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# In-Silico Drug Designing & Computational Study of Various Novel-Analogues against Novel Therapeutic Targets in Alzheimer's Disease

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***Abstract:*** ***Alzheimer's disease (AD) treatment and management significantlyremain an unaddressed medical challenge, with limited disease-modifying therapeutic options. In this study, we employed an integrated in silico computational strategy to identify and characterize novel compound analogues with potential anti-Alzheimer's activity. A rational analogue design approach was applied to a selected lead scaffold, followed by virtual screening to evaluate target binding affinity against key AD-associated proteins implicated in amyloidogenic processing, tau pathology, and neuroinflammation. Molecular docking and binding interaction analyses were conducted to elucidate structure–activity relationships and prioritize high-affinity candidates. Top-ranking analogueswere further assessed using molecular dynamics simulations to examine complex stability and conformational behaviour under physiological conditions. Several novel analoguesdemonstrated improved binding affinity, favourable interaction patterns, and enhanced predicted pharmacological properties compared to the parent compound. These findings highlight promising lead candidates for further optimization and experimental validation andprove the utility of computational approaches in accelerating early-stage drug discovery for Alzheimer's disease.***

***Keywords: Alzheimer's disease, Molecular docking, Human Phospholipase-D3, Amyloid precursor protein, Indoleamine 2,3-dioxygenase 1, Tryptophan 2,3-dioxygenase, Soluble epoxide hydrolase, STING Database.***

## I. INTRODUCTION

Alzheimer's disease is a devastating neurodegenerative disorder that affects millions of people worldwide. The multitude of biochemical progress of the disease is now taking hold in recent years and has led to promising new discoveries through a plethora of diverse molecular targets[1].One of the key findings is the mechanism through which the β-amyloid peptide aggregates through immense biochemical crosstalk. Traditional therapeutic interventions mainly focus on enzymes that cleave APP (amyloid precursor protein) rather than providing a targeted approach. However, recent research has shown that targeting other molecular pathways, such as inflammation and oxidative stress, may also hold promise in treating Alzheimer's disease. By exploring these alternative targets, researchers hope to develop more effective and personalized treatment strategies for this complex and challenging condition[2]. Additionally, targeting synaptic dysfunction and neuroinflammation has also shown potential in slowing down the progression of Alzheimer's disease. By broadening the scope of therapeutic interventions beyond traditional targets, researchers aim to address the multifaceted nature of the disease and improve patient outcomes. Phospholipase D has been proposed as a therapeutic target for Alzheimer's disease. A study using a Caenorhabditis elegans model showed that ablation of PLD in an AD-like model improved various phenotypes and had a protective effect, suggesting a significant role in neurodegeneration.The Amyloid-β (Aβ) peptides are synthesized through a biochemical process that typically involves sequential proteolytic cleavage of type-I transmembrane Amyloid precursor protein (APP) by β- and γ-secretases. The first and rate-limiting step in the cleavage of the β-amyloidogenic pathway is mediated by B-Site APP-cleaving enzyme-1 (BACE1)[3].

