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RESEARCH PAPERS

In *silico* screening of anti-Parkinsonian multi-target drugs from natural compounds

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Highlights

- QSAR models trained for PD targets and BBB permeability using public datasets
- Identified 107,825 BBB-permeable compounds and ranked the top 100 using QSAR models
- Docking revealed top candidates with multitarget potential against PD targets
- The top 10 compounds showed strong binding to multiple key targets for Parkinson's disease

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KEYWORDS
Parkinson's Disease;
Drug Discovery;
Chemoinformatics;
Virtual Screening.

Abstract: Parkinson's disease (PD), a neurodegenerative condition, manifests with tremors, muscle rigidity, and movement difficulties, primarily in individuals over 60 years old. The exact cause is unknown, but it involves the gradual loss of dopamine-producing neurons in the brain. Current treatments include medications like levodopa and dopaminergic agonists, as well as therapies such as physiotherapy and deep brain stimulation surgery. However, the main challenge of PD lies in managing the disease progression and its adverse effects over time. To address the therapeutic bottleneck of the disease, *in silico* strategies, such as quantitative structure-activity relationships (QSAR) and molecular docking, are particularly effective. In this study, we employed *in silico* techniques to identify natural compounds with multi target potential for the treatment of PD. The core computational methodologies employed included molecular docking, which predicted the binding affinities of compounds to key PD-related protein targets, followed by molecular dynamics (MD) simulations to assess the stability of these protein-ligand complexes over time. Crucially, the analysis incorporated comprehensive ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) prediction to evaluate the drug-likeness and pharmacokinetic profiles of potential candidates, with a particular emphasis on their predicted blood-brain barrier permeability, a critical factor for central nervous system (CNS) drugs. The investigation successfully identified several natural compounds with significant potential, notably Luteolin, which exhibited strong predicted multi-target activities. These activities include potent inhibition of Monoamine Oxidase-B (MAO-B), a well-established target for symptomatic relief in PD, alongside predicted antioxidant and anti-inflammatory properties, addressing the neurodegenerative aspects of the disease. Despite promising *in silico* results, we emphasize the need for experimental validation, such as *in vitro* and *in vivo* studies to confirm binding, assess neuroprotective effects, and analyze ADMET properties, advancing these compounds as potential treatments for Parkinson's disease.

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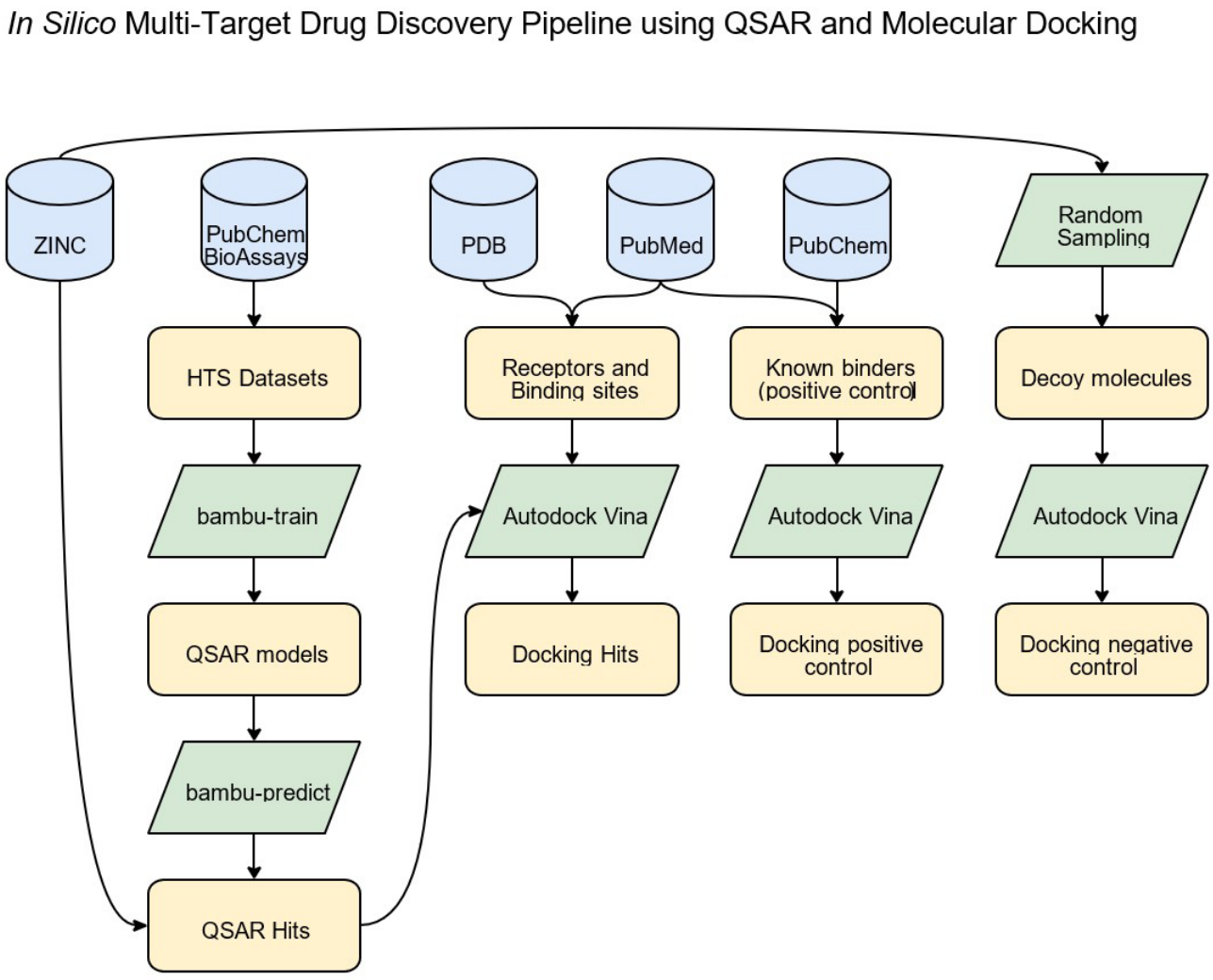
Graphical Abstract



Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world. The degeneration of dopaminergic neurons in the substantia nigra (SN), as well as the intracellular accumulation of the protein α-synuclein in the nervous system, forming inclusions known as Lewy Bodies are some of the main characteristics of the disease (Balestrino & Schapira, 2020). Current projections estimate that the global prevalence of Parkinson's disease will rise to about 9 million cases by 2030. Some risk factors for this cognitive decline include age, oxidative stress, and environmental and genetic factors. Physicians diagnose PD through a medical evaluation that confirms at least two of the following primary motor symptoms: rigidity, bradykinesia, tremor, and postural instability (Gonzalez-Latapi et al., 2021; Koszła et al., 2021).

There is still no cure for PD, that is, no therapy is capable of inhibiting the progression of the disease, but there are several resources available to help control its symptoms (Tolosa et al., 2021). Treatment focuses predominantly on the dopaminergic pathway. Currently, the gold standard therapy for this disease is the dopamine precursor levodopa. Other therapies used to manage the pathology include dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, and deep brain stimulation (DBS), among others (Armstrong & Okun, 2020).

Given the multifactorial nature of PD and the limitations of current symptom-based treatments, there is a growing interest in identifying compounds that can target multiple pathological pathways. The use of *in silico* methods to identify multitarget natural compounds remains limited (Aarón et al., 2025). Few studies integrate techniques such as QSAR and molecular docking to discover bioactive molecules

that target multiple pathways of disease progression. This limited exploration slows the development of more effective, disease-modifying therapies (Boulaamane et al., 2022).

In vitro and *in vivo* assays are commonly used in the initial identification of new and more effective pharmacotherapies. However, the discovery of new therapeutic agents through experimental methods is a time-consuming and costly process. For this reason, computational methods (*in silico*) are extensively employed, particularly in early stages, such as hit identification (Silva Rocha et al., 2019). One of the most effective methodologies for drug design and optimization is quantitative structure-activity relationship (QSAR) modeling. QSAR's main objective is to build mathematical models that can relate chemical structure to the biological activity of analogous compounds. In other words, it identifies chemical structures that have satisfactory inhibitory effects and low toxicity on specific targets (Almeida et al., 2010; Mao et al., 2021).

