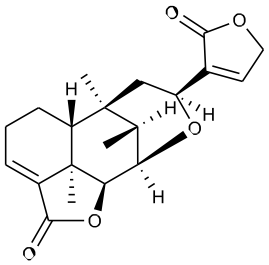
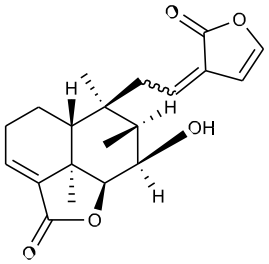
Compound	Name	Structure	Binding Energy (kcal/mol)
6	**Peronemin B3**		-10.1
7	**Peronemin C1**		-10.0
8	**Peronemin D1**		-9.6

2.2. Retrieval of Protein Structure

The three-dimensional crystal structure of the human dopamine transporter (DAT) (PDB ID: 4M48) was retrieved from the Protein Data Bank (PDB) [https://www.rcsb.org/] [19]. Protein preparation was conducted using AutoDockTools 1.5.7, which involved removing water molecules, adding polar hydrogens, assigning Kollman united atom charges, and optimizing the structure for docking simulations. The protein was then saved in PDBQT format [10].

2.3. Preparations of Ligands

Ligand structures were energy-minimized and prepared using Open Babel GUI and AutoDockTools 1.5.7. Gasteiger charges were assigned, and rotatable bonds were defined to allow torsional flexibility [20, 21]. The ligands were saved in PDBQT format to ensure compatibility with the docking protocol.

2.4. Molecular Docking Simulations

Molecular docking simulations were carried out using AutoDock Vina (version 1.2.3), employing a rigid receptor–flexible ligand approach [22]. The docking grid box was centered on the active site of DAT, encompassing the major substrate-binding pocket (S1) and the surrounding allosteric regions, based on the crystallographic analysis and mutational studies reported in previous literature [19, 23]. The grid box dimensions were set to 25 × 25 × 25 Å, and grid centers were set to -39 × -2 × 55 Å with a spacing of 0.375 Å, ensuring complete coverage of the binding pocket. The exhaustiveness parameter was set to 10 to improve sampling accuracy. AutoDock Vina's iterated local search global optimization algorithm was used to explore ligand binding conformations.

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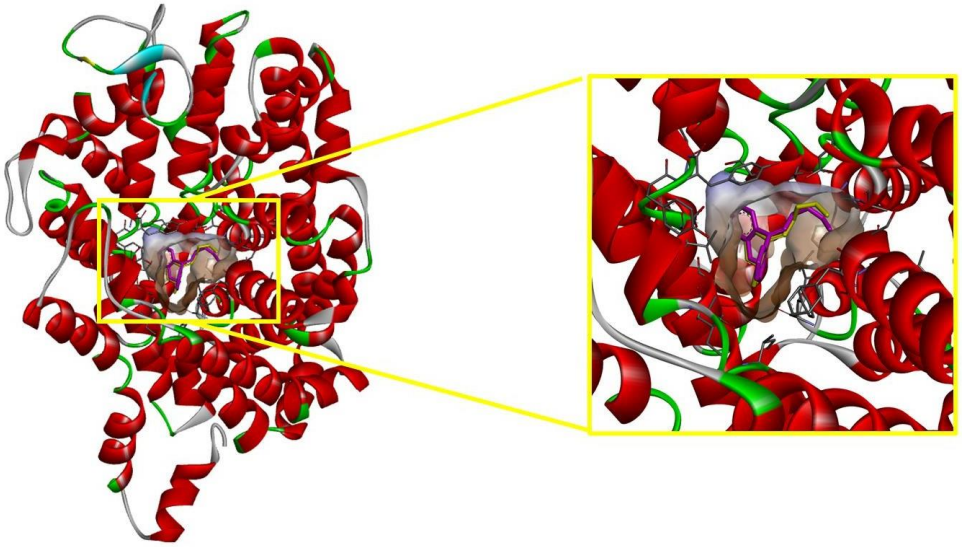

Figure 1. 3D visualization of nortriptyline's re-docking result with the Dopamine Transporter (DAT). Nortriptyline's original pose is colored in magenta, while its redocking outcome is marked in gold.