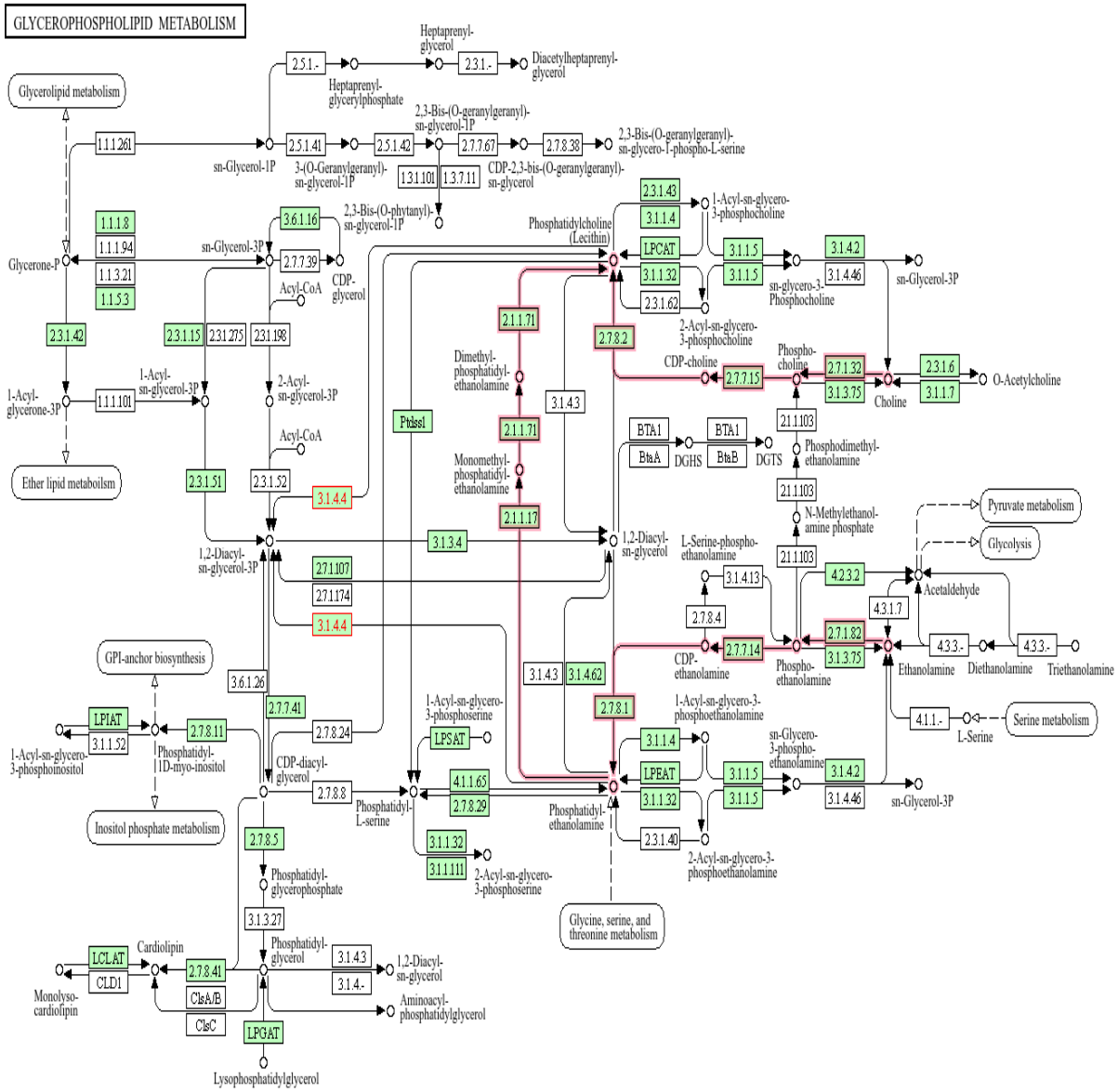
## II. NOVEL TARGETS IN ALZHEIMER'S DISEASE

### *A. Human Phospholipase-D3 (PD3) as Target*

Phospholipase $A_2$ is associated with Alzheimer's disease because it contributes to the synthesis of amyloid-beta peptides, which are known to aggregate and form plaques in the brains of individuals with Alzheimer's.

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Inhibiting the activity of phospholipase $A_2$ may provide a viable therapeutic approach for the treatment or prevention of Alzheimer's disease development. Pathogenesis occurs through their roles in neuroinflammation, oxidative stress, and synaptic dysfunction[4].These enzymes are important for understanding the molecular basis of Alzheimer's disease because they help break down phospholipids and send signals through lipids[5]. Comprehending the precise pathways via which phospholipase $A_2$ influences Alzheimer's pathogenesis may facilitate the creation of targeted medicines designed to inhibit its activity. Moreover, additional investigations into the control of phospholipase A2 in the brain may reveal innovative therapeutic approaches for Alzheimer's disease.Whole-exome sequencing has identified an uncommon missense variant in the PLD3 gene (rs145999145) linked to late-onset Alzheimer's disease (AD)[6].This variation is substantially more common in people with Alzheimer's disease than in people who don't have it. Still, the link is still up for debate, and not much is known about what PLD3 does in AD. More research is needed to investigate exactly how this change in the PLD3 gene might cause Alzheimer's disease that starts later in life. Comprehending the function of PLD3 in Alzheimer's disease may facilitate the identification of novel therapeutic targets for the management of this debilitating neurodegenerative condition. PLD3 encodes a phospholipase that might have a role in digesting amyloid precursor protein (APP). This indicates that PLD3 may contribute to the buildup of amyloid plaques, a characteristic feature of Alzheimer's disease. Stopping PLD3 from working could be a new way to stop or slow down the course of Alzheimer's disease[7].



