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RESEARCH ARTICLE

Computational Screening of Heterocyclic L-Type Calcium Channel Blockers for Potential Anti-Parkinson's Activity

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ABSTRACT

Treating cardiovascular disorders like hypertension, arrhythmias, angina pectoris, and congestive heart failure involves using calcium channel blockers that bind allosterically to Cave L-type channels in myocytes in cardiac muscle. The heterocyclic compounds like 1, 4 dihydropyridines, phenyl alkyl amines, and benzodiazepines are calcium antagonists for cardiac diseases. The receptor protein CavAb in complex with Br- Verapamil was selected as a target for studying the interaction and prediction of calcium channel blocking activity of five heterocyclic compounds based on chemical structural features. using two popular software's, Auto Dock and PyRx. The results predicted the activity of "2-(3, 4-methoxyphenyl)-5-(2, 2-phenylethylamine)-2-propan-2-ylpentanenitrile" and was chosen as the best score -6.9 – (strong) by auto dock and -9.8 by PyRX compared to the standard verapamil. Verapamil: - PyRX: -6.5, - Auto Dock: -5.22, Higher anticipated activity compounds (strong): 1. [(3R, 4S)-1-[2-ethyl (dimethylamine)]-4 (four-methoxyphenyl)5-dihydro-3H-1-benzazepin-3-yl, -7-methylsulfanyl-2-oxo-4] Acetate: - PyRX: -7.9, 2. 2-(3,4-ethoxyphenyl) - Auto Dock: -5.37(2) Phenyl ethylamine -5-2-propane-2-ylpentanenitrile:- PyRX: -9.8 molecules with weak estimated activity - Auto Dock: -6.251. 5-dicarboxylate, 4-dihydropyridine-3, 6-dimethyl-4-(3-nitrophenyl)-1, diethyl 2, PyRX: -7.2, 2. 4'- hydroxy-3'-methoxy acetophenone, Auto Dock: -3.81 PyRX: -5.6, Auto Dock: -4.31, 3. 1,4-dihydropyridine-3,5-dicarboxylate is diethyl 2,6-dimethyl-4-(4-nitrophenyl):PyRX: -6.8, Auto Dock: -4.52.Calcium channel blockers antiparkinson's effect is under recent global investigations. The ADME parameters studied for the compound were Inhibition of CYP1A2, BBB permeability, distribution, total clearance, oral rat acute toxicity (LD50), and toxicity with Swiss-ADME software. Lead optimization by identifying a molecule's salient characteristics will contribute to toxicity and building safer analogs.

Keywords: Docking; Parkinson's; Heterocyclic; Auto dock Vina; PyRX

INTRODUCTION

Parkinson's disease is an illness that involves the progressive deterioration of the nervous system. It was considered a loss of axonal projections of dopamine neurons in the substantia naigra neuronal cytoplasmic aggregate of Alpha syn and Ubiquitin, indicating this disease's existence[1]. A recent study suggests that mitochondrial dysfunction is a course of Parkinson's disease. Heterocyclic compounds have medicinal properties and considering the various pharmacophore groups and rings responsible for biological activity, they can be selected from an existing chemical database for in-silico testing and prediction of biological activity based on the docking scores. Mitochondrial regulation, reactive oxygen species, neuronal damage, and intracellular calcium homeostasis are the possible mechanisms of the formation of Parkinson's disease. Controlling the reactive calcium through "voltage-gated calcium channels" is one of the methods to prevent Parkinson's disease. The "L-type calcium channels" are targeted for drug development of Parkinson's disease. The activation of L-type voltage channels penetrates holes on the surface of the plasma membrane. The deactivation of L-type channels is a strategy for controlling Parkinson's disease and Alzheimer's disease. The heterocyclic compound that modulates calcium channels is a promising candidate for lead compounds for drug development. Calcium channel drugs have been used extensively for cardiovascular diseases. The chemical classes

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of drugs used for Calcium channel blocking activity for cardiovascular disorders are 1 4 dihydropyridines, phenyl alkyl amines, and benzodiazepines. They bind to different calcium channels. The dihydropyridines and phenyl alkyl amines bind CavAb[2].

