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A Computational Approach towards Targeting Parkinson's Disease: The Discovery of Potential Inhibitors against Alpha-Synuclein and Pten-Induced Putative Kinase 1 Protein

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Abstract

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease caused by the degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNpc), which influences the basal ganglia network that results in a host of the motor and cognitive deficits. The autosomal dominant and recessive form of Parkinson's disease caused by the abnormal aggregation of Alpha-synuclein and PTEN- induced putative kinase 1 protein. The present study focuses on developing lead compounds and antibody mimetic oligopeptides for inhibiting PD targets such as SNCA and PINK1. Virtual screening and docking were performed to find the best lead compounds further the docked complex were subjected to a molecular dynamics approach to predict the stability and the lowest conformation energy of the compounds. Nearly 5780 Similar compounds of carbidopa/levodopa are used to predict the potential lead molecules inhibiting the target proteins. Four potential lead compounds selected from a total of 1865 compounds based on their drug likeness properties and docking score. Biological activity prediction and statistical analysis were used for validating the inhibition of lead molecules against target protein.

Keywords: Alpha-synuclein • PTEN- putative kinase 1 • Parkinson's disease • Computational drug design • Protein aggregation • Gene mutation

Introduction

Parkinson's disease is one of the common complex progressive neurodegenerative diseases. This devastating neurodegenerative disease that predominately affects the dopamine producing neurons in a specific area of the brain called Substantia Nigra (SN) [1]. The lossof dopaminergic neurons in the Substantia Nigra pars compacta (SNpc) leads to the characteristic motor and non-motor symptoms. The pathophysiological changes associated with PD may start before the onset of motor features such as progressive involuntary tremors, gait, fatigue, complications in walking, speech, swallowing [2] and may include numerous NMS that encompass behavioral changes, autonomic dysfunction, sleep disorders, depression, sensory abnormalities, and cognitive changes [3,4]. The Parkinson's disease Foundation reports that approximately 1 million Americans currently have the disease. The incidence rates (IRs) in different countries vary from 1.5 to 20 per 100,000 per year [5].

Recently a few advances in the understanding of the pathogenesis of the disease [6]. The autosomal dominant PD caused by the mutations in SNCA, LRRK2, and VPS35 genes and PINK1, DJ-1, and Parkin are responsible for an autosomal recessive form of PD. SNCA and PINK1 proteins have a remarkable contribution in the disease enhancement of Parkinson's disease. It also associated with the early onset form of the disorder, which begins before the age of 50 [7,8].

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Alpha-synuclein protein, that is enormously present in neurons. It is highly conserved proteins, which controls the vesicular neurotransmission as well as regulate the dopamine neurotransmission [1]. A point mutation and missense mutation have been reported in the gene SNCA at PARK1 locus and the Cytogenetic Location: 4q22.1, which is the long (q) arm of chromosome 4 at position 22.1. The numerous mutational changes in the SNCA gene disturb the normal function of the Alpha-synuclein protein. It regulates the abnormal aggregation of protein to form insoluble fibrils associated with lewy bodies [9]. The unusual accumulation of the protein leads to cell damage and ultimately neuronal death.

PINK1 encodes 581 amino acid protein called phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) protein. It is a serine/threonine kinase protein, which maintains the regulation and health quality of entire mitochondria by removal of dysfunctional mitochondria [10]. Numerous types of mutations occur in the gene at the locus of PARK6 and the Cytogenetic Location: 1p36.12, which is the short (p) arm of chromosome 1 at position 36.12 [11]. This mutation induces the mitochondrial dysfunction and finally causes the dopamine depletion. PINK1-Parkin pathway controls mitochondrial function and autophagy. The formation of Parkin aggregates and enhanced the accumulation of PINK1 during the pathogenesis of PD [12].

Although Parkinson's disease can't be cured, the subsequent introduction of carbidopa and levodopa has revolutionized the field of PD therapeutics [13]; medications might significantly improve the symptoms. Treatment for each person with Parkinson's is based on his or her symptoms. There is still a need to improve current strategies of treating these symptoms, together with a need to alleviate non-motor symptoms of the disease [14]. At some instinct non-motor symptoms play a dominant role in the management of Parkinson's disease [15].

