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COMPUTATIONAL INSIGHTS INTO *Piper retrofractum* CONSTITUENTS TARGETING MAO-B IN PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease, characterized as a progressive neurodegenerative condition, represents a significant contributor to mortality in Indonesia. *Piper retrofractum*, a *Piperaceae* species rich in alkaloids, has been reported to contain compounds with neuroactive potential, similar to other *Piper* species in which Monoamine Oxidase-B (MAO-B) inhibition has been documented. However, no computational study has evaluated the interaction between *Piper retrofractum* bioactive compounds and MAO-B. = aimed to evaluate the MAO-B inhibitory potential of bioactive compounds from *Piper retrofractum*. Ten bioactive compounds from *Piper retrofractum* were screened and analyzed using Lipinski's rules, PreADMET, pharmacophore modeling (Ligandscout 4.4.5), and molecular docking (AutoDock 4.2.6). The findings revealed that all test compounds met Lipinski's rule of Five. From the PreADMET results, Alismoxide showed a high Blood-Brain Barrier (BBB) crossing capacity of 4.59529. Trans-fagaramide was identified as the optimal pharmacophore match, displaying a fit score of 34.57. Meanwhile, from the molecular docking results, the most promising pharmacological candidate was piperolein-B, which formed a hydrogen bond with the amino acid residue LEU: A56, similar to the native ligand, with an inhibition constant of 0.015 μM and a binding energy of -10.6 kcal/mol. From these results, the bioactive compounds from *Piper retrofractum* can interact with the MAO-B receptor. These findings are computational predictions and require further experimental validation to confirm their potential for Parkinson's disease treatment.

Keywords: Molecular Docking; Monoamine Oxidase-B (MAO-B); Parkinson's Disease; Pharmacophore Screening; Piper retrofractum

INTRODUCTION

The degenerative neurological disorder known as Parkinson's disease is brought on by the death or degeneration of dopamine-producing neurons in the substantia nigra pars compacta. In most cases, the oxidative stress plays a central role in the pathogenesis of Parkinson's disease through excessive production of reactive oxygen species (ROS) that cause mitochondrial dysfunction and impaired antioxidant defenses contribute to neuronal damage and α-synuclein aggregation. The brain's high oxygen consumption and lipid-rich composition further increase its vulnerability to oxidative injury, accelerating neurodegeneration in Parkinson's disease (Chang and Chen, 2020). Parkinson's disease induces bradykinesia and muscle rigidity because reduced dopamine production throws off the basal ganglia's direct and indirect route balance (Alia et al., 2022). In Indonesia, Parkinson's disease is estimated to affect approximately 200,000–400,000 people, with projections suggesting that the number may reach 876,665 out of a total population of 238,452,952. According to the Global Burden of Disease Study, the prevalence of Parkinson's disease in Indonesia was estimated between 117,531 and 178,755 cases in 2016, while an estimated 211,296 deaths worldwide were attributed to the disease in the same year (PERDOSNI, 2024).

Dopamine metabolism is largely regulated by specific enzymatic systems, particularly Monoamine Oxidase (MAO). MAO helps tyramine and monoamine neurotransmitters such as dopamine, phenethylamine, serotonin (5-hydroxytryptamine), and norepinephrine undergo oxidative deamination. The two MAO isoenzymes are MAO-A and MAO-B. Dopamine is metabolized by MAO-B, released into the synaptic cleft, and then absorbed by glial cells. MAO-B inhibitors improve dopamine signaling, block MAO-B mobility in the brain, stop dopamine catabolism, and raise dopamine levels in the synaptic cleft only. For early Parkinson's patients whose quality of life is unaffected by motor adverse effects, MAO-B inhibitors are recommended as the initial line of treatment (Tan et al., 2022).

Safinamide is a new generation selective MAO-B inhibitor that is 5,000 times more selective against MAO-B than MAO-B itself due to its sodium and calcium channel blocking capabilities. Safinamide not only inhibits dopamine reuptake but also inhibits glutamate release, opens voltage-dependent sodium channels, and modifies non-dopaminergic systems as calcium tracts to produce therapeutic effects (Tan et al.,

2022). However, the use of these synthetic drugs has the potential for side effects such as nausea, hypertension, digestive disorders, and dyskinesia (Cruz, 2017). Therefore, it is essential to conduct research on candidate drugs from therapeutic plants. These therapeutic plants are anticipated to be an adjuvant treatment for Parkinson's treatment with generally lower side effects.