The receptor 5KMH is classified as a transporter protein. It is a complex of CavAb and verapamil with four chains ABCD of voltage-gated cation and sodium family, voltage-depended on channel Super family and ion transport domain with Alpha helical structure[3]. It is a Calcium Ion selective protein created by mutation of the NaVAb channel. Dihydropyridines and phenyl alkaylamines inhibit these. The phenyl alkaylamines for the Br Verapamil bind to the combined cavity of protein receptors, blocking the Ion conducting pathway. The heterocyclic compound selection was based on structure similarity mode with compounds of similar rings like phenyl alkaylamines and dihydropyridines[4].

The compounds selected are. "Diethyl 2, 6-dimethyl-4-(3-nitrophenyl) - 1, 4-dihydropyridine-3, 5-dicarboxylate" of PubChem id 282663[5], "[6], 4'-Hydroxy-3'- methoxide acetophenone", (acetovanilone) of PubChem id 2214 is an aromatic ketone used as anti-inflammatory anti-rheumatic[6]. "Diethyl 2,6-dimethyl-4-(4-nitrophenyl)- 1,4-dihydropyridine-3,5-dicarboxylate", with a hydrogen bond donor count one, and PubChem id 210905[7], "2,(3,4-methoxyphenyl)-5-[2-(3,4-methoxyphenyl)ethyl-methylamino]-2-propan-2-ylpentanenitrile" (VERAPAMIL) with a PubChem id 2520 is an approved calcium channel blocker standard drug[8] "[(3R,4S)- 1-[2-(dimethylamine)ethyl]-4-(4-methoxyphenyl)-7-methylsulfanyl-2-oxo-4,5-dihydro-3H-1-benzazepin-3-yl]" acetic acid with a PubChem id 14156293 with a hydrogen bond donor count 0[9] "2-(3,4-methoxyphenyl)- 5-(2,2-phenylethylamine)- 2-propan-2-ylpentanenitrile" with a PubChem id -10719948 with hydrogen bond donor count one and acceptor count 4[10].

MATERIALS AND METHODS

Computational techniques such as auto dock 4.2.7 and PyRX docking software were used for this in-silico study. The docking scores were calculated and compared. This comparison of the two complementary values will substantiate the accuracy of this study. The ADMET parameters were predicted using pkCSM.

"Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures" tool. The aforementioned computational tools predicted ant-Parkinsonism activity and their drug penetration to biological cavities for desired biological activity with a comparative result. The standard used to compare the docking scores of selected heterocyclic compounds was a well-established calcium channel blocker and anti-

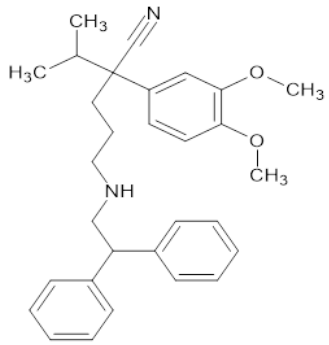

Fig. 1: 2-(3, 4-Dimethoxyphenyl)-5-(2, 2-phenylethylamine)-2-propane-2-ylpentanenitrile

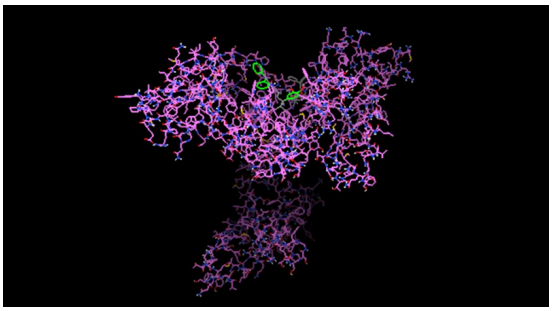

Fig. 2: 2-(3, 4-methoxyphenyl)-5-(2, 2-phenylethylamine)-2-propane-2-ylpentanenitrile docked image with CavAb (PDBID 5KMH)

hypertensive drug, verapamil. The protein target used for this study was CavAb (PDBID 5KMH) in complex with Br Verapamil[11]. The protein receptor was downloaded from RCSB PDB, and the ligands were selected based on a structure similarity with Phenylalkylamines and dihydropyridines. They were downloaded from the Pub chem database after citations. The files were saved in a separate folder containing Biovia Discovery Studio and auto dock tools. Biovia Discovery Studio visualizer cleaned and visualized the ligands and target.