Novel drug targets will be uncovered through pathophysiological insights gained from the identification of the role of genetic mutations that are responsible for hereditary forms of PD, and future therapies targeted

towards these mutations will have broader efficacy against sporadic PD than the currently available symptomatic treatments [16]. The present study emphasizes to gain adequate knowledge about the underlying mechanism of disease progression and discover potential inhibitors against Parkinson's disease through molecular docking and dynamics approaches. Prediction of novel drug molecules against the aggregation of SNCA and PINK1 proteins will have a great impact in the management of PD.

Materials and Methods

Retrieval of target Protein

Alpha-synuclein (SNCA) protein (PDB ID: 1XQ8) and PTEN induced putative kinase 1(PINK1) protein (PDB ID: 5TR5) [17] retrieved from Protein Data Bank (PDB) [18]. The human SNCA protein contains 140 amino acids. Val3-Val7 and Lys45-Thr92 form curved α-helices followed by the short extended region Gly93-Lys97 and a highly mobile tail Asp98-Ala140 [19]. PINK1 protein consists of 76 amino acids in sequence. The lowest energy structures possess four beta sheets and two α-helices [20]. These two targets didn't have any heteroatoms/ligand inhibitors and both are the NMR (Nuclear Magnetic Resonance Spectroscopy) solved structures.

Active site Prediction

The active site of protein targets was predicted using Computed Atlas of Surface Topography of Proteins (CASTp). It shows the different possible pockets of active sites on the protein chains [21].

Retrieval of Inhibitory Compounds

Inhibitory compounds are the small molecules which act against the PD targets. Similar Compounds of Carbidopa and levodopa drugs have chosen for this study. Totally 1252 carbidopa 4526 levodopa molecules were retrieved from PubChem database [22].

Prediction of ADMET properties

ADMET prediction is an essential procedure for the identification of lead molecules. It checks whether the small molecules having drug-likeness properties or toxic compounds. The ADMET properties of dietary compounds were computed using Qikprop programme from Schrodinger suite. Properties of the compound revealed Absorption, Distribution, Metabolism, Excretion, and Toxicity of the compound [23]. It facilitates to compare the molecular properties of a specific compound with those of 95% of known drugs.

Molecular Docking

Preparation of Protein

The downloaded proteins are prepared by protein preparation wizard from Maestro 11.7. The protein is carried out for preprocess to update the missing side chains. Then refine and modify the protein structure through preferring the correct chain and delete the unwanted water molecules. Hydrogen optimization is given enough resolution to fix the orientation. Energy minimization was performed in the presence of restraints, which helps to relax the side chain of the protein. The newly generated protein model was saved to a PDB file for docking.

Preparation of Ligand

Ligands are prepared using LigPrep Programme from Schrodinger suite. The ligand was prepared by addition of hydrogen molecule and removal of a salt/water molecule. Structural conformations of all the small molecules were done by ligand preparation. Further, the prepared ligand structure has taken to docking studies.

Glide docking

The prepared targets were subjected to receptor grid generation. The grid was generated at the active site region of the target protein [2]. All the prepared ligand molecules attempted to dock with the target protein at this region. Molecular docking of the target protein and similar compounds of Carbidopa and Levodopa were carried out using Glide module from Schrodinger suite. Initially, the Carbidopa and Levodopa molecules screened using SP (Standard Precision) docking followed by XP (Extra Precision) docking. The XP method weeds out false positives and provides a better correlation between good poses and good scores. Glide was run in rigid mode; the latter automatically generates conformations for each inhibitory compounds. Final scoring is then carried out on the energy-minimized poses. The scoring function is used to score the poses. Glide Score was selected as the scoring function to rank the poses of each inhibitory compound.