Piper retrofractum is a type of medicinal plant belonging to the Piperaceae family with a high alkaloid content (Hikmawanti et al., 2021). Alkaloids can work by inhibiting MAO, reducing adrenocorticotropic hormone, increasing the concentration of Brain Derived Neurotrophic Factor (BDNF) and serotonin (5-HT) in the brain, so that they can treat several diseases of the neurotransmitters (Sahetapy et al., 2021). Based on research conducted by Dhiman et al, (2020), the piperine compound in black pepper, which belongs to the Piperaceae family, contains compounds reported as MAO-B inhibitors (Dhiman et al., 2020). Until now, there has been no computational research using pharmacophore modeling and molecular docking methods that specifically discuss the interaction between compounds in *Piper retrofractum* and MAO-B for Parkinson's disease therapy. Based on these findings, this research seeks to determine whether *Piper retrofractum* can function as an MAO-B inhibitor for candidate drugs for Parkinson's disease using the molecular docking method of bioactive compounds from *Piper retrofractum*.

METHODS

Tool and Materials

All computational analyses were performed using Intel i5-based computers with Windows operating system. The programs utilized are ChemDraw Ultra Program, Chem3D, Ligandscout 4.4.5, AutoDock 4.2.6., and BIOVIA Discovery Studio 2021 Client. Among the websites that are utilized are Protein Data Bank (PDB) of the RCSB (https://www.rcsb.org/), DUD-E (Directory of Useful Decoys: Enhanced) (https://dude.docking.org) for decoy compounds, PreADMET (https://preadmet.webservice.bmdrc.org/) for ADMET prediction, chemical information from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and Mcule (https://mcule.com/dashboard/) for compound selection.

The materials used in this study included bioactive compound found in *Piper retrofractum* (Table 1), as reported by Tang et al., (2019). The complex structure of MAO-B protein with safinamide from the RCSB PDB website with PDB ID: 2V5Z,

and the 2D structure of the test compound that has been downloaded via PubChem.

Table 1. Bioactive compound found in *Piper retrofractum*

Compound	PubChem ID
Piperolein-B	21580213
Trans-fagaramide	5281772
Piperine	638024
Alismoxide	10988340
2'-O-Methyluridine	102212
Dihydropiperlonguminine	12682184
Pipernonaline	9974595
Piperanine	5320618
Methyl piperate	9921021
Piperidine	966720

Research Path

1. Lipinski's Rule of Five Predictions

The 2D structures of the test compounds were taken from PubChem and analyzed using Lipinski's Rule of Five. Further predictions of physicochemical properties including molecular weight, log P, Hydrogen Bonds Donor (HBD), and Hydrogen Bonds Acceptor (HBA) on the test compounds using Mcule.

2. Determination of ADMET

The evaluation of ADMET parameters (Absorption, Distribution, Metabolism, Excretion, and Toxicity) is crucial in drug development to prevent potential failures. For this purpose, the PreADMET tool was used, which predicts various properties such as drug-likeness, Human Intestinal Absorption (HIA), permeability in Caco-2 cells (human colon adenocarcinoma), Plasma Protein Binding (PPB), Blood-Brain Barrier (BBB) penetration, and potential toxicity.

3. Pharmacophore Modeling

The active, decoy, and test compound databases were prepared by visiting the DUD-E site and converted into .ldb format. In pharmacophore modeling with Ligandscout, the minimized active database file was clustered and one training type was obtained in each cluster. The results of 10 pharmacophore models were obtained which were saved in pmz format. In pharmacophore validation, 10 pharmacophore models were transferred to the screening perspective and marked the green color for the active database and the red color for the decoy. The best Receiver Operating Characteristics (ROC) curve plot was produced. In pharmacophore screening, the test compound database was entered in the screening

perspective. The test compound was marked in green and the active and decoy databases were made colorless. Screening was done by pressing perform screening to get hit compounds.