Here, we present the development of QSAR models for the PD molecular target, along with the virtual screening of drugs using these models in combination with other *in silico* methods, aiming to identify molecules with potential activity against multiple molecular targets of PD.

Materials and methods

Data acquisition

We obtained the data for this study from multiple public databases, which were selected to comprehensively cover molecular targets implicated in PD, as well as natural compounds for virtual screening. Initially, we retrieved bioactivity data against PD-related targets from the PubChem BioAssays database (National Library of Medicine, 2024), a large repository maintained by the National Institutes of Health (NIH) that includes high-throughput screening results. Table 1 presents the molecular targets, their associated BioAssay IDs, and the number of active and inactive compounds evaluated for each target.

To evaluate the ability of compounds to cross the blood-brain barrier (BBB), we utilized data from the B3DB dataset (Meng et al., 2021). Moreover, we downloaded an extensive collection of natural compounds in SDF format from the ZINC database (ZINC, 2024), encompassing 224,205 different molecules.

Each of the molecular targets selected from the PubChem BioAssays HTS datasets plays a relevant role in PD pathogenesis. The α-Synuclein protein is a known target in PD for its contribution to its pathogenesis through anomalous conformations that cause cellular dysfunction and neuronal death (Calabresi et al., 2023); CDC25B (Cell Division Cycle 25B) is one of three human phosphatases that play a key role in controlling the activation of cyclin-dependent kinases. It regulates the entry into mitosis and responses to DNA damage checkpoints. Disruptions can lead to cancer and possibly PD (Sharma et al., 2017); CHRM1, the Muscarinic Acetylcholine Receptor Subtype M1, regulates basal ganglia function and motor control. Targeting M1 receptors may help treat motor symptoms and cognitive impairments in Parkinson's disease (Sabbir et al., 2022); DRD1 (Dopamine Receptor type 1), DRD2 (Dopamine Receptor type 2), and DRD3 (Dopamine Receptor type 3) play crucial roles in regulating several physiological functions mediated by the neurotransmitter dopamine, including the control of voluntary movement, reward processes, hormonal regulation and blood pressure. Medications that target dopaminergic neurotransmission are widely used in the treatment of a variety of neurological disorders, such as PD (Eryilmaz et al., 2020); HTR2A (Serotonin 2A Receptor), a protein located in the cell membrane that is involved in the transmission of serotonin signals in the brain, This serotonin receptor is involved in mood, sleep, cognition, and motor control. It may be linked to impulsive behavior in PD patients (Vuletić et al., 2021); MAPK10/JNK3 (Mitogen-Activated Protein Kinase 10/c-Jun N-terminal Kinase 3) is involved in cell signaling

Table 1. Data obtained from PubChem BioAssays for training of QSAR (Quantitative Structure-Activity Relationship) models for Parkinson's Disease molecular targets.

Molecular Target	PubChem BioAssays ID	Number of Compounds	
		Active	Inactive
α-Synuclein	652106	501	362,541
α-Synuclein (gene expression)	1671193	173	135,948
CHRM1	588852	4,555	354,661
DRD1	641	3,413	54,292
DRD2	485358	1,779	333,884
MAPK10	746	366	59,422
Nrf2	624171	1,243	394,692
PINK1	624263	823	396,204
TAAR1	624466	5,374	357,211
TAAR1	651783	1,972	428

related to apoptosis and neurodegenerative disorders. JNK3 inhibitors are promissing candidates for Parkinson's disease treatment (Shuai et al., 2023); Nrf2 (Nuclear Factor Erythroid 2-Related Factor 2) is a protein that plays a crucial role in regulating the cellular response to oxidative stress as well as other cellular damage, making it a promising therapeutic target in several conditions associated with oxidative stress (Gureev & Popov, 2019); PINK1 (PTEN-Induced Protein Kinase 1) is a mitochondrial protein essential for maintaining mitochondrial function. Mutations in PINK1 may lead to hereditary PD, and it is a target for therapies aimed at restoring mitochondrial function (Pickrell & Youle, 2015). TAAR1 (Trace Amine-Associated Receptor 1) is a type of neurotransmitter receptor present in the central nervous system. This receptor regulates monoamine transmission and is a potential target for treating neuropsychiatric and neurodegenerative disorders, including Parkinson's disease (Rutigliano et al., 2018).

Model training and validation

The BAMBU tool (GitHub, 2024), developed to train, run, and straightforwardly validate QSAR models, was used to train specific models for molecular targets of PD based on the PubChem BioAssays High-Throughput Screening (HTS) datasets (Guidotti et al., 2023, 2024). Additionally, BAMBU was used to train models based on the B3DB dataset to evaluate which molecules have an affinity to overcome the blood-brain barrier (Meng et al., 2021). Due to the imbalanced nature of HTS datasets, we employed Random Undersampling for class balancing (Saripuddin et al., 2022). All substances were then transformed into 1024-bit Morgan Fingerprints, a molecular representation that converts chemical substructures into binary vectors, enabling classification algorithms to associate these characteristics with a target characteristic. The preprocessed datasets were randomly split into training (75%) and testing (25%) datasets. To train the predictive models, we have evaluated different classification algorithms, including Logistic Regression (LR), Extremely Randomized Trees (ET), and Gradient-Boosting Trees (GB). For each molecular target, BAMBU utilized the training dataset for both training and hyperparameter optimization. Finally, we evaluated the best model for each algorithm using the testing datasets to identify the final models.

Analysis with data from natural compounds

To identify potential new medications for PD, the ZINC database (ZINC, 2024) was utilized, which indexes a wide range of compounds, including natural molecules. Models previously trained with the BAMBU tool were used to select molecules that demonstrated relevant activity. In this study, we downloaded the structures of 224,205 natural compounds from ZINC and employed the QSAR models trained using BAMBU to score each one. Then, we computed a consensus score using the individual probabilities of activity for each target and selected the top 100 molecules for further analysis.

Molecular docking

We have utilized the molecular docking software Autodock Vina (Eberhardt et al., 2021) to assess the affinity between the selected natural compounds and different targets of PD, using proteins previously characterized in the literature. The structures of these targets were obtained from the Protein Data Bank (RCSB, 2024), when experimentally derived structures were available, or from AlphafoldDB otherwise (EMBL-EBI, 2024).

From the literature, residues relevant to interaction with these targets were identified (Table 2) and used to construct a grid box to cover them during the docking process, with a 20 Å padding around the binding site. Additionally, for each target, 100 decoy molecules were randomly selected from the ZINC natural compound dataset and used as a negative control for the docking analysis. Positive controls were derived from literature and include endogenous molecules with known biological activity or synthetic inhibitors with well-established activity. For the decoy molecules, we calculated a significance threshold by considering the mean binding energy minus two standard deviations ($\mu - 2\sigma$). In this analysis, we considered a candidate compound with a score below this threshold as a statistically rare event and thus a potential hit, as it falls outside the range where approximately 95% of non-binding decoys would score, assuming a normal distribution (De-la-Torre et al., 2024).

Workflow

An overview of the virtual screening strategy, comprising the steps for data collection, QSAR model training, QSAR-based and molecular docking-based virtual screening, and molecular docking positive controls, is presented in Figure 1.

Results

QSAR modelling

The search for targets with potential anti-Parkinson activity was conducted using the PubChem BioAssays database (see Table 1). The models produced by the BAMBU tool, based on the selected targets, were ranked based on the F1 Score metric. Table 3 presents the validation results of the best models for each target, including the metrics accuracy, recall, precision, F1 Score, and ROC AUC.

After the model training and validation stage using the BAMBU tool, we employed it in the virtual screening process to identify promising molecules. At this stage, the selection of substances took into account not only their potential effectiveness against PD but also their ability to cross the blood-brain barrier. Then, aiming to prospect new drug candidates for PD, the previously chosen targets were used as filtering criteria for natural compounds obtained from the ZINC database. A total of 107,825 molecules from the natural compounds dataset were predicted to be able to pass the blood-brain barrier and were ranked based on the average probability of activity for the molecular targets. We have selected the top 100 natural compounds based on the average probability of activity computed by the QSAR models.

