

Xanthoangelol Mitigates Neuroinflammation and Hypoxia via MAPK and HIF-1 Signaling Modulation: Network Pharmacology and In-Vivo Approach in a Haloperidol-Induced Model of Parkinson's Disease

Amber Sani

Quaid-i-Azam University

Chunyu Liu

Hospital of the Joint Support Force

Jawad Azam

Quaid-i-Azam University

Salman Khan

skhan@qau.edu.pk

Quaid-i-Azam University

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Computational Elucidation of Neuroprotective Pathways of Terpenoids and Coumarins from *Saposhnikovia divaricata* in Alzheimer's Disease: A Network Pharmacology and Docking Study

Abstract

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder that is produced by a network of interdependent pathophysiological processes, such as oxidative stress, neuroinflammation, ferroptosis, pyroptosis, apoptosis, autophagic failure, endocrine dysregulation, and aberrant neuronal signalling. Therefore, multitarget pharmacological natural products have potential therapeutic uses in alleviating this heterogeneity of mechanisms. *Saposhnikovia divaricata* is a common medicinal herb that contains a wide array of bioactive compounds, which have been reported to exhibit antioxidant, anti-inflammatory, and neuroprotective effects. Eight key terpenoids and coumarins: scopoletin, fraxidin, isofraxidin, 5-O-methylvisamminol, deltoin, anomalin, α -pinene, and panaxydol were chosen in this investigation after ADME filtration to evaluate their suitability in AD. We employed integrative network pharmacology, mechanistic target profiling, protein interaction network construction, identification of hub genes, KEGG pathway enrichment for Alzheimer's disease, and in silico docking to systematically elucidate the mechanistic relevance of each compound. Fraxidin, panaxydol, deltoin, and 5-O-methylvisamminol showed the most significant common targets between them and the main regulatory nodes, including AKT1, MTOR, CASP3, MAPK, INS, and NFKB1. Molecular docking made an emphasis on strong ligand protein interactions, and deltoin, panaxydol, and anomalin binding PTGS2 (ΔG -8.03 kcal mol⁻¹), MTOR (ΔG -7.65 kcal mol⁻¹), and INS (ΔG -7.74 kcal mol⁻¹) were found to have a strong binding affinity. Altogether, these data present several *S. divaricata* constituents as promising multitarget modulators of AD pathophysiology, which gives a solid foundation in terms of the future experimental validation and emphasizes the therapeutic value of coumarins and terpenoids in the modification of neurodegenerative diseases.

Keywords

Saposhnikovia divaricata; Coumarins; Terpenoids; Alzheimer's disease; Network pharmacology; Molecular docking.

Introduction

Alzheimer's disease (AD) is the most widespread and multifactorial neurodegenerative disease, which is clinically characterized by progressive memory loss, cognitive degradation, and behavioral disruption (1). Although conventionally typified by extracellular amyloid-2 (A2) plaques (2) and intracellular neurofibrillary tangles of hyperphosphorylated tau (3), these classical hallmarks are only a part of a much larger and more multifaceted pathological pathway. Modern studies have shown that the AD is a result of the interplay of various interconnected pathways, such as oxidative stress, neuroinflammation, mitochondrial dysfunction, impaired autophagy, dysregulated apoptosis, ferroptosis, pyroptosis, and hormonal disequilibria (4). The disruption of any of these pathways spreads to other pathways sequentially, creating a positive-feedback loop of neuronal damage, synaptic impairment, and downward and outward cognitive decline (5). This complex interplay of mechanisms is why traditional single-target therapeutic approaches have produced small disease-modulating effects and why multi-target agents that have the potential of simultaneously adjusting multiple pathological axes are desperately needed (6).

Natural products have become one of the potential candidates of multi-mechanistic intervention because of their structural diversity and integrative pharmacological effects (7). *Saposhnikovia divaricata* (8), also referred to as Fangfeng, is a commonly used traditional medicinal plant, which harbors an abundance of well-known anti-inflammatory, antioxidant, anti-apoptotic, immunomodulatory, and neuroprotective effects of the two compound classes of terpenoids and coumarins (9). NF- κ B -activation, reactive oxygen species (ROS) inhibition, autophagic homeostasis, and microglial-induced neuroinflammation have been reported to be suppressed by coumarins, including scopoletin, fraxidin, and isofraxidin. Terpenoids that contain TPH 6: α -pinene and panaxydol have a strong impact on mitochondrial homeostasis, oxidative regulation, cell-survival pathways, and autophagy activation (10). These various activities are exactly consistent with major processes involved in AD pathogenesis that place *S. divaricata*-derived compounds in an ideal position to be attractive as multi-target neuroprotectants.