4. Molecular Docking

Receptor and compound preparation was performed on the MAO-B target protein, downloaded from RCSB PDB with ID: 2V5Z. The natural compounds and receptors were removed from their water molecules and separated using the BIOVIA program. In AutoDock, the receptor was assigned polar hydrogen atoms and Kollman charges, while the natural compounds and test compounds were added hydrogen atoms, combined into non-polar compounds, and given Gasteiger charges, then saved in .pdbqt format. During validation, grid box parameters and docking parameters were created in AutoDock and saved in .gpf (grid) and .dpf (docking) formats. The grid box in the docking process was used to determine the binding region for the compound. Determination of the grid box size was depended on the binding site and the size of the compound being tested. The center coordinates of the grid box for safinamide were X = 52.144; Y = 156.171; Z = 28.035, with dimensions of 90 × 90 × 90. Validation was carried out through a redocking procedure using the native ligand, and the docking results were evaluated using the Root Mean Square Deviation (RMSD) criterion (acceptable RMSD ≤ 2 Å) to ensure the reliability of the docking protocol. Molecular docking was then performed via the command prompt and produced results in .glg and .dlg output files. The docking results were analyzed using AutoDockTools and BIOVIA Discovery Studio, including analysis of amino acid residues, binding free energy, predicted inhibition constants, and ligand protein interactions with amino acid residues of MAO-B in both 2D and 3D visualization using BIOVIA.

RESULTS AND DISCUSSION

1. Lipinski's Rule of Five Predictions

A compound is considered to have characteristics similar to a drug and can be given orally if it meets Lipinski's rule of five. Estimated results based on Lipinski's rule of five are presented (Table 2). The molecular weight obtained for each test compound meets the Lipinski's rule of five criteria and the most fulfilling is the compound Piperidine with a value of 217.3062. The smallest log P or partition coefficient is the compound 2'-O-Methyluridine with a value of -1.4. The smaller the log P value, the lower the lipophilicity of the compound (Dyanira et al., 2022). The compound Piperidine is identified as the optimal HBD and HBA, with a donor value of 0 and an acceptor value

of 2. HBD and HBA values, aligned with Lipinski's criteria, imply that the substance maintains conformational stability with the intended protein (Suryana et al., 2022). From the test results, it was found that 10 compounds in *Piper retrofractum* fruits have met Lipinski's rule of five criteria so that they can be used as drug candidates and given orally.

In addition, *Piper retrofractum* is one of Indonesia's native spice plants and has been widely used as an ingredient in herbal medicine for health and wellness. It is found that approximately 77 traditional herbal medicine packages use *Piper retrofractum* as one of their raw materials (Bahruddin et al., 2021). These findings indicate that *Piper retrofractum* has also been widely consumed orally by the community.

Table 2. Lipinski's rule of five prediction result

Compound	Weight	Log P	HBD	HBA	Drug Likeness
Piperolein-B	343.4589	4.7195	0	4	Suitable
Trans-fagaramide	247.2890	3.0410	1	4	Suitable
Piperine	285.3368	2.9351	0	4	Suitable
Alismoxide	238.3651	2.8908	2	2	Suitable
2'-O-Methyluridine	258.23	-1.4	3	6	Suitable
Dihydropiperlonguminine	275.3421	3.5166	1	4	Suitable
Pipernonaline	341.4430	4.4955	0	4	Suitable
Piperanine	287.3527	2.8545	0	4	Suitable
Methyl piperate	232.2311	2.8545	0	4	Suitable
Piperidine	217.3062	2.5696	0	2	Suitable

2. Determination of ADMET

The ADMET evaluation was conducted to assess the pharmacokinetic behavior and safety profile of the selected compounds (Table 3) (Sufi et al., 2022). Most compounds showed favorable absorption characteristics, with 9 exhibiting high HIA values (>70%), indicating strong intestinal absorption. Only 2'-O-Methyluridine demonstrated moderate absorption (Wulandari et al., 2023). All compounds showed moderate Caco-2 permeability (4–70 nm/s), suggesting acceptable intestinal epithelial transport (Hasan & Khalid, 2021).