Biological Activity Prediction

Therapeutic activity of top ten best docked compounds was predicted using PASS (prediction of activity spectra for biologically active substances) Server [24,25]. The server predicts the activity of compounds based on the active threshold value. Possible activity (Pa) and inactivity (Pi) of the compounds were predicted. The compound which has Pa>0.7 is quite prone to show the activity in the experiment, If the value of Pa lies between 0.5 < Pa < 0.7, the compound is liable to display the activity in an experiment. All the compounds have good expected biological activity.

Validation of Docked Complex

Validation of docking is the useful method to pick the best docked complex among a number of docked complexes. Binding energy and Inhibit constant of the compound identified using Autodock 4.0 tool. Docked complex are validated by the linear regression method. The linear regression analysis is performed using the statistical package of SPSS server. The linear regression graph is obtained from the docking score (X-Axis) versus inhibits constant (Y-Axis). Based on the docking score, biological activities and linear regression graph, best compounds were selected for further dynamic studies.

Molecular Dynamics

Molecular Dynamic Simulation was performed by GROMACS. The GROMOS43a1 force field was used for simulation and energy calculation. The constant temperature was 300 K and an integration step of 2.0 fs was given. MD simulation has carryout for 10 ns time with the presence of water molecules in the system. Finally, Root Mean Square Deviation (RMSD) was calculated for checking the stability of the target protein with their native motion.RMS graphs used to understand the residue fluctuation of the receptor protein.

Result and Discussion

Identification of active site

The active site regions of the target protein has predicted by CastP programme. The active site residues of SNCA is Lys10, Ala17, Lys21, Ala69, Val70, Gly73, Ala76, Val77, Lys80, Glu83, Gly84, Ser87 and Val3, Val5, Glu16, Asp18, Thr21, Ile23, Val30, Lys32, Val43, Ile44, Val67, Ile69 are the binding residues of PINK1.

ADME-Toxicity Prediction

Totally 5780 small molecules were retrieved from Pubchem database. These are selected based on the criteria of 90% similarity of carbidopa and levodopa structures. Among these 1252 compounds related to carbidopa remaining 4526 of them related to Levodopa. Further, these compounds preferred for the ADMET prediction to check the druglikeness properties. 426 carbidopa and 1234 levodopa molecules selected based on the Lipinski's rule of five. These screened compounds taken for further docking studies.

Glide XP Docking

Screened compounds were subjected to dock against target proteins where all the inhibitory compounds were searched for best orientation and conformation which can inhibit target proteins and compared to the docked

complex of commercially availed drugs.

Docking: SNCA with Carbidopa and similar compounds of Carbidopa

Carbidopa and similar compounds of carbidopa (426 screened compounds) were subjected for docking against human SNCA. Initially, based on scoring function, all compounds were screened. Glide score of carbidopa was -3.5. The carbidopa interacted with THR81 and LYS80 residue of SNCA forming five hydrogen bonds. Top ranking ten compounds have good glide score and also potentially interacted with SNCA. Out of ten compounds CID69584858 docking score was -6.3 that formed 5 hydrogen bonds (Figure 1a) interacting with an already predicted active site residues such as Lys80, Gly84, Ser87. (Table 1).

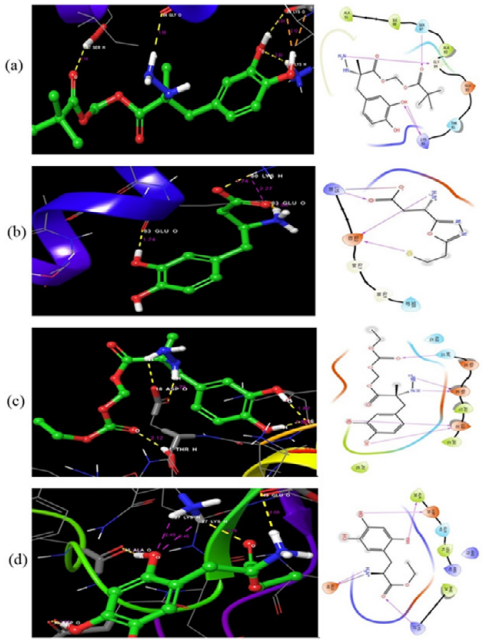

Figure 1: Molecular interaction of the best inhibitors against target proteins and the Ligand interaction diagram
SNCA inhibitors: a) SNCA with CID69584858; b) SNCA with CID101744537
PINK1 inhibitors: c) PINK1 with CID69584883; d) PINK1 with CID55270478
Ribbon structure indicates the target protein, ball and stick structure represent the ligand and the dotted lines represent the H bonds.

