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Exploring molecular interactions and ADMET profiles of novel MAO-B inhibitors: toward effective therapeutic strategies for neurodegenerative disorders

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Abstract

Background Neurodegenerative disorders (NDs), primarily affecting the elderly, are marked by complex pathophysiological processes and are projected to become the second leading cause of death. Parkinson's disease (PD), one of the most common NDs, is characterized by motor impairments due to reduced dopamine levels in the substantia nigra (SN), a crucial midbrain region involved in motor control and reward mechanisms. PD also impacts cognitive functions, potentially leading to depression and sleep disturbances. Recent research highlights the importance of MAO-B inhibitors in PD management, as these enzymes play a critical role in regulating neurotransmitter levels by catalyzing the oxidative deamination of intracellular amines and monoamine neurotransmitters.

Result Computational virtual screening of several quinoline-based ligands against the target protein MAO-B (PDB ID: 1OJA) was performed using molecular docking simulation and ADMET studies to identify promising inhibitors for neurodegenerative disease treatment. The most active hit, Compound PA001, exhibited a MolDock score of − 207.76 kcal/mol. Subsequent investigation of 6-methoxy-2-(4-phenylpiperazin-1-yl)quinoline (Compound PA001) using molecular dynamics (MD) simulations with GROMACS revealed potent inhibition and significant interactions at key active site residues. MD simulations confirmed the stability of the Compound PA001-MAO-B complex under physiological conditions. Additionally, ADMET analysis demonstrated that Compound PA001 possesses favorable drug-like properties, including absorption, distribution, metabolism, excretion, and toxicity profiles. These findings underscore 6-methoxy-2-(4-phenylpiperazin-1-yl)quinoline (Compound PA001) as a promising candidate for developing new MAO-B inhibitors to treat neurodegenerative diseases.

Conclusion The research highlighted 6-methoxy-2-(4-phenylpiperazin-1-yl)quinoline (Compound PA001) as a promising MAO-B inhibitor, exhibiting strong binding affinity, stability, and desirable drug-like characteristics for the treatment of neurodegenerative diseases. Among the top ten molecules, Compound PA001 was selected for molecular dynamics (MD) simulation using GROMACS. The compound showed potent inhibition, significant interactions with key active site residues, and stable complex formation under physiological conditions. ADMET analysis further confirmed its favorable pharmacokinetic profile.

Keywords MAO-B, Parkinson's disease, Docking, ADMET, MD simulation

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Background

Neurodegenerative disorders (NDs) predominantly affect the elderly, marked by their prevalent incidence and intricate pathophysiological processes [1]. With projections indicating that NDs may soon become the second leading cause of death, there is an urgent need for focused research and interventions in this field [2]. Parkinson's disease (PD) [3], one of the most common neurodegenerative conditions, primarily manifests through motor impairments due to a reduction in dopamine levels in the substantia nigra (SN). The SN, a critical midbrain region, plays a vital role in modulating motor control and reward mechanisms within the basal ganglia circuitry [4]. PD also affects cognitive functions, potentially leading to issues such as depression and sleep disturbances [5, 6]. A recent study by Oertel and Schulz highlights the importance of incorporating MAO-B inhibitors as supplementary therapeutic interventions in PD management [7]. Monoamine oxidases (MAOs) function as enzymatic catalysts facilitating the oxidative deamination of intracellular amines and monoamine neurotransmitters [8]. This process is crucial for controlling neurotransmitter levels within the brain and peripheral tissues, thereby contributing to their regulatory mechanisms [9, 10]. MAOs, enzymes containing flavin adenine dinucleotide (FAD), are predominantly found in glial and neuronal cells, especially in the liver and brain [11]. Two isoforms of MAOs, MAO-A and MAO-B, exhibit 70% genetic similarity and are encoded by genes located on the X chromosome. These isoforms differ in substrate specificity and responsiveness to inhibitors [12]. MAOs hold significant pharmacological importance due to their role in the breakdown of specific neurotransmitters. Selective MAO-A inhibitors are used to treat depression and anxiety disorders, while MAO-B inhibitors are used to slow the progression of PD and manage symptoms of Alzheimer's disease [13]. MAO-B inhibitors are increasingly recognized as viable therapeutic options for neurodegenerative conditions due to their ability to regulate neurotransmitter levels such as dopamine [14]. These inhibitors work by impeding the catalytic activity of MAO-B, preventing the breakdown of critical neurotransmitters and potentially alleviating symptoms associated with neurodegenerative diseases [15]. Molecular docking is a widely used computational method in the early stages of drug discovery, assessing the interaction between a drug candidate (ligand) and a target (receptor) to predict binding affinity and orientation [16]. The Protein Data Bank contains over 40 crystallographic structures of MAO, predominantly featuring MAO-B, along with various reversible and irreversible inhibitors [17]. These structures were elucidated using X-ray diffraction techniques, with refinement resolutions ranging from 3.0 to 1.7 Å. Notably, MAO-A has a distinct monopartite cavity (~ 550 Å), while MAO-B has a bipartite cavity (~ 290 Å). The "aromatic cage," encompassing the hydrophobic binding pocket with the FAD cofactor, is recognized as the active site [13, 18]. The FAD molecule forms a covalent bond with a cysteine residue on the protein via an 8a-thioether linkage. A hypothesis suggests that the catalytic role of two tyrosine residues, Tyr398 and Tyr435, in hMAO-B, is linked to their capacity to induce polarization in the amine nitrogen pair of the substrate [19].