Although there is growing evidence on their pharmacological promise, the exact molecular pathways through which the *S. divaricata* constituents mediate AD-related mechanisms, especially ferroptosis, pyroptosis, autophagy, mitochondrial control, and estrogen-regulated neuroprotection, are still not clearly understood. Since AD is a systemic failure of interlinked regulatory networks, other than solitary lesions, there is a necessity to explain the relationships between compounds and mechanisms to understand the molecules that can generate significant

therapeutic outcomes (11). The formation of such mechanistic maps is particularly relevant to coumarins and terpenoids, whose interactions with different molecular targets are known, although they have not been studied in the context of multi-mechanistic AD modulation in detail (12).

Network pharmacology offers a general computational approach to decomposing multi-target and multi-pathway networks of bioactive compounds in multi-dimensional biological systems (13). It can be used to conduct a systematic search of potential targets, functional modules, and signaling pathways related to therapeutic effects by combining molecular docking and bioinformatics studies. Network pharmacology with docking structural validation can provide both functional and binding plausibility, and provide mechanistic information to inform preclinical prioritization (14).

The current study will be able to explain computationally the neuroprotective effects of terpenoids and coumarins that are derived from *S. divaricata* against AD. In particular, their regulation of inflammation, oxidative stress, apoptosis, autophagy, ferroptosis, pyroptosis, and hormonal dysregulation are the areas of this research. The study aims to define key hub genes, pathways, and interactions underlying these effects through network pharmacology and molecular docking and, as a result, should offer a mechanistic understanding of the multi-target potential of *S. divaricata* constituents and their potentially important role in sex-specific neuroprotection in AD.

Materials and Methods

2.1 Compound Selection and ADME Screening

Thirty-one phytochemical constituents previously reported in *Saposhnikovia divaricata* were collected from published phytochemical studies and reference databases. To prioritise compounds with potential central nervous system activity, all molecules were evaluated using SwissADME. The screening applied standard criteria for oral drug-likeness and neurological relevance, including oral bioavailability of at least 30%, drug-likeness index above 0.1, topological polar surface area below 90 Å² for predicted blood–brain barrier permeability (or below 140 Å² for acceptable oral absorption), LogP values between –0.4 and 5.6, molecular weight not exceeding 500 Da, high predicted gastrointestinal absorption and no more than one Lipinski rule violation. Compounds also had to be predicted as blood–brain barrier permeable to ensure suitability for Alzheimer’s disease mechanisms. Sixteen compounds satisfied all pharmacokinetic criteria, and from these, eight were selected for deeper mechanistic

investigation. The final selection was based on their prevalence in the plant, their representation of the phytochemical classes most associated with neuroactivity (coumarins and terpenoids), and their documented antioxidant, anti-inflammatory, or neuroprotective effects. The eight compounds analysed in this study were scopoletin, fraxidin, isofraxidin, 5-O-methylvisamminol, deltoin, anomalin, α -pinene, and panaxydol [1].

2.2 Mechanistic Target Identification for Alzheimer's Disease

To reflect the multifactorial nature of Alzheimer's disease, eight mechanistic domains strongly implicated in the disorder were selected: Alzheimer's disease core targets, hormonal dysregulation, pyroptosis, ferroptosis, neuroinflammation, oxidative stress, apoptosis, and autophagy. Gene sets for each mechanism were retrieved from the GeneCards database. The inference score system was used to extract high-confidence genes with strong mechanistic relevance, avoiding inflation by low-evidence associations. These curated gene sets formed the mechanistic framework for evaluating each compound's biological relevance to Alzheimer's pathology. [2].

2.3 Drug Target Prediction

To determine the potential protein targets of the eight selected compounds, three independent target-prediction platforms were used: PharmMapper, SwissTargetPrediction, and the Similarity Ensemble Approach. PharmMapper generated reverse pharmacophore matches against human proteins, while SwissTargetPrediction provided ligand–target relationships based on structural similarity and known pharmacology. The Similarity Ensemble Approach identified chemically similar ligand interactions through its statistical similarity model. Target lists from all three tools were combined for each compound, and duplicate entries were removed. [3].

2.4 Identification of Common Mechanistic Targets

The predicted targets for each compound were compared with the eight Alzheimer's-related mechanistic gene sets. Intersection analyses identified the common genes between each compound and each mechanism. This allowed quantification of how strongly each molecule interacted with each mechanistic domain. A second, more integrative intersection was performed by combining all eight mechanisms into a single gene pool. Common genes shared across all mechanisms for each compound represented the compound's multi-mechanistic relevance. [4].

2.5 Protein–Protein Interaction Network Analysis

Protein–protein interaction (PPI) networks for each compound's multi-mechanism common targets were generated using the STRING v11.5 database. Only interactions involving human proteins and meeting a high-confidence threshold of at least 0.70 were included. Interaction

evidence derived from curated databases, experimental studies, co-expression, and text-mining. Nodes with no interactions were removed to maintain a coherent network structure. Each network was imported into Cytoscape for further analysis, and descriptive parameters such as node number, network density, clustering coefficients, and connectivity patterns were recorded. [5].

