**Bulletin of Environment, Pharmacology and Life Sciences**
Bull. Env. Pharmacol. Life Sci., Vol 12 [6] May 2023 : 168-174

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

**ORIGINAL ARTICLE** **OPEN ACCESS**

# Identification of Lead Moiety to Inhibit Catechol-O-Methyl Transferase in the Treatment of Parkinson's Disease: A Computational Approach

**Srinivas G[1], Soundarya R[1], Basavanagowda H D[1], Brundha S N[1], Agasa Ramu Mahesh[1], Debanjan Sen[2], Veerasamy Ravichandran[3], M Aynul Rifaya[4], Parasuraman Pavadai[1]***

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
M.S. Ramaiah University of Applied Sciences, Bangalore-560054, Karnataka, India
[2]BCDA college of Pharmacy & Technology, Hridaypur, Kolkata 700127, West Bengal, India
[3]Faculty of Pharmacy, AIMST University, Semeling, Kedah, Malaysia
[4]Department of Chemical Engineering, Erode Sengunther Engineering College, Erode-638057, Tamil Nadu, India
E-Mail: pvpram@gmail.com

**ABSTRACT**

*The gradual loss of the structure or functionality of neurons, or neurodegeneration, is the root cause of neurodegenerative diseases. Parkinson's disease is a brain disorder that is caused due to degradation of dopamine and presence of Lewy bodies and misfolding of protein alpha-Synuclein. COMT [catechol-o-methyl Transferase] is an enzyme which degrades the dopamine is a potential target to discover newer Anti-Parkinson drugs. Present marketed drugs have major side effects like Sleepiness and fainting, Impulsive and compulsive behaviours, hallucinations and delusions, Blood pressure changes so there is a need for development of new drugs. Hence, the present study aims to identify lead moieties to inhibit COMT through ligand-based pharmacophore modelling. Ligand-based pharmacophore model was developed by using Pharmagist webserver. Based on the model developed, novel ligands were obtained from Zinc-Pharmer Database. The server has identified 1000 best possible ligands with high pharmacophoric similarity. Based on Lipinski rule it was screened through Using data warrior tool, the identified ligands were filtered and subjected for Molecular Docking studies using Auto Dock Vina. Based on binding affinity and amino-acid interaction top ten compounds was subjected to ADMET Studies by using PKCSM Webserver. ZINC12218382 was identified as best compound with high binding affinity and good amino acid interactions when compared with standard drug.*

***Keywords:*** *Parkinson, COMT, Pharmacophore modelling, Molecular docking*

Received 12.03.2023 Revised 20.04.2023 Accepted 20.05.2023

## INTRODUCTION

The gradual loss of the structure or functionality of neurons, or neurodegeneration, is the root cause of neurodegenerative diseases. Cell death may ultimately result from such neural injury. Amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple system atrophy, and prion disorders are a few examples of neurodegenerative illnesses [1,2].Parkinson's disease [PD] is a complicated, progressive neurological condition marked by tremor, stiffness, and bradykinesia. As the condition worsens, some individuals may have postural instability. it is characterised by a variety of motor issues, including bradykinesia, resting tremor, stiffness, flexed posture, "freezing," and loss of postural reflexes. Parkinson's is a neurodegenerative illness with several factors, including inParkinson's disease, a variety of Factors contribute to neurodegeneration[3].Protein misfolding is a condition where normal protein changes to 3-Dimensional structure in the nerve cell mutations in genes like SNCA, PARK2, PINK1, DJ-1 and LRRK2 leads to protein misfolding and effects the neural function the aggregation of this protein is also called as LEWY BODY [LB's] [4-7]. The main component of this LB's is "Alpha synuclein "its main function involves axonal transport, synaptic function, and neuronal plasticity The mutation of genes and oxidative and nitrosative stress causes aggregation of the protein and protein further leads to neurodenegration by obstructing the mitochondrial function [8-10].The main function of the mitochondria is generation of the energy in the form of ATP disfunction of mitochondria causes PD For example, environmental neurotoxin 1-methyl-4-phenyl-1,2,3,4 - tetrahydropyridine [MPTP] produces parkinsonism. It is converted into toxin named as 1- methyl-4-