Molecular docking

The execution of molecular docking was conducted using residues derived from the targets, previously identified in the

Table 2. Molecular targets used in the molecular docking analysis for the screening of candidate natural compounds with multi-target activity against Parkinson's Disease, including Accession Codes on PDB or Alphafold DB, and the Residues used to define the grid-box.

Molecular targets	PDB/AlphafoldDB	Binding site residues
α-synuclein	1XQ8	Ala30, Val37, Ala56, Val63, Leu38, Thr44, Gly93, Lys97, Val95, Gln99
CDC25B	1QB0	Glu431, Met531, Tyr528, Glu474, Arg479, Phe475, Ser476, Glu478, Ser477, Lys394
CHRM1	5CXV	Trp164, Leu167, Val168, Glu170, Leu174, Gln177, Phe182, Ser184, Gln185, Pro186, Ile188, Glu397, Trp400, Glu401, Tyr404
DRD1	7CKX	Asp103, Ser107, Ser198, Ser202, Phe288, Phe289, Asn292, Trp321
DRD2	6VMS	Cys182, Ile183, Phe110, Val111, Asp114, Cys118, Thr119, Ile122, Val190, Ser193, Ser197, Trp386, Phe389, Phe390, Tyr408, Ser409, The 412, Tyr416
DRD3	3PBL	Tyr365, Phe345, Ile183, His349, Val189, Phe106, Val86, Tyr373, Asp110, Thr369, Trp342, Val111, Cys114, Ser196, Phe346, Ser193, Ser192, Val350
HTR2A	6WGT	Arg137, Glu318, Trp336, Phe332, Gly369, Ser242, Asp155, Val156, Val235, Phe339, Phe340
MAPK10	1JNK	Ser30, Glu402, Phe48, Glu397, Leu317, Lys328, Ser217, Thr226, Gly71, Val78, Phe209, Leu210, Phe218, Met220 Arg227, Arg230, Tyr223, Thr226, Arg188, Asn194, Asp207, Ala211, Asp189, Asp207, Ser40, Ala218, Ser40, Glu402
NRF2	7O7B	Arg456, Leu464, Val470 - Asn475, Val478, Lys487, Glu492, Gly505, Ala452, Met484, Arg499, Asp500, Arg503, Asn482, Arg456, Ala510, Lys506, Val509, Arg512, Lys518
PINK1	6EQI	Ser 65, Ser 228, Ser 230, Tyr 198, Ile 44, Val 70, Gly 47, Thr 305, Arg 282, Asn 283, Ala 46, Arg 333, Ser 375, Lys 380, Asp 379, Arg 374, Gln 378, TYr 404
TAAR1	Q96RJ0	Trp89, Asp103, Cys182, Trp264, Phe267, Phe268, Asn286, Trp291, Tyr294

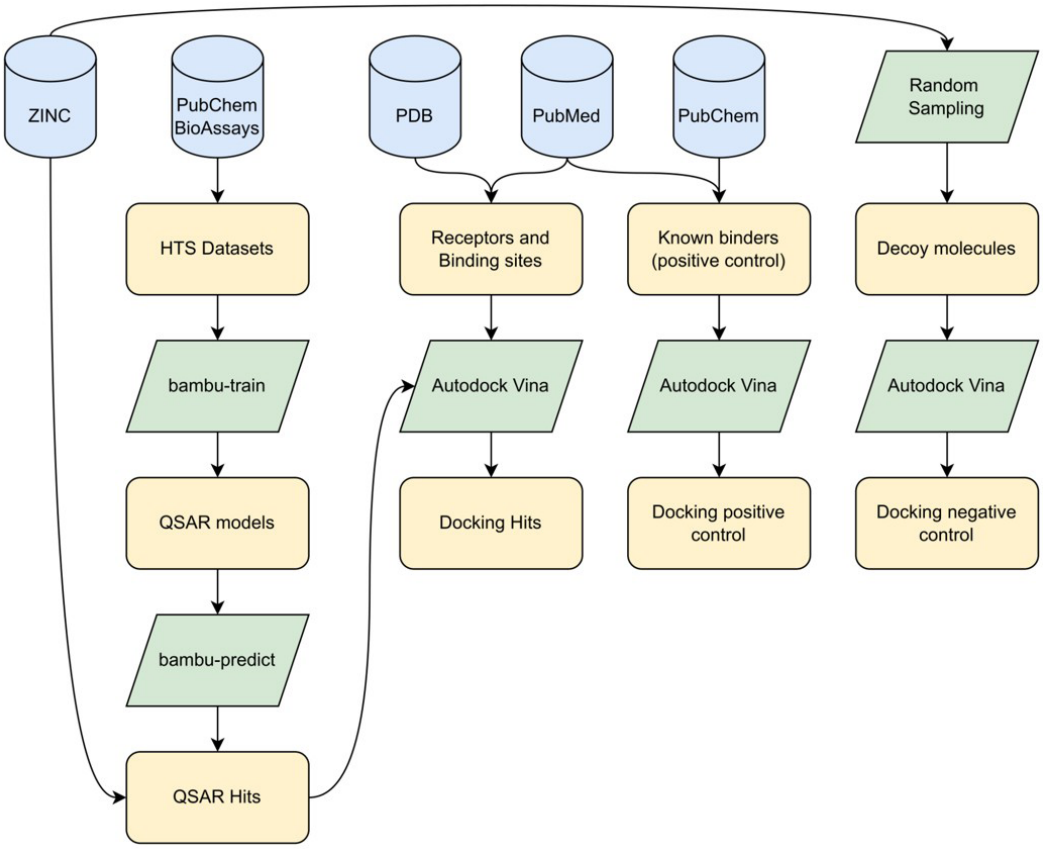


Figure 1. Workflow used for the virtual screening of natural compounds against multiple Parkinson's Disease molecular targets using QSAR and Molecular Docking.

Table 3. Results of the evaluation of predictive models trained by the BAMBU tool.

Molecular Target	Pubchem BioAssays ID	Algorithm	Accuracy (%)	*Recall* (%)	Precision (%)	F1 (%)	ROC AUC (%)
α-Sinucleine	652106	LR	68.53	71.30	64.06	67.49	72.93
α-Sinucleine (gene expression)	1671193	LR	78.16	81.25	79.59	80.41	84.13
CHRM1	588852	ET	68.96	61.65	72.72	66.73	75.35
DRD1	641	ET	67.31	60.10	69.19	64.32	72.78
DRD2	485358	ET	76.63	64.99	83.78	73.2	81.74
MAPK10	746	GB	72.13	69.23	73.26	71.19	78.73
Nrf2	624171	LR	65.27	32.8	95.37	48.82	85.84
PINK1	624263	ET	68.69	66.23	74.38	70.07	74.49
TAAR1	624466	LR	70.75	73.29	69.44	71.31	76.99
TAAR1	651783	ET	63.08	72.92	56.91	63.93	67.88

LR: Logistic Regression; ET: Extremely Randomized Trees; GB: Gradient-Boosting Trees.

literature as crucial for the protein's activity and essential for pharmacological action. For this purpose, we created grid boxes that covered all selected residues for each target, with a 20 Å padding around them. The average docking energy was used as a consensus score to rank the compounds and select potential multi-target compounds. Table 4 presents the results of this phase, where negative values indicate the energy resulting from docking. Table 5 includes the docking results for the negative (decoy) molecules and positive controls.

Discussion

James Parkinson's seminal study of "tremulous palsy" remains relevant today, with many of the original clinical insights still valid. In addition to characteristic motor symptoms such as tremors, Parkinson's disease is now recognized for a range of non-motor manifestations including cognitive problems, sleep disturbances, and depression. Advances in understanding the underlying pathology and neurophysiological mechanisms have led to the development of effective therapies such as L-DOPA administration and deep brain stimulation. However, these therapies are palliative, and the disease continues to be progressive and debilitating, highlighting the urgent need for research to find ways to slow its progression and identify early signs before motor symptoms appear (Balestrino & Schapira, 2020; Bloem et al., 2021; Poewe et al., 2017).