2.6 Identification of Hub Genes for AD

Hub genes were identified using the CytoHubba plugin in Cytoscape. The Maximal Clique Centrality (MCC) algorithm was selected because of its strong performance in distinguishing essential regulatory genes in biological networks. For each compound, the ten highest-ranking MCC genes were identified. These genes represented the dominant signalling hubs through which each compound may modulate Alzheimer's-related pathology [6, 7].

2.7 KEGG Pathway Matching for Alzheimer's Disease

Using the STRING pathway enrichment tool, KEGG Alzheimer's disease pathway genes were identified. Overlap analysis was performed between these KEGG-annotated Alzheimer's genes and each compound's MCC-ranked hub genes. Only targets appearing in both datasets were selected for molecular docking to ensure biological relevance to AD progression. This filtering step provided a disease-specific ligand–target docking set for each compound. [8, 9].

2.8 Molecular Docking Procedure

Molecular docking studies were performed using Molecular Operating Environment (MOE) 2019. Crystal structures of relevant AD-associated proteins were obtained from the RCSB Protein Data Bank. Protein preparation included removal of crystallographic water, addition of hydrogen atoms, assignment of physiologically relevant protonation states, and energy minimisation using the AMBER10:EHT forcefield. Ligands were energy-minimised using the MMFF94x model and standardised with respect to protonation state and charge. Docking was conducted using the Triangle Matcher placement method with London dG scoring for initial pose ranking, followed by refinement with GBVI/WSA dG scoring. For each protein–ligand pair, the best-scoring poses were retained, and interaction details, including S-scores, binding energies, interaction distances, and hydrogen bonding patterns, were extracted. Key interacting residues were recorded. Docking results from the provided dataset were used to interpret the results in the Results section. [10, 11].

Results

3.1 Overview of Mechanism-Specific Target Intersections

Intersection analysis between predicted drug targets and mechanism-specific Alzheimer's disease gene sets demonstrated substantial variability across the eight compounds. Fraxidin displayed the broadest coverage across mechanistic domains, while isofraxidin showed the narrowest range of interactions. When comparing the number of overlapping genes within each mechanism, the highest degree of mechanistic enrichment was observed for autophagy in α -pinene, ferroptosis in deltoin and anomalin, neuroinflammation in isofraxidin and scopoletin, and apoptosis in 5-O-methylvisamminol. Conversely, oxidative stress and pyroptosis displayed more uniform and moderate coverage across all compounds. Descriptively, the comparative radar trends indicated that fraxidin, panaxydol, deltoin, and 5-O-methylvisamminol demonstrated the greatest mechanistic breadth, whereas isofraxidin and α -pinene were more selective in their influence.

3.2 Total Multi-Mechanism Common Targets

When all eight mechanistic domains were combined into a unified Alzheimer's-related gene pool, the number of shared targets per compound allowed assessment of generalised multi-pathway involvement. Fraxidin showed the highest number of multi-mechanism common targets, with a total of 191 genes. Panaxydol followed with 142, scopoletin with 134, anomalin with 127, deltoin and 5-O-methylvisamminol each with 116, and isofraxidin with 109 (Figure 1). These values suggested that fraxidin was the most broadly interactive compound across Alzheimer's disease-related molecular axes, while isofraxidin exhibited the most selective target profile. This ranking provided the initial prioritisation framework for deeper network interrogation.

3.3 PPI Network Characteristics

STRING-based protein-protein interaction networks generated from each compound's multi-mechanism gene set produced densely interconnected regulatory clusters enriched in signalling proteins, kinases, transcription factors, and metabolic enzymes. All networks demonstrated high node centrality, dense intermodular communication, and significant clustering coefficients, consistent with typical Alzheimer's disease regulatory landscapes. Fraxidin's network demonstrated the highest node count and network density, congruent with its large number of common targets. Panaxydol and scopoletin displayed intermediate levels of complexity, while isofraxidin and deltoin produced smaller but still highly structured interaction clusters. Visual inspection of network topology (not shown here) indicated the presence of large central hubs surrounded by peripheral regulatory modules, suggesting multi-layered signalling influence (Figure 2).

