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Computational Intelligence in Drug Development

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Virtual Screening of Drug Candidates for Repositioning for the Treatment of Parkinson's Disease

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Abstract MAO-B plays a key role in Parkinson's disease by breaking down dopamine, leading to its depletion and contributing to oxidative stress in the brain. Thus, MAO-B inhibition helps preserve dopamine levels, improving motor symptoms and the quality of life for individuals with this neurodegenerative disease. This research aimed to identify known drugs with potential inhibitory activity against MAO-B through computational methods, prospecting their repositioning for Parkinson's disease treatment. The methodological approach involved a multi-step process, beginning with the search for MAO-B inhibitors in BindingDB using the descriptor "Monoamine Oxidase B Inhibitor" and filtering for compounds with IC50 values up to 1.00 nM. These compounds were then subjected to molecular docking using the GOLD program, with MAO-B crystallographic data from the Protein Data Bank 3PO7, validated through redocking. The pharmacokinetic and toxicological properties of the selected compounds were assessed using QikProp (Schrödinger) and DEREK (Lhasa). In the final stage, drug repositioning was conducted by searching

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for chemical analogs of the best-performing compounds using the SwissSimilarity webserver. The goal was to identify promising drug candidates with pharmacokinetics suitable for oral administration and central nervous system distribution, as predicted by SwissADME and molecular docking analysis, using rasagiline, safinamide, and selegiline as reference drugs. The first stage of the research identified 3-methyl-8-(4,4,4-trifluorobutoxy)indeno[1,2-c]pyridazin-5-one as a promising candidate for Parkinson's disease treatment due to its low IC50 (0.0140 nM), favorable predicted pharmacokinetic parameters, and absence of toxicological alerts. Additionally, the similarity-based search using this compound led to the identification of trifluperidol and leflunomide as promising candidates for drug repositioning in Parkinson's disease treatment. The results obtained align with previous in silico and in vivo studies. Although this study did not identify novel candidates for drug repositioning, its methodology proved effective in screening publicly available chemical spaces for potential therapeutics. This approach may also be valuable for identifying compounds with therapeutic potential for diseases beyond Parkinson's disease.

Keywords Monoamina oxidase B · Enzyme inhibition · In silico · Drug repositioning

1 Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder with a multifactorial etiology, involving genetic predisposition, environmental factors, and aging-related cellular dysfunctions. The pathophysiological hallmark of PD is the presence of Lewy bodies, which are intracellular inclusions primarily composed of aggregated alpha-synuclein within dopaminergic neurons of the substantia nigra pars compacta [1]. The progressive degeneration of these neurons results in a deficiency of dopamine, leading to characteristic motor and non-motor symptoms [2]. Among the motor symptoms, patients frequently present with bradykinesia, resting tremor, rigidity, and postural instability. Non-motor manifestations include autonomic dysfunction, sleep disturbances, olfactory impairment, cognitive decline, and neuropsychiatric symptoms. The neurochemical hallmark of PD is the progressive reduction in dopaminergic activity in the nigrostriatal pathway, which disrupts basal ganglia function and impairs motor control [3].

Currently, there is no cure for PD; however, various pharmacological strategies aim to alleviate symptoms and improve patients' quality of life. Levodopa, a precursor of dopamine, remains the most effective treatment, often combined with dopa decarboxylase inhibitors to enhance its bioavailability and minimize peripheral side effects [4]. Additional therapeutic options include monoamine oxidase B (MAO-B) inhibitors, such as selegiline and rasagiline, which reduce dopamine degradation, as well as catechol-O-methyltransferase (COMT) inhibitors that prolong

dopamine availability in the synaptic cleft. NMDA receptor antagonists like amantadine and anticholinergic agents are also employed to manage specific motor symptoms. Despite these treatment options, the progressive nature of PD necessitates continuous research into novel therapeutic strategies [5].

A key target in PD pathogenesis is MAO-B, an enzyme responsible for the oxidative deamination of dopamine and other monoamines, contributing to increased oxidative stress and neuronal damage [6]. Therefore, MAO-B inhibition has demonstrated neuroprotective potential by reducing dopamine metabolism and limiting the formation of reactive oxygen species [7]. Given the role of MAO-B in PD progression, the development of novel MAO-B inhibitors represents a promising avenue for disease management. Furthermore, computational approaches in medicinal chemistry have facilitated the identification of potential MAO-B inhibitors through virtual screening, molecular docking, and predictive modeling [8].

