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Target-based Virtual Screening of Natural Compounds as Promising Anti-Parkinson's Agents

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Abstract

Background: Parkinson's disease (PD), the second most common neurodegenerative disease among the elderly, is caused by the death of dopaminergic neurons, resulting in dopamine depletion. Monoamine oxidase B (MAO-B) is an important enzyme in PD because it degrades dopamine. Dopamine levels can be elevated by inhibiting MAO-B, especially in the early stages of the disease.

Methods: This study involves virtual screening (docking) of ZINC database natural compounds (N = 200) against MAO-B, followed by ADME and drug-likeness analysis of the top hits.

Results: ZINC899884, ZINC4098705, ZINC14764165, and ZINC18847036 compounds exhibited strong binding to MAO-B and interacted with key MAO-B residues. The Cys172, Ile198, Phe168, Ile199, Leu171, Gln206, Gly58, Tyr326, Leu328, Phe343, Tyr398, Ser59, Tyr60, Gly434, and Tyr435 residues of MAO-B were important in binding with these compounds. In addition, these compounds, like the control Rasagiline, interact with MAO-B via several common residues. Furthermore, ADME and drug-like prediction resulted in promising results, indicating that these compounds have a high gastrointestinal absorption property.

Conclusion: ZINC899884, ZINC4098705, ZINC14764165, and ZINC18847036 can be used as MAO-B inhibitors for PD. However, experimental validation is required to optimize them as MAO-B inhibitors.

Introduction

The increased prevalence of neurodegenerative disorders (NDs), particularly among elderly people in wealthier nations, has become a major global health concern [1,2]. Parkinson's disease (PD), which is defined by the degradation of the nigrostriatal dopaminergic system, causes important motor symptoms such as bradykinesia, tremor, and stiffness [3]. Nondopaminergic therapies are increasingly recognized as important components of the PD treatment landscape [4-6], given that long-term use of dopamine replacement therapies has been linked to complications such as decreased drug efficacy, dyskinesias, and the onset of psychosis and depression [7]. Hence, the study of nondopaminergic medicines is becoming increasingly important in PD research, emphasizing the need for innovative therapeutic techniques in medicinal chemistry.

Monoamine oxidase (MAO) contains two isoforms: MAO-A and MAO-B, which are extensively expressed in the brain and gut. These isoforms have a high sequence similarity but differ in substrate-inhibitor recognition sites and tissue distribution [8]. Overexpression of MAO-B and dopamine insufficiency are major pathogenic variables in ND such as PD. Inhibiting MAO-B reduces dopamine breakdown, raising its levels in the brain, especially in early illness stages, and has anti-Parkinson's benefits by exclusively targeting the striatum [9].

The process of discovering and developing novel medications is difficult and resource-intensive. Computer-aided drug design (CADD) techniques are being used more frequently to improve efficiency. Structure-based and ligand-based drug design techniques are highly effective and are frequently used in conjunction with molecular docking and virtual screening to identify and optimize leads. Computational technologies have become indispensable in the pharmaceutical industry and research, greatly boosting the drug discovery and development pipeline [10]. Natural products (NP) are a vast and diverse source of bioactive compounds, and some have been used in traditional medicine for hundreds of years, distinguishing them from synthesized small molecules [11]. NPs and traditional medicines are important sources of therapeutic agents and structural diversity, with many modern medications coming from these natural reservoirs. They have historically been valuable tools for discovering possible therapeutic leads [12,13]. This study aimed to find the natural MAO-B inhibitors to combat the PD.

Methods

MAO-B structure preparation

The crystal structure of MAO-B (PDB ID: 2C65) was obtained from the Protein Data Bank. The co-crystal ligand was removed, and the prepared protein was saved as pdb format.

Ligands preparation

ZINC, a freely available library of commercially available compounds for virtual screening [14], was used to obtain 200 natural compounds in SDF format. These compounds were then converted to pdbqt format to aid in the virtual screening procedure.

Virtual screening

Structure-based virtual screening has achieved several major achievements in recent years [15-17], making it a commonly used technique in early-stage drug development by most pharmaceutical corporations and several academic institutions. In this investigation, the prepared library was screened against MAO-B using PyRx 0.8 software [18]. The SWISSADME online application was used for ADME computations.