3.4 Identification of Hub Genes Across Compounds

CytoHubba MCC analysis consistently identified several regulatory genes as dominant hubs across multiple compounds. For scopoletin, key hubs included GAPDH, HIF1A, AKT1, NFKB1, CCND1, ALB, SRC, ESR1, MMP9, and PTGS2. Fraxidin produced a set of genes that were highly overlapping but distinct, including ALB, AKT1, BCL2, ESR1, CTNNB1, TGFB1, MMP9, SRC, and NFKB1, thus highlighting its very strong contribution to anti-apoptotic and pro-survival signaling pathways. Isofraxidin, in its turn, showed a hub profile that is both AKT1-enriched and CTNNB1-enriched with CCND1, EGFR, HDAC1, FOS, BCL2, GSK3B, ESR1, and CCNA2, which underscores its central position in the processes of transcriptional regulation and synaptic signaling. Panaxydol mostly acted on the targets of STAT1, MMP9, INS, ESR1, AKT1, ANXA5, HSP90AB1, and MTOR, suggesting a high involvement in metabolic control and stress-response pathways. The profile of Anomalins included MMP2, MDM2, ALB, CASP3, HSP90AB1, INS, MMP9, ESR1, ACTB, and CCND1, thus demonstrating its effect on the apoptotic and extracellular matrix dynamics. Lastly, Deltoin generated a hub that comprised CASP3, SRC, INS, ESR1, STAT3, PPARG, PTGS2, EGFR, ALB, and CYCS, which is indicative of good control of inflammatory and proliferative pathways. α -Pinene's hubs included MAPK1, RHOA, ESR1, PPARG, TGFB1, ACTB, ALB, EGFR, HSP90AA1, and SRC; however, its enriched genes did not show statistically significant alignment with KEGG Alzheimer's disease pathways, reducing its prioritisation (Figure 3).

3.5 KEGG Alzheimer's Pathway Alignment

Comparison between the MCC-ranked hub genes and KEGG Alzheimer's pathway enrichment revealed that most compounds demonstrated substantial overlap with AD-relevant nodes. Fraxidin, panaxydol, and deltoin showed the highest concordance, particularly through genes such as AKT1, MTOR, TGFB1, PPARG, NFKB1, MMP9, and EGFR. 5-O-methylvisamminol also displayed strong alignment through MAPK1, STAT1, EGFR, CREB1, and MTOR, indicating involvement in synaptic plasticity, neuroinflammation, and survival signalling. α -Pinene showed minimal KEGG pathway alignment, which was consistent with its lower mechanistic relevance despite its high initial target count (Table 1).

3.6 Molecular Docking of Hub Genes with Selected Compounds

Docking analyses conducted using MOE revealed several high-affinity ligand–target interactions across the compound panel (Table 2).

3.6.4. Molecular Docking of Scopoletin with Overlapping Genes

Docking analysis showed that the protein has stable binding interactions with GAPDH and PTGS2, with the predicted affinities of between -4.7 and -6.0 kcal mol⁻¹; and there was no stable

interaction with residues of AKT1. The adherence to GAPDH is an indication that this pathway may affect oxidative stress and energy metabolism processes, which are typically impaired in Alzheimer's disease of Alzheimer. Also, the affinity towards PTGS2 indicates the possibility of anti-inflammatory action, which confirms the scopoletin action in suppressing neuroinflammation (Figures 4 & 5).

3.6.6. Molecular Docking of Fraxidin with Overlapping Genes

Docking analysis showed no stable interaction with AKT1, but fraxidin has good and stable binding to CTNNB1 and NFKB1, with predicted affinities of -4.8 to -5.7 kcal mol⁻¹. NFKB1 Interaction implies possible anti-inflammatory activity, and the interaction with CTNNB1 suggests possible regulation of neuroprotective transcriptional pathways associated with cell survival and synaptic maintenance (Figures 6 & 7).

3.6.7. Molecular Docking of Isofraxidin with Overlapping Genes

Molecular docking showed strong and energetically stable interactions with AKT1, CTNNB1, and GSK3b with a binding affinity of -7.8 and -8.9 kcal mol⁻¹. GSK3b inhibition is also specifically relevant because it can alleviate an indicator of Alzheimer's disease, tau hyperphosphorylation. The interaction with CTNNB1 indicates a possible increase in the Wnt/ β -catenin signalling, which is also known to protect against amyloid- β -induced neurotoxicity. Moreover, communication with AKT1 suggests the potential to reinforce neuronal survival and anti-apoptotic pathways, which means that isofraxidin can partially have certain neuroprotective effects, despite its low coverage of the entire pathway (Figures 8, 9 & 10).

3.6.2. Molecular Docking of 5-O-Methylvisamminol with overlapping genes

Docking of 5-O-Methylvisamminol showed stable and favorable interactions with CASP3, INS, MAPK1, and mTOR with binding energies of -5.8, -6.2, -6.4, and -6.9 kcal mol⁻¹. The binding to CASP3 suggests the ability to regulate apoptotic cell death, and the binding to mTOR and MAPK1 suggests that it can have an effect on neuronal survival, autophagic processes, and synaptic signaling. A potential involvement in the correction of the insulin-related metabolism malfunction, which is one of the factors in the development of Alzheimer's disease, is additionally supported by the moderate affinity to INS (Figures 11, 12, 13 & 14).