This procedure involved redocking native ligands in the direction of the protein receptor (Figure 1). When redocking with the binding pose from the crystal structure, the observed result was represented as root mean square deviation (RMSD), which measures the divergence from the binding location. A lower RMSD value suggests a greater pose quality obtained during docking. An acceptable RMSD should have a value lower than 2 Å [RMSD < 2 Å]. The RMSD value from this experiment was calculated using the PyMOL program. Nortriptyline, a natural ligand for DAT (PDB ID: 4M48), demonstrated a redocking outcome at 0.76 Å. These findings lead us to conclude that the locations of active sites in the main chain are almost comparable [24].

2.5. Visualization of Protein-Ligand Interactions

Moreover, the docking results were ranked by predicted binding affinity (kcal/mol), and the best-scoring poses were selected for analysis. Protein-ligand interactions were visualized and analyzed using Biovia Discovery Studio Visualizer (version 2021) and PyMOL (version 2.5), focusing on hydrogen bonding, hydrophobic contacts, andπ-π stacking to assess binding stability and interaction specificity [25, 26].

In addition to molecular docking, the drug-likeness of Peronemin derivatives was assessed using Lipinski's Rule of Five, which considers molecular properties such as molecular weight, hydrogen bond donors, hydrogen bond acceptors, and logP to determine whether the compounds have good oral bioavailability [27]. This review used HyperChem software, calculating the attributes required to estimate the compounds' potential as orally active medicines.

3. RESULTS AND DISCUSSION

According to the molecular docking study, Peronemin derivatives have comparable or better binding affinity to the 4M48 dopamine transporter (DAT) protein when compared to the natural ligand, nortriptyline. Peronemin A2 (-10.6 kcal/mol), Peronemin A3 (-10.5 kcal/mol), and Peronemin B2 (-10.3 kcal/mol) all had higher or comparable binding energies than nortriptyline (-10.1 kcal/mol), as seen in Table 2. Among them, Peronemin A2 had the lowest binding affinity. Although the energy difference with nortriptyline was minor (0.5 kcal/mol), Peronemin A2 indicated an altered and enhanced interaction profile at the DAT binding site, indicating that it might be a viable lead drug for future optimization. Notably, the increased binding energy alone may not be statistically significant; nevertheless, structural complementarity and residue-level interaction studies give more evidence for its potential. It is commonly acknowledged that a lower (i.e., lower) binding energy in molecular docking frequently corresponds with increased binding strength and biological activity,

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implying a more thermodynamically advantageous and stable ligand-receptor complex formation [28, 29]. As a result, Peronemin A2's more interaction with critical active site residues and lower docking score point to more powerful pharmacological activity than the native ligand.