Methodology

A molecular docking study was conducted using Molegro Virtual Docker (MVD) [20], version 6.0, installed on a machine equipped with an Intel i5 8th-generation processor and Nvidia GeForce 940mx graphics card, operating on Windows 11 Home. MVD [21] provides various tools for molecular docking, including protein visualization, data analysis, and protein–ligand interaction study. These features enhance the accuracy of the results, eliminate false positives, and yield the best docking scores.

Target selection

The protein crystal structure of the MAO-B inhibitor was obtained from the RCSB Protein Data Bank (PDB ID: 1OJA) [22]. This protein was selected based on crucial parameters such as resolution, R-value, R-free factor, and mutation. The selected protein was used for virtual screening and docking studies [23].

Virtual screening

The crucial step of ligand selection was undertaken with great care. Quinoline-based [24] ligands, vital for our investigation into MAO-B inhibitors, were sourced from the extensive repository of chemical compounds in PubChem [25], as shown in Fig. 1. To ensure a focused and relevant dataset, we meticulously downloaded a library of quinoline-based molecules. The selection process involved applying stringent filters, where one of the paramount criteria was adherence to Lipinski's rule of five [26]. These five fundamental rules, proposed by Christopher Lipinski, encompass parameters that evaluate a compound's potential for oral bioavailability and drug-like properties. The rules include (1) a molecular weight less than 500 Da, (2) a partition coefficient (log P) not exceeding 5, (3) a hydrogen bond donor count not surpassing 5, (4) a hydrogen bond acceptor count less than 10, and (5) a polar surface area of no more than 140 Å [2, 26]. The application of these criteria ensured that the selected quinoline-based ligands possessed properties conducive to drug development and oral administration, enhancing the relevance of our study in the context of MAO-B inhibition and neurodegenerative disorders.

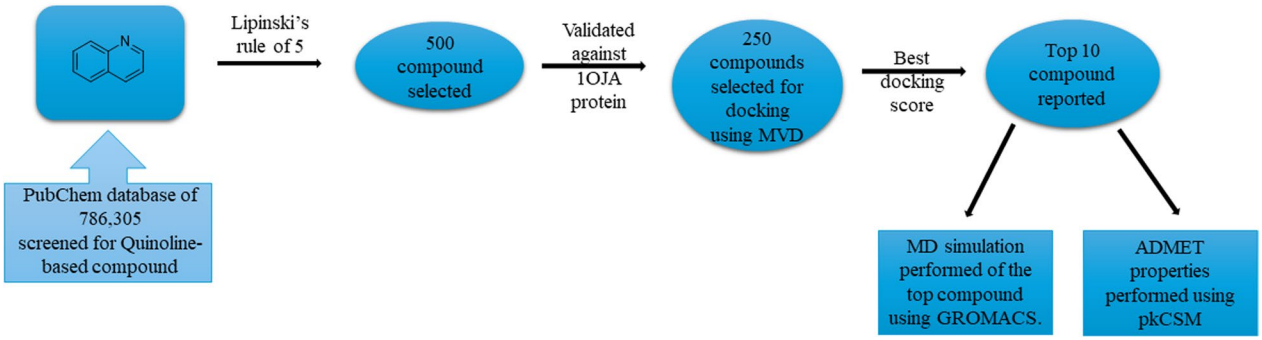


Fig. 1 Methodology used for screening, docking study, and ADMET study

Furthermore, we performed docking and ran a molecular dynamic (MD) simulation along with that we evaluated the Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties of the selected ligands [27]. This comprehensive assessment provided insights into their pharmacokinetic and pharmacodynamic profiles, ensuring their suitability for further drug development and clinical application. By integrating Lipinski's rule of five and ADMET analysis into our virtual screening process [28], we aimed to identify promising MAO-B inhibitors with the potential to address neurodegenerative disorders effectively.