3.6.1. Molecular Docking of Deltoin overlapping genes

Molecular docking analysis of deltoin showed constant and energetically feasible contacts with the hub genes CASP3, INS, and PTGS2, with binding affinities of -6.2, -7, and -8 kcal mol⁻¹. The strong affinity to PTGS2 highlights its possible anti-inflammatory capacity, but the binding with CASP3 indicates the possible existence of regulation in the apoptotic cell death. Furthermore, the INS binding suggests a potential future connection to metabolic dysfunction and disruptions of the insulin signaling that are common in the pathology of Alzheimer's disease (Figures 15, 16 & 17).

3.6.3. Molecular Docking of Anomalin with Overlapping Genes.

Docking analysis was noted to exhibit constant interaction with CASP3 and INS with a binding energy of between -6.8 and -7.7 kcal mol⁻¹. The interaction with CASP3 indicates a potential future implication in the regulation of apoptosis, which would possibly improve neurodegenerative disease. At the same time, the identified preference towards INS suggests a potential impact on insulin resistance and metabolic dysfunction, which is becoming a more and more active part of the Alzheimer's disease pathology (Figures 18 & 19).

3.6.5. Panoxydol Molecular Docking with Overlapping Genes.

The docking analysis showed that there existed stable and favorable interactions with AKT1 and mTOR, with binding energies of -6.5 to -7.6 kcal mol⁻¹, but no stable bond existed between Panaxydol and INS residues. The existence of interaction with AKT1 and mTOR indicates that it may have a neuroprotective effect, especially when it regulates cell survival, autophagy, and metabolic processes that are often dysregulated in Alzheimer's disease (Figures 20 & 21).

3.7. Comparative Evaluation of Compound Activity Across Key Alzheimer's Pathways

Mechanistic intersection data, absence of hubs, dominance of a hub, Alzheimer-associated alignment of KEGG, and docking affinities suggest that Fraxidin, panaxydol, 5-O-Methylvisamminol, and deltoin are the best compounds to modulate Alzheimer's disease. Fraxidin was ranked first with the highest number of targets and network centrality; panaxydol had a strong alignment to the AD pathway and high binding to MTOR; deltoin had strong single-target binding affinity; and 5-O-Methylvisamminol made a significant contribution to the oxidative stress and apoptosis pathways. Isofraxidin and scopoletin were also moderately but significantly involved, and α -pinene had low levels of KEGG alignment, limiting its relevance in translation despite high levels of autophagy targeting.

3.8. Compound-Pathway Interaction Map.

The pathway map was used to visualize the pathways covered by each compound related to Alzheimer's disease, with 5-O-Methylvisamminol the only pathway to cover all major ones, including APP and presenilin processing, tau phosphorylation, autophagy-lysosomal signaling, mitochondrial dysfunction, oxidative stress, and neuroinflammation. The common coverage of inflammatory, synaptic, and apoptotic pathways was common to Panaxydol and scopoletin. Deltoin had high apoptotic and MAPK-related pathway activation but poor autophagy signalling. Anomalin and fraxidin were not well covered and did not have any important neuroprotective pathways. Isofraxidin only interacted with a fraction of the amyloidogenic and apoptotic pathways and did not interact with oxidative and synaptic targets (Figure 22).

3.9. Ranking of Compounds in terms of the Strength of Enrichment.

Bubble-chart analysis, which combines enrichment strength, the number of AD genes involved, and logFDR, showed the biggest and strongest bubble 5-O-Methylvisamminol (23) with the highest number of AD genes, the strongest pathway enrichment (1.04), and the strongest statistical value (logFDR =14.94). The panaxydol generated a huge albeit less intense bubble of reflection of the broad involvement of genes, but with a slightly lesser statistical power. Deltoin, scopoletin, and anomalin had a moderate size of bubbles that portrayed moderate performance. Fraxidin exhibited a humble participation. The weakest overall profile was confirmed by isofraxidin, which produced the smallest bubble (Figures 23 & 24).

Discussion

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is characterized by a gradual decline of cognitive functions, including memory, reasoning, language, and behavior (26). Our overall results included ADME screening, target identification, protein-protein interaction (PPI) mapping, hub-gene analysis, KEGG Alzheimer pathway enrichment, and molecular docking, all of which were carried out in a comprehensive network pharmacology approach in order to evaluate the therapeutic potential of bioactive constituents of *Saposhnikovia divaricate* (27). Combined with analyses revealed that even though all the analyzed compounds demonstrated some level of neuroprotective property, their mechanistic input varied significantly in depth, breadth, and specificity in the context of biological networks of AD origin.

