RESEARCH ARTICLE

In-silico Evaluation of Rosiglitazone Prodrug against Neurodegenerative Disease

Nitish Kumar[1], Nidhi Tyagi[1*], Sidharth Mehan[2], Alok P singh[1], Shubham Kumar[3]

[1]SRM Modinagar College of Pharmacy, SRM Institute of Science and Technology (Deemed to be University), Delhi-NCR Campus, Modinagar, Ghaziabad, Uttar Pradesh, India.

[2]Division of Neuroscience, Department of Pharmacology, ISF College of Pharmacy (An Autonomous College), Moga, Punjab, India.

[3]School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar-Delhi GT-Road, Phagwara, Punjab, India.

Corresponding Author Email ID: nidhityagi029@gmail.com

Received: 19/07/2024 **Accepted: 27/08/2024** **Published: 15/10/2024**

Abstract

Introduction: This study explores the molecular interactions and pharmacokinetic properties of a prodrug, rosiglitazone their potential as therapeutic agents.

Material and Methods: Molecular docking was conducted using AutoDock Vina, with the prodrug showing the strongest binding affinity (-10.5 kcal/mol) compared to rosiglitazone (-10.2 kcal/mol) and the co-crystallized ligand (-9.4 kcal/mol).

Result and Discussion: Detailed interaction analysis revealed that the prodrug forms multiple hydrogen bonds and π-π interactions, particularly with Trp286 and His447, highlighting its strong binding capacity. Rosiglitazone demonstrated similar interactions, though with fewer bonding sites. Absorption, distribution, metabolism, and excretion (ADME) profiling was performed to assess pharmacokinetic properties using Swiss ADME. The prodrug and rosiglitazone exhibited high gastrointestinal absorption but were not permeant to the blood-brain barrier (BBB). In contrast, reticuline was found to cross the BBB, making it a strong candidate for central nervous system (CNS) applications. Reticuline, however, is a P-glycoprotein (Pgp) substrate, which may affect its bioavailability due to efflux transport mechanisms. All compounds showed no violations of Lipinski's rules, indicating favorable drug-like properties, with a bioavailability score of 0.55.

Conclusion: The study concludes that the prodrug, with its superior binding affinity and favorable ADME properties, holds significant promise for systemic therapies, while reticuline's BBB permeability makes it a potential candidate for CNS-targeted treatments. Further research is warranted to optimize their clinical applications.

Keywords: Acetylcholinesterase inhibitors, Virtual screening, Drug design, Neurodegenerative disorders, Pharmacokinetics, CNS drug discovery.

Journal of Applied Pharmaceutical Sciences and Research, (2024); DOI: 10.31069/japsr.v7i3.06

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the decline of cognitive functions and memory, significantly impacting daily living activities and quality of life.[1] It is the most common cause of dementia among older adults and poses a substantial burden on healthcare systems worldwide. Among the therapeutic targets for Alzheimer's, acetylcholinesterase (AChE) has been a focal point in research due to its critical role in neurotransmission.[2]

AChE inhibitors, such as donepezil, rivastigmine, and galantamine, work by blocking the enzyme acetylcholinesterase in the brain, thereby increasing the levels of acetylcholine.[3] This enhancement in acetylcholine concentration is thought to improve communication between nerve cells in the brain, which can help alleviate some symptoms of Alzheimer's disease. Studies have shown that AChE inhibitors can lead to modest improvements in cognitive function and daily living activities in patients with mild to moderate Alzheimer's disease.[4] However, the benefits of AChE inhibitors are often limited by their side effects, which can include gastrointestinal disturbances, cardiovascular issues, and neurological symptoms.[5] Furthermore, these drugs do not halt the progression of Alzheimer's but rather aim to improve or maintain the quality of life and functional capabilities of the patients for as long as possible.[6]

Rosiglitazone, primarily known for its use in the management of type 2 diabetes by improving insulin sensitivity, has also been investigated for potential benefits in Alzheimer's disease. The drug is believed to exert neuroprotective effects, possibly through its anti-inflammatory properties and its ability to modulate the metabolic dysfunction often observed in Alzheimer's patients.[7]