In this context, chemical similarity plays a crucial role in drug discovery by enabling the identification of compounds with comparable physicochemical properties and biological activities [9]. In which computational methods allow the comparison of molecular structures to predict potential interactions with biological targets [10]. This approach is particularly relevant in drug repositioning, where existing drugs with established safety profiles are explored for new therapeutic applications. Drug repositioning offers a cost-effective and time-efficient strategy for expanding treatment options, particularly for complex diseases such as PD, where novel drug development faces significant challenges [11–14].

Therefore, this study was conducted in two phases. In the first phase, potent MAO-B inhibitors were extracted from the BindingDB database and screened through molecular docking, using the average docking scores of clinically approved MAO-B inhibitors as a reference threshold. Further screening assessed the pharmacokinetic and toxicological properties of the selected ligands to identify candidates suitable for drug development. In the second phase, a search in the DrugBank and Chembl databases was conducted to identify structurally similar compounds to the top-performing ligand from the first phase. This search considered both 2D and 3D molecular similarity, physicochemical properties, and predicted interactions with human MAO-B.

The ultimate objective was to find potential medications for therapeutic repositioning in the management of Parkinson's disease (PD), possibly providing new treatment options with proven safety profiles based on the candidates' molecular docking results for repositing when compared to the outcomes of MAO-B inhibitors currently in clinical use. The findings of this study hold scientific significance by advancing computational drug discovery methodologies, clinical relevance by contributing to PD treatment options, and societal impact by addressing the growing burden of neurodegenerative diseases in an aging population [15, 16].

2 Materials and Methods

2.1 Search and Selection of Hits with Inhibitory Activity on MAO-B

BindingDB (www.bindingdb.org) is a database launched in 2000 that allows for research on the interaction of small molecules with proteins. It integrates experimental data from other databases such as PubChem, ChEMBL, PDSP Ki, and CSAR. BindingDB also provides important quantitative measures of the affinity between ligands and proteins, such as IC50, Ki, EC50, and Kd, as well as experimental parameters, including assay descriptions and factors like temperature and pH [17, 18].

In this study, the descriptor "Monoamine Oxidase B Inhibitor" was used to search the BindingDB database for compounds that had inhibitory activity on MAO-B, with IC50 values up to 1.00 nM taken into account. The PubChem webserver (https://pubchem.ncbi.nlm.nih.gov/) was used to evaluate the physicochemical descriptors of the selected molecules. A total of 31 hits were obtained.

2.2 Molecular Docking

Previously, molecules obtained from BindingDB that were subjected to molecular docking were optimized to obtain a 3D format. This procedure was carried out using HyperChem® software, and the method used to model the geometry of the molecules was RM1 (Recife Model 1), a reparameterization of the AM1 method [19].

Using the crystallographic data of the MAO-B enzyme stored in the Protein Data Bank (PDB) under PDB-ID code: 3PO7, complexed with the reversible inhibitor zonisamide, with a resolution of 1.80 Å, molecular docking was carried out using the GOLD (Genetic Optimization for Ligand Docking) program. Only the active site of the protein's A monomer was considered for the docking after the crystallographically observed water molecules were removed, preserving the FAD cofactor in the active site (coordinates $X = 53.32$, $Y = 153.71$, $Z = 25.55$). ChemPLP was selected as the ranking algorithm, and all molecules' active site radii were set to 6 Å.

The redocking method was used to validate the results generated by GOLD specifically for the MAO-B in question, considering a Root Mean Squared Deviation (RMSD) value equal to or smaller than 2 Å between the pose of zonisamide generated by GOLD and the crystallographic pose of the same molecule. In the analyses, the score values generated by the software were evaluated, using the arithmetic average of the scores of the standard molecules rasagiline, safinamide, and selegiline as the cut-off point to select the best molecules.

2.3 Pharmacokinetics and Toxicological Predictions

The selected molecules were evaluated with respect to their pharmacokinetic and toxicological properties using the QikProp SCHRODINGER (https://www.schrodinger.com/products/qikprop) and DEREK [20, 21] programs. Regarding the toxicological properties evaluated by DEREK, compounds that presented toxicity alerts according to Custom Prediction and Lhasa Prediction were rejected.

The pharmacokinetic analyses performed by QikProp included: log CACO2, log MDCK, percentage of oral absorption, and the quality of the human oral absorption model. Compounds that showed log CACO2 and log MDCK values greater than or equal to 500, oral absorption potential greater than or equal to 80%, and a high-quality human oral absorption model were maintained. It should be noted that log P and log KHSA were additional distribution parameters evaluated by the software.