Using a combination of QSAR modelling and molecular docking, we were able to identify molecules with potential activity against the molecular targets of PD. The most promising molecules are listed below, along with their descriptions, mechanisms of action, and relationship to Parkinson's disease.

QSAR modelling

The comprehensive evaluation of predictive models, as detailed in Table 3, underscores the performance of the QSAR models trained using the BAMBU tool. These targets range from neurological components, such as α-Synuclein and dopamine receptors (DRD1, DRD2), to essential cellular regulators, including MAPK10, Nrf2, and PINK1. We have assessed the model's efficacy using a suite of standard classification metrics, including Accuracy, Recall, Precision, F1-score, and ROC AUC, which provide a multifaceted perspective on its predictive capabilities and robustness across various biological contexts. A detailed analysis of the results reveals a heterogeneous landscape of model performance, contingent on both the specific molecular target and the chosen machine learning algorithm. Notably, the Logistic Regression (LR) model applied to α-Synuclein (gene expression) demonstrated exceptional performance, achieving the highest accuracy (78.16%) and F1-score (80.41%), alongside a strong ROC AUC (84.13%), indicating its particular suitability for this prediction task. Conversely, the Nrf2 model, also employing LR, presented a unique scenario with an outstanding ROC AUC (85.84%) and near-perfect precision (95.37%), yet a significantly lower recall (32.8%). Therefore, these results highlight a critical trade-off: while the model's optimistic predictions are highly reliable, it concurrently misses a substantial number of actual positive instances. Such divergent performances underscore the imperative of selecting and optimizing models based on the specific objectives and the relative importance of minimizing false positives versus false negatives in a given research or clinical application. The study further highlights the practical application of various machine learning algorithms. Extremely Randomized Trees (ET) emerged as a frequently deployed algorithm, demonstrating competitive performance across multiple targets, including CHRM1, DRD1, DRD2, PINK1, and TAAR1, suggesting its broad applicability and robustness for diverse biological datasets. These varied algorithmic performances, coupled with the target-specific nuances, collectively emphasize the need for a thorough, context-dependent evaluation when developing and applying predictive models in molecular biology, ensuring that the

Table 4. Analysis of natural compounds against selected targets trained by the BAMBU tool and their respective energies generated by molecular docking.

ZINC ID	Drug Name	Molecular Docking Binding Energy (kcal/mol)											
		α-Sinuclein	CBC25B	CHRM1	DRD1	DRD2	DRD3	HTR2A	MAPK10	NRF2	PINK1	TAAR1	Mean
ZINC000085626058	(1S,2R,7S,10S,14R,15S)-15-benzyl-2-(3,4-dihydroxyphenyl)-7,10-dihydroxy-14-(4-hydroxy-3-methoxyphenyl)tricyclo[8.8.0.02,7]octadec-16-yn-12-one	-7.3	-8.9	-7.1	-9	-11.6	-10.2	-9	-7.5	-8	-8.5	-10.1	-8.83
ZINC000095909830	1-[(7-Hydroxy-5-methoxy-9,10-dihydrophenanthrene-2-yl) oxy]-4-methoxy-9,10-dihydrophenanthrene-2,7-diol	-7.4	-7.5	-7.2	-8.8	-11.7	-9.8	-9.1	-7.7	-8.4	-11.6	-8.5	-8.88
ZINC000001799340	1-[2-(1H-indol-3-yl)ethyl]-2,4,6-triphenylpyridinium	-7.2	-8.2	-7.1	-8.9	-11.4	-9.6	-9.8	-7.1	-7.9	-11.6	-9	-8.89
ZINC000015968006	(1S,3S,3aR,6aS)-7'-chloro-1-(1H-indol-3-ylmethyl)-5-(2-phenylethyl)spiro[1,2,3a,6a-tetrahydropyrrolo[3,4-c] pyrrole-3,3'-1H-indole]-2',4,6-trione	-8	-8.6	-6.8	-8.5	-11	-10.2	-9	-7.2	-8.2	-11.7	-9.9	-9.00
ZINC000015969573	(1R,3R,3aR,6aS)-1-(1H-indol-3-ylmethyl)-5-(2-phenylethyl) spiro[1,2,3a,6a-tetrahydropyrrolo[3,4-c]pyrrole-3,3'-1H-indole]-2',4,6-trione	-7.8	-8.8	-7.9	-8.8	-11.3	-9.5	-9.1	-8.5	-7.6	-12.1	-8.8	-9.10
ZINC000015968013	(1R,3R,3aR,6aS)-7'-chloro-1-(1H-indol-3-ylmethyl)-5-(2-phenylethyl)spiro[1,2,3a,6a-tetrahydropyrrolo[3,4-c] pyrrole-3,3'-1H-indole]-2',4,6-trione	-7.7	-8.9	-8	-8.4	-11.5	-10.2	-9.2	-7.2	-8	-12	-9.3	-9.12
ZINC000085567782	(2S,3R,4S,14R,19S,22R)-7-cyclohexyloxy-9,30-dimethoxy-19-methyl-35-oxa-15,16-dithiaheptacyclo[20.10.2.14,32.02,14.05,10.023,28.029,33]pentatriaconta-1(33),5,7,9,23(28),24,26,29,31-nonaen-12-yne-3,8,25-triol	-7.6	-8.8	-6.6	-8.9	-12.5	-10.7	-10.4	-7.4	-9.1	-11.2	-8.1	-9.20
ZINC000828327486	(3Z)-3-({[3-(2-oxo-2H-chromen-3-yl)phenyl]amino} methylidene)-2H-chromene-2,4(3H)-dione	-7.6	-7.9	-5.9	-9.5	-11.3	-10.1	-9.1	-10	-8.8	-11.7	-9.9	-9.25
ZINC000002117475	9-(9-ethyl-9H-carbazol-3-yl)-4-(4-methoxyphenyl)-2H,8H,9H,10H-chromeno[8,7-e][1,3]oxazin-2-one	-8	-8.1	-6.8	-9.1	-12.8	-10.3	-10.1	-7.9	-9.4	-11.5	-8.7	-9.33
ZINC000002121309	13-(2-{8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(13),2,4,6,9,11-hexaen-4-yl}hydrazin-1-ylidene)-8-oxa-14-azatetracyclo[7.7.0.0^{2,7}.0^{11,15}]hexadeca-1(16),2,4,6,9,11(15)-hexaen-12-one	-7.6	-8.7	-6.4	-10.1	-11.9	-10.5	-9.5	-8.6	-8.7	-11.6	-9.9	-9.40

Table 5. Negative and Positive controls used for the docking studies.

Target	Negative Control Binding Energies (kcal/Mol)			Positive Control Binding Energies (KCal / Mol)		Reference
	mean	standard deviation	threshold	Molecule	Binding Energy	
α-Sinuclein	-5.99776	1.038920	-8.075599	Synuclean-D	-6.036	Peña-Díaz et al. (2022)
CDC25B	-6.71143	1.015351	-8.742133	ethyl 3-((3-methoxynaphthalen-1-yl)amino)benzoate	-6.218	Cerchia et al. (2019)
CHRM1	-4.98297	0.965017	-6.913004	Dicyclomine	-6.905	Wang et al. (2024b)
DRD2	-8.78078	1.700788	-12.182355	Dopamine	-4.720	Beaulieu & Gainetdinov (2011)
DRD1	-7.05852	1.043366	-9.145252	Dopamine	-5.256	Beaulieu & Gainetdinov (2011)
DRD3	-7.96998	1.362163	-10.694307	Dopamine	-4.766	Beaulieu & Gainetdinov (2011)
HTR2A	-7.14645	1.119327	-9.385104	Serotonin	-5.303	Parajulee & Kim (2023)
MAPK10	-6.28831	1.085737	-8.459783	SP600125	-8.308	Zhang et al. (2021)
NFR2	-6.53026	1.091089	-8.712437	ML385	-7.866	Lv et al. (2024)
PINK1	-8.43227	1.478935	-11.390141	PRT062607	-8.364	Rasool et al. (2024)
TAAR1	-7.12747	1.096570	-9.320611	EPPTB	-7.946	Kong et al. (2021)

Negative controls are derived from a random sample of 100 natural compounds extracted from the ZINC database (ZINC, 2024), serving as a decoy to estimate the mean and standard deviation of the binding energy of natural compounds for the selected targets. Positive controls are molecules with activity already demonstrated by experimental methods, and when available, those with usage already approved by the U.S. Food and Drug Administration (FDA).

chosen model aligns optimally with the scientific question at hand.