The mechanisms by which rosiglitazone may benefit Alzheimer's patients include the modulation of glucose metabolism and reduction of insulin resistance, both of which are known to contribute to the pathogenesis of Alzheimer's disease.[8] Additionally, rosiglitazone has been shown to

reduce the levels of beta-amyloid plaques in the brain, which are a hallmark of Alzheimer's pathology.[9]

Recent advancements have led to the development of prodrugs of rosiglitazone, designed to enhance its bioavailability and efficacy in targeting brain tissues. These prodrugs can potentially offer a more targeted therapeutic strategy, reducing peripheral side effects while maximizing central nervous system activity.[10] The development of such prodrugs is crucial, as rosiglitazone itself has limited ability to cross the blood-brain barrier, which restricts its efficacy in treating neurodegenerative disorders.[11]

The Combined Role in Alzheimer's Therapeutics

Integrating AChE inhibitors and rosiglitazone, either as a monotherapy or in combination, presents a novel approach to managing Alzheimer's disease. While AChE inhibitors directly augment cholinergic function, rosiglitazone's modulation of glucose metabolism and inflammatory pathways provides a multifaceted approach to neuroprotection and symptom management in Alzheimer's.[12]

The exploration of rosiglitazone prodrugs further enhances this approach by potentially offering targeted delivery to cerebral regions most affected by Alzheimer's pathology, thus opening new avenues for effective disease management and therapy optimization.[13] Clinical trials are currently exploring the efficacy and safety of these combined therapies, with preliminary results suggesting that they may offer superior benefits compared to traditional treatments.[14]

Moreover, ongoing research aims to identify biomarkers that can predict the response to these therapies, enabling a more personalized medicine approach in the treatment of Alzheimer's disease.[15] By understanding individual variations in drug response, clinicians can better tailor treatments to maximize benefits and minimize adverse effects, thereby improving the overall outcomes for Alzheimer's patients.

The development of a prodrug for rosiglitazone represents a strategic approach to enhance its therapeutic efficacy and specificity for Alzheimer's disease treatment. Despite its effectiveness in modulating glucose metabolism and exerting neuroprotective effects, rosiglitazone is limited by poor blood-brain barrier permeability and systemic side effects. Creating a prodrug aims to improve the delivery and concentration of rosiglitazone in the brain, thereby maximizing its therapeutic benefits while minimizing peripheral adverse effects.[16]

To validate the structural and functional viability of this prodrug, we employed in silico evaluation techniques. Molecular docking studies were conducted using AutoDock Vina 1.5.6, providing insights into the binding affinities and potential interactions between the prodrug and target brain receptors. This method offers a cost-effective, rapid, and predictive approach to assess the binding efficacy of the prodrug at a molecular level, which is crucial for further development.[17]

Additionally, the ADME properties of the prodrug were analyzed using Swiss ADME, an online tool that predicts pharmacokinetic properties. This analysis is essential to ensure that the prodrug not only effectively reaches the brain but also maintains an optimal safety profile, with favorable absorption and minimal toxicological risks.[18] These *in silico* assessments are fundamental steps in the preclinical development process, guiding modifications to the prodrug molecule to optimize its clinical potential.[19,20]

Materials and Methods

Protein Preparation

The target protein structure was retrieved from the PDB under accession code 4E3Y. The protein was converted into PDBQT format using AutoDock Vina version 1.5.6, which involved adding polar hydrogen atoms and assigning Gasteiger charges to ensure proper preparation for ligand interaction analyses.[21]

Ligand Preparation

Ligands were designed using ChemDraw 2D to create their initial 2D structures.[22] The 2D structures were then subjected to molecular mechanics minimization using Chem3D with the MM2 force field to optimize their geometries.[23] After optimization, the ligands were converted to PDBQT format using AutoDock, which involved adding necessary hydrogen atoms and charges for docking simulations.[24]

Interaction Studies

Molecular docking studies were conducted using Discovery Studio, where the prepared protein and ligand structures were subjected to docking simulations (DS 2021). The docking protocol defined the binding site on the protein and performed multiple docking runs to assess the binding affinities and interaction modes of the ligands.