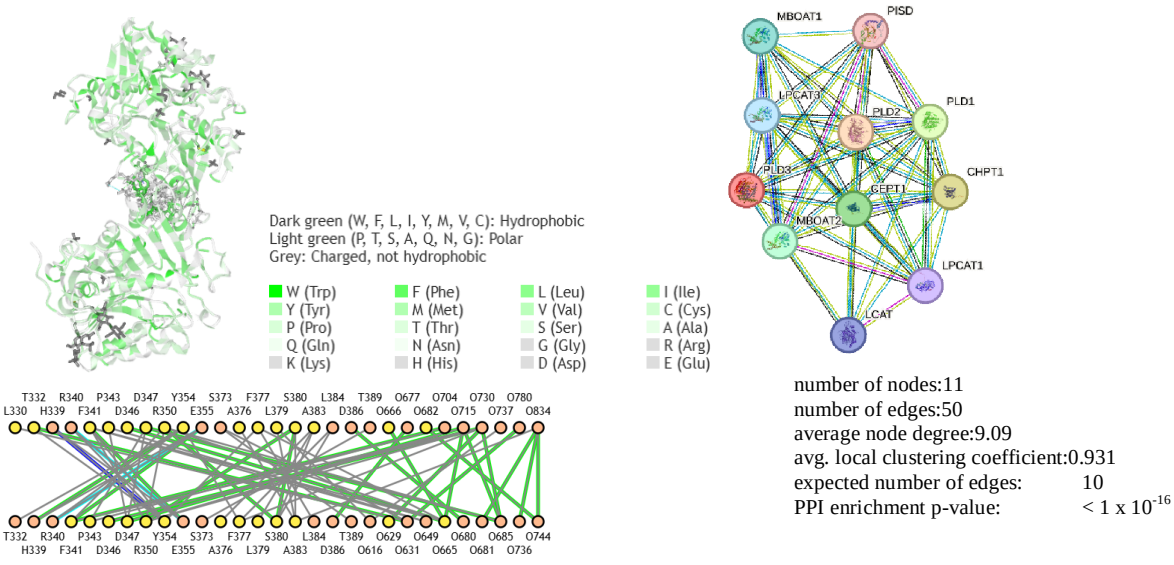



Fig-1: The image depicts the hydrophobic, hydrophilic and polar residues of Human Phospholipase-D3 along with interactions among two chains A and B respectively along with Protein-Protein Interaction (PPI) from Interaction Network Analysis.

The compounds N-{2-[3-(furan-2-yl)-6-oxopyridazin-1(6H)-yl]ethyl}acetamide,1-{1-[6-(furan-2-yl)pyridazin-3-yl]piperidin-4-yl}ethan-1-one,N,N-dimethyl-4a,6,7,8,9,9b-hexahydro-1H-benzo[4,5]thieno[3,2-c]thiopyran-3-carboxamide, andN-methyl-3-(3-(4-methyl-3,5-dioxo-2-(p-tolyl)-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)-1,2,4-oxadiazol-5-yl)propenamide were screened against the following receptor (PDB-ID:8V5T ) against potential inhibition activity in MOE 2015.01. The following interaction with best free energy and binding score conformer is selected and analyzed for descriptor calculations and correlation-matrix plot is generated and analyzed for best scores interrelation among the descriptors.