Natural compounds as potential targets

The molecular docking results reveal distinct groups of drugs based on their primary targets, suggesting diverse mechanisms of action for potential therapeutic applications in PD. Key targets include dopamine receptors (DRD1, DRD2, DRD3), proteins involved in oxidative stress and mitochondrial regulation (NRF2, PINK1), as well as other relevant proteins such as α-synuclein and MAPK10.

Potential dopamine receptor modulators, such as compounds ZINC000015968006, ZINC000015969573, ZINC000002121309, ZINC000002117475, and ZINC000828327486, demonstrate strong binding affinities to dopamine receptors, particularly the D2 receptor (DRD2). These receptors play a crucial role in motor control and cognitive function, which are significantly affected in PD. For example, ZINC000002121309 exhibits high binding energy with DRD2 and DRD1, suggesting it could modulate dopaminergic signaling pathways. The affinity of these compounds for multiple dopamine receptors also indicates potential utility in managing the non-motor symptoms of PD by providing broader dopaminergic modulation.

Compounds such as ZINC000085626058, ZINC000095909830, ZINC000001799340, ZINC000015968006, and ZINC000085567782 are potential modulators of oxidative stress and mitochondrial function, exhibiting significant affinities for targets like NRF2 and PINK1. These proteins are crucial for the cellular response to oxidative stress and maintaining mitochondrial health, which is essential in preventing PD neuronal death (Pickrell & Youle, 2015). ZINC000015968006 and ZINC000085567782, for instance, bind strongly to PINK1, suggesting a role in promoting mitochondrial quality control and reducing oxidative damage, which are crucial in PD pathogenesis (Moon & Paek, 2015).

Drugs targeting protein aggregation and neuroinflammation, such as ZINC000085626058 and ZINC000015969573, also show promising results. These compounds exhibit binding to α-synuclein, a protein that aggregates in the brains of patients with PD and plays a key role in disease progression. By inhibiting α-synuclein aggregation, these compounds could potentially slow or prevent the spread of toxic aggregates in the brain, providing a novel approach to PD therapy (Horne et al., 2024).

ZINC000085626058 - This compound belongs to the class of diarylheptanoids, a class of lipophilic natural compounds found in plants, which are distinguished by having two aromatic rings connected by a linear aliphatic chain composed of seven carbon atoms (Ganapathy et al., 2019), and are found in the botanical genera *Zingiber*, *Curcuma*, *Alpinia*, *Alnus* and *Myrica*. These compounds have gained increasing recognition due to their diverse biological and pharmaceutical properties, being considered promising as therapeutic agents. Its medicinal properties encompass a wide range of effects, including anti-inflammatory, antitumor, antioxidant, antiestrogenic, and hepatoprotective activities, as well as action against leishmaniasis and neuroprotective effects (Sun et al., 2020).

A study led by Mohamed Nadjib Boukhatem examines the neuroprotective potential of natural compounds found in plants, including flavonoids and diarylheptanoids. Some proposed biological activities include improvements in brain health due to their antioxidant, anti-inflammatory, and neuroprotective properties. This study addresses several

literature reviews. Diarylheptanoids were tested using cell lines stressed with oxygen peroxide (H_2O_2) and glutamate. This test mimics the oxidative stress attributed to the development of neurodegenerative disorders. A variety of plants, such as *Girsium setidens*, *Aster scaber*, *Passiflora actinia*, *Ginkgo biloba*, *Acel nikoense*, *Alnus glutinosa*, *Panax ginseng*, *Schisandra chinensis*, *Rehmannia glutinosa*, *Flammulina velutipes*, *Rhododendron fortune*, *Morusalba*, and *Carya cathayensis* Sarg., have recently been identified as containing flavonoids and/or diarylheptanoids that can neutralize the neurodegenerative effects of oxidative stress. The antioxidant capacity of flavonoids and diarylheptanoids is crucial in the search for effective therapies and the prevention of diseases, especially Parkinson's disease. These compounds offer new perspectives for the development of innovative treatments that target the mechanisms underlying neurodegenerative diseases, due to the limitations of current therapies (Boukhatem, 2017).

Another study, conducted by Guangmiao Fu et al., investigated how diarylheptanoids derived from the rhizomes of the plant *Alpinia officinarum* can interfere with the aggregation of the protein α-synuclein, a process associated with the progression of neurodegenerative diseases such as Parkinson's. Using laboratory tests and computer simulations, the researchers investigated the impact of these compounds on the formation of α-synuclein aggregates. The results indicated that certain diarylheptanoids have the potential to prevent this aggregation, suggesting that they could be explored as treatments for neurodegenerative conditions. Researchers extracted and purified diarylheptanoids from the rhizomes of Alpinia officinarum. They then conducted a series of *in vitro* experiments to investigate how these compounds might affect the aggregation of the α-synuclein protein. This included aggregation tests, fluorescence spectroscopy analysis, and electron microscopy observation to examine the formation of α-synuclein aggregates in the presence of the diarylheptanoids.

Furthermore, *in silico* studies were conducted using molecular modeling to explore the possible interaction mechanisms between the compounds and α-synuclein. As a result, they discovered that certain diarylheptanoids extracted from Alpinia officinarum can significantly reduce the formation of clumps of the protein α-synuclein, associated with Parkinson's disease. Laboratory tests have shown a notable reduction in both the quantity and size of these clumps in the presence of these compounds. Additional analyses confirmed these results, suggesting that diarylheptanoids have the potential to be developed as therapies to halt the progression of neurodegenerative diseases (Fu et al., 2017).

In addition to the cited studies, Anna Santarsiero et. al. investigated the potential of new, recently synthesized diarylheptanoid polyoxygenates in combating neuroinflammation triggered by lipopolysaccharide (LPS). The researchers synthesized polyoxygenated diarylheptanoids and tested them in *in vitro* and *in vivo* experiments to evaluate their effect on inflammation. Using microglial cell cultures in *in vitro* experiments and animal models in *in vivo* experiments, the researchers investigated the effects of the compounds on both the inflammatory response and brain function. This comprehensive approach enabled a thorough analysis of the potential of these compounds to mitigate LPS-induced neuroinflammation and to gain a better understanding of the mechanisms underlying this effect. Following the study, polyoxygenated diarylheptanoids demonstrated remarkable efficacy in reducing neuroinflammation induced by LPS, both in *in vitro* experiments and in an in vivo model. They were able to reduce the production of inflammatory substances. Additionally, they demonstrated benefits in preserving brain function and reducing histopathological damage, with results suggesting that these compounds have therapeutic potential for treating neuroinflammatory conditions (Santarsiero et al., 2020). ZINC000085626058 exhibited strong binding affinities across several key targets, including DRD2 (-11.6 kcal/mol), DRD3 (-10.2 kcal/mol), HTR2A (-9.0 kcal/mol), and TAAR1 (-10.1 kcal/mol). Notably, its affinity for DRD2 (-11.6 kcal/mol) approaches the negative control threshold of -12.18 kcal/mol. It significantly surpasses the positive control Dopamine (-4.72 kcal/mol), suggesting a potent interaction with this crucial dopaminergic receptor. Similarly, its binding to DRD3 (-10.2 kcal/mol) and HTR2A (-9.0 kcal/mol) is more favorable than that of their respective positive controls, Dopamine (-4.766 kcal/mol) and Serotonin (-5.303 kcal/mol), further supporting its potential for modulating dopaminergic and serotonergic pathways. While its binding to α-Synuclein (-7.3 kcal/mol) did not meet the stringent negative control threshold (-8.076 kcal/mol), it still demonstrated a more favorable interaction than the α-Synuclein positive control Synuclean-D (-6.036 kcal/mol).