Results

In this study, 200 natural compounds were screened against the MAO-B. Rasagiline was used as the control compound. The screening of the compound library resulted in 11 hit compounds with binding energy values more favorable than the Rasagiline. Among these 11 compounds, the top four compounds (ZINC899884, ZINC4098705, ZINC14764165, and ZINC18847036) were taken for further details interaction analysis.

S. No.	Compounds	Binding energy (kcal/mol)
1.	ZINC899884	-8.4
2.	ZINC4098705	-8.2
3.	ZINC14764165	-8.1
4.	ZINC18847036	-8.0
5.	ZINC40461617	-7.9
6.	ZINC491073	-7.9
7.	ZINC898013	-7.7
8.	ZINC3872070	-7.6
9.	ZINC2031813	-7.3
10.	ZINC2561256	-7.3
11.	ZINC3861630	-7.0
12.	Rasagiline	-6.3

Table 1: Binding energy values of top compounds and control compound (Rasagiline) with MAO-B.

ZINC899884 interacted with Tyr326, Leu171, Leu328, Phe343, Tyr60, Tyr398, Ser59, Gly58, Gly434, Cys172, Tyr435, Ile198, Gln206, and Ile199 residues of MAO-B (Figure 1A), with a binding energy of -8.4 kcal/mol. ZINC4098705 interacted with Tyr398, Ser59, Gly58, Tyr60, Phe343, Leu328, Leu171, Gln206, Ile199, Tyr326, Cys172, Phe168, Ile198, and Tyr435 residues of MAO-B (Figure 1B), with a binding energy of -8.2 kcal/mol. ZINC14764165 interacted with Cys172, Ile199, Phe168, Ile198, Tyr435, Lys296, Gly58, Ser59, Gly57, Tyr60, Tyr398, Phe343, Tyr326, Gln206, Leu328, and Leu171

residues of MAO-B (Figure 1C), with a binding energy of -8.1 kcal/mol. ZINC18847036 interacted with Ile199, Phe168, Ile198, Cys172, Tyr435, Gly434, Gly58, Tyr398, Tyr60, Phe343, Gln206, Leu171, and Tyr326 residues of MAO-B (Figure 1D), with a binding energy of -8.0 kcal/mol. Further, the positive control Rasagiline was found to interact with Cys172, Ile198, Phe168, Ile199, Leu171, Gln206, Tyr326, Phe343, Tyr398, Tyr60, and Tyr435 residues of MAO-B (Figure 1E), with a binding energy of -6.3 kcal/mol.

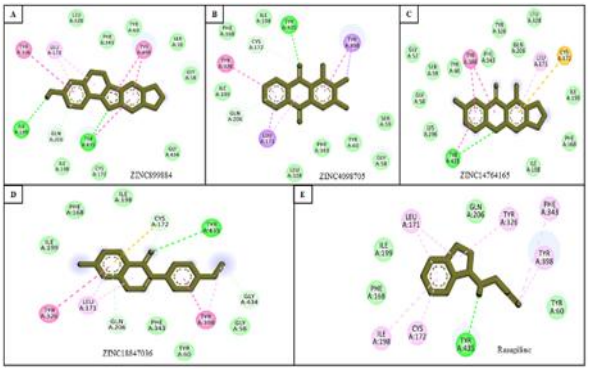

Figure 1: Interacting residues of MAO-B with ZINC899884 (A), ZINC4098705 (B), ZINC14764165 (C), ZINC18847036 (D), and Rasagiline (E).

The physicochemical properties and adherence to drug-like criteria of the top 11 compounds demonstrated that they have the necessary characteristics for future drug candidates (Table 2 and Table 3).

Compounds	Physico -Chemical Properties				Lipophilicity		Pharmacokinetics	
	MW (g/mol)	Num Rotatable Bonds	Num H-Bond Acceptors	Num H-Bond Donors	MLOGP	WLOGP	GI Absorption	BBB Permeant
ZINC899884	284.26	0	5	1	1.71	2.41	High	Yes
ZINC4098705	254.24	0	4	2	0.92	2.18	High	Yes
ZINC14764165	272.21	0	6	2	0.43	2.09	High	No
ZINC18847036	268.26	2	4	1	1.33	3.17	High	Yes
ZINC40461617	254.41	2	2	2	3.13	3.36	High	Yes
ZINC491073	287.35	1	4	1	1.74	1.32	High	Yes
ZINC898013	270.28	2	4	1	2.14	3.75	High	Yes
ZINC3872070	254.24	1	4	2	1.08	2.87	High	Yes
ZINC2031813	303.36	0	1	1	3.16	2.23	High	Yes
ZINC2561256	296.23	0	6	1	1.60	3.13	High	No
ZINC3861630	254.24	0	4	2	0.92	2.18	High	Yes

Table 2: Physico-chemical properties (molecular weight, number of rotatable bonds, number of H-bonds accepters, and number of H-bonds donors) and pharmacokinetics (GI absorption, and BBB permeability) of top 11 compounds.