Ligand preparation

The process of ligand preparation was meticulously executed to ensure the structural integrity and suitability of the selected quinoline-based ligands for subsequent analyses. The software tool Chem 3D played a pivotal role in this regard. To optimize the ligands' conformations and overall stability, energy minimization was conducted utilizing the MM2 force field, a widely recognized script for energy minimization within Chem 3D. This crucial step involved the systematic adjustment of bond lengths, bond angles, and torsional angles, aiming to reach a state of minimal potential energy while preserving the ligands' chemical integrity. By employing the MM2 force field in Chem 3D, we rigorously prepared the ligands, ensuring that they were in the most energetically favorable conformation for subsequent molecular docking and ADMET property predictions [29], ultimately enhancing the reliability of our research findings in the realm of MAO-B inhibition and neurodegenerative diseases.

Docking study and data analysis

We conducted molecular docking studies to gain insights into the binding interactions between quinoline-based ligands and the MAO-B protein. Molegro Virtual Docker, a robust molecular docking software, was employed for this purpose. The docking process involved several critical steps. Firstly, grids were generated around the active site of MAO-B, with dimensions carefully chosen to encompass key binding residues. These grids served as guides for the ligand placement within the binding pocket. Subsequently, several docking simulations were conducted to investigate different conformations and orientations of the ligands, thereby ensuring comprehensive coverage of the binding space. The docking software evaluated and scored each ligand–receptor interaction based on binding affinity and interaction energy. Following the docking simulations, data analysis was a crucial phase. We meticulously analyzed the results to identify the most favorable binding poses and interactions. This involved scrutinizing the binding affinities of ligands with MAO-B, with lower binding energies indicating stronger ligand–protein interactions. Additionally, we explored the precise molecular interactions occurring between the ligands and the amino acid residues within the active site of MAO-B. Our emphasis was on identifying key hydrogen bonds, hydrophobic interactions, and π–π stacking events crucial for comprehending the binding mechanisms. By thoroughly examining these interactions and assessing binding affinities, we obtained significant insights into the potential of ligands based on quinoline as inhibitors of MAO-B, contributing to our understanding of their role in neurodegenerative disorder therapeutics.

Molecular dynamics simulations

The molecular simulation was conducted to investigate the stability of the examined docked complex, of the protein in physiological conditions using GROMACS software [30] version 2024.1.

Results

The study was initiated by shortlisting ten top hits based on MolDock scores through virtual screening of the PubChem database. To elaborate on the filtration process, several criteria were applied to narrow down