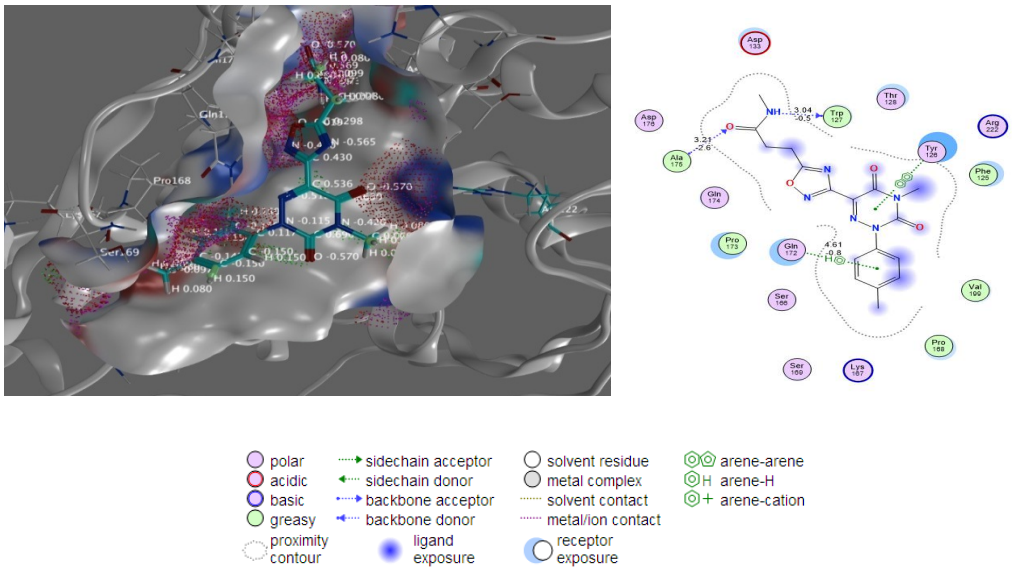



Fig-2: Three-dimensional interaction analysis revealed that compound N-{2-[3-(furan-2-yl)-6-oxopyridazin-1(6H)-yl]ethyl}acetamideis stably accommodated within the catalytic pocket of the target protein. The ligand adopts an extended conformation that enables optimal surface complementarity with the binding cavity. The pyridazinone carbonyl group forms a hydrogen bond with the backbone of Pro168, while the acetamide moiety engages in additional hydrogen-bond interactions with Ser165. The furan ring is positioned within a hydrophobic sub-pocket, establishing favourable van der Waals contacts with surrounding residues. Electrostatic surface mapping further indicates strong charge complementarity between the ligand and the active-site environment, supporting the observed binding stability

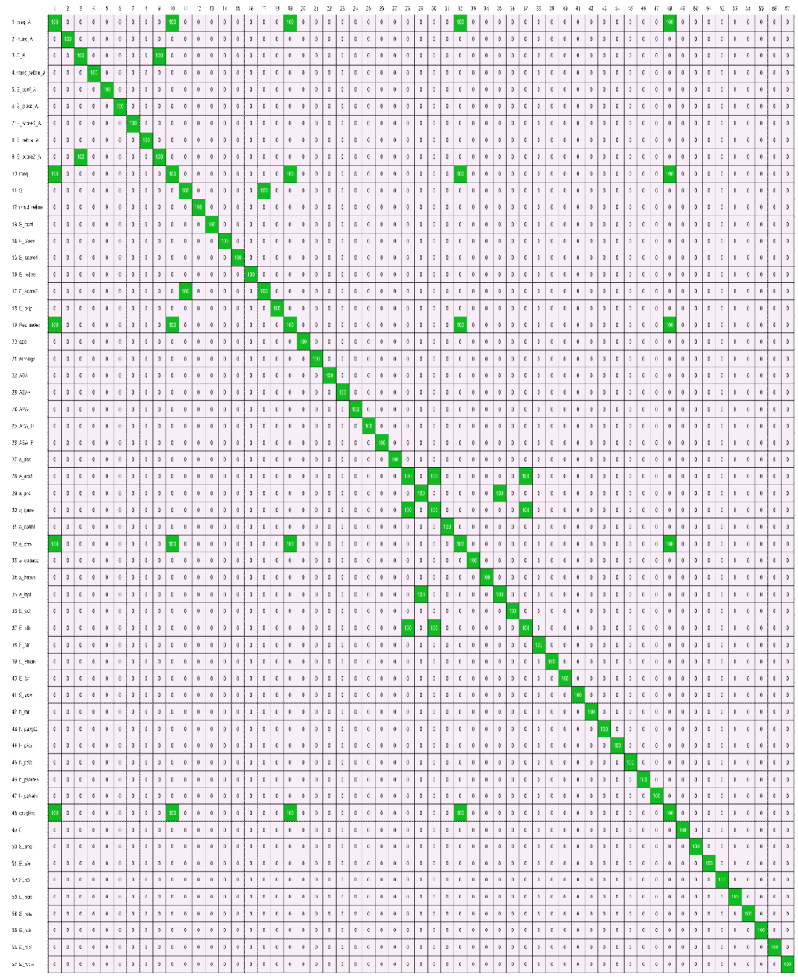


Fig-3: The MOE descriptor correlation-matrix indicates that molecular size, lipophilicity, and surface-based descriptors constitute the dominant features of the dataset, with molecular weight, lipophilic surface area (SlogP, VSA), and volume-related descriptors showing consistently high intensities across compounds. Polar surface and hydrogen-bonding descriptors contribute moderate variability, while electronic descriptors display comparatively lower influence, suggesting that steric and hydrophobic factors primarily govern ligand behaviour in the present study.