Among the molecules under investigation, 5-O-methylvisamminol was the most promising multi-target candidate that was found several times (28). It showed the highest number of AD-associated genes, interacted with the broadest range of biological pathways, and had strong

docking affinities with key neuronal survival regulators. Its interactome involved important processes involved in AD pathogenesis, such as amyloid precursor protein processing, tau phosphorylation, neuroinflammation, oxidative stress, apoptosis, mitochondrial dysfunction, and autophagy. It is also worth noting that it undergoes strong interaction with AKT1, the members of the MAPK family, along with other neuroprotective kinases, so that they have the ability to stabilize the AKT/mTOR and MAPK signaling axes, which are largely disrupted in AD. These observations highlight the compound to control interconnected neurodegenerative effects that cumulatively cause disease pathology (29).

Panaxydol took the second place in the therapeutic relevance category, showing robust interaction with signalling pathways and having strong interactions with the AD-associated genes. It was particularly effective in the processes that control glutamatergic neurotransmission, NMDA receptor regulation, mitochondrial homeostasis, and oxidative phosphorylation (30). MTOR, NFKB1, and synaptic regulatory protein docking affinities also contribute to the prospects of the compound in restoring synaptic plasticity and neuroenergetics, which are significantly impaired in AD (31, 32).

Deltoid and scopoletin showed moderate therapeutic value, which could be explained mainly by their involvement in MAPK signalling, the regulation of oxidative stress, neuroinflammatory process, and apoptosis (33, 34). Deltoid exhibited a strong docking interaction with PTGS2 and an interesting interaction with CASP3, involving anti-inflammatory and anti-apoptotic parameters (35). Scopoletin's modulation of NF- κ B-associated inflammatory signalling aligns with established neuroprotective actions of coumarin derivatives and reinforces its relevance in regulating chronic Neuroinflammation [12].

Fraxidin, anomalin, and isofraxidin showed more limited but still meaningful mechanistic contributions. Fraxidin engaged with pathways related to oxidative stress, pyroptosis, and inflammatory signalling; anomalin modulated ER-stress and apoptotic mechanisms. [13]; and isofraxidin, despite strong docking affinity for GSK3 β , AKT1, and CTNNB1, demonstrated weak pathway enrichment [14]. This suggests potent target-specific binding but insufficient broader systems-level engagement in AD networks.

Across all compounds, convergent interactions with core hub genes, including AKT1, ESR1, MTOR, CTNNB1, MMP9, PPARG, NFKB1, TGFB1, and CASP3 [15], were evident. These nodes regulate neuronal survival, synaptic plasticity, mitochondrial stability, inflammatory responses, and proteostasis. Their recurrent identification highlights a shared mechanistic axis

underpinning the activity of multiple compounds and suggests potential synergy among the coumarin and terpenoid constituents of *S. divaricata* [16].

Molecular docking supported the network-pharmacology predictions by revealing favourable binding energies. [17] And functionally relevant hydrogen-bond interactions for high-performing compounds such as deltoin, panaxydol, anomalin, and 5-O-methylvisamminol. These structural insights enhance the plausibility of direct protein modulation and reinforce the mechanistic coherence of the integrated findings.

The current research paper shows that the medicinal activity of *S. divaricata* could be explained by its ability to modulate various signaling pathways and targets of the complex neurobiological systems involved in the pathogenesis of Alzheimer's disease. The compound with the most comprehensive mechanistic profile in the tested compounds was 5-O-methylvisamminol, followed by panaxydol, and in contrast, the activity of deltoin, scopoletin, and anomalin seems to be mainly focused on anti-inflammatory and anti-apoptotic activity. Such data predict that these compounds should be prioritized for experimental validation in future preclinical models of AD.

Conclusion

Combined results of multi-mechanistic target overlap, Protein-protein Interaction network analysis, Hub-gene identification, enriching Alzheimer pathways, as well as molecular docking, concluded that Fraxidin, Panaxydol, Deltoin, anomalin, as well as 5-O-methylvisamminol, are the most promising *Saposhnikovia divaricata* derivatives to intervene in AD. These compounds were shown to continuously react with major regulatory systems involved in the pathogenesis of AD and showed desirable binding with essential proteins in AD. Scopoletin and Isofraxidin had moderate yet significant mechanistic relevance, whereas α -pinene, despite its high autophagy-related activity, had a relatively weak specificity to the pathways in the case of AD. On the whole, this paper provides a systematic and thorough analysis of eight significant phytochemicals of *S. divaricata*, the most promising biologically active molecules, and a strong basis of experimental and pharmacological confirmation of the findings in future in the study of AD.

