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Research Article

IDENTIFICATION OF POSSIBLE MOLECULAR TARGETS OF POTENTIAL ANTI-PARKINSON DRUGS BY PREDICTING THEIR BINDING AFFINITIES USING MOLECULAR DOCKING TECHNIQUE

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ABSTRACT

Objective: Mechanistic study of newly reported anti-Parkinson agents by molecular docking to predict possible target.

Methods: Structures of newer drugs known anti-Parkinson agents were drawn using ChemBioDraw 2D software. Thereafter, they were converted to 3D structures using ChemBioDraw 3D software in which they were subjected to energy minimization using the MM2 method and then saved as PDB extension files, which can be accessed using the AutoDock Vina (ADT) interface. ADT 1.5.6 software version was used for molecular docking study.

Results: Various molecular targets were selected (D2/D3, D2, A2A, and MAO-B) and studied for Pardoprunox, Istradefylline, Rasagiline, and Bromocriptine. Pardoprunox, Istradefylline, and Bromocriptine had more affinity with their corresponding receptor with −6.9, −8.5, and −9.4 kcal/mol binding affinity, respectively, except Rasagiline, who has less affinity with its corresponding receptor (−6.4kcal/mol) and shown better affinity with 3pbl receptor (−6.7 kcal/mol).

Conclusion: Pardoprunox, Istradefylline, and Bromocriptine were found to act on D2/D3 (3pbl), A2A (3pwh), and D2 (4yyw), respectively, whereas Rasagiline found to be act on D2/D3 (3pbl) receptor. The results help in prediction of mechanism and interaction to various Parkinson's disease targets.

Keywords: Anti-Parkinson, Mechanism, Molecular docking, Autodock Vina.

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INTRODUCTION

Neurological disorders cause significant morbidity, mortality, disability, and socioeconomic losses and reduce the quality of life [1]. Few Indian neuroepidemiological studies have estimated the load of neurological diseases [2,3]. Nearly 33 million Indians have neurological disorders and they occur twice as often in rural areas [4]. Parkinson's disease (PD) is one of the neurological diseases that affect the ability to perform common daily activities. Most of the people with the PD will experience affect motor and non-motor movement. The most common motor symptoms of PD are tremor (a form of rhythmic shaking), rigidity of the muscles, and slowness of movement (called bradykinesia). A person with PD may also have trouble with posture, fatigue, anxiety, bad facial expression, loss of smell, poor balance, depression, failure in walking, sleep problems, and constipation, which are common non-motor symptoms of PD among others [5,6].

The cause of PD is still unknown; till, however, there is some evidence that genetics and environmental factors or a combination of both have a big role in PD [7]. It is also possible that there may be more than one cause of PD. PD is a multifaceted disease involving the activation of several cellular pathways in dopaminergic neurons. These pathways include MPTP toxicity, alterations in neurotransmitter levels, oxidative stress, glutamate toxicity, mitochondrial dysfunction, neuroinflammation, alterations in gene regulation, protein aggregation, and heavy metal poisoning [8]. These mechanisms share overlapping and redundant features and cause injury to the neurons. Diagnosis of PD in population-based studies is another important issue, and the presence of at least two of the three cardinal features of PD resting tremor, bradykinesia, rigidity without other causes of Parkinsonism is acceptable [9]. There is no curative therapy for PD till date. The two main approaches to treatment practiced are symptomatic therapy and protective therapy. Dopamine analogs and anticholinergic agents help to restore the dopamine levels this results in improving the movement disabilities, thus these drugs come under symptomatic therapy. Anticholinergic agents carry with them serious central nervous system adverse effects such as cognitive impairment and hallucination; other side effects are constipation and dryness of mouth. Protective therapy helps to reduce the side effects of drugs by their free radical scavenging properties, selegiline, and Vitamin E comes under this category [10]. The introduction of levodopa proved a landmark discovery in the treatment of PD, but the peripheral decarboxylation is a major limitation of the drug. Adjuvant therapy carbidopa is given to increase the bioavailability of levodopa in the brain. The present therapies although good for the management of the disease but as long-term use side effects occur. There is the tremendous research going on the new drugs approaches for the treatment of PD, which is believed to carry the minimum side effects. As per the several studies, it is concluded that one of the reasons of PD pathogenesis is oxidative damage. A lot of antioxidant drugs such as selegiline, bromocriptine, ropinirole, pramipexole, and many more are used to treat the oxidative stress, as with great benefits they have a long list of side effects that cannot be controlled during the therapy, so the new drugs under the studies will be taken and will show more effect in the treatment of the disease (Fig. 1) [10]. Recent years, atypical antipsychotics, such as phenothiazines and butyrophenones, which block postsynaptic receptors for dopamine receptor and cause extrapyramidal symptoms generally, resemble Parkinsonism. Antiemetics such as prochlorperazine and metoclopramide may also cause Parkinsonism. Reserpine produces a Parkinsonism-like symptoms by depleting dopamine available for release by the presynaptic neurons [11,12].