phenylpyridinium [MPP+] By the enzymatic action of MAO-B which obstructs the electron transport chain [ETC], leading to mitochondrial dysfunction. This accumulates in the dopaminergic neurons causing neuronal death. this leads to the formation of ROS species which increases oxidative stress and decreased ATP production which causes High intracellular calcium concentration, nitric oxide [No] and excitotoxicity-mediated neuronal damage. Genetic mutations also cause mitochondrial dysfunction. For example, in patients with PD, the mutation in maternally inherited 12SrRNA which reduces the activity of cytochrome coxidase activity which is Necessary for normal mitochondrial functioning [10-11].Cure for the Parkinson's disease is still unknown but surgery, medications, and physical treatment may deliver relief and it may increase quality of patient's life. Practice of the exercise in the middle age may reduce the risk of the disease even caffeine acts protective and vitamin C and E which are antioxidants has protective action against the disease.The significance of in silico tools has much importance in advanced pharmaceutical research. Computer-aided drug discovery [CADD] tools provide virtual shortcut, in reducing the long process and cost of research and development. Now a days CADD has become an effective and indispensable tool in therapeutic development CADD technologies are powerful tools that mainly decreases the number of ligands that are required to be screened in experimental assays CADD tools identify lead drug molecules for testing, can predict effectiveness and possible side effects, and assist in improving bioavailability of possible drug molecules [12].

A pharmacophore is the collection of steric and electronic properties required for the best supramolecular interactions with a particular biological target and for inducing [or inhibiting] the target's biological response.These molecular structures can be classified as hydrophobic, hydrophilic, cationic, anionic, donors or acceptors of hydrogen bonds, or any possible combinations of these. The few features that make up a pharmacophore model are arranged in a particular 3D manner[13].Putting molecules in the best possible positions to engage with a receptor is a process known as docking. A mechanism known as "docking" occurs in a cell when molecules are linked together to create a durable complex.Successful docking methods search high-dimensional spaces effectively and use a scoring function that correctly ranks candidate dockings The ligand is docked onto the receptor and the interactions are checked. The scoring function generates score, depending on which the best fit ligand is selected. The ADMET [absorption, distribution, metabolism, excretion, and toxicity] characteristics play a crucial role in deciding a molecule's fate inside the body. When a molecule is administered orally, a good absorption is sought.The distribution and absorption of a molecule throughout the system will be governed by the balance of lipophilic and hydrophilic groups in the structure. From a therapeutic standpoint, effectiveness and toxicity are important[14].

Hence the present work focuses to identify novel molecules to inhibit the COMT enzyme for the treatment of Parkinson's disease through the application of computational tools.

## MATERIAL AND METHODS

**Identification and preparation of the Target:** The target protien was identified and retrieved from the PDB[Protien drug bank] with PDB ID 4XUC with the resolution of 1.80Å in the protien preparation water molecules, hetero groups and unwanted ligands were removed by using the software known as SPBDV and saved in the PDB format[15].

**Identification of the ligands:** The Drugs which are available in the market are selected through literature survey which are used as standard and the structures are Dopamine [681], Entacapone [5281081], Epinephrine [5816], isoprenaline [3779], L-dopa [6047], Methyldopa [38853], Nebicapone [9838389], Nor-epinephrine [439260], Opicapone [135565903], Rimiterol [36283], Selegiline [26757], Tolcapone [4659569] are downloaded by the NCBI PubChem website In SDF format [15,16].

**Ligand based Pharmacophore modelling:** The above molecules were introduced to pharmacophore modelling by using a web server known as pharmagist which helps to generate pharmacophore features for a set of molecules here sybyl Mol2 format was submitted with valid Email-Id the server generates multiple combinations of the submitted molecules and it is downloaded in Jmol format.The pharmacophoric features obtained as Jmol format is then subjected to ZINC harmer which is a web server which is used to screen ZINC database with the pharmacophoric features obtained for the set of molecules by this we can recognise the molecules which fulfil the required features it is filtered, and Top hits are selected and downloaded as SDF file. The results obtained through the Zinc pharmer is further filtered using the software known as Data Warrior based on the Input variables such as Molecular weight, RMSD, number of rotatable bonds, Hydrogen Bond donars, Hydrogen bond acceptors etc the results are downloaded as SDF file and used for the Docking studies[16].