Study Limitations

This paper uses purely computational techniques, such as predictive target discovery, reconstruction of protein-protein interaction networks, and molecular docking simulations. Despite the useful mechanistic information provided by these methods, they cannot be used in

place of experimental validation. The biological relevance and therapeutic potential of the identified compounds should be confirmed with the help of in vitro or in vivo studies in the context of Alzheimer's disease models. Moreover, molecular docking gives only a structural approximation of binding affinity and does not entirely consider protein flexibility, metabolism transformation, pharmacokinetics, and bioavailability in physiological conditions. The sets of mechanistic genes were based on the GeneCard database, which might add a bias of literature dependence, since not all genes are equally visible in the research. In spite of these underlying drawbacks, the integrative computational workflow applied in this research provides a vigorous and thorough mechanistic framework that can be successfully used in future laboratory-based research.

Authorship contribution statement

Amber Sani: Conceptualization, Methodology, Investigation, Visualization. **Chunyu Liu:** Methodology, Investigation **Jawad Azam:** Writing – original draft. **Salman Khan:** Conceptualization, Visualization, Validation, Data curation, Writing – review & editing, Project administration, Supervision.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Figure 1. Compound–Target Network of Coumarins and Terpenoids from *Saposhnikovia divaricata*.

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Figure 22. Radar Plot Comparing Compound Activity Across Eight Alzheimer's Disease Mechanisms.

Radar plot illustrating comparative mechanistic engagement of all compounds across eight Alzheimer's disease pathways: core genes, hormonal dysregulation, pyroptosis, ferroptosis, neuroinflammation, oxidative stress, apoptosis, and autophagy. Larger polygon areas correspond to broader mechanistic involvement.

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Heatmap representing the degree of overlap between each compound and eight mechanistic categories. Higher intensity indicates a larger number of shared targets.

Figure 24. Bubble Plot of KEGG Pathway Enrichment.
Bubble plot showing KEGG pathway enrichment for all compounds combined. Bubble size denotes enriched gene count, colour reflects log FDR, and horizontal placement indicates enrichment strength. Pathways with larger, deeper-coloured bubbles represent the most significant biological routes.

<i>Compound</i>	<i>Genes Involved</i>	<i>Background Genes</i>	<i>Strength</i>	<i>Signal</i>	<i>FD R</i>	<i>Genes Enriched in Alzheimer's Disease</i>
<i>Deltoin</i>	22	354	1.02	2.26	1.0 1×10^{-1} 4	MAPK1, CSNK2A1, MAPK3, MAP2K1, INSR, GRM5, CYCS, ADAM17, CASP3, BACE1, GSK3B, NOS2, MAP3K5, PTGS2, CASP7, AKT2, MAPK8, INS, BRAF, CDK5, APAF1, AKT3
<i>5-O-Methylvisaminol</i>	23	354	1.04	2.39	1.1 5×10^{-1} 5	MAPK1, PIK3R2, MAPK3, PIK3CA, NCSTN, INSR, CYCS, CASP3, BACE1, PSEN1, NOS2, MAP3K5, MTOR, APH1A, AKT2, MAPK8, INS, MME, BRAF, CDK5, PSENEN, LPL, AKT3
<i>Anomalin</i>	19	354	0.92	1.76	2.5 8×10^{-1} 1	MAPK1, MAPK3, PIK3CA, CASP3, BACE1, GSK3B, NOS2, PSMB5, PSEN2, CASP7, AKT2, MAPK8, INS, BRAF, CDK5, PIK3R1, IKBKB, PSENEN, NOS1
<i>Scopoletin</i>	20	354	0.92	1.80	1.2 7×10^{-1} 1	MAPK1, CSNK2A1, NFKB1, MAP2K1, INSR, BACE1, GSK3B, NOS2, MAPT, PTGS2, SDHB, AKT2, GAPDH, ERN1, RAF1, MME, BRAF, APAF1, AKT1, NOS1
<i>Panaxydol</i>	23	354	0.95	2.05	1.3 2×10^{-1} 3	MAPK3, MAP2K1, INSR, GRM5, CYCS, ADAM17, CDK5R1, BACE1, GSK3B, NOS2, GRIN2A, CASP8, MAP3K5, MTOR, CASP7, GRIN1, INS, MME, CDK5, PIK3R1, AKT1, LPL, AKT3
<i>Fraxidin</i>	21	354	0.79	1.48	4.3 7×10^{-1} 0	TNFRSF1A, CSNK2A1, NFKB1, APP, MAP2K1, INSR, BACE1, GSK3B, MAPT, CASP8, PTGS2, ERN1, RAF1, HRAS, MME, BRAF, PIK3R1, TUBA1A, APAF1, AKT1, CTNNB1

<i>Isofraxidin</i>	14	354	0.86	1.25	1.4	7×10^{-7}	<i>CSNK2A1,APP,CDK5R1,BACE1,GSK3B,CASP9,CASP8,AKT2,ERN1,BRAF,CDK5,APAF1,AKT1,CTNNB1</i>
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Table 1. KEGG Alzheimer’s Disease (hsa05010) Pathway Enrichment of Compound-Associated Hub Genes

Pathway enrichment results showing the number of involved genes, background size, enrichment strength, signal score, false discovery rate (FDR), and Alzheimer’s disease–related genes for each compound.