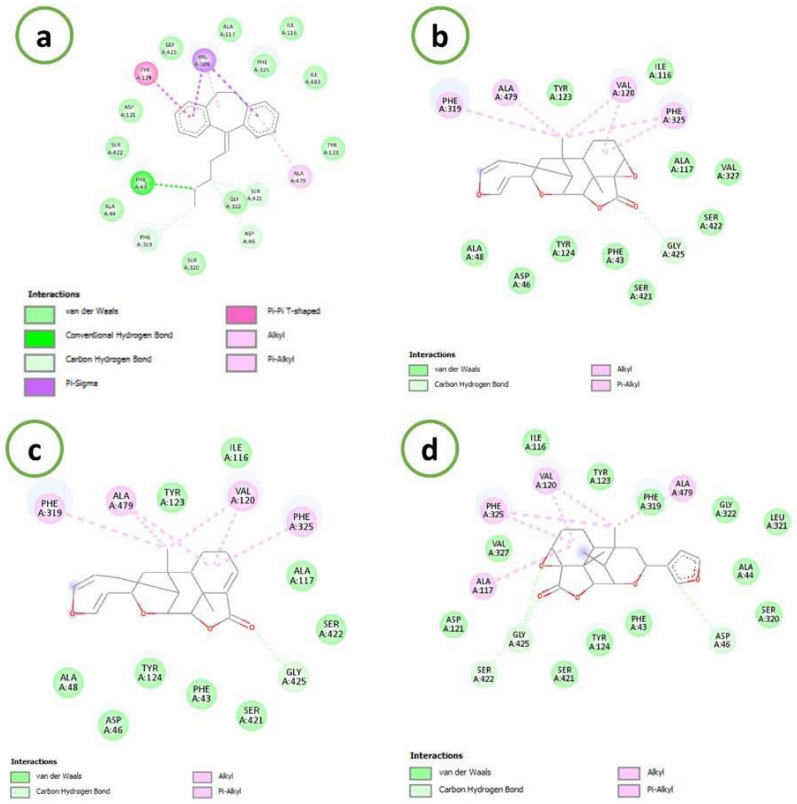

Figure 2. 2D visualization of the top-ranked *P. canescens* bioactive compounds and the native ligand nortriptyline toward the Dopamine Transporter (DAT) protein. (a) Nortriptyline (native ligand) (−10.1 kcal/mol), (b) Peronemin A2 (−10.6 kcal/mol), (c) Peronemin A3 (−10.5 kcal/mol), (d) Peronemin B2 (−10.3 kcal/mol). Key interactions include van der Waals, hydrogen bonds, and alkyl/π-alkyl contacts with DAT active site residues.

The binding affinity of these compounds is a significant factor determining their capacity to influence DAT activity. The lower binding energies of Peronemin A2, A3, and B2 indicate a more persistent association inside the DAT active site, which might lead to increased pharmacological effectiveness. Given DAT's pivotal significance for dopamine modulation, these findings possess significant implications regarding managing stroke-related pain and sedation. By inhibiting DAT, these drugs may increase synaptic dopamine levels, reducing pain while encouraging neurological rehabilitation in stroke patients. This is consistent with prior data showing that DAT inhibitors improve dopamine signaling, critical for motor and cognitive recovery in neurological disorders [30].

Hydrogen bonding and hydrophobic interactions contributed to ligand stability within the DAT binding site. The active site of DAT, which is responsible for dopamine reuptake inhibition, is located in the central transmembrane region, particularly between transmembrane domains (TMs) 1, 3, 6, and 8, which constitute the substrate translocation pathway [19]. Key amino acid residues in this binding region include PHE43, ALA44, ASP46 (TM1), TYR123, TYR124 (TM3), SER320, PHE319, PHE325, LEU321, VAL327 (TM6), and SER421,
GLY425 (TM8)—all associated with ligand binding stabilization through hydrophobic or polar interactions [30, 31].

Figure 2 shows the 2D interaction profiles, which highlight the particular residues implicated in

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Ligand binding. Nortriptyline, the native ligand, formed a hydrogen bond with PHE43 and other hydrophobic contacts with residues such as SER320, PHE319, ALA44, and ASP121, all of which have been identified as crucial for DAT ligand stability. This reaffirms its orientation within the canonical binding pocket [19].

Peronemin B2 has the most significant binding similarity to nortriptyline of any Peronemin derivative (94.4%). It interacted with critical residues such as PHE43, TYR124, SER421, and GLY425, which are required for ligand stability. This high degree of similarity indicates that Peronemin B2 might serve as a competitive DAT inhibitor, potentially mimicking nortriptyline's mode of action. Notably, B2 also interacts with ILE116 and LEU321, giving further hydrophobic stability [32].