**Molecular docking studies:** The protein is downloaded and prepared and ligands are downloaded and made cluster using Discovery studio in the form Mol SDF File and made ready for the docking studies.The docking studies was done using PyRx in which protein is loaded and made macromolecule and then Drug

cluster is loaded and energy minimisation is done the protein and drug cluster is converted in to pdbqt format the grid box is identified and allowed for the docking and result is downloaded in the pdbqt form [17].

**Building the protein -ligand complex:** By using the PYMOL software which is used for the visualisation and to make complex here particular drug and protein is made complex and saved as PDB format [18]

**Studying the protein -ligand interactions:** The Discovery studio software is used for for both clustering the ligands and visualisation of the protein ligand interactions the complex obtained is loaded in the discovery studio and analysed for the interactions in the form of 2D and 3D structures [19].

**ADMET STUDIES**

Based on the results obtained through molecular docking studies Drug likeliness was determined using the webserver known as PKCSM[20].

## RESULTS AND DISCUSSION

**Ligand based Pharmacophore modelling:** The pharmacophore hypothesis was done using PharmaGist server the pharmacophore features obtained consists of 3 features that is 1 aromatic ring 1 hydrogen bond donor, 1 hydrogen bond acceptor based on the output file from Pharma Gist it was introduced into Zinc Pharmer to screen and identify compounds with similar pharmacophoric features here we got 1000 hits and results was downloaded in Mol2 format. This was then introduced into Data Warrior which is a screening tool based on the input variables like LogP, Molecular weight, Hydrogen Bond donor, Hydrogen Bond Acceptor, number of Rotatable Bonds, polar surface area of standard drugs was compared with the drugs obtained through the zinc database and it was filtered it was downloaded in SDF format.

**Molecular docking studies:** The molecular docking studies of COMT inhibitors was done the main intention was to determine the major binding sites in the protein's active pocket with PDB ID 4XUC using Auto Dock Vina molecular docking was carried out. The Drugs which are used as standard and the structures are Dopamine [681], Entacapone [5281081], Epinephrine [5816], isoprenaline [3779], L-dopa [6047], Methyldopa [38853], Nebicapone[9838389], Nor-epinephrine[439260], Opicapone[135565903], Rimiterol[36283], Selegiline[26757], Tolcapone[4659569]

Are currently used in the market and among this Inhibitors Tolcapone was found with the Docking score of -7.7Kcal/mol and has conventional hydrogen bonding with MET90, GLU249 Pi-Pi stacked interaction with TRP193 Pi-Cation interaction with LYS194 Pi-Alkyl interaction with TRP193, LYS194, MET90 Therefore this interaction helps to understand inhibitory properties of the COMT inhibitors.

**Table: 1** DOCKING SCORE AND TYPE OF INTERACTION OF STANDARD DRUGS

| Compound | Docking score | Interacting residues | Type of Interaction |
|---|---|---|---|
| ENTACAPONE | -5.8 | TRP193, LYS194, GLU249 MET90 | Conventional hydrogen bond, Pi- cation, Pi-Alkyl, unfavourable Acceptor-Acceptor |
| EPINEPHRINE | -6.6 | ASP191, GLU140, GLY167, TRP193, HIS192, ILE141, SER169, GLN170 | Conventional hydrogen bond, Pi-sigma, Pi-Pi Tshaped, Carbon Hydrogen bond |
| LEVODOPA | -6.8 | ASP191, ILE139, HIS192, TRP193, ILE141, GLU140, TYR118 | Conventional hydrogen bond, Pi-Sigma, Pi-Pi T shaped, unfavoured Acceptor- Acceptor |
| NEBICAPONE | -7.3 | PRO224, LYS194, MET90, ASN220, GLU249, ASP219 | Conventional hydrogen bond, Unfavourable Donor-Donor, unfavourable Acceptor- Acceptor, Pi-Cation, Pi-Alkyl |
| NITECAPONE | -6.2 | LYS194, GLU249, MET90, ASP191 | Conventional Hydrogen bond, Unfavourable Acceptor-Acceptor, Pi-Cation, Pi-Alkyl |
| NOREPINEPHRINE | -5.6 | GLU249, MET90, ASP191 LYS194 | Conventional Hydrogen bond, Carbon Hydrogen bond, Pi-Cation, Pi-Alkyl |
| OPICAPONE | -7.5 | MET90, PRO224, TRP193, ASN220, GLU249 | Conventional Hydrogen bond, Pi-Cation, Pi-Sigma, Pi-Pi stacked, Pi-Alkyl |
| SELEGILINE | -4.7 | GLU77, THR81, ASP94, LYS95, GLU84 | Carbon Hydrogen Bond, Pi-Anion Pi-Alkyl |
| TOLCAPONE | -7.7 | TRP193, LYS194, GLU249 MET90 | Conventional Hydrogen bond, Pi-Cation, Pi-Pi Stacked, Pi-Alkyl |
| DOPAMINE | -5.8 | TRP193, LYS194, GLU249, MET90 | Conventional Hydrogen Bond, Unfavourable Acceptor-Acceptor, Pi-Alkyl, Pi-Cation |