For distribution, several compounds Piperolein-B, Piperine, Alismoxide, Dihydropiperlonguminine, Pipernonaline, and Piperanine showed PPB values above 90%, indicating strong binding affinity and prolonged systemic circulation (Apriali et al., 2022). A key finding relevant to MAO-B

inhibitor potential was the high BBB permeability of Alismoxide, which demonstrated a BBB score >2 (Purwaniati, 2020). Since MAO-B is predominantly expressed in the Central Nervous System (CNS) and Parkinson's therapy requires CNS penetration, Alismoxide's strong BBB permeability significantly enhanced its pharmacological relevance (Damayanti et al., 2022). Regarding toxicity, Alismoxide was predicted to be non-mutagenic based on the Ames test. However, it exhibited carcinogenicity in mouse models, highlighting the need for further toxicity validation before progressing into advanced drug development (Az-Zahra et al., 2022).

Overall, the ADMET analysis identified Alismoxide as the most pharmacokinetically favorable compound for MAO-B targeted Parkinson's therapy due to its strong absorption and CNS penetration, although its predicted carcinogenicity warranted caution and further validation.

Table 3. ADMET determination results

Compound	Absorption		Distribution		Toxicity		
	%HIA	Caco-2	%PPB	BBB	Mutagens	Carcinogens	
						Mouse	Rat
Piperolein-B	98.059592	55.7786	96.018200	0.830059	Mutagens	No	No
Trans-fagaramide	95.030584	39.1781	67.311418	0.328725	Mutagens	No	No
Piperine	98.180182	52.383	90.448927	0.050316	Mutagens	Yes	No
Alismoxide	90.685820	33.9066	100.000	4.59529	No Mutagens	Yes	No
2'-O-Methyluridine	46.292985	2.53115	11.704265	0.152406	Mutagens	Yes	No
Dihydropiperlonguminine	95.175231	41.4854	95.377153	1.12729	Mutagens	Yes	Yes
Pipernonaline	98.042871	55.7544	96.663912	0.76008	Mutagens	Yes	No
Piperanine	98.269843	52,453	100,000	0.0875913	Mutagens	No	No
Methyl piperate	98.195147	31.8019	86.022642	0.0219478	Mutagens	Yes	No
Piperidine	100.0000	49.0629	78.51349	0.242114	Mutagens	No	No

3. Pharmacophore Modeling

Pharmacophore modeling was conducted to identify the essential structural features required for optimal interaction between the compounds and the MAO-B target. A total of 100 active compounds and 400 decoys were obtained from the DUDE database (https://dude.docking.org) and used for model generation in Ligandscout. This process produced ten pharmacophore

models, each of which was validated using ROC curve analysis to assess their ability to distinguish active compounds from decoys.

The Area Under the Curve (AUC) values ranged from 0.67 to 0.70 (Table 4). AUC values above 0.7 indicate acceptable discriminatory performance (Sangande et al., 2020), while values above 0.5 are considered valid (Arba et al., 2020). Among the generated models, Model 4 demonstrated the highest AUC value (0.70) and produced the greatest number of hits (182 compounds), indicating superior capability in identifying potential MAO-B inhibitors. Therefore, Model 4 was selected for subsequent virtual screening.

Table 4. Pharmacophore validation results in the form of ROC curves

Pharmacophore Model	ROC Hits	AUC 100%
1	181	0.70
2	181	0.70
3	179	0.70
4	182	0.70
5	184	0.69
6	176	0.69
7	176	0.69
8	174	0.67
9	176	0.67
10	179	0.68

The same process for validation was carried out again but this time for the test compound database. With this model, screening identified Model 2 (Trans-fagaramide) as the best fit for the test compounds, yielding a pharmacophore fit score of 34.57 (Figure 1). The pharmacophore fit score reflects the degree to which a compound satisfies the essential features of the pharmacophore, where values >50% indicate strong activity and values between 30-50% suggest moderate activity (Muchtaridi et al., 2017). Thus, the obtained score suggests moderate pharmacological relevance and justifies further docking analysis. As shown in Figure 1, the aromatic ring of Trans-fagaramide corresponded to the aromatic ring (AR) feature, the non-polar region aligned with the hydrophobic (H) feature, and the amide group engaged the HBD/HBA features, demonstrating proper feature matching within the generated pharmacophore model.