Table 1 Docking score of top ten compounds and standard

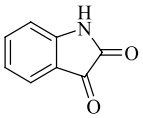
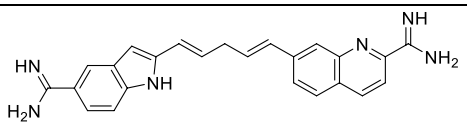
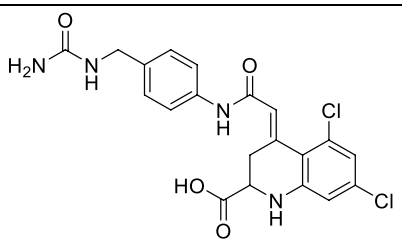
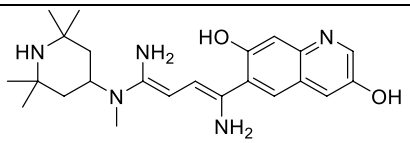
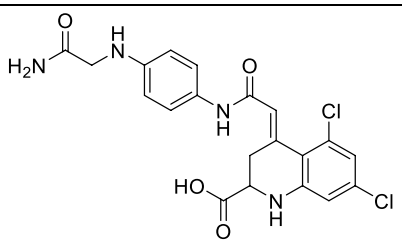
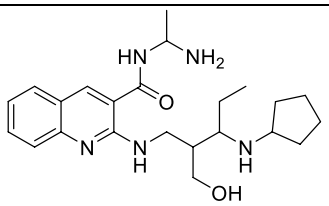
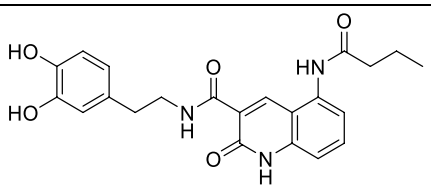
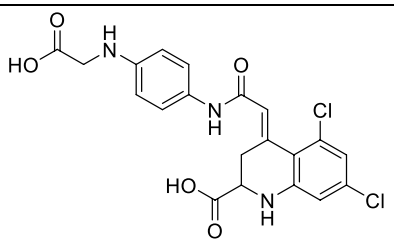
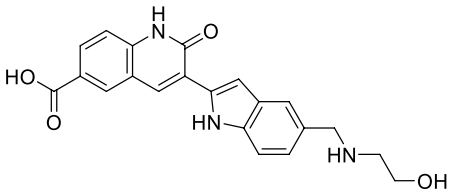
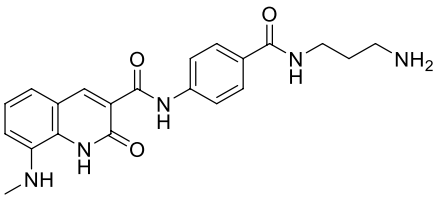
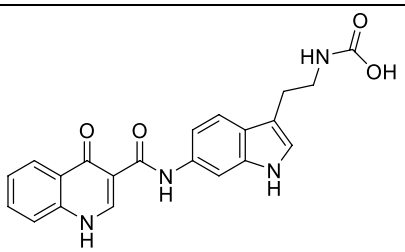
S.No.	Ligand	MolDock Score (kcal/mol)	Re-rank Score	H Bond
1.	 **Isatin**	-81.29	-69.83	-2.50
2.	 **PA001**	-207.76	-158.05	-2.71
3.	 **PA002**	-200.29	-167.64	-7.92
4.	 **PA003**	-198.40	-158.44	-9.73
5.	 **PA004**	-198.35	-164.84	-6.92
6.	 **PA005**	-196.47	-148.45	-2.98

Table 1 (continued)

7.	 **PA006**	-195.70	-164.06	-11.07
8.	 **PA007**	-195.09	-161.72	-6.47
9.	 **PA008**	-194.93	-159.84	-1.13
10.	 **PA009**	-194.87	-163.04	-10.97
11.	 **PA010**	-194.44	-157.14	-5.82

the selection of molecules. Initially, Lipinski's rule of five was employed to assess the drug-likeness of the compounds, considering parameters such as molecular weight, lipophilicity, hydrogen bond donors, and hydrogen bond acceptors [26]. This step aimed to prioritize compounds with physicochemical properties conducive to oral bioavailability and permeability across biological membranes. Additionally, compounds exhibiting undesirable structural features or violating specific criteria were excluded to enhance the likelihood of identifying promising candidates. Following the initial filtration based on drug-likeness, the remaining compounds underwent further evaluation through molecular docking simulations using MVD. The MolDock

Table 2 Steric and H-bond interaction with amino acid fragments

S. No	Ligand Code	Steric interaction	Hydrogen bond interaction
1	PA001	Ala 263, Tyr 393, Trp 388, Val 294, Cys 397	Leu 56, Glu 34
2	PA002	Tyr 435, Phe 343, Gly 58	Cys 397, Arg 42, Thr 426, Ala 263
3	PA003	Thr43, Tyr 60	Tyr 398, Gly 40, Ile 14, Tyr 60
4	PA004	Gly 58, Phe 343, Tyr 435	Cys 397, Arg 42, Thr 426, Ala 263
5	PA005	Cys 397, Trp 388, Gly 58, Tyr 398, Tyr 60, Tyr 435	Gly 434, Arg 42
6	PA006	Tyr 435, Gly 57, Gly 58	Tyr 60, Met 436, Gly 434, Gly 40, Arg 42, Lys 296
7	PA007	Phe 343	Trp 388, Cys 397, Ala 263, Arg 42, Thr 426
8	PA008	Gly 58, Trp 388	Gly 58
9	PA009	Thr 43, Gly 434, Met 436	Ala 263, Arg 42, Met 436, Tyr 60, Ser 59, Met 436
10	PA010	Ala 263, Gly 13, Gly 40, Met 436, Tyr 398	Arg 42, Cys 397, Leu 56, Trp 388
11	Isatin	Phe 343	–

scores generated from these simulations served as a quantitative measure of the binding affinity between the ligands and the MAO-B protein. The highest-ranking compounds were chosen for further examination and evaluation of their binding interactions and were compared to the reference compound isatin. The structures of the top ten hits against 1OJA are presented in Table 1 for comparison. In the docking studies, compounds with MolDock scores exceeding -192 kcal were identified as potential hits against their respective targets. As depicted in Table 1, all ten compounds demonstrated MolDock scores surpassing − 192 kcal against the target 1OJA. The hydrogen bond score evaluates the contribution of hydrogen bonds to the overall binding affinity of the ligand, a higher hydrogen bond score generally indicates stronger, and more favorable hydrogen bonding interactions between the ligand and the receptor all docked compound showed the H-bond interaction in the range of − 11.07 [31].