Docking: SNCA with Levodopa and similar compounds of Levodopa

Levodopa and 1234 similar compounds carried out for docking against human SNCA protein. The glide score of Levodopa is -2.0. GLY85 and SER87 are the protein residues interacted with levodopa compounds using two hydrogen bonds. Top ten compounds glide score ranges between -4.9 to -7.5. Among the ten molecules CID101744537 considered as the best inhibitor based on the criteria of docking score -7.5 and four hydrogen bonds (Figure 1b) stabilizes the ligand- receptor complex. The hydrogen bond connects the ligand molecule with the target protein at the active site residue of Lys80 and Glu83 (Table 1).

Docking: PINK1 with Carbidopa and similar compounds of Carbidopa

Similar docking was performed with carbidopa and 426 similar compounds of carbidopa against human PINK1 protein. The carbidopa docked to the target by 2 hydrogen bonds with glide score -3.2 (Figure 1c). The top ten ranked docked inhibitors have high potential inhibition activity against the target. Out of these ten CID69584883 has good binding energy and glide score is -6.8. Five hydrogen bonds were formed between the ligand and Glu16, Asp18, Thr21 residues of protein. The interacting residues as well as hydrogen bonds were listed in (Table 1).

Docking: PINK1 with Levodopa and similar compounds of Levodopa

Carbidopa and similar compounds of carbidopa (1234 screened compounds) were subjected for docking against human PINK1. Initially, based on scoring function, all compounds were screened. Glide score of levodopa was -4.1 (Figure 1d). The levodopa interacted with Lys35 residue of PINK1 forming one hydrogen bond. Top ranking ten compounds have good glide score and also potentially interacted with SNCA. Out of ten compounds CID55270478 docking score was -7.5 that formed 2 hydrogen bonds interacting with an already predicted active site residues such as Lys32. (Table 1).

Finally, we are targeted SNCA and PINK1 protein using different carbidopa/ levodopa inhibitory compounds. When compared to the existing drug molecules, the newly predicted lead compounds such as CID69584858, CID101744537, CID69584883, CID55270478 compounds posess good binding affinity towards the target proteins .Therefore, the proposed interactions of these compounds with SNCA and PINK1 suggest a possibility to inhibit the catalytic function of the enzyme. In addition to the observations of the interactions between SNCA and potential inhibitors, it can be seen that

Table 1: Molecular interaction of best compounds with target proteins.

Docking result of Ligands against SNCA				
Compound ID	**Docking score**	**No of H bonds**	**Residues**	**H-bond Distance**
69584858	-6.3	5	87 SER H : O	2.14
			84 GLY O: H	1.98
			80 LYS O : H	2.01
			80 LYS H : O	2.30
			80 LYS O : H	2.10
101744537	-7.5	4	83 GLU O : H	1.55
			80 LYS H : O	1.74
			80 LYS H : O	2.27
			83 GLU O : H	1.74
Docking result of Ligands against PINK1				
69584883	-6.8	5	16 GLU O : H	1.82
			16 GLU O : H	1.87
			18 ASP O : H	1.75
			18 ASP O : H	2.12
			21 THR H : H	2.50
55270478	-7.5	2	32 LYS H : O	1.96
			32 LYS H : O	2.45

the combination of pharmacophore, virtual screening and molecular docking efforts is successful for discovering more effective inhibitory compounds against PD.