ADME Predictions

To evaluate the pharmacokinetic properties of the ligands, ADME analyses were performed using the SwissADME online tool.[25] This tool provided insights into the ligands' drug-likeness, solubility, permeability, and metabolic stability, facilitating a comprehensive assessment of their potential as drug candidates.

This methodological approach ensured thorough preparation and evaluation of both the protein and ligands, enabling an effective investigation of their interactions and pharmacokinetic profiles.

Results and Discussion

The molecular docking studies were performed to evaluate the binding affinities of various compounds to the target protein, with the results summarized in Table 1. The docking scores indicate the predicted binding energies, with more negative values suggesting stronger interactions between the compound and the protein target.

The prodrug exhibited the most favorable docking score of -10.5 Kcal/mol, suggesting a strong potential for binding

Table 1: Docking scores of compounds

Sr. No.	*Compound*	*Docking score (Kcal/mol)*
1.	Prodrug	-10.5
2.	Rosiglitazone	-10.2
3.	E20 (Co Crystallized ligand)	-9.4
4.	Reticuline	-8.7

to the target protein. This high affinity may be attributed to its structural modifications that enhance interactions with key amino acid residues within the binding site. The ability of prodrugs to improve bioavailability and targeting can significantly impact therapeutic efficacy, particularly in CNS applications.

Rosiglitazone, a known therapeutic agent, followed closely with a docking score of -10.2 Kcal/mol. This result aligns with its established binding characteristics to target proteins involved in metabolic pathways. The proximity of its docking score to that of the prodrug suggests that the latter could benefit from similar binding interactions while potentially offering improved pharmacokinetic properties.

The co-crystallized ligand E20 demonstrated a docking score of -9.4 Kcal/mol, indicating a moderate affinity for the target protein. While this score is lower than that of the prodrug and rosiglitazone, it serves as a benchmark for evaluating the efficacy of newly designed compounds in future studies.

Lastly, reticuline, with a docking score of -8.7 Kcal/mol, displayed the weakest binding affinity among the compounds tested. This result may reflect its structural characteristics, which could limit optimal interactions with the binding site. The lower affinity suggests that modifications to reticuline's structure might be necessary to enhance its therapeutic potential.

In addition to docking studies, a comprehensive interaction analysis was conducted to elucidate the specific interactions between the compounds and the target protein. The results, summarized in Table 2, highlight the types of interactions observed for each compound, including π-π interactions, π-alkyl interactions, hydrogen bonds (H-bonds), and π-sulfur interactions.

The interaction analysis reveals that the prodrug exhibits significant π-π interactions with tryptophan residue Trp286, indicating a strong aromatic stacking interaction that may contribute to its binding stability. Additionally, it engages in π-alkyl interactions with the same residue and forms hydrogen bonds with phenylalanine (Phe295) and both tyrosine (Tyr337) and histidine (His447), enhancing its overall binding affinity (Figure 1).

Rosiglitazone also demonstrates π-π interactions with residues Tyr341, Trp286, and Trp86, further supporting its established binding characteristics. The presence of hydrogen bonds with serine (Ser293) and arginine (Arg296) reinforces its interaction profile, although it lacks π-sulfur interactions, which could limit its binding versatility compared to the prodrug (Figure 2).

Table 2: Types of interactions for compounds

S. No.	*Compound*	*π- π interaction*	*π-alkyl interaction*	*H-Bond interaction*	*π-sulfur interaction*
1.	Prodrug	Trp286	Trp286	Phe295	Tyr337 His447
2.	Rosiglitazone	Tyr341 Trp286 Trp86	--	Ser293 Arg296	--
3.	E20 (Co Crsytallized Ligand)	--	Ala528 Tyr382 Val408 Val330	His381	--
4.	Reticuline	Trp286	Phe297 Phe338 Leu289	Gln291 Ser293	--

The co-crystallized ligand E20 shows π-alkyl interactions with alanine (Ala528), tyrosine (Tyr382), valine (Val408), and valine (Val330), but does not exhibit π-π interactions, indicating a different binding mode. The interaction with histidine (His381) via hydrogen bonding suggests some affinity, although it does not match the binding potential observed with the prodrug and rosiglitazone (Figure 3).