The investigation delved into the inhibitory activity of these compounds as a potential MAO-B inhibitor via quantitative data, which included MolDock scores and Re-rank scores, which were generated to provide a rigorous assessment of binding affinities. PA001, with a remarkable MolDock score of − 207.76 kcal (Table 1), emerged as a lead compound with high binding potential.

Further, the analysis primarily centered on two key aspects: steric interactions and hydrogen bond interactions. Steric interactions, a pivotal determinant of ligand–receptor binding, were meticulously examined. PA001 showed interaction with key amino acid residues such as Ala 263, Tyr 393, Trp 388, Val 294, and Cys 397 (Table 2 and Fig. 2). These findings shed light on the specific molecular moieties and orientations that optimize binding to MAO-B. In parallel, the study rigorously assessed hydrogen bond interactions with the amino acid helps in understanding how well the ligand forms hydrogen bonds with the receptor amino acid a critical component of ligand–receptor recognition.

Molecular dynamic (MD) simulation [32] was performed on the top compound PA001/1OJA complex for 10 ns, and the root-mean-square deviation (RMSD) value was crucial indicators used to evaluate the stability of the top ligand PA001/1OJA complex. The RMSD values during the MD simulation are presented in Fig. 3. The RMSD value tended toward relative equilibrium states with an average range of 0.05–0.40 nm throughout the 10 ns simulation. Therefore, the plot suggests that the protein backbone remained relatively stable during the MD simulation. The RMSD only increased by approximately 0.4 nm over the course of the simulation, which is small amount, indicating that the examined docking complex exhibited good stability.

Structure–activity relationship (SAR)

The SAR analysis in Fig. 4 shows that electron-withdrawing groups show steric interactions with target amino acids, while electron-donating groups facilitate hydrogen bond interactions. The quinoline core is crucial for binding affinity, outperforming other structures. Compared to the reference compound, isatin [33], quinoline-based compounds show stronger and more essential interactions within the active site. Higher molecular weight compounds (> 500 Da) fit less snugly within the protein cavity, whereas those in the 400–500 Da range exhibit optimal binding affinity. These findings highlight the superior binding properties of quinoline-based compounds, making them promising candidates for MAO-B inhibition.