*B. Indoleamine 2,3-dioxygenase (IDO) Related Targets*

The KynurinePathway is turned on by inflammatory signals and has been linked to the development of several neurodegenerative illnesses, such as Alzheimer's and Parkinson's disease [8].The kynurenine pathway is responsible for approximately 95% of dietary tryptophan breakdown. Human post-mortem studies consistently demonstrate upregulation of IDO1 in AD brains, particularly in hippocampus and cortex[9]. IDO immunoreactivity colocalizes with amyloid plaques, activatedmicroglia, reactive astrocytes.Altered kynurenine metabolite profiles leads to decreased tryptophan levels, increased KYN/tryptophan ratios, elevated QUIN concentrations, and relative insufficiency of KYNA [10]. IDO-driven tryptophan depletion and QUIN accumulation synergize with proteotoxic stress, exacerbating synaptic and neuronal vulnerability, support the concept of presence of this pathway in AD. The first stage in the process is changing tryptophan into N-formyl-L-kynurenine. This is done by IDO-1, IDO-2, or TDO[11]. Targeting this route may provide innovative treatment approaches for addressing these disorders and safeguarding cognitive function. Indoleamine 2,3-dioxygenase 1 (IDO1), indoleamine 2,3-dioxygenase 2 (IDO2), and tryptophan 2,3-dioxygenase (TDO) are all enzymes that are at the entry point of the KP. TDO primarily regulates the balance of tryptophan in the human body, but IDO1 is additionally switched on in immunological and brain cells when there is inflammation. This makes it fundamentally important for AD. Chronic neuroinflammation, a defining characteristic of Alzheimer's disease (AD), serves as a persistent catalyst for indoleamine 2,3-dioxygenase (IDO) activation, leading to persistent modifications of kynurenine metabolites that significantly impact neuronal viability and synaptic functionality[12].

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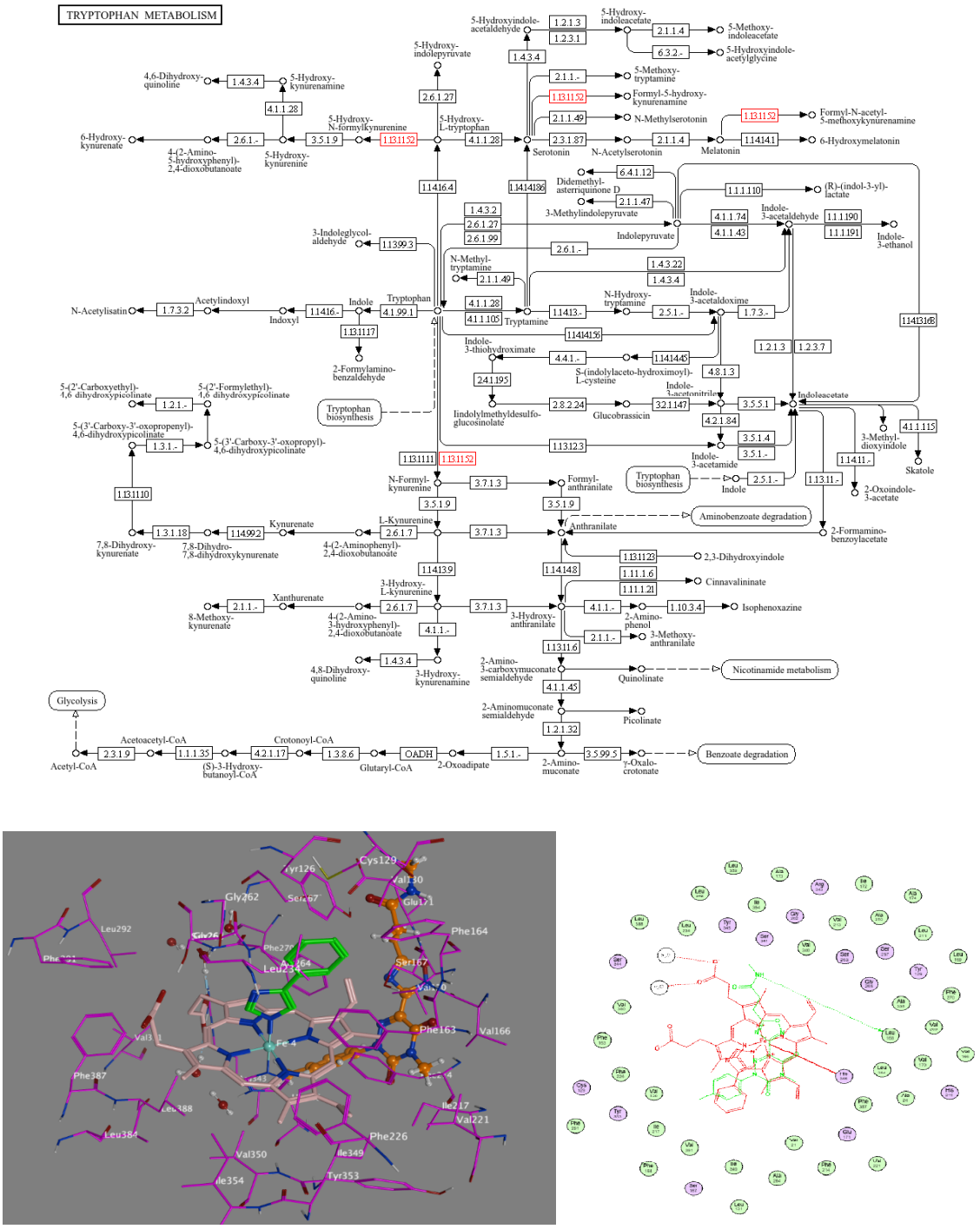