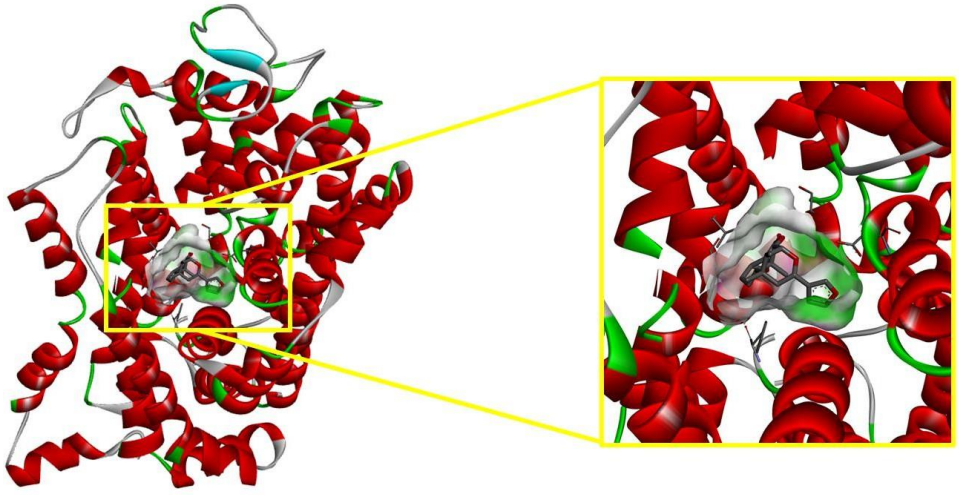

Figure 3. 3D visualization between ligand (Peronemin B2) and the DAT protein (PDB: 4M48). This visual representation highlights the spatial conformation and binding pocket.

Peronemin A2 and A3 had a slightly lower binding similarity (72.2%) but interacted with key residues, including PHE319, TYR123, PHE325, and GLY425, indicating their ability to stabilize inside the DAT binding pocket. Peronemin A2's greater binding affinity may be assigned to more intense hydrophobic interactions with residues such as ALA117, VAL327, and ASP46, residues involved in substrate recognition and ligand anchoring. The presence of these residues within the transmembrane channel confirms their functions in the binding event [33]. These interactions indicate that Peronemin derivatives are well-positioned inside the DAT substrate-binding cavity and might operate as potent inhibitors by limiting dopamine reuptake. This may result in increased synaptic dopamine levels, which might have therapeutic advantages for stroke-related pain, drowsiness, or depression. Importantly, their distinct interaction patterns may overcome the drawbacks of current DAT-targeting drugs, such as addiction risk and reduced effectiveness [34]. Furthermore, Peronemin derivatives' structural flexibility allows for lead tuning. For example, A2's hydrophobic contacts with ALA117 and VAL327 may inspire analog design with improved selectivity, while B2's dual interaction with ILE116 and LEU321 may be used to increase binding stability and pharmacokinetic features. This strategy is consistent with using natural product scaffolds to build novel central nervous system (CNS) active medicines [35, 36].

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Table 2. Binding energy, interaction sites, and binding similarity (%) of *P. canescens* compounds compared to native ligand nortriptyline at the DAT active site.

Compound	Binding energy (kcal/mol)	Binding site		Binding Similarity %
		Hydrogen bonding	Hydrophobic interaction	
Nortriptyline (Native Ligand)	-10.1	**phe43**	**ser320, phe319, ala44, ser422, asp121, tyr124, gly425, val120, ala117, phe325, ile116, ile483, tyr123, ala479, ser421, gly322, asp46**	100
Peronemin A2	-10.6		**phe319, ala479, tyr123, val120, ile116, phe325, ala117,** val327, **ser422, gly425,ser421,phe43, tyr124, asp46,** ala48	72.2
Peronemin A3	-10.5		**phe319, ala479, tyr123, ile116, val120, phe325, ala117, ser422, gly425, ser421, phe43, tyr124, asp46,** ala48	72.2
Peronemin B2	-10.3		**ile116,val120, tyr123, phe319, ala479, gly322,** leu321, **ala44, ser320, asp46, phe43, tyr124, ser421, gly425, ser422, asp121, ala117,** val327, **phe325**	94.4