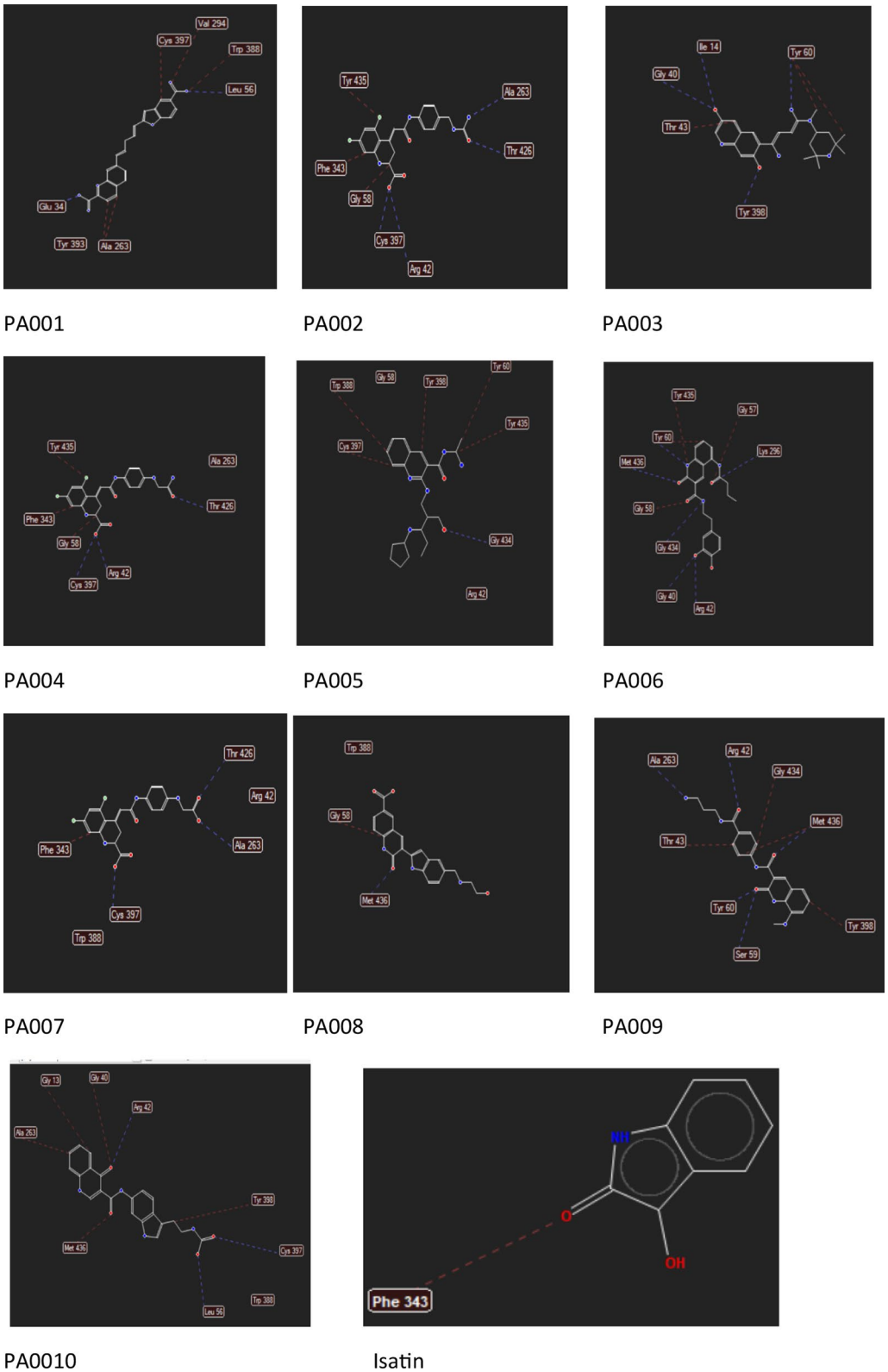


Fig. 2 Interaction with amino acid, blue indicates the H-bond interaction, and red indicates the steric interactions