In addition to the therapeutic challenges, other antipsychotics like clonidine were found to be safe in the treatment of PD psychosis without degenerating Parkinsonism or causing other adverse effects, there are challenges related conducting the trials and many issues pertaining to optimal trial design, inclusion/exclusion criteria, subject recruitment, and study completion PD psychosis. Apart from these atypical antipsychotic drugs, other drugs which are not yet in the market, but under phase III such as SLV308 (Pardoprunox) and KW6002 (Istradefylline) was also found to be effective to treat PD [13]. The current research work was aimed to evaluate the mechanism of anti-Parkinson's drugs, which are approved or under clinical trials.

METHODS

To evaluate the mechanistic aspect of anti-Parkinson drugs under clinical trial, it is necessary to have the knowledge of the binding interaction of existing drugs with their respective target receptors. By taking into the considerations of various aspects of ligand-receptor interaction, a new scaffold can be developed. This can be achieved by computer-aided drug design, especially molecular docking [14-17]. Hence, we used Autodock Vina (ADT) 1.5.6 software [18] to find out the binding affinity (Kcal/mol) and compared with various targets. The selected anti-Parkinson agent's structure was drawn by ChemBioDraw ultra and thereafter converted to the 3D structure using ChemBioDraw 3D. All structures were optimized

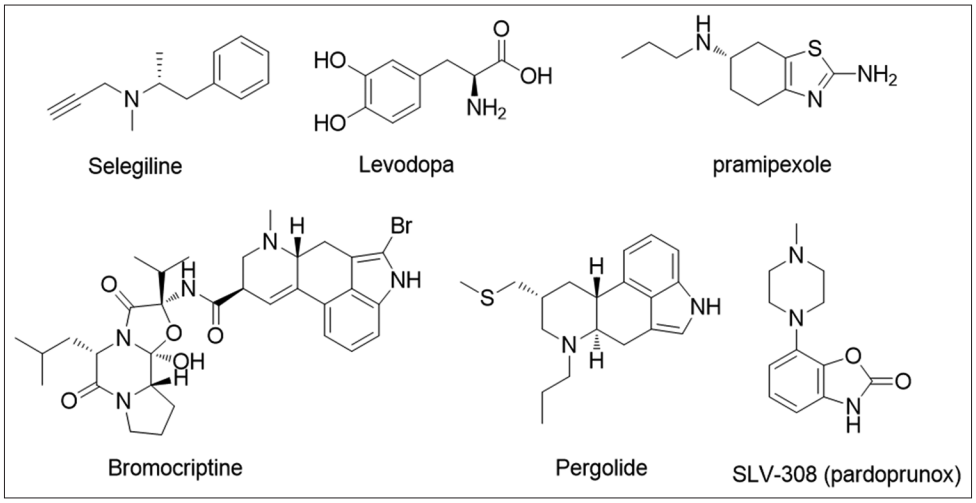


Fig. 1: Common anti-Parkinson's agents

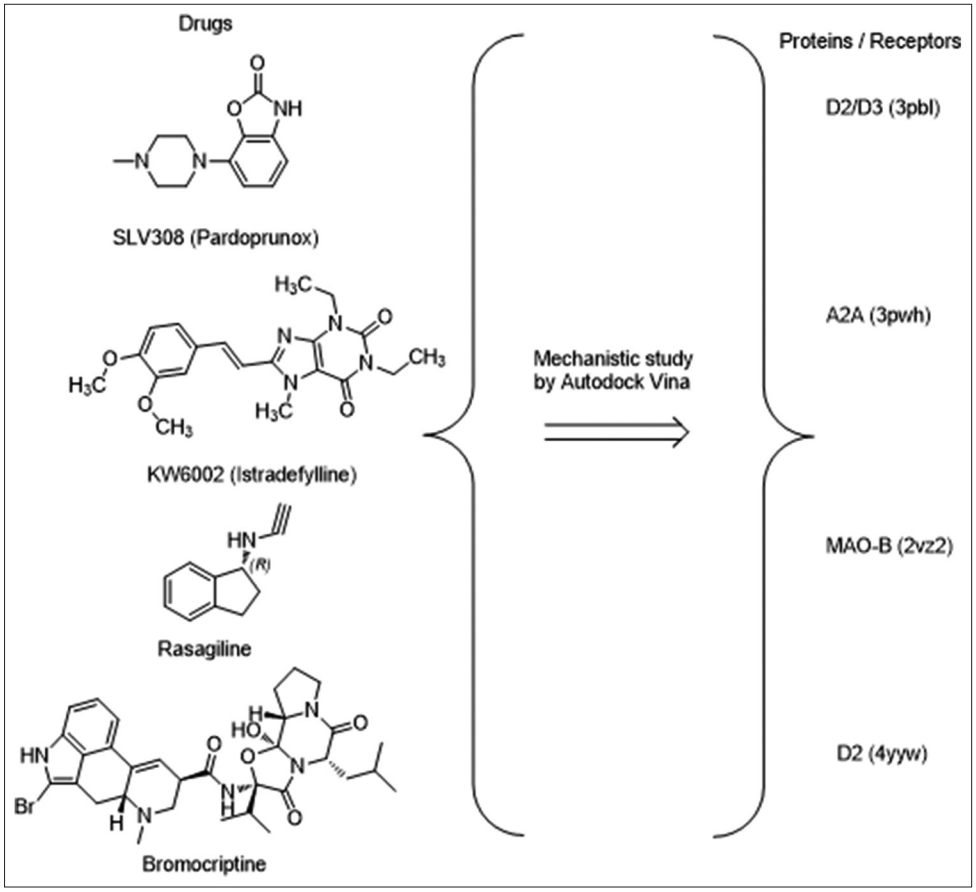
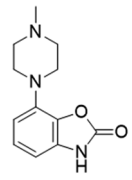
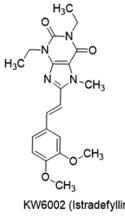