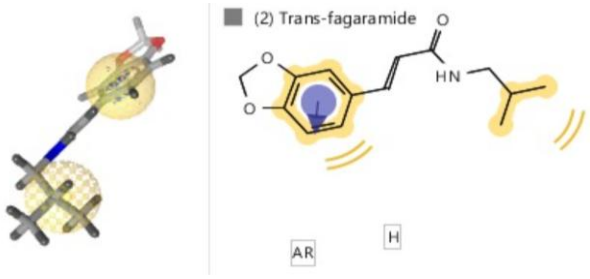

Figure 1. Pharmacophore fit score of Trans-fagaramide

4. Molecular Docking

The selected receptor was MAO-B with PDB code 2V5Z, as shown in **Figure 2**. This receptor was chosen because it used the X-ray diffraction method, which was the most optimal technique for describing the 3D structure of macromolecular compounds, and had a resolution below 2 Å (1.60 Å). A smaller resolution value indicated a better structural representation, making the model increasingly similar to the native structure (Az-Zahra et al., 2022). Redocking safinamide on the MAO-B receptor was performed to validate the docking protocol.

Safinamide ((s)-(+)-2-[4-(fluorobenzyloxy-benzylamino)propionamide]) was the native ligand present in the receptor (Figure 2) and was known as a selective MAO-B inhibitor (Cilia et al., 2023). This compound was capable of inhibiting MAO-B in degrading dopamine, thereby contributing to Parkinson's disease therapy.

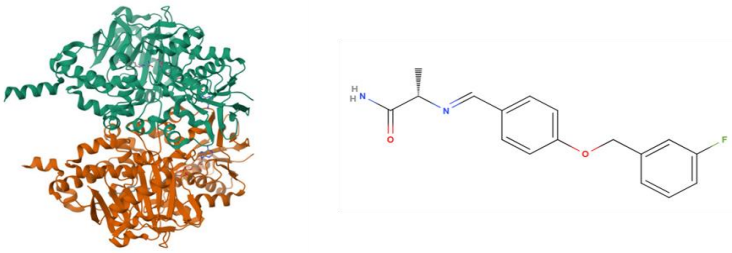

Figure 2. Structure of MAO-B and its native ligand Safinamide (PDB ID: 2V5Z)

Method validation was used to evaluate specific parameters required in the study, and these parameters had to meet defined criteria before the method could be applied (Sagitasa et al., 2021). The RMSD was an essential validation parameter; values ≤2 Å indicated that the docking protocol was valid for further MAO-B studies. Larger deviations indicated a higher error in predicting ligand protein interactions (Muttaqin, 2019). The safinamide redocking resulted in an RMSD of 1.78 Å, confirming that no significant deviations occurred and prediction errors were minimized.

The best conformation from the molecular docking results was determined by the binding energy, where the ligand conformation with the lowest energy represented the most stable interaction (Mohanty & Mohanty, 2023). The affinity

between each test ligand and the protein was reflected by the binding free energy (ΔG) and inhibition constant (Ki). A lower ΔG indicated higher interaction stability (Marques et al., 2019), while a smaller Ki indicated that a lower ligand concentration was required to inhibit receptor activity, reflecting a stronger compound receptor binding affinity (Puspita et al., 2022).

Molecular docking between 10 compounds from *Piper retrofractum* and the MAO-B receptor was carried out, and the results were presented in Table 5. According to recent studies (Ajala et al., 2024), effective MAO-B inhibition relies on interactions with crucial active site residues, particularly TYR435, CYS397, CYS172, and LYS296. While Safinamide exhibited a binding affinity of -9.26 kcal/mol anchored by a hydrogen bond at LEU A56 , Piperolein-B emerged as the superior candidate with the lowest binding energy of -10.66 kcal/mol. Notably, Piperolein-B mimicked the binding mechanism of the native ligand by forming the identical hydrogen bond at LEU A56 , and it successfully established stabilizing interactions with the critical residues CYS A172 and TYR A435, thereby demonstrating a more robust and stable inhibitory profile than the other tested compounds. The strong binding affinity of Piperolein-B is likely due to the presence of a conjugated aromatic system and an amide functional group, which enable multiple stabilizing interactions within the MAO-B active site. These include π–π stacking with aromatic residues (Pacureanu et al., 2023).