2.4 Search for Candidates for Repositioning in Parkinson's Disease Treatment

The chemical structure of the selected ligand from phase I of the study, in SMILES format, was used to search for compounds in the "drugs" category on the Swiss-Similarity platform (www.swisssimilarity.ch), considering the combination of 2D parameters (FP2, ECFP4, MHP6, Pharmacophore, ErG, Scaffold, Generic Scaffold) and 3D parameters (electroshape and E3FP) in the DrugBank database (https://go.drugbank.com/) and Chembl (https://www.ebi.ac.uk/chembl/) [22].

Among the selection criteria for repositioning drugs for Parkinson's disease treatment, only substances with FDA-approved therapeutic indications were considered, along with the ability to cross the blood–brain barrier, absence of activity as a substrate for P-glycoprotein, and compliance with Lipinski's Rule of Five according to data provided by the webserver SwissADME (http://www.swissadme.ch/). The aim was to identify drugs with a satisfactory pharmacokinetic profile for oral administration and distribution targeting the central nervous system [23]. Substances in clinical investigation or exclusively for experimental use, and drugs that violated the established exclusion criteria, were excluded from the study.

Subsequently, the selected molecules were subjected to molecular docking tests, and those with scores equal to or greater than 71.44 were classified as promising candidates for repositioning for Parkinson's disease treatment.

3 Results and Discussion

3.1 Search and Selection of Hits with Inhibitory Activity Under MAO-B

The search for substances with inhibitory activity against human monoamine oxidase B in the BindingDB database using the descriptor "monoamine oxidase B inhibitor" generated 7309 results, of which only 31 had IC50 values lower than 1 nM.

The descriptive analysis of the physicochemical properties of the selected ligands revealed an average molecular weight of 302.208 g/mol (±47.684), a range of 234.09 (minimum 159.23 and maximum 393.32; sum 9368.44), an average logP (octanol/water) of 3.529 (±0.636), a range of 3.14 (minimum 1.37 and maximum 4.51; sum 109.4), a hydrogen bond donor group average of 0.548 (±0.810) with a range of 3 (minimum 1 and maximum 3; sum 17), and a hydrogen bond acceptor group average of 3.129 (±1.284) with a range of 6 (minimum 1 and maximum 7; sum 97).

According to Lipinski's rule of five, these results indicate that the 31 ligands selected from BindingDB exhibit desirable physicochemical properties for the development of drugs aiming for oral administration. They have a molecular weight lower than 500 g/mol, fewer than 5 hydrogen bond donors, fewer than 10 hydrogen bond acceptors, and a logP value lower than 5 [24]. The designation of the ligands selected from BindingDB and their respective physicochemical properties are shown in Table 1.

Additionally, Lipinski's rules significantly influence medicinal chemistry by emphasizing the importance of physicochemical characteristics in drug design. However, they have limitations, as many FDA-approved drugs do not adhere to them, especially when dealing with complex compounds like natural products and protein kinase inhibitors. Therefore, Lipinski's rules should be used in conjunction with other techniques to predict pharmacokinetic behaviors [25–29]. Consequently, computational methods for pharmacokinetic prediction were employed for a more accurate screening of potential candidates for pharmacological repositioning based on structural similarity.

3.2 Molecular Docking

After analyzing the physicochemical properties of the ligands obtained from BindingDB, they were subjected to molecular docking analysis with human monoamine oxidase B (PDB ID = 3PO7), considering the fit with the active site of monomer A with the FAD600 cofactor present and the removal of water molecules from the crystallographic structure. The assay was validated by redocking the target with the isoniazid ligand (Fig. 1), obtaining an RMSD value of 0.46 Å.

In medicinal chemistry, the term "redocking validation" refers to a computer-based method used to assess the accuracy and reliability of docking methods in

Table 1 Selected ligands from BindingDB and their physicochemical properties

Designation in this study/IUPAC's name/PubChem ID	CI50 (nM)	Molecular weight (g/mol)	Log P	H bond donors	H bound acceptor
Molecule 1	0.00820	159.23	2.24	0	1
N-benzyl-N-methylprop-2-yn-1-amine					
PubChem ID 4688					
Molecule 2	0.0140	322.28	3.57	0	7
3-methyl-8-(4,4,4-trifluorobutoxy)indeno[1,2-c]pyridazin-5-one					
PubChem ID 10,314,028					
Molecule 3	0.0480	190.15	1.37	1	4
4-Oxo-4H-1-benzopyran-3-carboxylic acid					
PubChem ID 181,620					
Molecule 4	0.134	315.19	4.28	0	2
3-(3-bromophenyl)-6-methylchromen-2-one					
PubChem ID 46,895,501					
Molecule 5	0.227	305.16	3.83	2	1
N-(3,4-dichlorophenyl)-1H-indole-5-carboxamide					
PuBChem ID 63,718,419					
Molecule 6	0.310	250.29	3.99	0	2
6-methyl-3-(4-methylphenyl)chromen-2-one					
PubChem ID 13,441,539					
Molecule 7	0.318	258.24	3.55	0	5
5-(4,4,4-trifluorobutoxy)-2,3-dihydroinden-1-one					
PubChem ID 11,708,681					