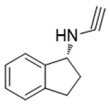
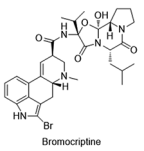


Fig. 2: Selected anti-Parkinsonism agents for comparative study of mechanism

Table 1: Comparison of estimated free energy of binding of the investigated ligands with different receptors

S. No.	Receptors	Drugs	Binding affinity (Kcal/mol) Target receptors			
			3pbl	3pwh	2vz2	4yyw
	D2/D3 agonist	 SLV308 (Pardoprunox)	−6.9	NA	NA	−6.3
	A2A antagonist	 KW6002 (Istradefylline)	−8.5	−8.5	NA	−7.4
	MAO-B selective inhibitor	 Rasagiline	−6.7	−2.9	−6.4	−4.8
	Pure D2	 Bromocriptine	−8.3	−3.9	NA	−3.9

*NA: No binding

by energy minimization using MM2 method [19] before ligand preparation and saved to pdb format. For comparative mechanistic study, proteins (receptor) such as D2/D3 (3pbl), A2A (3pwh), MAO-B (2vz2), and D2 (4yyw) were selected and downloaded from Protein Data Bank [20]. The results were analyzed for various interactions between ligand and target receptor by ADT.

RESULTS AND DISCUSSION

The main purpose of this study is to find out the mechanism of anti-Parkinson agents by investigated them to target proteins (receptors). Various molecular targets were selected, i.e. D2/D3, D2, A2A, and MAO-B and studied for Pardoprunox, Istradefylline, Rasagiline, and Bromocriptine as shown in Fig. 2.

All structures were drawn through ChemBioDraw 2D software to study the stereochemical effect and then converted to 3D structures using ChemBioDraw 3D software a later saved as pdb files so that it can be accessed by the ADT software. Different proteins were downloaded from the Protein Data Bank site rcsb.org specifically protein with code D2/D3 (3pbl), A2A (3pwh), MAO-B (2vz2), and D2 (4yyw) for this study.