ZINC000095909830 - This compound belongs to the class of phenanthrenes and derivatives, an uncommon class of aromatic compounds that may be formed during the oxidative combination of aromatic rings found in stilbene precursor compounds. These compounds are found in a wide variety of plants, primarily within the Orchidaceae family. Other botanical families, such as Hepaticae, Betulaceae, Dioscoreaceae, and Combretaceae, also present some varieties of these compounds (Tóth et al., 2018). Phenanthrenes exhibit a diverse range of biological effects, including antiproliferative activities, antimicrobial properties (against viruses, bacteria, and fungi), and functions as anti-inflammatory, antioxidant, antiallergic, muscle relaxant, and anxiolytic agents (Tóth et al., 2018). A study conducted by Ankita Rajput et al. investigated the neuroprotective activity of a phenanthrene derivative isolated from the *Grewia tiliaefolia* plant, where chemical components were extracted from the leaves and roots of the *Grewia tiliaefolia* plant and purified to obtain the desired phenanthrene derivative. The chemical structure was determined by analyses such as nuclear magnetic resonance spectroscopy and mass spectrometry. *In vitro* tests were conducted on neuronal cells to assess the neuroprotective properties of the compound, including cell viability assays and analysis of inflammatory cytokine expression. *In silico* studies were conducted to investigate the mechanisms of analysis of the phenanthrene derivative, using molecular modeling and computer simulation techniques. The results obtained in *in vitro* and *in silico* studies provide strong evidence of the neuroprotective activity of the synthesized phenanthrene derivative. This discovery opens the way for the development of new therapeutic approaches with significant potential in the treatment of neurodegenerative diseases, such as Parkinson's disease. Furthermore, *in silico* studies

were fundamental in elucidating the molecular mechanisms underlying the compound's neuroprotective effect, offering crucial insights for the development of more specific and effective therapeutic interventions (Rajput et al., 2023).

ZINC000095909830 showed a favorable multi-target binding profile in our docking analysis, with a mean binding energy of -8.88 kcal/mol. This compound exhibited strong affinities for DRD2 (-11.7 kcal/mol) and PINK1 (-11.6 kcal/mol). For DRD2, its binding energy of -11.7 kcal/mol is very close to the stringent negative control threshold of -12.18 kcal/mol and significantly outperforms the positive control Dopamine (-4.72 kcal/mol), suggesting a potent interaction. Similarly, its affinity for PINK1 (-11.6 kcal/mol) surpasses the negative control threshold of -11.39 kcal/mol. It is more favorable than the positive control PRT062607 (-8.364 kcal/mol), indicating a strong potential for modulating mitochondrial function. While its binding to other targets, such as α-Synuclein (-7.4 kcal/mol), did not reach the decoy threshold, it was still more favorable than the α-Synuclein positive control Synuclean-D (-6.036 kcal/mol).

ZINC000001799340 - This compound belongs to the class of Pyridines and derivatives. They have a six-membered heterocyclic ring that contains a nitrogen atom and are present in a variety of natural compounds, in addition to being used in therapeutic applications, such as niacin (nicotinic acid) and Nicotinamide Adenine Dinucleotide (NAD+), playing roles such as substrate or cofactor in biological processes (Prachayasittikul et al., 2017). Its biological activity is extensive, containing antiviral, antibacterial, anticancer, antifungal, antidiabetic, antimicrobial, antitubercular, and antioxidant action (De et al., 2022). A study conducted by Ghobadian et al. (2018) explored the creation and analysis of new compounds known as tetrahydrocarbazole benzyl pyridine hybrids, designed to act as highly effective and selective inhibitors of butyrylcholinesterase (BChE). Furthermore, the capability of these compounds to exert neuroprotective and ß-secretase inhibition activities, both critical therapeutic targets in neurodegenerative conditions, was also evaluated. Tetrahydrocarbazole-benzyl-pyridine hybrids were synthesized and structurally characterized using techniques such as NMR spectroscopy and mass spectrometry. They were then tested to selectively inhibit BChE and evaluate its neuroprotective activity in neuronal cells. In parallel, previous studies also evaluated their inhibitory activity on ß-secretase, a key enzyme associated with Alzheimer's disease (AD), through specific biochemical assays. Although the trial was aimed at AD, the researchers concluded that tetrahydrocarbazole benzyl pyridine hybrids showed promise as candidates for the development of new therapies. The results highlighted the remarkable ability of these compounds to selectively inhibit BChE, an enzyme related to neurodegenerative disorders such as AD, in addition to exhibiting neuroprotective activity in neuronal cells, indicating a significant potential in mitigating cellular damage associated with neurodegenerative conditions (Ghobadian et al., 2018), which could be of great value for PD. A recent study conducted by Ahmadi et al. (2024) aimed to develop new potent and selective inhibitors of cyclooxygenase-2 (COX-2), a central enzyme in the production of prostaglandins from arachidonic acid that is associated with several pathophysiological conditions, including DP, based on imidazo[1,2-a]pyridine derivatives, through a rational design process. Furthermore, researchers evaluated the biological activities of these compounds, including their COX-2 inhibitory effects, analgesic activity, and antiplatelet potential, to contribute to the development of more effective and safe therapies. The investigations were conducted using molecular docking, specifically with the AutoDock Vina software, to analyze the interaction of the designed compounds with COX-2. A total of 15 synthesized derivatives were obtained through a series of five reaction steps. COX-2 inhibitory activities were assessed using a Cayman fluorescent kit, while analgesic effects were determined using behavioral tests, and antiplatelet activity was evaluated using the Born method. The results suggest that the developed compounds have potential as selective and effective COX-2 inhibitors, in addition to demonstrating analgesic and antiplatelet effects. These findings could provide important insights to advance the development of more effective treatments for conditions related to COX-2 activity, such as inflammation and pain (Ahmadi et al., 2024).

ZINC000001799340 demonstrated a compelling binding profile across multiple PD targets, with an overall mean binding energy of -8.89 kcal/mol. This compound exhibited powerful interactions with DRD2 (-11.4 kcal/mol) and PINK1 (-11.6 kcal/mol). Its DRD2 binding affinity of -11.4 kcal/mol, while slightly less negative than the -12.18 kcal/mol threshold, remains substantially more favorable than the positive control Dopamine (-4.72 kcal/mol), indicating a robust interaction. More notably, for PINK1, ZINC000001799340 achieved a binding energy of -11.6 kcal/mol, which surpasses the negative control threshold of -11.39 kcal/mol and is considerably more favorable than the positive control PRT062607 (-8.364 kcal/mol). This strong affinity for PINK1 suggests its potential role in mitochondrial quality control. Furthermore, its binding to HTR2A (-9.8 kcal/mol) also exceeded the negative control threshold of -9.385 kcal/mol and was superior to the positive control Serotonin (-5.303 kcal/mol).

Carboxylic acids: ZINC000015968006, ZINC000015968013 and ZINC000085567782

ZINC000015968006, ZINC000015968013, and ZINC000085567782 belong to the class of Carboxylic Acids. They have been extensively employed as versatile attachment points in modifications and the formation of carbon structures. They are a class of organic compounds that contain the carboxyl functional group (COOH). They have a wide range of applications across various sectors, including the food industry, medicine, chemistry, and materials manufacturing (Wu & Zheng, 2017).

The functional group of carboxylic acids plays a crucial role in the biochemistry of living organisms and the development of pharmaceuticals. Several natural substances, such as amino acids, triglycerides, and prostanoids, have the carboxyl group. Furthermore, this functional group is common in different classes of drugs. More than 450 drugs containing carboxylic acid have been launched on the market worldwide, ranging from non-steroidal anti-inflammatory drugs (NSAIDs) to antibiotics, anticoagulants, and cholesterol-lowering statins. The ability of the carboxylic group to form hydrogen bonds and electrostatic interactions is crucial for its functions in drug-target interactions (Bharate, 2021). These compounds

demonstrated significant binding affinities to several key PD targets. Notably, all four compounds showed exceptionally strong binding to DRD2, with energies ranging from -11.0 to -11.5 kcal/mol for ZINC000015968006 (-11.0 kcal/mol), ZINC000015969573 (-11.3 kcal/mol), ZINC000015968013 (-11.5 kcal/mol), and ZINC000085567782 (-12.5 kcal/mol). For DRD2, the negative control threshold is -12.18 kcal/mol, and the positive control is Dopamine at -4.72 kcal/mol. ZINC000085567782, in particular, achieved an impressive -12.5 kcal/mol, surpassing the negative control threshold and demonstrating a superior affinity compared to Dopamine. All four also showed robust binding to PINK1, with values ranging from -11.2 to -12.1 kcal/mol. Specifically, ZINC000015969573 (-12.1 kcal/mol), ZINC000015968013 (-12.0 kcal/mol), and ZINC000015968006 (-11.7 kcal/mol) all surpassed the PINK1 negative control threshold of -11.39 kcal/mol, and all four were more favorable than the positive control PRT062607 (-8.364 kcal/mol).