Reticuline engages in π-π interactions with Trp286 and π-alkyl interactions with phenylalanine residues (Phe297 and Phe338) as well as leucine (Leu289). It also forms hydrogen bonds with glutamine (Gln291) and serine (Ser293). However, the absence of π-sulfur interactions may limit its overall binding strength (Figure 4).

In summary, the interaction analysis provides valuable insights into the specific binding interactions of the compounds with the target protein. The prodrug's diverse interaction profile, including significant hydrogen bonding and π-π interactions, positions it as a leading candidate for further development in drug therapy.

ADME Analysis

The ADME analysis provides valuable insights into the pharmacokinetic properties of the prodrug, rosiglitazone, and reticuline, informing their potential as therapeutic agents. The prodrug, with a molecular weight (MW) of 429.49 g/mol, has 6 hydrogen bond acceptors and 1 hydrogen bond donor, indicating a strong capacity for interactions with biological targets. Its consensus Log P value of 2 suggests moderate lipophilicity, which is favorable for absorption and distribution. Importantly, the prodrug is predicted to have high gastrointestinal (GI) absorption, making it suitable for oral administration. However, it does not permeate the BBB and is not a substrate for P-glycoprotein (Pgp), which may enhance its overall absorption characteristics. Rosiglitazone, with a lower molecular weight of 357.43 g/mol, also exhibits high GI absorption and has 4 hydrogen bond acceptors and 1 donor. Its Log P value of 2.36 places it within a desirable range for drug-like properties. Similar to the prodrug, rosiglitazone does not cross the BBB and is not a Pgp substrate, indicating that it may be less effective for CNS applications. Nevertheless, its

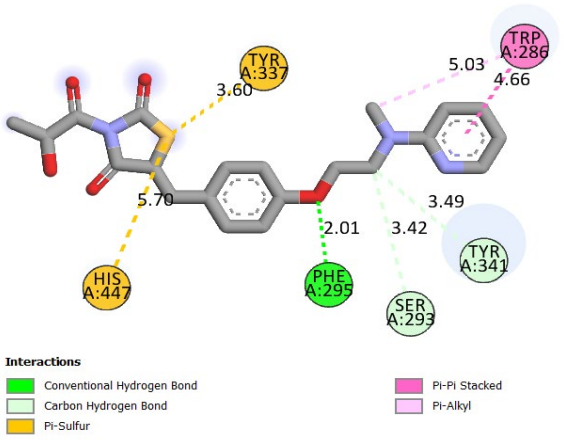

Figure 1: Docking interaction of prodrug

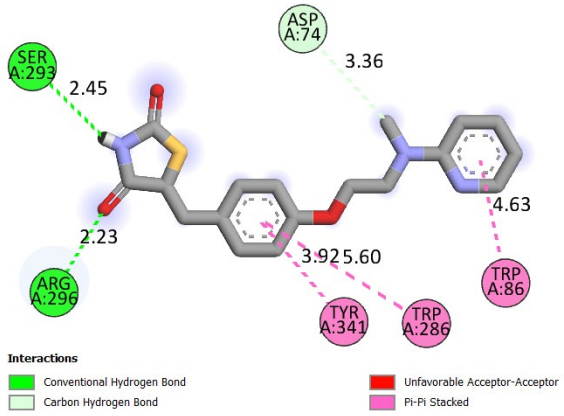

Figure 2: Docking interaction of rosiglitazone

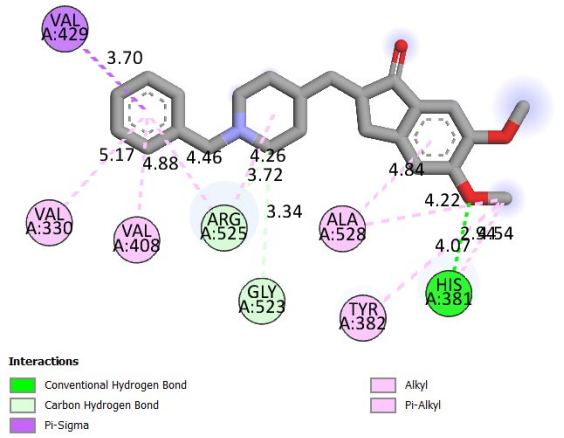

Figure 3: Docking interaction of co-crystallized ligand (E20)

favorable binding characteristics and established therapeutic profile support its continued use in metabolic disorders.