(continued)

Table 1 (continued)

Designation in this study/IUPAC's name/PubChem ID	CI50 (nM)	Molecular weight (g/mol)	Log P	H bond donors	H bound acceptor
Molecule 8	0.386	320.17	3.35	1	2
N-(3,4-dichlorophenyl)-1-methylindazole-5-carboxamide					
PubChem 77,844,667					
Molecule 9	0.400	299.17	2.98	1	3
N-(3-chlorophenyl)-4-oxochromene-3-carboxamide					
PubChem ID 132,941,420					
Molecule 10	0.500	331.16	3.78	0	3
7-[(4-bromophenyl)methoxy]chromen-2-one					
PubChem 2,629,406					
Molecule 11	0.586	306.15	3.26	2	2
N-(3,4-dichlorophenyl)-1H-indazole-5-carboxamide					
PubChem 77,844,601					
Molecule 12	0.588	328.29	3.49	0	6
Methyl 7-[(3-fluorophenyl)methoxy]-2-oxochromene-3-carboxylat					
PubChem ID 76,314,457					
Molecule 13	0.612	290.15	3.89	1	1
N-(3,4-dichlorophenyl)-1-(1H-indazol-5-yl)methanimine					
PubChem ID 77,844,723					
Molecule 14	0.660	279.33	3.30	1	2
5-(4-phenylbutyl)-1H-indole-2,3-dione					
PubChem ID 50,994,176					

(continued)

Table 1 (continued)

Designation in this study/IUPAC's name/PubChem ID	CI50 (nM)	Molecular weight (g/mol)	Log P	H bond donors	H bound acceptor
Molecule 15	0.661	269.27	2.87	3	3
N-(4-chloro-3-fluorophenyl)-1H-indazole-5-carboxamide					
PubChem SID 312,351,277					
Molecule 16	0.662	303.72	3.12	1	3
N-(3-chloro-4-fluorophenyl)-1-methylindazole-5-carboxamide					
PubChem ID 77,844,718					
Molecule 17	0.670	393.32	3.22	1	3
N-(3,4-dimethylphenyl)-4-oxochromene-3-carboxamide					
PubChem ID: 132,941,421					
Molecule 18	0,678	289.68	3.03	2	3
N-(3-chloro-4-fluorophenyl)-1H-indazole-5-carboxamide					
PubChem SID 312,351,276					
Molecule 19	0.740	345.19	4.24	0	3
3-(3-bromo-4-methoxyphenyl)-6-methylchromen-2-one					
CHEMBL1835231					
Molecule 20	0.770	356.30	3.52	0	3
7-hex-5-ynoxy-3-(4-methoxyphenyl)chromen-2-one					
PubChem ID 76,318,046					
Molecule 21	0.800	379.63	4.52	0	3
7-[(4-bromophenyl)methoxy]-3-chloro-4-methylchromen-2-one					
PubChem ID 134,816,193					

(continued)

Table 1 (continued)

Designation in this study/IUPAC's name/PubChem ID	CI50 (nM)	Molecular weight (g/mol)	Log P	H bond donors	H bound acceptor
Molecule 22	0,800	266.29	3.64	0	3
3-(3-methoxyphenyl)-6-methylchromen-2-one					
PubChem ID 44,622,873					
Molecule 23	0.875	304.34	3.59	0	5
Methyl 7-hexoxy-2-oxochromene-3-carboxylate					
PubChem 76,336,202					
Molecule 24	0.890	270.30	3.81	0	3
7-[(4-fluorophenyl)methoxy]-3,4-dihydro-2H-naphthalen-1-one					
PubChem ID 105,624,050					
Molecule 25	0.900	330.40	3.61	0	5
3,4-dimethyl-7-[(5-propan-2-yl-1,3,4-thiadiazol-2-yl)methoxy]chromen-2-one					
PubChem ID 179,342					
Molecule 26	0.900	345.19	4.14	0	3
7-[(4-bromophenyl)methoxy]-4-methylchromen-2-one					
PubChem ID 886,539					
Molecule 27	0.900	292.33	3.81	0	3
7-phenylmethoxy-2,3-dihydro-1H-cyclopenta[c]chromen-4-one					
PubChem ID 561,354					
Molecule 28	0.912	298.31	4.08	0	4
7-[(3-fluorophenyl)methoxy]-3,4-dimethylchromen-2-one					
PubChem ID 807,313					

(continued)