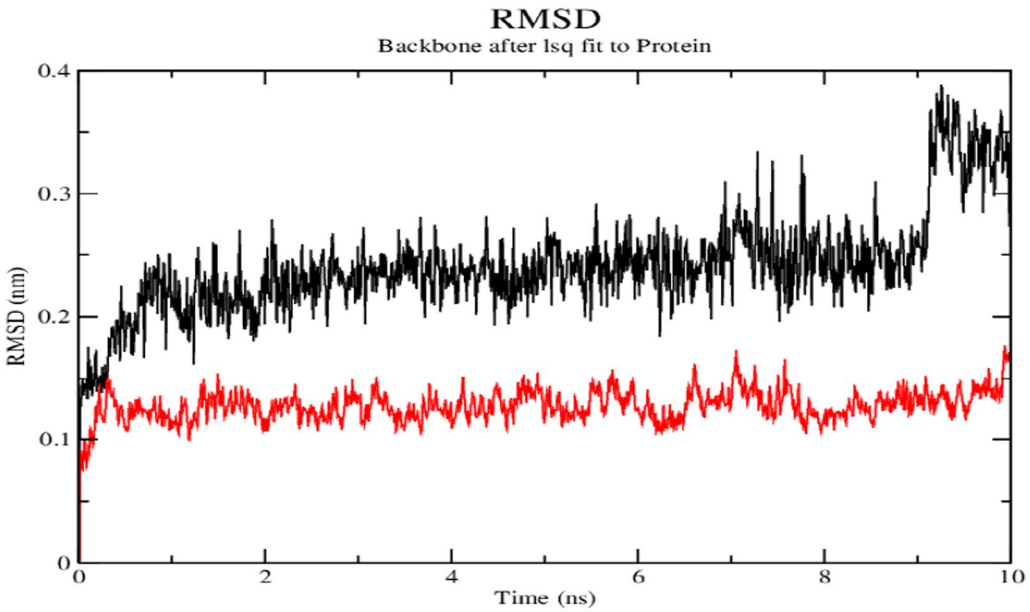


Fig. 3 Plot of RMSD of ligand–protein complex PA001/1OJA for 10 ns MD simulation

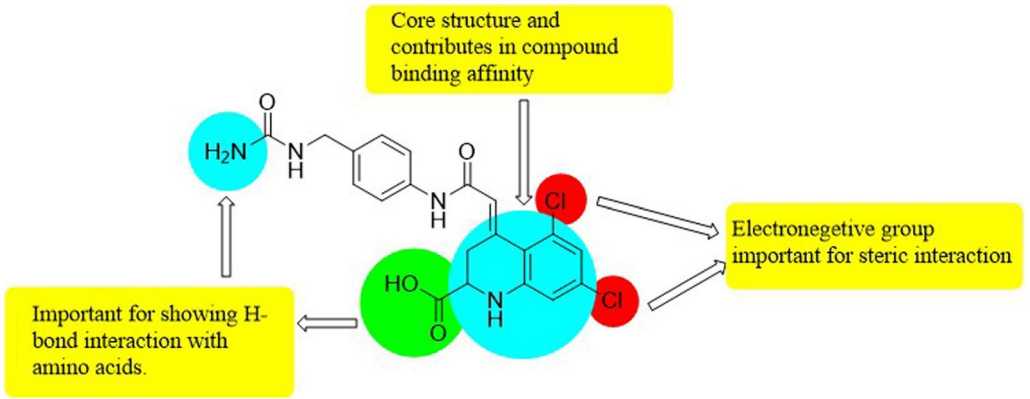


Fig. 4 SAR of quinoline-based MAO-B inhibitors

ADMET

In our study, we also conducted an in-depth analysis of the ADMET properties [34] of our top 10 compounds using pkCSM [35]. We placed a strong emphasis on relevant parameters crucial for drug suitability while ensuring minimal toxicity. The parameters we examined in our study for absorption encompassed water solubility, Caco2 permeability, intestinal absorption, and skin permeability. In the distribution category, we meticulously assessed VDss, fraction unbound, BBB permeability, and CNS permeability. For metabolism, our scrutiny focused on CYP2D6 inhibition and CYP3A4 interactions. Excretion considerations involved the evaluation of total clearance and renal OCT2 substrate. To gauge toxicity, we considered critical factors such as the maximum tolerated dose, oral rat acute toxicity (LD50), oral rat chronic toxicity, T. Pyriformis toxicity, and minnow toxicity.

After a comprehensive evaluation of the ADMET properties for the ten compounds, it becomes apparent that these compounds exhibit diverse characteristics that significantly influence their potential as MAO-B inhibitors. Notably, compounds PA001, PA002, and PA004 displayed relatively favorable attributes in several key categories, including water solubility, intestinal absorption, and distribution as shown in Table 3. In terms of BBB permeability, PA001 (− 1.02), PA004

Table 3 ADMET study of top 10 compounds

S.No	Ligand code	Property and values															
		Absorption				Distribution					Metabolism	Excretion		Toxicity			
		Water solubility (log mol/L)	Caco2 permeability (Papp in 10^{-6} cm/s)	Intestinal absorption (% absorption)	Skin permeability (log K_p)	VDss (log L/kg)	Fraction unbound (Fu)	BBB permeability (log BB)	CNS permeability (log PS)	CYP2D6	CYP3A4	Total clearance	Renal OCT2 substrate	Max. tolerated dose	Oral rat acute toxicity (LD50)	Oral Rat Chronic Toxicity	*T. Pyriformis* toxicity
1	Isatin	− 1.40	1.18	87.72	− 2.98	− 0.02	0.49	− 0.23	− 2.16	No	No	− 0.06	No	0.91	1.93	2.55	0.54
2	PA001	− 3.74	0.22	83.43	− 2.73	− 0.31	0.01	− 1.02	− 2.22	No	Yes	0.75	No	0.39	2.57	2.61	0.30
3	PA002	− 3.26	0.19	56.09	− 2.73	− 1.03	0.25	− 1.52	− 2.48	No	No	− 0.37	No	0.30	2.42	2.19	0.28
4	PA003	− 3.32	0.63	68.09	− 2.79	0.84	0.29	− 1.46	− 3.83	Yes	No	0.46	No	0.91	2.29	1.79	0.28
5	PA004	− 3.43	0.29	57.62	− 2.73	− 0.98	0.15	− 1.04	− 2.63	No	No	− 0.25	No	0.3	2.63	3.1	0.28
6	PA005	− 2.56	0.64	67.94	− 2.78	1.89	0.4	− 0.9	− 3.09	No	No	1.02	No	− 0.04	2.17	0.83	0.28
7	PA006	− 3.03	0.13	72.27	− 2.73	0.03	0.14	− 1.3	− 2.79	Yes	No	0.19	No	0.68	2.23	3.22	0.3
8	PA007	− 2.92	− 0.24	40.4	− 2.73	− 1.52	0.14	− 1.44	− 2.53	No	No	− 0.2	No	0.56	2.53	2.44	0.28
9	PA008	− 2.97	0.21	57.44	− 2.73	− 0.23	0.15	− 1.32	− 2.81	No	No	0.95	No	1.08	2.59	2.85	0.28
10	PA009	− 3.13	0.29	71.6	− 2.73	0.81	0.19	− 1.05	− 2.78	Yes	No	1.01	No	0.8	2.44	3.49	0.28
11	PA010	− 2.97	0.57	56.36	− 2.73	− 0.94	0.13	− 1.46	− 2.46	0.43	No	No	No	0.91	2.29	1.79	0.28