After obtaining molecule from the Zinc Pharma based on the pharmacophore modelling 10 molecules were selected and subjected to docking to the protein with PDB ID 4XUC Based on the binding interactions the compound are identified the docking score ranges from -8.2 to to- 4.7kcal/mol by docking a compound ZINC12218382 was identified with highest binding score of -8.2Kcal/mol which exhibits Conventional hydrogen bond with GLU106, Carbon hydrogen bond interaction with ALA102, Pi-Sigma interaction with ALA102, The binding interaction between Docked molecules and the protein was done using Discovery studio Docking study showed that these compounds can bind similarly as that of the standard therefore this compound can inhibit COMT Interaction of the Ligands with the protein is given in Table2.

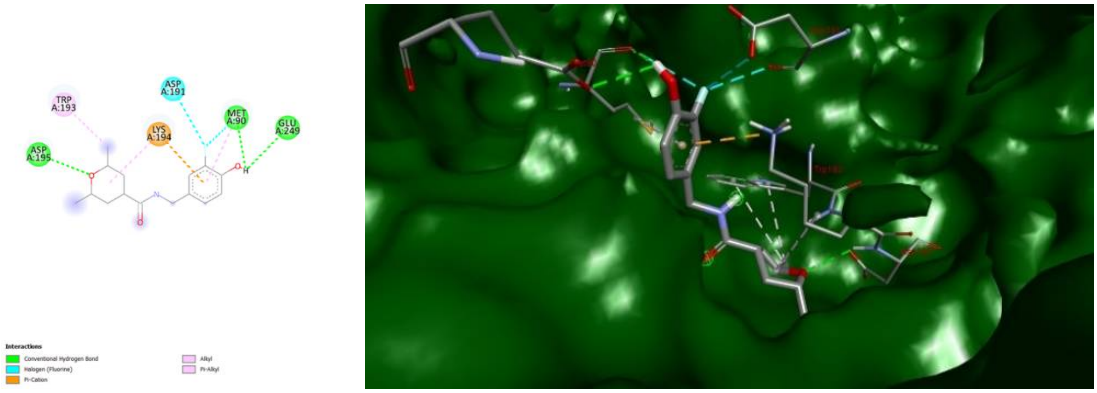


**Fig1: 2D AND 3D STRUCTURE OF ZINC92764435**

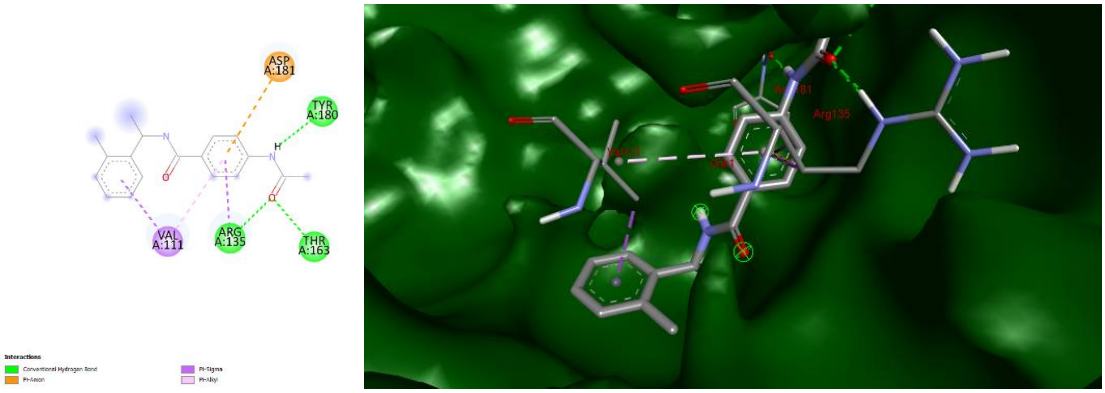


**Fig2: 2D AND 3D STRUCTURE OF ZINC09257056**

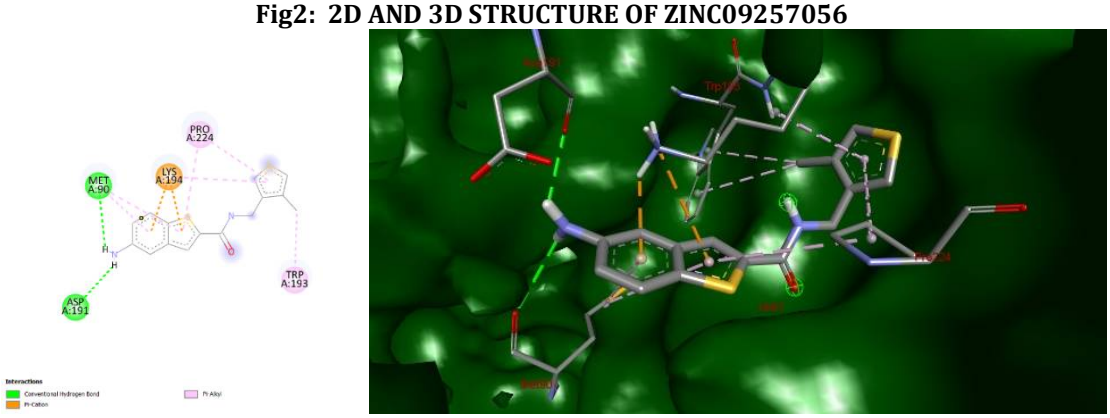


**Fig3: 2D AND 3D STRUCTURE OF ZINC94873487**

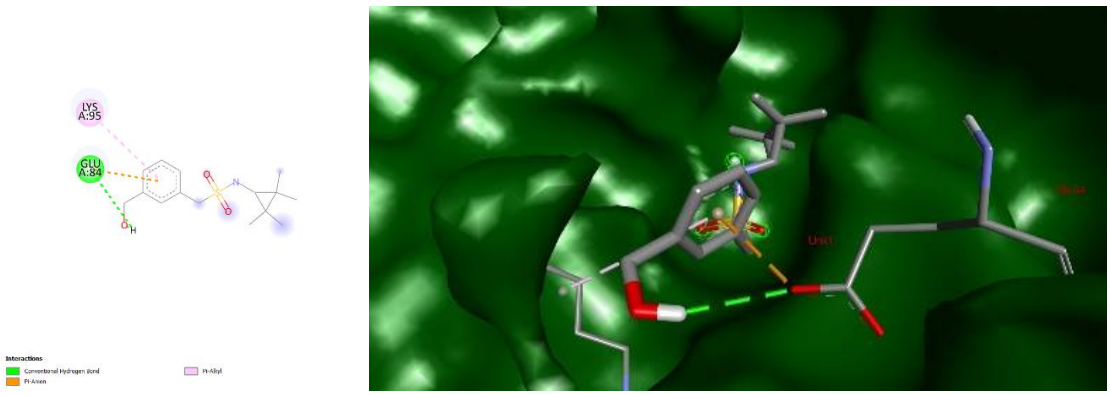


**Fig4: 2D AND 3D STRUCTURE OF ZINC92833078**

**Table 2:** Binding Affinity and Type of interaction of ligand with protein

| Compound | Docking score | Interacting residues | Type of Interaction |
|---|---|---|---|
| **ZINC92764435** | -7.2 | TRP193, ASP195, LYS194, ASP191, MET90, GLU249 | Convention hydrogen bond interaction<br>Halogen [Flourine]<br>Pi-Cation interaction<br>Alkyl interaction<br>Pi-Alkyl interaction |
| **ZINC92508175** | -4.7 | MET90, LYS194, GLU249 | Attractive charge interaction<br>Pi-Pi Cation interaction<br>Conventional Hydrogen bond interaction<br>Pi-Pi alkyl interaction |