Compounds	Drug-likeness			
	Lipinski	Ghose	Veber	Egan
ZINC899884	Y	Y	Y	Y
ZINC4098705	Y	Y	Y	Y
ZINC14764165	Y	Y	Y	Y
ZINC18847036	Y	Y	Y	Y
ZINC40461617	Y	Y	Y	Y
ZINC491073	Y	Y	Y	Y
ZINC898013	Y	Y	Y	Y
ZINC3872070	Y	Y	Y	Y
ZINC2031813	Y	Y	Y	Y
ZINC2561256	Y	Y	Y	Y
ZINC3861630	Y	Y	Y	Y

Table 3: Drug-likeness (Lipinski, Ghose, Veber, and Egan) of top 11 compounds showing that they met the necessary characteristics for future drug candidates. Y = Yes.

Discussion

Neurons are essential for brain function and play a critical role in communication [19]. Neurodegeneration is the fundamental pathogenic alteration in many brain illnesses [20], the most common of which being Alzheimer's disease and PD. Although there are various medications available to treat NDs, the majority of them focus on symptoms rather than the underlying cause. This is largely due to the blood-brain barrier, which prevents roughly 99% of foreign substances from entering the brain. PD is a degenerative neurological ailment marked by tremors, muscle rigidity, and poor balance and coordination. Both hereditary and non-genetic variables contribute to PD, and age is a key risk factor [21,22]. MAO-B overexpression and dopamine deprivation are key pathogenic factors. Inhibiting MAO-B lowers dopamine breakdown and increases its levels in the brain, especially in the early phases, and has anti-Parkinson's effects via targeting the striatum [9]. In docking studies, high negative binding energy indicates a strong interaction between the ligand and target protein complexes [23-26]. Interestingly, the top-hit compounds have more favorable negative binding energy than Rasagiline (control), indicating that they bind more strongly to MAO-B and can be employed as MAO-B inhibitors. Rasagiline is a strong, irreversible, and selective second-generation MAO-B inhibitor used to treat PD. It has demonstrated significant benefits as a monotherapy in early PD and has neuroprotective effects that are independent of MAO-B inhibition [27]. In this study, Cys172, Ile198, Phe168, Ile199, Leu171, Gln206, Tyr326, Phe343, Tyr398, Tyr60, and Tyr435 residues of MAO-B were found to be important in binding to Rasagiline. Interestingly, the top four compounds (ZINC899884, ZINC4098705, ZINC14764165, and ZINC18847036) were found to bind with the majority of these MAO-B residues, implying that these hits bind to the same MAO-B pocket as Rasagiline.

NPs and traditional medicines are important because of their therapeutic potential in treating a variety of ailments, including cardiovascular problems, diabetes, hypertension, cancer, and NDs [28]. Extensive studies have been undertaken on natural sources such as plants, animals, microorganisms, and marine organisms because they contain a diverse range of bioactive chemicals with complex structures and distinct pharmacological effects [29]. NPs and their isolated molecules have been extensively studied as a main source for drug discovery in the search to generate more effective medications, particularly those that improve human brain function [30]. The compounds identified in this study are natural and have a strong binding energy for MAO-B, making them potential MAO-B inhibitors for the treatment of PD.

This study screened natural compounds against MAO-B. ZINC899884, ZINC4098705, ZINC14764165, and ZINC18847036 compounds exhibited strong binding to MAO-B and interacted with key MAO-B residues. These compounds, like the control Rasagiline, interact with MAO-B via several residues. Furthermore, ADME and drug-like prediction resulted in promising results, indicating that these compounds have a high gastrointestinal absorption property, implying that they could be effective MAO-B inhibitors for PD.

Conflict of Interest Statement

The author declare that there is no conflict of interest regarding this research paper.

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