(− 1.04), and PA009 (− 1.05) showed relatively higher values among the PA series, but still significantly lower than the standard isatin (− 0.23). However, compound PA001 emerges as the most promising candidate, primarily due to its remarkable human intestinal absorption rate (83.439%), suggesting efficient uptake. Despite its lower BBB permeability, PA001 strikes a favorable balance between various properties, positioning it as a robust contender for further development as an MAO-B inhibitor.

Discussion

The identification of PA001 as a potent MAO-B inhibitor offers promising insights into developing new therapeutic agents for neurodegenerative diseases like Parkinson's and Alzheimer's. PA001's strong binding affinity, stability, and favorable drug-like properties underscore its potential for further drug development, complementing previous research on MAO-B inhibitors in managing such conditions. However, this study has limitations, including the need for experimental validation of computational predictions and the unexplored potential off-target effects. Practical challenges included the substantial computational resources required for molecular docking and dynamics simulations, as well as integrating Lipinski's rule of five and ADMET analysis. Future research should focus on experimental validation, structural optimization of PA001, and comprehensive pharmacokinetic and toxicity assessments to fully realize its therapeutic potential.

Conclusion

In conclusion, this study presents a thorough examination of MAO-B inhibitors, combining computational and pharmacological approaches to identify promising candidates for the treatment of neurodegenerative disorders. The research elucidated the intricate binding mechanisms between inhibitors and the MAO-B protein, providing valuable insights into structure–activity relationships and potential therapeutic avenues. PA001 emerged as a lead compound, exhibiting high binding affinity and favorable ADMET properties, positioning it as a robust contender for further development as an MAO-B inhibitor. The study underscores the significance of comprehensive ADMET profiling in the drug discovery process and emphasizes the importance of molecular dynamics simulations in evaluating the stability of ligand–protein complexes. Moving forward, the findings pave the way for the rational design and optimization of MAO-B inhibitors, offering new possibilities for the development of effective treatments for neurodegenerative diseases. Further preclinical and clinical studies are warranted to validate the efficacy and safety of PA001 and other promising compounds, ultimately translating these findings into tangible therapeutic interventions for patients suffering from neurodegenerative disorders.

Future prospective

Moving forward, this research article sets the stage for further investigation into MAO-B inhibitors by highlighting PA001 as a promising lead compound for the treatment of neurodegenerative disorders. Future studies may focus on optimizing PA001 and other lead compounds using state-of-the-art molecular dynamics simulations, such as those employing advanced algorithms like accelerated molecular dynamics or enhanced sampling techniques. Additionally, employing cutting-edge docking models, such as deep learning-based approaches or ensemble docking strategies, could aid in the identification of novel binding sites and the design of more potent inhibitors.

Abbreviations

MAO-B	Monoamine oxidase B
MVD	Molegro Virtual Docker
SAR	Structure–Activity Relationship
RMSD	Root-mean-square deviation

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Author contributions

AR designed the manuscript and worked on docking software; JC conducted studies on GROMACS software; AAK evaluated the manuscript, performing thorough reviews to enhance the scientific merit of the final document; and MS was involved in interpreting the results to ensure scientific accuracy and robustness in the study's findings. DK provided guidance throughout the project, offering strategic insights and technical advice that directed the research toward achieving its objectives; AM secured financial support that enabled the comprehensive research and development activities; and PW mentored the project, delivering expert mentorship and oversight, guiding the team through various phases of the research with his extensive knowledge and experience.

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Availability of data and materials

Data and supplementary material will be provided on demand.

Declarations

Ethics approval and consent to participate

NA.

Consent for publication

Yes.

Competing interests

Authors declare no conflict of interest.

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