Fig-4: Pathway analysis confirmed the central role of indoleamine-2,3-dioxygenase-1 (IDO1) in regulating tryptophan metabolism linked to neuroinflammatory processes in Alzheimer's disease. Molecular docking revealed stable accommodation of the ligandcompound N-{2-[3-(furan-2-yl)-6-oxopyridazin-1(6H)-yl]ethyl}acetamide within the IDO1 active site, with favourable surface complementarity and orientation toward the catalytic region. Two- and three-dimensional interaction analyses indicated the formation of multiple hydrogen bonds and hydrophobic interactions with key active-site residues, suggesting effective inhibition of enzymatic activity. Collectively, these findings support IDO1 as a viable therapeutic target and highlight the studied compound as a potential modulator of kynurenine pathway dysregulation in AD.The observed binding profile suggests that the compound may attenuate inflammation-driven neurodegeneration, positioning IDO1 inhibition as a promising disease-modifying approach rather than symptomatic intervention.

### *C. Soluble epoxide hydrolase (sEH) Related Targets*

Recent years have seen a major change in AD research, moving away from theories that focus on amyloid and toward models that in clude neuroinflammation, vascular dysfunction, lipid metabolism, and problems with neurovascular coupling.Soluble epoxide hydro lase (sEH), encoded by the EPHX2 gene, has garnered considerable attention as a potential molecular target due to its pivotal role at the nexus of lipid signaling, inflammation, vascular control, and neuronal survival[13]. Human genetics, post-mortem brain analysis, animal models, and pharmacological research now indicate that dysregulated sEH activity plays a role in the etiology of Alzheimer's disease. Inhibiting sEH has been demonstrated to mitigate neuroinflammation, restore cerebral blood flow (CBF), decrease amyloid load, and enhance cognitive performance, establishing sEH as a prospective therapeutic target for Alzheimer's disease and Alzheimer's disease-related dementias (ADRD)[14].The brain has a lot of polyunsaturated fatty acids (PUFAs), especially arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Cyclooxygenase (COX), Lipoxygenase (LOX), and Cytochrome P-450 epoxygenase (CYP) are the three main enzyme routes that break down these PUFAs[15].EpFAs serve as endogenous anti-inflammatory and neuroprotective lipid mediators in the brain, where they help manage synaptic plasticity and reduce oxidative stress. The enzyme sEH converts EpFAs into diols, which possess significantly lower biological activity and can even have pro-inflammatory and neurotoxic effects. Increased sEH activity leads to a reduction in protective EpFAs and an accumulation of inflammatory diols, contributing to a pro-inflammatory environment. This dysregulation is particularly relevant in Alzheimer's disease, indicating its role in neurovascular and neuroinflammatory pathology[16].