Biological activity prediction

Biological activity prediction and linear regression analysis is used to validate the top scoring compounds. All the compounds showed some significant biological activities such as Antiparkinsonian, rigidity reliever, Dopamine release stimulant, Dopamine precursors, Neuotrophic factor enhancer, anti-acute neurologic disorders, Neuotransmitter antagonist etc. So biological activity analysis is justifying, our top scoring compounds has not only binding affinity but also has good biological activity which can be used for treating against target proteins (Table 2).

Regression-correlation of top scoring compounds

The linear regression analysis between the independent variable inhibit constant and dependant variable binding energy reveals the efficiency of inhibit constant against the target. The regression graph of the top scoring compounds shows good inhibition effect against the receptor protein (Figure 2). The linear regression analysis performed for all top scoring compounds resulted in regression correlation (R2) of the carbidopa related compound CID69584858 is 0.831 (Figure 2a); followed by the R^2 value of compound CID101744537 had 0.620 (Figure 2b). R^2 value of the compound CID 69584883 against PINK was 0.670 (Figure 2c) and the regression coefficient (R^2) of CID55270478 was 0.767 (Figure 2d). Specifically, these four compounds were lies near to the regression line among all ten compounds.

Table 2: Possible activity and inactivity of top scoring compounds against target proteins.

Compound ID	Pa> Pi		Activity
	Pa	Pi	
69584858	0,230	0,075	Dopamine release stimulant
	0,039	0,017	Dopamine precursors
	0,207	0,062	Neuotrophic factor enhancer
	0,710	0,001	DOPA decarboxylase inhibitor
101744537	0,696	0,001	DOPA decarboxylase inhibitor
	0,690	0,004	Neurotransmitter antagonist
	0,048	0,025	Neuraminidase inhibitor
	0,172	0,090	Antiparkinsonian, tremor relieving
	0,104	0,095	Neurotrophic factor
69584883	0,039	0,017	Dopamine precursors
	0,625	0,002	DOPA decarboxylase inhibitor
55270478	0,338	0,144	Neurotransmitter antagonist
	0,290	0,133	Prion diseases treatment
	0,140	0,051	Neuropsin inhibitor
	0,196	0,110	Dopamine release stimulant
	0,172	0,090	Antiparkinsonian, tremor relieving
	0,250	0,223	Dementia treatment
	0,039	0,031	Neuropathy treatment

Compound id – PubChem database ID, Pa – possible activity, Pi – Possible inactivity, Activity – Activity of the compound. The compound which has Pa>0.7 is quite prone to show the activity in experiment, If the value of Pa lies between 0.5 < Pa < 0.7, the compound is liable to display the activity in experiment. Activity of all the compounds was showed efficient inhibition to the target. All the compound showed possible activity against the PD.

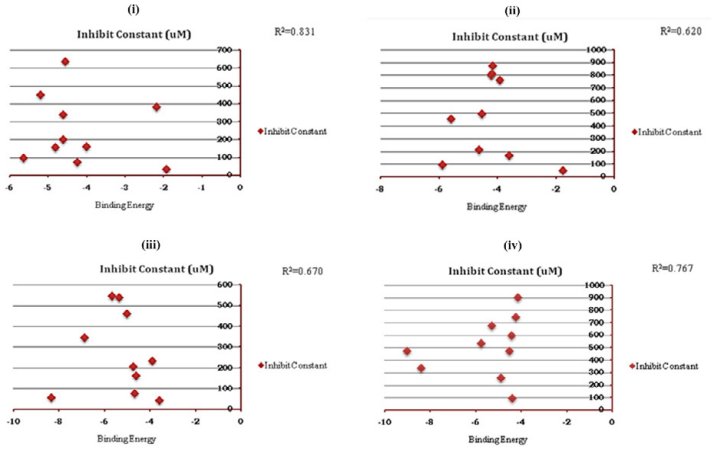

Figure 2 :Linear Regression Analysis Graph

Top ten docked complex subjected for regression correlation analysis, X axis – Binding energy, Y axis – inhibiting constant.