Table 5. Molecular docking results

Compound	Binding Energy (k.cal/mol)	Ki (μM)	Amino Acid Interactions		
			Hydrogen Bonds	Van der Waals Bonds	Others
Safinamide (ligand)	-9.26	0.163	LEU A56	-	LYS A296, MET A436, VAL A294, TYR A398, TRP A388, CYS A397
Piperolein-B	-10.66	0.015	LEU A56	GLY A58	CYS A397, GLY A57, VAL A294, LYS A296, TRP A388, TYR A60, LEU A171, CYS A172, ILE A198

Compound	Binding Energy (k.cal/mol)	Ki (μM)	Amino Acid Interactions		
			Hydrogen Bonds	Van der Waals Bonds	Others
Trans-Fagaramide	-8.0	1.36	TYR A188	-	TYR A435, LEU A171, ILE A198, CYS A172, ILE A199, TYR A326
Piperine	-9.8	0.0652	TYR A188	-	CYS A172, TYR A43, TYR A398, ILE A316, LEU A164, LEU A167, ILE A199, ILE A198, LEU A171
Alismoxide	-8.63	0.4724	LYS A296, GLY A57, GLY A434	-	TYR A60, PHE A343, TYR A398, TYR A435, MET A436
2'-O-methyluridine	-6.98	7.68	TYR A60, GLY A57, LYS A296, SER A59, TYR A60, MET A436, GLN A206	-	-
Dihydropiperlonguminine	-9.15	0.195	LYS A296	-	TRP A388, LEU A171, ILE A199, TYR A398, PHE A343, VAL A294, CYS A397, TRP A388, LYS A296
Pipernonaline	-11.27	0.00553	ILE A14 ARG A42 LYS A296	-	ALA A439, ILE A14, ARG A42, MET A436, TYR A435, TYR A398, CYS A397, TRP A388, TRS A296
Piperanine	-9.72	0.075	ILE A14 ARG A42	-	ILE A14, ALA A439, ARG A42, TRP A388,

Compound	Binding Energy (k.cal/mol)	Ki (μM)	Amino Acid Interactions		
			Hydrogen Bonds	Van der Waals Bonds	Others
Methyl piperate	-8.23	0.92	CYS A172 SER A59 LYS A296	-	LYS A296, TYR A398, CYS A397 LEU A171, TYR A60, PHE A343, TYR A398
Piperidine	-7.92	1.56	LEU A56 LYS A296	-	LYS A296, MET A436, VAL A294, TYR A398, TRP A388, CYS A397

The pharmacophore modelling results indicated that Trans-fagaramide was the hit compound that best matched the pharmacophoric features. However, the molecular docking analysis showed that Piperolein-B exhibited the highest binding affinity and the most favorable interaction profile as an MAO-B inhibitor. This difference was caused because pharmacophore modeling was based on a set of ligand molecules known to be active, but the detailed structure of the target protein was not considered, relying only on mathematical models to match ligand pharmacophore features with the provided database. Meanwhile, molecular docking took into account the structures of both the ligand and the target protein to directly simulate their physical interactions, allowing analysis of more specific and detailed binding characteristics (Macalino et al., 2015).

From the findings, it showed that *Piper retrofractum* had MAO-B inhibiting activity, indicating its potential use as a candidate drug for orally administered Parkinson's therapy. However, because this study was purely computational, *in vitro* and *in vivo* experiments were required to verify the ability of *Piper retrofractum* to suppress MAO-B.

CONCLUSIONS

Based on *in silico* molecular docking studies of *Piper retrofractum* on MAO-B receptors, Piperolein-B demonstrates strong potential as an MAO-B inhibitor. This compound exhibits a Gibbs free energy of –10.66 kcal/mol and an inhibition constant (kI) of 0.015 μM, forming a hydrogen bond

with the amino acid residue LEU A56. In comparison, the selective MAO-B inhibitor Safinamide shows a binding energy of -9.26 kcal/mol and a kI of 0.163 μM. The presence of this hydrogen bond, together with additional hydrophobic interactions commonly observed in MAO-B ligand binding, provides a mechanistic basis for the predicted inhibitory activity of Piperolein-B. These findings highlight the potential of *Piper retrofractum* as a natural lead source for the development of anti-Parkinson's drugs. While this study only limits the utilization of computational-based analysis in predicting the molecular interaction between the bioactives and the target protein, the current finding holds promising development, and further *in vitro* to *in vivo* studies are necessary to validate its MAO-B inhibitory effect and neuroprotective potential.

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