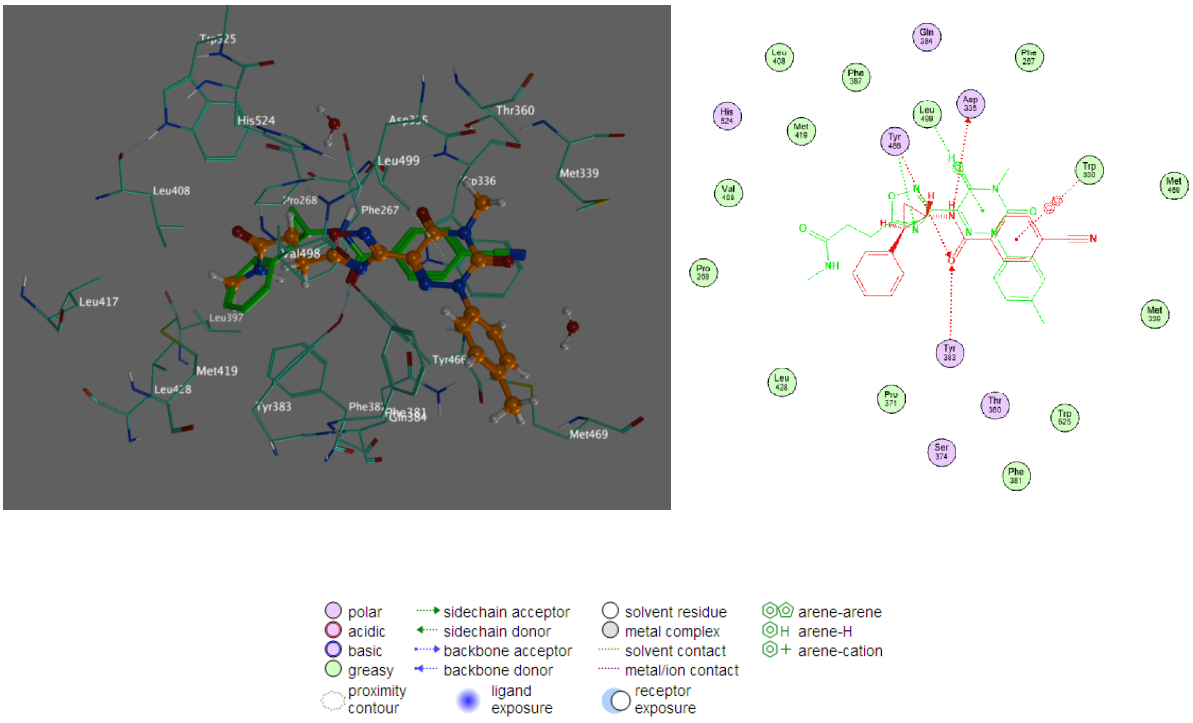



Fig-5:Molecular docking revealed stable accommodation of the ligand compound N-{2-[3-(furan-2-yl)-6-oxopyridazin-1(6H)-yl]ethyl}acetamide within active site of soluble epoxide hydrolase (PDB-ID:3ANS), with possible overlayconserved region towards the inhibitor4-Cyano-N-[(1S,2R)-2-Phenylcyclopropyl]benzamide. Two- and three-dimensional interaction analyses indicated the formation of different interactions between the ligand and receptor.