(a) Regression correlation of carbidopa related SNCA inhibitor
Regression correlation (R^2) is 0.831

(b) Regression correlation of levodopa related SNCA inhibitor
Regression correlation (R^2) is 0.620

(c) Regression correlation of carbidopa related PINK1 inhibitor
Regression correlation (R^2) is 0.670

(d) Regression correlation of levodopa related PINK1 inhibitor
Regression correlation (R^2) is 0.767

The numerous validations suggest these inhibitory compounds having good docking quality and have an inhibitory effect against the target (Table 3). The R^2 value is more than 0.6 suggests strong and positive correlation between the two continuous variables. The selected complexes are further considered for dynamics studies.

Molecular dynamics (MD) studies of the docked complexes

To study the stability of the docked complexes, Molecular dynamics simulation of best docked complex was performed using Gromacs. After the careful validation of docking, four best complexes have chosen as the representative candidate for molecular dynamics simulation. The complexes are energy minimized and equilibrated followed by MD simulation carried out for 10 ns time. The complex stability during dynamics can be checked by plotting RMSD and RMSF graphs of the protein studied (Figure 3).

Molecular Dynamics of SNCA and their carbidopa related inhibitor

The trajectory files obtained during simulation was used to calculate RMSD and RMSF. RMSD plot shows that SNCA with CID69584858 has attained

Table 3: Regression correlation of best inhibitors.

SNCA Inhibitors				
Compound	R	R Square	Adjusted R Square	Std.Error of the Estimate
CID69584858	0.912[a]	**0.831**	0.810	0.52738
CID101744537	0.787[a]	**0.620**	0.573	0.73450
PINK1 Inhibitors				
CID69584883	0.819[a]	**0.670**	0.629	0.86038
CID552704878	0.876[a]	**0.767**	0.738	0.90417

The linear regression correlation of inhibit constant and binding energy of the inhibitors are computed by SPSS package.

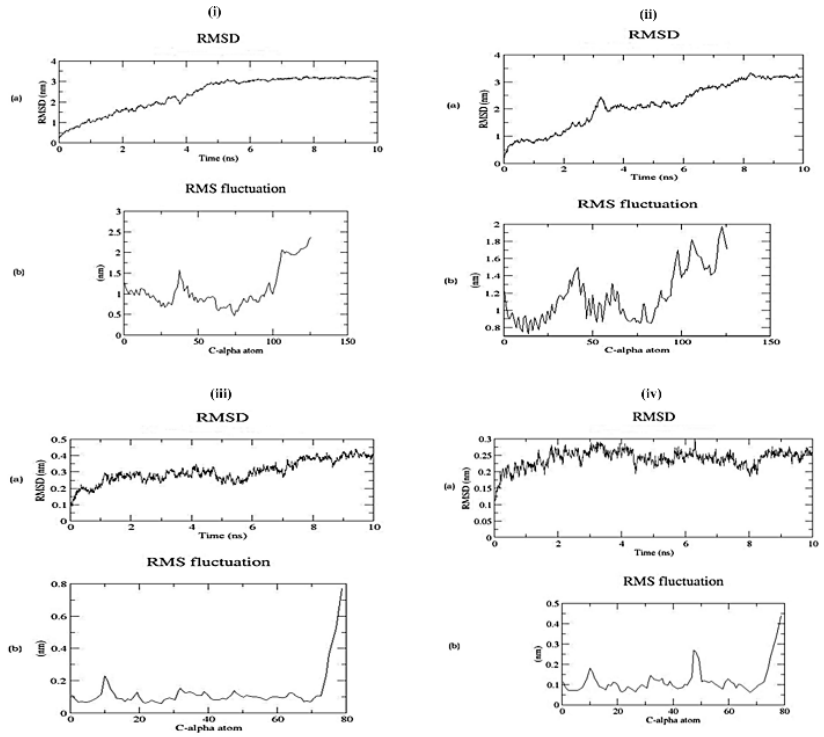

Figure 3: MD simulation of best docked complex.