Peronemin A2, A3, and B2's potential as DAT inhibitors is demonstrated by their ability to interact with vital residues in the DAT binding pocket. These substances could increase dopamine levels in synapses by modifying DAT activity, providing a new treatment approach for sedation and discomfort associated with stroke. This is especially important considering the shortcomings of the available DAT-targeting medications, which frequently have negative side effects, including addiction or decreased effectiveness [37].

Peronemin derivatives' structural diversity offers opportunities for further optimization. For example, the increased hydrophobic interactions obtained with Peronemin A2 could potentially be employed to develop analogs with lower binding affinity and specificity. Similarly, Peronemin B2's additional interactions with ILE116 and LEU321 may serve as a platform for designing molecules with enhanced pharmacokinetic features. This method is consistent with recent advances in drug development, which use natural products as scaffolds for designing novel therapeutics [38].

Beyond binding affinity, the drug-likeness of these compounds was evaluated using Lipinski's Rule of Five, which remains a widely accepted guideline for predicting oral bioavailability [39]. All three compounds exhibited zero violations of Lipinski and lead-likeness criteria, indicating a high probability of pharmacokinetic compatibility. Furthermore, their molar refractivity (88.18–90.15 m^3/mol) and topological polar surface area (TPSA 44.76–61.2 $Å^2$) fall within optimal ranges for blood-brain barrier penetration, a critical property for CNS-targeting agents [40]. Synthetic accessibility scores below six further suggest that these scaffolds are amenable to practical chemical synthesis, supporting their potential as lead compounds for further development [41].

Even though these *in silico* results are encouraging, more experimental validation is required to verify the compounds' potential for therapeutic applications. Evaluating the effectiveness of Peronemin derivatives in modifying DAT activity will need in vitro research using techniques including binding assays and functional testing. In vivo research is also necessary to assess their pharmacokinetic characteristics, safety, and effectiveness in animal models of stroke. Despite the useful insights that molecular docking offers, experimental confirmation is still essential to guarantee translational relevance [42].

Furthermore, possible off-target effects must be investigated. Despite their promising binding affinity to DAT, Peronemin derivatives' interactions with other neurotransmitter transporters or receptors may influence their therapeutic efficacy. A comprehensive ADMET (absorption, distribution, metabolism, excretion, and toxicity) investigation will be required to determine their drug likeness and uncover any safety issues. This is especially significant considering natural products' complicated pharmacokinetic and pharmacodynamic properties [43].

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Table 3. Physicochemical and drug-likeness properties of selected Peronemin derivatives (A2, A3, and B2).

Compound	MW	#H-bond acceptors	#H-bond donors	Molar Refractivity (m3/mol)	TPSA Å²	Lipinski #violations	Leadlikeness #violations	Synthetic Accessibility
Peronemin A2	348.43	5	0	89.63	57.29	0	0	5.58
Peronemin A3	332.43	4	0	90.15	44.76	0	0	5.3
Peronemin B2	344.4	5	0	88.18	61.2	0	0	5.76

Molecular Weight (MW); Topological Polar Surface Area (TPSA)

4. CONCLUSION

In conclusion, the molecular docking study highlights the potential of Peronemin derivatives as promising DAT inhibitors, especially Peronemin A2, A3, and B2. They are excellent options for managing stroke-related pain and sedation because of their lower binding affinity, good interaction profiles, and interaction resemblance to the natural ligand. Optimizing their structural characteristics, confirming their effectiveness through experimental study, and evaluating their clinical applicability should be the main goals of future investigations. These discoveries lay the groundwork for developing the bioactives of *P. canescens* as innovative treatments that target the dopamine system.

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