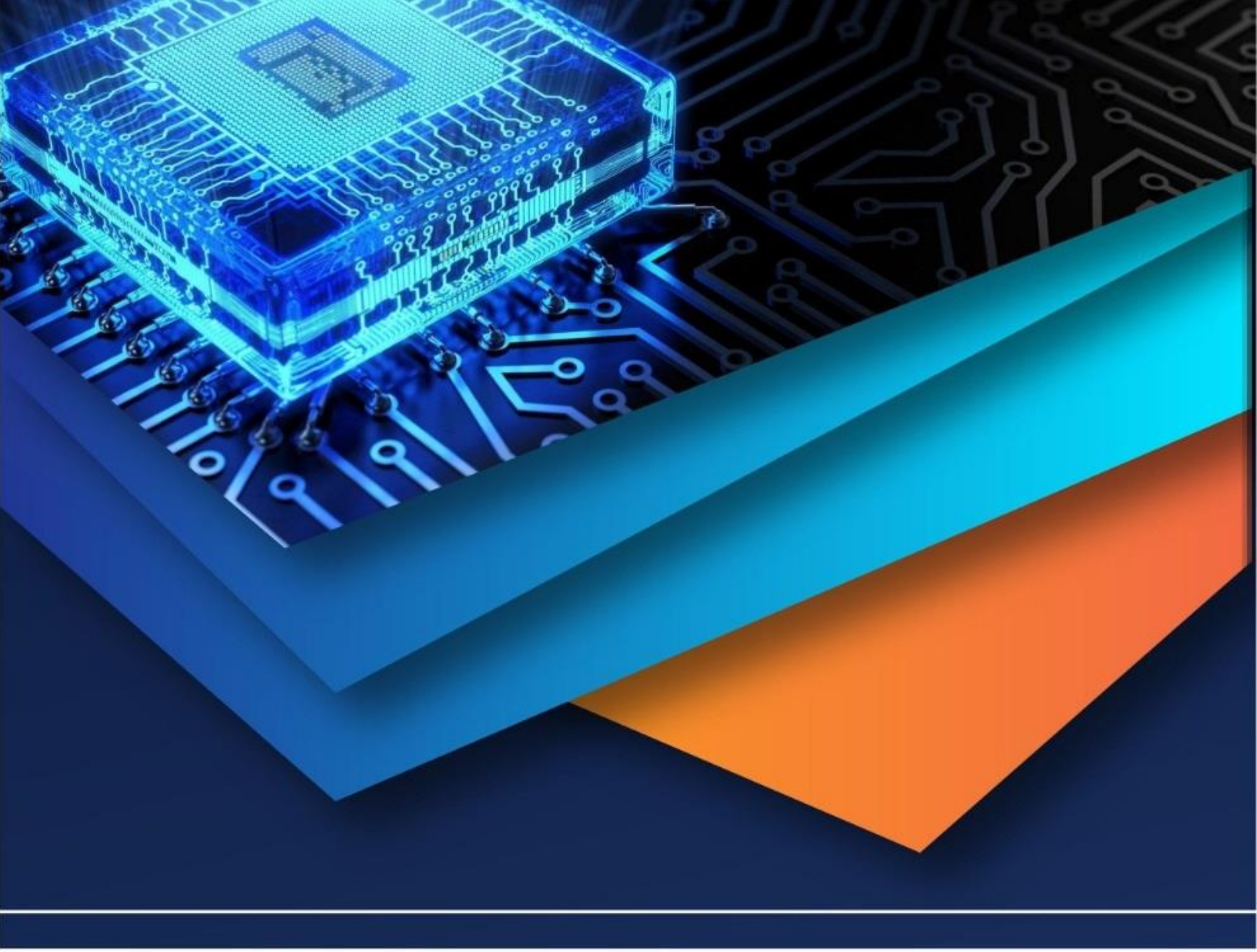
## III. CONCLUSION

The study emphasized the significance of docking analysis involving novel compounds targeting newly identified proteins that are increasingly associated with neurodegenerative diseases such as Alzheimer's. By focusing on these novel targets, the research not only broadens the understanding of molecular interactions critical to disease progression but also suggests potential therapeutic strategies. These targets may serve as adjuncts to existing standard treatments, offering palliative benefits and possibly enhancing overall efficacy. This approach opens new pathways for drug development and encourages further exploration of molecular mechanisms underlying neurodegeneration. Docking analysis targeting novel proteins implicated in neurodegenerative diseases such as Alzheimer's represents a pivotal advancement in therapeutic research.

By identifying and characterizing these previously unexplored molecular targets, the study enhances our comprehension of the intricate protein-ligand interactions that drive disease pathology. This detailed understanding facilitates the rational design of compounds with improved specificity and efficacy, potentially overcoming limitations associated with conventional treatments. Importantly, these novel targets provide opportunities to intervene at various stages of neurodegeneration, which could slow or modify disease progression rather than merely alleviating symptoms. Furthermore, integrating these newly identified targets into therapeutic strategies may complement existing standard-of-care treatments, thereby offering synergistic effects that enhance patient outcomes. The adjunctive use of novel compounds could improve palliative care by addressing molecular pathways not targeted by current drugs, ultimately contributing to a more holistic management of neurodegenerative disorders. This approach also encourages ongoing exploration of the molecular mechanisms underpinning these diseases, fostering innovation in drug discovery and development. Collectively, these efforts open promising avenues for creating more effective and personalized interventions against Alzheimer's and related neurodegenerative conditions.

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