Steroids: ZINC000085567782

This compound belongs to the Steroids class. Steroids are complex organic molecules formed by four rings that perform a wide range of functions in multicellular organisms. They are part of the structure of cell membranes, including dietary cholesterol, and play multiple regulatory roles, acting as internal endocrine hormones through structural modifications of cholesterol (Cole et al., 2019). Neuroactive steroids, including estrogens, progesterone, and their metabolites, play a role in modulating brain functions and may influence PD risk and symptoms. PD, primarily idiopathic, is more prevalent in men, who experience earlier onset and more severe neurodegeneration than women. Evidence suggests that ovarian hormones, such as 17ß-estradiol and progesterone, provide neuroprotective effects on dopaminergic neurons, with more prolonged exposure to endogenous ovarian hormones associated with reduced PD risk. However, the benefits of postmenopausal hormone therapy remain inconclusive due to conflicting observational studies influenced by various factors. Animal studies support the neuroprotective effects of these hormones, including their metabolites, which modulate GABAA receptors. Androgens have not shown consistent protective or harmful effects in PD, though testosterone therapy may benefit energy levels and physical function in testosterone-deficient men (Bourque & Di Paolo, 2022; Bourque et al., 2024). ZINC000085567782 exhibited one of the most potent binding profiles among the screened compounds, with an overall mean binding energy of -9.20 kcal/mol. Its exceptional affinity for DRD2 at -12.5 kcal/mol not only significantly surpasses the positive control Dopamine (-4.72 kcal/mol) but also exceeds the highly stringent negative control threshold of -12.18 kcal/mol, indicating a particularly strong and favorable interaction with this critical receptor. The compound also demonstrated compelling binding to PINK1 (-11.2 kcal/mol), a target crucial for mitochondrial health, showing an affinity comparable to the negative control threshold (-11.39 kcal/mol) and more favorable than the positive control PRT062607 (-8.364 kcal/mol). Furthermore, its binding to DRD3 (-10.7 kcal/mol) aligns perfectly with the negative control threshold of -10.69 kcal/mol and significantly outperforms Dopamine (-4.766 kcal/mol).

ZINC000828327486- This compound belongs to the class of isoflavonoids, also known as isoflavones, which constitute a category of phenolic compounds widely present in plants from the Fabaceae family (such as soybeans, chickpeas, and red clover). From a structural point of view, isoflavonoids have a B ring connected to the C-3 position of the C ring, which has a 3-phenylchroman skeleton (Al-Maharik, 2019; Křížová et al., 2019). Isoflavonoids have shown antioxidant properties due to their ability to neutralize free radicals by donating hydrogen atoms from the hydroxyl group linked to the benzene ring. This mechanism helps protect against damage caused by oxidation and damage to macromolecules, leading to a reduction in low-density lipoprotein (LDL) levels (Wang et al., 2024a). Additionally, isoflavonoids stimulate the activation and expression of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD) and glutathione (GSH), while decreasing the activation and expression of hepatic malondialdehyde (MDA) through regulation of the Nrf2 and Peroxisome Proliferator-Activated Receptor-gamma (PPARγ) pathways (Suraweera et al., 2020). A study conducted by Biswas et al. (2021) aimed to identify potential flavonoids with activity against the Parkin protein, which is associated with Parkinson's disease. To achieve this, the researchers obtained Parkin's crystal structure and performed structural modifications to correct the missing residues. They then evaluated the stereochemical quality of the modified Parkin model, as well as its relationship with the amino acid sequence and the three-dimensional structure. This approach allowed the identification of potential flavonoids with therapeutic potential for PD. In this study, a variety of ligand molecules, including baicalein, apigenin, epicatechin, chrysin, daidzein, and quercetin, among others, were recovered and optimized. These molecules are flavonoids recognized for their neuroprotective properties, as reported in previous studies. Afterwards, ADMET and Lipinski filtering of the selected candidate flavonoids were performed. The structure of the Parkin protein was submitted to the CASTp server to identify ligand-binding sites within the protein. Subsequently, the protein and ligand molecules were prepared using Discovery Studio 2.5 to optimize angles and binding to the Parkin protein, followed by molecular docking. In conclusion, scientists highlight the potential of flavonoids as therapeutic agents for Parkinson's disease, highlighting their ability to interact with the Parkin protein. The presence of -OCH3 and -OH groups in flavonoid molecules facilitates a variety of interactions with Parkin's amino acid residues, contributing to its therapeutic efficacy.

Furthermore, our results suggest that flavonoids may protect Parkin against mutations associated with the development of PD, potentially slowing its progression. However, the exact mechanism by which flavonoids exert their effects in Parkinson's disease requires further investigation. However, this research concluded that the therapeutic potential of flavonoids in Parkinson's disease warrants further exploration, paving the way for the development of new treatment strategies (Biswas et al., 2021). Searches carried out in the literature indicate that studies relating less common phenolic compounds, such as isoflavonoids and neoflavonoids, have not been conducted in depth.

ZINC000828327486 presented a noteworthy multi-target binding profile with a mean binding energy of -9.25 kcal/mol. This compound demonstrated powerful interactions with DRD1 (-9.5 kcal/mol), DRD3 (-10.1 kcal/mol), MAPK10 (-10.0 kcal/mol), and PINK1 (-11.7 kcal/mol). For DRD1, its binding energy of -9.5 kcal/mol surpasses the negative control threshold of -9.145 kcal/mol and is considerably more favorable than the positive control, Dopamine (-5.256 kcal/mol). Similarly, for DRD3, its -10.1 kcal/mol affinity, while just shy of the -10.69 kcal/mol threshold, still dramatically outperforms the positive control Dopamine (-4.766 kcal/mol). Its interaction with MAPK10 (-10.0 kcal/mol) stands out as particularly strong, surpassing the negative control threshold of -8.46 kcal/mol and being substantially more favorable than the positive control SP600125 (-8.308 kcal/mol). Furthermore, for PINK1, ZINC000828327486 exhibited a binding energy of -11.7 kcal/mol, exceeding the negative control threshold of -11.39 kcal/mol and outperforming the positive control PRT062607 (-8.364 kcal/mol).

ZINC000002117475 - This compound belongs to the class of Neoflavonoids (NFs). They are a notable category of flavonoids present in nature, characterized by their distinct molecular structure of C6–C3–C6 (4-phenylcoumarin). Although they are not commonly found in foods and consumable plants, they are widely distributed, occurring in more than 50 plant species belonging to several botanical families, including Fabaceae, Clusiaceae, Leguminosae, Rubiaceae, Passifloraceae, Thelypteridaceae, and Polypodiaceae. NFs have been associated with a wide range of health benefits, exhibiting a diversity of biological activities. These activities include actions against osteoporosis, anti-inflammatory properties, antimicrobial effect, antiparasitic activity, antiandrogenic effects, anti-allergic properties, antioxidant capacity, antifungal activity, antidiabetic potential, and anticancer effect (Umer et al., 2023).