(i) Molecular dynamic simulation of docked complex of CID69584858 with SNCA protein
  (a) RMSD plot of the complex CID69584858 with SNCA:The plot generated by RMSD value versus Time OPLS
  (b) RMS fluctuation Graph: The majority of C-alpha atoms fluctuated from 0.6nm to 1.75nm

(ii) Molecular dynamic simulation of docked complex of CID101744537 with SNCA protein
  (a) RMSD plot of the complex CID101744537 with SNCA:The plot generated by RMSD value versus Time OPLS
  (b) RMS fluctuation Graph: The majority of C-alpha atoms fluctuated from 0.8nm to 1.3nm

(iii) Molecular dynamic simulation of docked complex of CID69584883 with PINK1 protein
  (a) RMSD plot of the complex CID69584883 with PINK1:The plot generated by RMSD value versus Time OPLS
  (b) RMS fluctuation Graph: The majority of C-alpha atoms fluctuated from 0.09nm to 0.2nm

(iv) Molecular dynamic simulation of docked complex of CID55270478 with PINK1 protein
  (a) RMSD plot of the complex CID55270478 with PINK1:The plot generated by RMSD value versus Time OPLS
  (b) RMS fluctuation Graph: The majority of C-alpha atoms fluctuated from 0.05nm to 0.2nm

stability at 6ns around 3 nm and remained the same till the end of simulation. RMSF graph shows the fluctuations of the C-alpha atom of SNCA protein. RMSF graph shows highly fluctuating residues. So we consider residues having fluctuations above 1 nm to be crucial and may have a role in CID69584858 interactions Figure 3(i). Apart from terminal residues, the residues specifically from K23 to K32 are important for ligand interactions.

Molecular Dynamics of SNCA and their levodopa related inhibitor

The RMSD graph of SNCA with CID101744537 shows that the protein attains stability at 8ns around 3.2 nm and continues to remain the same till the end of simulation. RMSF plot shows that the residues from K32 to A27 and T67 to K80 show higher fluctuations and may be crucial for ligand interactions (Figure 3 (ii)).

Molecular Dynamics of PINK1 and their carbidopa reated inhibitor

MD simulation was performed to the complex PINK1 with CID69584883 compound. The RMSD plot shows that the PINK1 attained stability at 8ns around 0.4 nm. RMSF graph shows the fluctuations of the protein residues Figure 3(iii). Residues having fluctuations above 0.1 nm are considered to be significant. Residues V5, R6 and F7 have some ideal role to play in protein – ligand interactions.

Molecular Dynamics of PINK1 and their levodopa related inhibitor

MD simulation of PINK1 with CID55270478 complex was performed for 10 ns. The trajectory files obtained during the entire simulation were taken for calculating the RMSD and RMSF plots. The RMSD graph shows that the protein PINK1 attained stability at 2ns around 0.25 nm and remained the same until the end of simulation. In the RMSF plot, the residues having fluctuations above 0.1 nm are considered to be significant Figure 3(iv). Residues K5, R6, F7, V30, A31, K32, R33 and Q34 are considered to be crucial for ligand interactions.

Conclusion

Introduction of the drug levodopa revolutionized the medication system of PD. But levodopa is not a cure. Although it can reduce the symptoms of PD, it does not replace lost nerve cells and it does not stop the progression of the disease. This study exemplifies the screened molecules are novel potential inhibitors for targeting Alpha-synuclein and PTEN-putative kinase 1 protein. The biological activity prediction reveals the newly predicted lead compounds possess good antiparkinson activity and the statistical study proves the complex have enough correlation between them for inhibition. Molecular dynamics confirm the efficiency of the lead molecule and their stability against target. The in-silico study reported that the experimentally derived compounds such as CID69584858, CID101744537, CID69584883, and CID552704878 are used for the treatment against PD. Molecular dynamics simulation of SNCA/PINK1 with their best inhibitors show that the reported structures are stable, and these inhibitors can be considered for in vivo and in vitro studies.

Conflict of Interest

The author declares that there is no conflict of interest.

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