Method using Auto dock 4.2.7

The Br.-Verapamil was removed from this receptor protein target, and cleaning was done. Charges and polar hydrogens were added, and PDBQT FILES were generated for both target and ligands. The grid parameters were set, and GPF files were generated. The docking tools were utilized to create the PDF. The auto grid and dock executable files were used to run the docking. The auto grid run generated the map files, and the docking run generated the DLG file, which was opened in M.S notepad. To obtain the result, the histograms were checked in each case. The most favorable docking with a minimum binding energy was selected and tabulated[12].

Method using PyRX docking

PyRX is integrated software with a multiple-ligand docking program. The downloaded Receptor target and ligands were saved in a separate folder. The PyRX software downloaded from a reliable source on the internet was also saved in the same folder on the computer. The system was an HP Elite Book with an Intel Core 5 8th generation processor with a graphical interface. "Biovia Discovery Studio" was downloaded to clean and visualize the target and ligands in the same folder. The files were saved in PDB format. PyRX was opened and loaded the target file, the open babel tool added the ligands at once, energy minimization was done at once, and the PDBQT files were generated at once. Vina wizard was used, the grid parameters were set, and docking was performed. The results were obtained in a single step with the ease of convenience [13].

The results were compared against the standard in each case, and a software-wise comparison was done. The results of both methods were complementary. The difference in values may be due to using different force fields in each case.

RESULTS

Table 1: ADMET parameters of high-scoring compound 2-(3,4-dimethoxyphenyl)-5-(2,2-diphenylethylamino)-2-propan-2-ylpentanenitrile

Table 1: Docking Scores of heterocyclic compounds, which shows the predicted biological activity; maximum negative score shows maximum activity (N=10)

Compound	Score (Auto dock) 4.2.7	Score (PyRX)	PDBID
"Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate"	-3.81	-7.2	282663
"4'-Hydroxy-3'-methoxy acetophenone"	-4.31	-5.6	2214
"Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate"	-4.52	-6.8	210905
(VERAPAMIL)	-5.22	-6.5	2520
"[(3R,4S)-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-7-methylsulfanyl-2-oxo-4,5-dihydro-3H-1-benzazepin-3-yl]" acetate	-5.37	-7.9	1.4E+07
"2-(3,4-methoxyphenyl)-5-(2,2-phenylethylamine)-2-propane-2-ylpentanenitrile"	-6.25	-9.8	1.1E+07

DISCUSSION

The present study revealed that among the five heterocyclic compounds selected for the study, (2-(3, 4-methoxyphenyl)-5-(2, 2-phenylethylamine)-2-propan-2-ylpentanenitrileexhibited minimum binding energy which indicated a good predicted biological activity [Table 1]. The binding energies were calculated as -6.25 (Auto dock) and - 9.5 (PyRX). The values are complementary, and the difference exists due to the exhaustiveness parameter, the grid parameters, and the difference in force fields. The next compound of interest found is [(3R, 4S)-1-[2-(dimethyl amino) ethyl]-4-(4-methoxyphenyl)-7-methylsulfanyl-2-oxo-4, 5-dihydro-3H-1-benzazepin-3-yl] acetate. Binding energy -5.37 and -7.9 for auto dock and PyRX, respectively. PyRX always showed a high negative value for binding energy. The compound of choice that gave a good score can be considered as a lead compound for anti-parkinsonism drug development. It may inhibit the voltage-gated L-type calcium ion channels, decreasing calcium ion entry to cells and reducing neurons' hyper excitability.