ZINC000002117475 stands out for its exceptional binding affinity to the Dopamine D2 receptor (DRD2) at -12.8 kcal/mol. This binding energy is not only significantly more favorable than the positive control Dopamine (-4.72 kcal/mol) but also surpasses the stringent negative control threshold of -12.18 kcal/mol, positioning it as one of the most potent DRD2 binders identified. Beyond DRD2, it also showed strong binding to DRD3 (-10.3 kcal/mol), closely approaching the negative control threshold (-10.69 kcal/mol) and outperforming the positive control Dopamine (-4.766 kcal/mol). Furthermore, its affinity for HTR2A (-10.1 kcal/mol) significantly exceeded the negative control threshold of -9.385 kcal/mol and was much more favorable than the positive control Serotonin (-5.303 kcal/mol). The mean binding energy for this compound across all targets was -9.33 kcal/mol. While neoflavonoids are a less explored class in the context of PD compared to other flavonoids, their reported wide range of biological activities, including antioxidant and anti-inflammatory effects, combined with these outstanding docking results, strongly advocate for ZINC000002117475 as a prime candidate for further investigation into its therapeutic mechanisms in Parkinson's disease.

ZINC000002121309 - This compound belongs to the class of Benzofurans. Benzofurans are heterocyclic organic compounds that result from the combination of a benzene ring with a furan ring. This class of compounds is widespread and is also present in many artificially produced pharmaceuticals and agrochemicals. Due to their distinctive structure, these compounds have diverse applications in both industry and pharmaceuticals (Hiremathad et al., 2015). Benzofuran-derived compounds bring several benefits to human health. They have antifungal, vasodilatory, antituberculous, anti-inflammatory, antiprotozoal, antioxidant, anticonvulsant, anticancer, anti-HIV, analgesic, antiparasitic, lipid-lowering, antidiabetic, antihypertensive, antimalarial, anti-Alzheimer's, hypothermiantarrhythmic properties (Abdel-Wahab et al., 2009).

Chao Yi et al. (2023) conducted a study aimed at developing, synthesizing, and evaluating new monoamine oxidase B inhibitors with improved pharmacokinetic properties for the treatment of Parkinson's disease. To this end, they carried out the rational design of the compounds, utilizing molecular modeling and structure-activity approaches to design compounds with potential MAO-B inhibitory activity and ideal pharmacokinetic properties, followed by the synthesis of the compounds in the laboratory. Soon after, a pharmacological evaluation was conducted, in which the synthesized compounds were tested for their selective inhibitory capacity against MAO-B. Fifteen compounds were tested in comparison to safinamide, a medicine already known and used to inhibit MAO-B. For *in vivo* tests, the compound that showed the most benefits was compound 14 (C14), indicating that it dose-dependently inhibited MAO-B, and had easily crossed the blood-brain barrier within 15 minutes. They then concluded that C14 showed a notable inhibition of the MAO-B enzyme in the brain of rats. As a result, C14 demonstrated potential efficacy in ameliorating dopamine deficits in the MPTP-induced rat model by significantly increasing dopamine levels in the striatum. Furthermore, compared with safinamide, C14 exhibited more robust anti-Parkinson effects in mouse models of PD. Thus, C14 is seen as a promising candidate for drug development in the treatment of Parkinson's disease.

ZINC000002121309 emerged as a top candidate with the most favorable mean binding energy of -9.40 kcal/mol across the entire panel of PD targets, underscoring its significant multi-target potential. This compound exhibited strong interactions with DRD1 (-10.1 kcal/mol), DRD2 (-11.9 kcal/mol), DRD3 (-10.5 kcal/mol), and PINK1 (-11.6 kcal/mol). Its DRD1 affinity of -10.1 kcal/mol significantly surpasses the negative control threshold of -9.145 kcal/mol and is markedly more favorable than the positive control, Dopamine (-5.256 kcal/mol). Similarly, for DRD2, its binding energy of -11.9 kcal/mol approaches the negative control threshold of -12.18 kcal/mol and is far superior to Dopamine (-4.72 kcal/mol). For DRD3, its affinity of -10.5 kcal/mol closely aligns with the negative control threshold of -10.69 kcal/mol, again outperforming Dopamine (-4.766 kcal/mol). Moreover, its binding to PINK1 (-11.6 kcal/mol) surpassed the negative control threshold of -11.39 kcal/mol and was more favorable than the positive control PRT062607 (-8.364 kcal/mol).

Parkinson's disease multi-target drug discovery

The multifactorial nature of PD, which involves a complex interplay of genetic and environmental factors leading to dopaminergic neuron loss, α-synuclein aggregation, oxidative

stress, and neuroinflammation, has made it clear that single-target drugs are often insufficient for achieving a profound therapeutic effect. The development of multi-target-directed ligands has emerged as a promising strategy to address this complexity (Katsoulaki et al., 2025).

In recent years, several key molecular target combinations have been explored in the quest for effective multi-target drugs for PD. A prevalent strategy involves the dual inhibition of monoamine oxidase B (MAO-B) and the antagonism of the adenosine A2A receptor (Boulaamane et al., 2024). This combination is particularly attractive as MAO-B inhibitors can increase dopamine levels and may possess neuroprotective properties, while A2A antagonists have been shown to alleviate motor symptoms. Other successful approaches have focused on dual inhibitors of MAO-B and acetylcholinesterase (AChE), aiming to address both motor and cognitive deficits associated with PD (Carradori et al., 2018). Computational methods, including virtual screening and molecular docking, have been instrumental in identifying novel compounds, and as well used on the prospection of natural compounds (Boulaamane et al., 2024).

Our manuscript's findings align with and expand upon the current state-of-the-art in multi-target drug discovery for PD. The use of an *in silico* pipeline, initiated with QSAR modeling followed by molecular docking, is a contemporary and efficient approach for screening large compound libraries. A key strength and novelty of our work is the focus on natural products, a rich source of bioactive compounds that are increasingly being investigated for their therapeutic potential in neurodegenerative diseases. Various studies have demonstrated the neuroprotective effects of natural compounds like curcumin and resveratrol (Viegas et al., 2022), which are known to act on multiple pathways including oxidative stress and inflammation. The identification of promising candidates from natural sources like diarylheptanoids and phenanthrenes contributes to the growing body of evidence supporting the use of these compounds in PD treatment.

The results presented here compare favorably with the existing literature and, in some aspects, offer a more comprehensive approach. While many published studies focus on dual-target ligands, our identified lead candidates exhibit predicted binding affinities across a broader spectrum of key PD-related targets, including not only dopaminergic receptors (DRD2) but also proteins involved in mitochondrial function (PINK1) and oxidative stress (Nrf2). Targeting PINK1 is a particularly innovative strategy, as restoring mitochondrial quality control is a promising avenue for neuroprotection. This broader multi-target profile suggests the potential for a more profound disease-modifying effect. For instance, the high predicted binding affinities of our top compounds to DRD2 are comparable to or exceed those of known inhibitors, while their simultaneous predicted interactions with PINK1 and α-synuclein represent a more holistic therapeutic strategy than many dual-target agents currently under investigation. The novelty of the identified chemical scaffolds, combined with their promising multi-target profiles, positions our findings as a significant contribution to the ongoing search for more effective treatments for Parkinson's disease.

Conclusion

This study employed a computational approach to identify natural compounds with multi-target therapeutic potential for the treatment of PD. The application of an *in silico* pipeline, integrating QSAR models and molecular docking, enabled the screening of a vast library of molecules and the identification of 10 lead candidates with promising profiles. Among the most promising compounds, notably ZINC000002117475 demonstrated an exceptional binding affinity for the dopamine D2 receptor (-12.8 kcal/mol), a critical target in PD therapy. Furthermore, ZINC000002121309 exhibited the most favorable mean binding energy across a panel of multiple disease targets, suggesting strong multi-target potential.

The study's contribution to drug discovery lies in demonstrating an effective computational workflow that can accelerate the identification of viable candidates from natural sources. More importantly, this work points to novel chemical classes, such as diarylheptanoids and phenanthrenes, as rich sources of bioactive compounds that can serve as starting points for the development of disease-modifying therapies—an urgent need in the field.

However, despite the encouraging computational results, we emphasize the need for experimental validation. The identified compounds are promising leads that now require rigorous investigation. Subsequent in vitro and in vivo studies are an indispensable step to confirm binding affinity, assess neuroprotective effects, and determine the pharmacokinetic and safety profiles of these candidates, thereby paving the way for the development of novel and more effective treatments for Parkinson's disease.

Conflict of interests

None.

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