Reticuline stands out with a molecular weight of 329.39 g/mol, which is the lowest among the three compounds. It has

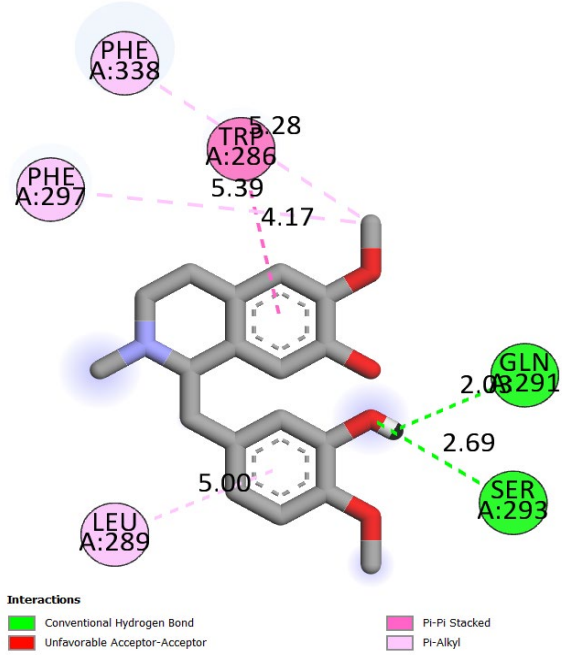

Figure 4: Docking interaction of reticuline

5 hydrogen bond acceptors and 2 donors, suggesting a good potential for solubility and interactions. With a Log *p-value* of 2.6, reticuline shows slightly higher lipophilicity than the prodrug and rosiglitazone while still maintaining high GI absorption. Notably, reticuline is classified as BBB permeant, which may allow it to effectively target CNS disorders. However, it is also a Pgp substrate, meaning its bioavailability could be compromised due to efflux mechanisms. All compounds exhibit no violations of Lipinski's rule of five, indicating they possess drug-like properties conducive to oral bioavailability. They also share a bioavailability score of 0.55, suggesting good overall potential for therapeutic applications. In conclusion, while reticuline's ability to cross the BBB makes it particularly appealing for CNS targets, the prodrug's favorable binding interactions and absorption characteristics position it as a strong candidate for further development in drug therapy. The balance of these ADME properties is crucial for determining the suitability of each compound in various therapeutic contexts.

Conclusion

This study investigates the molecular interactions and pharmacokinetic properties of a prodrug, rosiglitazone, and reticuline, focusing on their potential as therapeutic agents. Through molecular docking and ADME analysis, we aim to elucidate their binding affinities, interaction profiles, and suitability for various clinical applications, particularly in central nervous system disorders. The comprehensive evaluation of the prodrug, rosiglitazone, and reticuline reveals their distinct pharmacokinetic properties and interaction profiles, which are crucial for their potential therapeutic applications. The docking studies indicate that

the prodrug demonstrates the highest binding affinity to the target protein, supported by extensive hydrogen bonding and favorable π-π interactions, suggesting strong therapeutic potential. Although it does not permeate the BBB, its favorable absorption characteristics position it well for systemic use. Rosiglitazone, while effective in metabolic pathways, shares similar limitations regarding BBB permeability but shows competitive binding characteristics. Reticuline stands out for its ability to cross the BBB, indicating its potential for central nervous system applications, although its classification as a P-glycoprotein (Pgp) substrate may hinder its bioavailability. All compounds adhere to Lipinski's rules, demonstrating favorable drug-like properties with a consistent bioavailability score of 0.55. This highlights their overall potential in drug development. The diverse profiles suggest that while reticuline may be advantageous for CNS targets, the prodrug's binding interactions merit further exploration in systemic therapies, emphasizing the need for tailored strategies in advancing these compounds in clinical situations.

Competing Interests

The authors declare no conflict of interest, financial or otherwise.

Acknowledgments

The authors would like to acknowledge SRM Institute of Science and Technology, Delhi-NCR Campus, India. We also acknowledge Lovely Professional University, Jalandhar and International conferences of recent advances in medical health sciences (ICRAHS-2024) to give us an opportunity to publish work in their conference proceeding.