| **ZINC09257056** | -6.2 | TYR180, TYR163, TYR135<br>VAL111, ASP181 | Convention hydrogen bond interaction<br>Pi-Pi Sigma interaction<br>Pi-Alkyl interaction<br>Pi-Anion interaction |
| **ZINC94331900** | -5.9 | LYS95, GLU84, ASP94 | Unfavourable Donor-Donor Interaction, Pi-Anion Interaction, Alkyl Interaction |
| **ZINC92833078** | -5.9 | LYS95, GLU84 | Pi-Anion interaction<br>Pi-Alkyl interaction<br>Convention hydrogen bond interaction |
| **ZINC94873487** | -6.4 | MET90, LYS194, PRO224,<br>TRP193, ASP191 | Unfavourable Donor-Donor Interaction, Pi-Cation interaction,<br>Alkyl interaction, Convention hydrogen bond interaction |
| **ZINC12218382** | -8.2 | GLU106, LYS259, GLN105, TYR244, ALA102,<br>ILE99, LYS98 | Convention hydrogen bond interaction,<br>Pi- Sigma interaction,<br>Pi-Alkyl interaction,<br>Alkyl interaction, Amide-Pi stacked interaction |
| **ZINC9475994** | -7.2 | TRP88, ASN220, ASP219,<br>LEU248, LYS194 | Convention hydrogen bond interaction, Alkyl interaction<br>Pi-Alkyl interaction, Unfavourable Donor-Donor Interaction, Pi-Pi stacked interaction |

## ADMET studies

By Differentiating the ADMET properties of standard drug with the Zincdatabase drug I.e., ZINC1899064 has Commending properties like water solubility, $CaCo_2$ permeability, CNS permeability and it is non hepatotoxic molecule, while other molecules are showing hepatotoxicity. The zinc data base molecule, ZINC1899064 will obey the Lipinski rule of five, by this the molecule can Absorb well by orally and it can pass BBB and CNS to show its activity. The drug development process is speed up by the drug-likeness filters based on physicochemical characteristics. The drug-likeness rules/filters based on physicochemical features, however, have drawbacks, as demonstrated by several research. The physical properties of drugs which is screened as per Lipinski rule is given in Table 3.