All the chosen molecules were analyzed utilizing the ADT molecular modeling software. At first, the protein was validated by docking with the extracted ligand (Fig. 3). Ligands were prepared by the including of polar hydrogens, recognizing root, and changing over it to pdbqt, while proteins were set up by evacuating water molecules, repairing missing atoms, including polar hydrogens, as well as the Kollman charges. Further, the grid box was created keeping the ligand as middle; from that configuration file, "conf.txt" was prepared. At last, through command prompt docking was performed utilizing for ADT as "program files\the scripps research institute\vina\vina.exe --config conf.txt --log log.txt." It produced the record the docking score or output file with binding

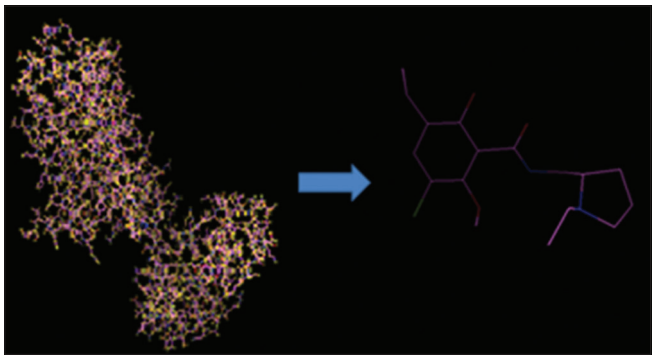


Fig. 3: Extracted and preparation of ligand from protein

affinity (Kcal/mol), comparative results were examined and presented in Table 1.

Binding interaction of Pardoprunox, Istradefylline, Rasagiline, and Bromocriptine was analyzed in detail. Pardoprunox, Istradefylline, and Bromocriptine had more affinity with their corresponding receptor binding and had scored −6.9, −8.5, and −9.4 Kcal/mol, respectively, except Rasagiline who has less affinity with its corresponding receptor (−6.4 Kcal/mol) but showed a better affinity with 3pbl receptor (−6.7 Kcal/mol). Therefore, cross-docking each ligand with different other receptors was analyzed and discussed below.

Pardoprunox has no affinity on 2vz2 and 3pwh receptor but has less affinity on 4yyw with a score of −6.3 Kcal/mol. Istradefylline has no affinity on 2vz2, less affinity with 4yyw (−7.4 Kcal/mol) compared to the affinity that it has with 3pbl (−8.5 Kcal/mol) which is same to that

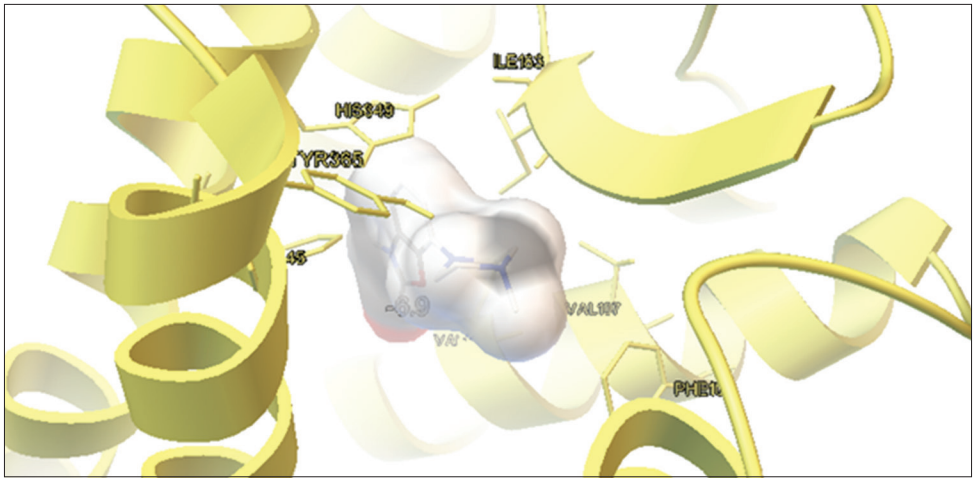


Fig. 4: SLV308 (Pardoprunox) and 3pbl receptor are showed as molecular surface and ribbon structure, respectively