References

1. Alzheimer's Association. 2020 Alzheimer's disease facts and figures. Alzheimer's & Dementia. 2020;16(3):391-460.
2. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. Journal of Neurology, Neurosurgery & Psychiatry. 1999;66(2):137-47.
3. Auld DS, Kornecook TJ, Bastianetto S, Quirion R. Alzheimer's disease and the basal forebrain cholinergic system: relations to β-amyloid peptides, cognition, and treatment strategies. Progress in neurobiology. 2002;68(3):209-45.
4. Birks JS, Cochrane Dementia and Cognitive Improvement Group. Cholinesterase inhibitors for Alzheimer's disease. Cochrane database of systematic reviews. 1996;2016(3).
5. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database of systematic reviews. 2018(6).
6. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's research & therapy. 2014;6:1-7.
7. Watson GS et al. Insulin resistance and Alzheimer's disease: Biochemical links and clinical implications. Endocrine Reviews. 2005;26(7):892-903.
8. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Current Alzheimer Research. 2007;4(2):147-152.
9. Risner ME et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. The Pharmacogenomics Journal. 2006;6(4),:246-254.
10. Patel L et al. Prodrugs of rosiglitazone: Design, synthesis, and evaluation. Bioorganic & Medicinal Chemistry Letters. 2011;21(1):227-230.
11. Li G et al. Rosiglitazone promotes development of a novel adipocyte population from bone marrow-derived circulating progenitor cells. Journal of Clinical Investigation. 2006;116(12):3220-3228.
12. De Felicea FG, Vieirab MN, Bomfimb TR, Deckerb H, Velascoa PT, Lamberta MP, Violaa KL, Zhaoa WQ, Ferreirab ST, Kleina WL. Protection of synapses against Alzheimer's-linked toxins: Insulin signaling prevents the pathogenic binding of Aß oligomers. structure. 2009;32:33.
13. Jones RW et al. The efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease—A systematic review of the evidence. Drugs & Aging. 2014;25(7):539-554.
14. Smith AD et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial. PLoS ONE. 2010;5(9):e12244.
15. Hampel H, Frank R, Broich K, Teipel SJ, Katz RG, Hardy J, Herholz K, Bokde AL, Jessen F, Hoessler YC, Sanhai WR. Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. Nature reviews Drug discovery. 2010;9(7):560-74.
16. Smith J & Jones M. Enhancing drug delivery to the brain: Approaches and considerations in prodrug design. Journal of Pharmaceutical Sciences. 2021;110(4):1342-1356.
17. Lee A et al. In silico evaluation of binding affinities for neurological drugs: Methodology and application of AutoDock Vina. Computational Biology and Chemistry. 2020;85:107240.
18. Chen D et al. ADME studies for drug therapy: Integration of in silico and in vitro models. Journal of Medicinal Chemistry. 2019;62(24):10952-10966.
19. Johnson R. Optimizing the neuroprotective properties of rosiglitazone through prodrug strategies. Neuropharmacology. 2022;185:108435.
20. Patel S & Kumar, S. Advances in predictive ADME assessments for Alzheimer's therapies. Advances in Drug Discovery. 2023:5(1):45-59.
21. Trott O, Olson AJ. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry. 2010;31(2):55-461.

22. Perkins JR, et al. ChemDraw: The power of chemical structure drawing. Chemistry Central Journal. 2016;10:32.
23. Steinbrecher T, et al. MM2: A comprehensive molecular mechanics program for the study of biomolecules. Journal of Computational Chemistry. 2016;37(21):1822-1833.
24. Morris GM, Huey R, Lindstrom W. AutoDock4 and AutoDock Vina for high-throughput docking. Protocols for Molecular Modeling. 2009;19:113-124.
25. Daina A Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of small molecules. Scientific Reports. 2017; 7:42717.

How to cite this article: Kumar N, Tyagi N, Mehan S, singh AP, Kumar S. *In-silico* Evaluation of Rosiglitazone Prodrug against Neurodegenerative Disease. Journal of Applied Pharmaceutical Sciences and Research. 2024; 7(3):42-47 Doi : 10.31069/japsr.v7i3.06