**Table3:**DRUG ABILITY STUDIES OF THE LIGANDS VIZ.., PARAMETERS OF LIPINSKI RULE OF FIVE

| Compound | Physical Properties | | | | | | Lipinski's Rule |
|---|---|---|---|---|---|---|---|
| | Molecular weight | Rotatable bonds | H-bond acceptors | H-bond donors | Surface Area | LOGP | |
| ZINC92764435 | 281.32 | 4 | 4 | 2 | 58.56 | 1.95 | 0 |
| ZINC92508175 | 289.19 | 4 | 2 | 3 | 44.90 | 2.03 | 0 |
| ZINC09257056 | 296.36 | 6 | 2 | 2 | 58.20 | 2.64 | 0 |
| ZINC94331900 | 297.41 | 4 | 4 | 2 | 74.78 | 2.50 | 0 |
| ZINC92833078 | 297.41 | 5 | 4 | 2 | 74.78 | 2.16 | 0 |
| ZINC94873487 | 302.41 | 4 | 1 | 2 | 111.60 | 3.41 | 0 |
| ZINC71899064 | 324.44 | 6 | 1 | 2 | 36.78 | 2.91 | 0 |
| ZINC12218382 | 410.53 | 4 | 2 | 2 | 40.80 | 5.29 | 1 |
| ZINC9475994 | 268.31 | 4 | 4 | 2 | 62.22 | -0.58 | 0 |

## CONCLUSION

The molecules which are in the market as an COMT inhibitor Which Dopamine[681], Entacapone [5281081], Epinephrine[5816], isoprenaline[3779], L-dopa[6047], Methyldopa[38853], Nebicapone [9838389], Nor-epinephrine[439260], Opicapone[135565903], Rimiterol[36283], Selegiline[26757], Tolcapone [4659569]used to get ligand-based pharmacophore model. The model gives molecules with similar pharmacophoric feature which is obtained from Zinc Data base and Data warrior, these molecules were subjected to docking by using Auto Dock Vina and based on docking score and binding interaction, 10 molecules are obtained. Next further ADMET studies were done by using PKCSM and Swiss ADME online software. Which predicts the drug-likeness feature and oral rat chronic toxicity and hepatotoxicity. Based on the result molecule ZINC1899064 were predicted as the COMT inhibitor.Further*in vitro* and *in vivo* evaluation on the selected compound will lead to identify a potent lead as COMT inhibitor.