Table 2: ADMET parameters of high-scoring compound 2-(3,4-methoxyphenyl)-5-(2,2-phenylethylamine) -2-propane-2-ylpentanenitrile

Table 2:

"Water solubility"	-5.047	log mol/L
"Caco2 permeability"	1.016	log Papp in 10^{-6} cm/s
"Intestinal absorption" (human)	93.507	% Absorbed
"Skin Permeability"	-2.766	log Kp
"BBB" permeability	-0.436	Numeric (log BB)
"Distribution"	CNS permeability	-1.934
"CYP1A2 inhibition"	Yes	Categorical (Yes/No)
"Total Clearance"	1.023	log ml/min/kg
"Oral Rat Acute Toxicity (LD50)"	2.688	$Mol.kg^{-1}$
"Toxicity"	Oral Rat Chronic Toxicity (LOAEL)	2.143
"Toxicity"	Hepatotoxicity	

pkCSM
"Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures"

Further structural modifications and in vivo studies must be done for better drug development. The ABMET parameters of these compounds were found satisfactory and are represented in [Table 2]. Calcium channel blockers as neuroprotective agents in Parkinson's disorder should be further investigated, and new molecules may be developed as potential drugs. Any discovery intended to improve human health is of high value.

Molecular docking is an Insilco technique that predicts the mode of interaction of small molecules.

Like drugs to macromolecular targets, the small molecule can be a phytochemical or a synthetic heterocyclic compound, a semisynthetic derivative, or a natural or marine chemical. This technique helps drug discovery, eliminating the non-significant compounds from further biological testing. It saves money and time in the research of drugs. We have selected five heterocyclic compounds and a standard drug, verapamil, for this Insilco study, which was based on the structure of the compounds. The receptor protein involved in the present study is 5KMH, which is CavAb bound to Br- Verapamil. It is a bacterial homotetrameric model. This receptor is inhibited dihydropyridines and phenyl alkyl amines. Br-Verapamil binds to the receptor's central cavity pocket and acts as a calcium ion channel blocker. Experimental evidence suggests that dihydropyridines act as calcium channel blockers by blocking L-type ion channels and may protect against Parkinson's disease. Another mechanism of action of antiparkinsonian drugs is to increase the dopamine levels in the brain. This may, in turn, decrease cholinergic activity, which may suppress the tremors associated with Parkinson's disease. Verapamil is an established drug for PD.

The present study revealed that among the five heterocyclic compounds selected for the study, (2-(3, 4-methoxyphenyl)-5-(2, 2-phenylethylamine)-2-propan-2-ylpentanenitrileexhibited minimum binding energy which indicated a good predicted biological activity [Table 1]. The binding energies were calculated as -6.25 (Auto dock) and - 9.5 (PyRX). The values are complementary, and the difference exists due to the exhaustiveness parameter, the grid parameters, and the difference in force fields. The next compound of interest found is "[(3R, 4S)-1-[2-(dimethyl amino) ethyl]-4-(4-methoxyphenyl)-7-methylsulfanyl-2-oxo-4, 5-dihydro-3H-1-benzazepin-3-yl] acetate". Binding energy -5.37 and -7.9 for auto dock and PyRX, respectively. PyRX always showed a high negative value for binding energy. The compound of choice that gave a good score can be considered as a lead compound for anti-parkinsonism drug development. It may inhibit the voltage-gated L-type calcium ion channels, decreasing calcium ion entry to cells and reducing neurons' hyper excitability.

CONCLUSION

Molecular docking is a valuable tool for drug discovery. Heterocyclic compounds with different pharmacophore groups or ring systems exhibit versatile biological activities when tested in silico and in vivo. Five compounds were tested Insilco for anti-parkinsonism activity, and a lead compound with the least binding energy was identified. The calcium channel-blocking activity of anti-parkinsonism drugs is a current topic under investigation. The potential compound selected may be modified and tested in vivo to establish the activity. More heterocyclic compounds with different biological activities must be identified as a part of high throughput screening before proceeding into in vivo animal models and clinical studies. Insilco drug development is vital; it will save money and time.

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