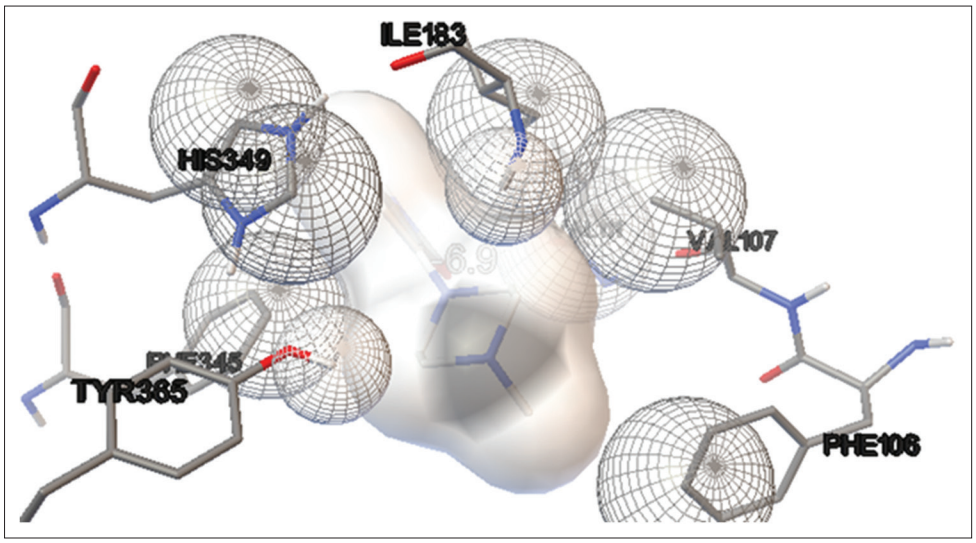


Fig. 5: Close interactions of SLV308 (Pardoprunox) with 3pbl receptor

with 3pwh. Rasagiline showed affinity with almost all the receptors with −6.7, −4.8, and −2,9 Kcal/mol binding affinities with 3pbl, 4yyw, and 3pwh, respectively. We found that Rasagiline has more binding affinity with 3pbl and therefore it can be a partial D2/D3 receptor agonist. Bromocriptine has no affinity with 2vz2 receptor, less affinity with 3pwh (−3.9 Kcal/mol), and better with 3pbl (−8.3 Kcal/mol) (Table 1).

To understand the binding interaction, and in-depth analysis was done for SLV308 (Pardoprunox) (Figs. 4 and 5). We found that Pardoprunox binds on the receptor 3pbl through interacting with various amino acid residues, i.e. ILE183, VAL107, PHE106, TYR365, PHE345, and HIS349. The NH group of Pardoprunox binds very closely to NH group of backbone of isoleucine 183 (ILE183) to form hydrogen binding; similarly, its carbonyl group has a hydrogen bonding to NH of histidine 349 (HIS349) present on its receptor. Although compared to other drugs interaction, it has more binding affinity with its receptor than Rasagiline ligand with 2vz2 receptor and Istradefylline ligand with 3pwh receptor, less than that of bromocriptine ligand with 4yyw receptor. By these interactions, we can understand that more is the interaction of the ligand with the receptor suggests the mechanism of drug.

CONCLUSION

We studied binding affinities of different novel anti-Parkinsonism drugs under clinical trials and compared with currently used drug Bromocriptine using ADT molecular software. However, the study has been done by docking each drug with its original receptor and by cross-docking them with different other receptors to determine on what receptor each drug has better affinity. Bromocriptine showed the maximum activity on 4yyw receptor (D2 receptor) with a binding affinity of −9.4 Kcal/mol. Rasagiline showed better affinity with receptor 3pbl (D2/D3 receptor) with a binding affinity of −6.7 kcal/mol and moderate affinity with receptor (2vz2 (MAO-B receptor). Istradefylline showed more binding affinity of −8.5 Kcal/mol to receptor 3phw (A2A receptor) and equally on 3pbl (D2/D3 receptor), whereas Pardoprunox showed −6.9 Kcal/mol binding affinity on receptor 3pbl (D2/D3 receptor). Therefore, we can suggest the mechanistic role of these drugs on the base of better binding affinities Bromocriptine, Istradefylline (KW6002), Rasagiline, and Pardoprunox (SLV308) as D2 and partial D2/D3 agonist.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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