## ACKNOWLEGEMENT

The authors are thankful to the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, M S Ramaiah University of Applied Sciences, Bengaluru for providing computational facility for research work.

## CONFLICT OF INTEREST

The authors declare that no conflict of interest.

## REFERENCES

1. Männistö, Pekka&Kaakkola, S. [2000]. Catechol-O-methyltransferase [COMT]: Biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. Pharmacological reviews. 51. 593-628.
2. da Silva, I. R., Parise, M. R., Pereira, M., & da Silva, R. A. [2021]. Prospecting for new catechol-O-methyltransferase [COMT] inhibitors as a potential treatment for Parkinson's disease: a study by molecular dynamics and structure-based virtual screening. *Journal of Biomolecular Structure & Dynamics*, *39*[16], 5872–5891.
3. Rajeshkumar, R.R., Kumar, B.K., Parasuraman, P., Panneerselvam, T., Sundar, K., Ammunje, D.N., Ram Kumar Pandian, S., Murugesan, S., Kabilan, S.J., &Kunjiappan, S. [2022]. Graph theoretical network analysis, in silico exploration, and validation of bioactive compounds from Cynodondactylon as potential neuroprotective agents against α-synuclein. ***BioImpacts***.
4. Hitge, R., Smit, S., Petzer, A., &Petzer, J. P. [2020]. Evaluation of nitrocatechol chalcone and pyrazoline derivatives as inhibitors of catechol-O-methyltransferase and monoamine oxidase. *Bioorganic & Medicinal Chemistry Letters*, *30*[12],
5. Palma, P. N., Bonifácio, M. J., Loureiro, A. I., Wright, L. C., Learmonth, D. A., & Soares-da-Silva, P. [2003]. Molecular modeling and metabolic studies of the interaction of catechol-O-methyltransferase and a new nitrocatechol inhibitor. *Drug Metabolism and Disposition: The Biological Fate of Chemicals*, *31*[3], 250–258.
6. Jayaraj, Richard &Ranjani, V & KRISHNAN, MANIGANDAN &Namasivayam, Elangovan. [2013]. Insilico docking studies to identify potent inhibitors of alpha-synuclein aggregation in parkinson disease. Asian Journal of Pharmaceutical and Clinical Research. 6.
7. Lee, Jee-Young & Baek, Sun-Hee& Kim, Yang-Mee. [2007]. Receptor-oriented Pharmacophore-based in silico Screening of Human Catechol O-Methyltransferase for the Design of Antiparkinsonian Drug. Bulletin of the Korean Chemical Society. 28. 10.5012/bkcs.2007.28.3.379.
8. Chakraborty, C., Pal, S., Doss, C. G. P., Wen, Z.-H., & Lin, C.-S. [2012]. In silico analyses of COMT, an important signaling cascade of dopaminergic neurotransmission pathway, for drug development of Parkinson's disease. *Applied Biochemistry and Biotechnology*, *167*[4], 845–860.
9. Moschovou, Kalliopi&Melagraki, Georgia &Mavromoustakos, Thomas & Zacharia, Lefteris&Afantitis, Antreas. [2019]. Cheminformatics and virtual screening studies of COMT inhibitors as potential Parkinson's disease therapeutics. Expert Opinion on Drug Discovery. 15. 1-10. 10.1080/17460441.2020.1691165.

10. Cruz-Vicente, P., Gonçalves, A. M., Ferreira, O., Queiroz, J. A., Silvestre, S., Passarinha, L. A., & Gallardo, E. [2021]. Discovery of small molecules as membrane-bound catechol-O-methyltransferase inhibitors with interest in Parkinson's disease: Pharmacophore modeling, molecular docking and in vitro experimental validation studies. *Pharmaceuticals [Basel, Switzerland]*, *15*[1], 51
11. Salman, M. M., Al-Obaidi, Z., Kitchen, P., Loreto, A., Bill, R. M., & Wade-Martins, R. [2021]. Advances in applying computer-aided drug design for neurodegenerative diseases. *International Journal of Molecular Sciences*, *22*[9], 4688
12. Chandrasekaran, J., Elumalai, S., Murugesan, V., Kunjiappan, S., Pavadai, P., &Theivendren, P. [2022]. Computational design of PD-L1 small molecule inhibitors for cancer therapy. *Molecular Diversity*.
13. Chaitra, R., Gandhi, R., Jayanna, N., Satyanath, S., Pavadai, P., &Murahari, M. [2022]. Computational design of MmpL3 inhibitors for tuberculosis therapy. *Molecular Diversity*. 12:67-71
14. Kalimuthu, A. K., Parasuraman, P., Sivakumar, P., Murugesan, S., Arunachalam, S., Pandian, S. R. K., Ravishankar, V., Ammunje, D. N., Sampath, M., Panneerselvam, T., &Kunjiappan, S. [2022]. In silico, in vitro screening of antioxidant and anticancer potentials of bioactive secondary metabolites from an endophytic fungus [Curvularia sp.] from Phyllanthus niruri L. *Environmental Science and Pollution Research International*, *29*[32], 48908–48925.
15. Saravanan, G., Panneerselvam, T., Kunjiappan, S., Parasuraman, P., Alagarsamy, V., Udayakumar, P., Soundararajan, M., Joshi, S. D., Ramalingam, S., &Ammunje, D. N. [2019]. Graph theoretical analysis, in silico modeling, prediction of toxicity, metabolism and synthesis of novel 2-[methyl/phenyl]-3-[4-[5-substituted-1,3,4-oxadiazol-2-yl] phenyl] quinazolin-4[3H]-ones as NMDA receptor inhibitor. *Drug Development Research*, *80*[3], 368–385.
16. Kamatchi, Sundara Saravavan&Arjunan, Selvam &Kunjiappan, Selvaraj &Pavadai, Parasuraman & Sundar, Lakshmi. [2021]. Phytoconstituents as Lead Compounds for Anti-Dengue Drug Discovery. Adv Exp Med Biol;1322:159-193. doi: 10.1007/978-981-16-0267-2_7.
17. Kalimuthu, A. K., Panneerselvam, T., Pavadai, P., Pandian, S. R. K., Sundar, K., Murugesan, S., Ammunje, D. N., Kumar, S., Arunachalam, S., &Kunjiappan, S. [2021]. Pharmacoinformatics-based investigation of bioactive compounds of Rasam[South Indian recipe] against human cancer. *Scientific Reports*, *11*[1], 21488.
18. Theivendren, P., Kunjiappan, S., Govindraj, S., Chandrasekarn, J., Pavadai, P., Saraswathy, G. R., & Murugan, I. [2019]. Graph Theoretical Analysis, InsilicoModeling and Formulation of Pyrimidine Nanoparticles as p38α MAP Kinases inhibitors: A Quantitative Proteomics Approach. *Drug research*, *69*[2], 100–110.
19. Saravanan, G., Panneerselvam, T., Alagarsamy, V., Kunjiappan, S., Parasuraman, P., Murugan, I., & Dinesh Kumar, P. [2018]. Design, graph theoretical analysis, density functionality theories, Insilicomodeling, synthesis, characterization, and biological activities of novel thiazole fused quinazolinone derivatives. *Drug Development Research*, *79*[6], 260–274.
20. Suresh, Jithya& C., Pushpalatha& P, Parasuraman & G, Dhananjaya. [2022]. An In-Silico Approach of the Antibacterial Activity of Coleus Amboinicus Against Streptococcus Mutans. ECS Transactions. 107. 18247-18254. 10.1149/10701.18247ecst.

**CITATION OF THIS ARTICLE**

Srinivas G, Soundarya R, Basavanagowda H D, Brundha S N, Agasa Ramu M, Debanjan S, Veerasamy R, M Aynul Rifaya, Parasuraman P. Identification of Lead Moiety to Inhibit Catechol-O-Methyl Transferase in the Treatment of Parkinson's Disease: A Computational Approach. Bull. Env. Pharmacol. Life Sci., Vol 12[6] May 2023: 168-174.