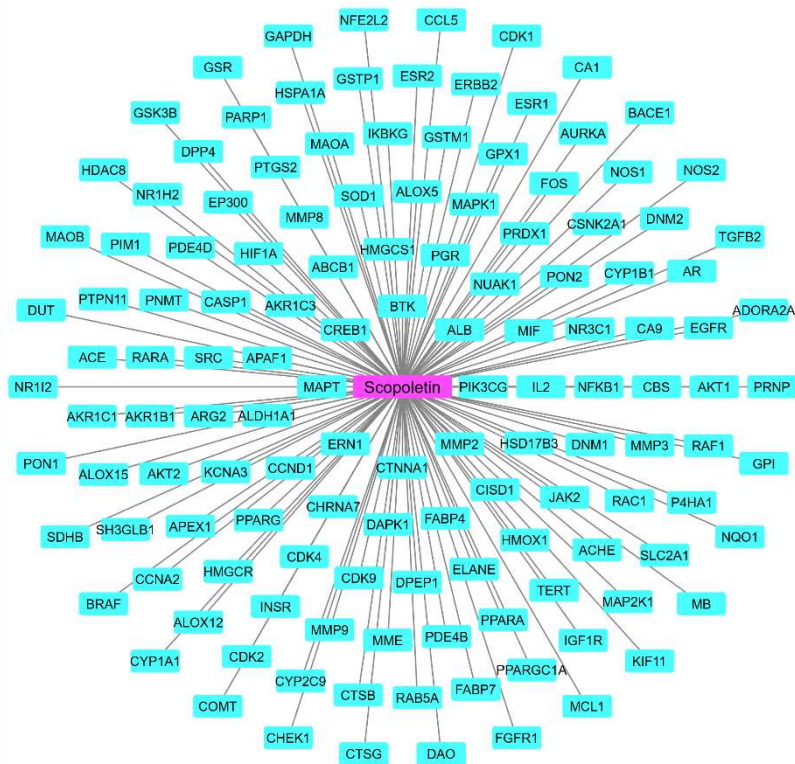
Ligand	Receptor	Residue(s)	Interaction Type	Distance (Å)	Energy (kcal/mol)	S-Score	RMSD
Scopoletin	GAPDH	ASP192	H-donor	2.53	−5.8	−4.7911	1.2013
Scopoletin	PTGS2	GLN327	H-donor	2.57	−1.5	−6.0117	0.7942
Isofraxidin	CTNNB1	GLN266	H-donor	2.87	−1.4	−4.7971	0.7268
Isofraxidin	GSK3β	VAL70	π-H	4.29	−0.6	−5.4041	1.5496
Isofraxidin	GSK3β	VAL70	π-H	4.13	−0.5	−5.4041	1.5496
Isofraxidin	AKT1	TYR315, ASP331	H-donor, H-donor	2.93, 2.76	−0.6, −1.1	−6.6819	0.8278
Fraxidin	CTNNB1	GLN266, LYS270	H-donor, π-H	3.50, 3.64	−0.5, 2.0	−4.8157	1.4207
Fraxidin	NFKB	ASN105	H-acceptor	3.49	−0.6	−5.7921	1.4696
5-O-Methylvisamminol	CASP3	LYS468	π-H	3.62	−1.0	−5.8217	1.4143
5-O-Methylvisamminol	INS	ASP1183, ARG1155	H-donor, H-acceptor	3.13, 2.98	−0.7, 3.1	−6.2413	1.2148
5-O-Methylvisamminol	MAPK	PHE169	H-donor / H-acceptor	3.32 / 2.88	−0.5 / −3.2	−6.4215	1.3538

5-O-Methylvisamminol	MTOR	ARG849	H-acceptor	2.89	−0.7	−6.9397	2.1977
Panaxydol	AKT1	ASN324	H-donor	2.95	−0.6	−6.5108	1.6611
Panaxydol	MTOR	ASP964	H-donor	3.21	−0.5	−7.6593	1.7240
Deltoidin	CASP3	MET61	H-donor	4.00	−0.6	−6.2822	1.7038
Deltoidin	INS	PHE1151	H- π	3.42	−0.6	−7.0565	1.2995
Deltoidin	PTGS2	LYS468	π -H	3.62	−1.0	−8.0316	2.1254
Anomalin	CASP3	HIS121, CYS163	H-acceptor, H-acceptor	3.36, 3.01	−0.5, 1.5	−6.8199	2.6852
Anomalin	INS	LYS1182	H-acceptor	2.90	−1.0	−7.7422	0.9172

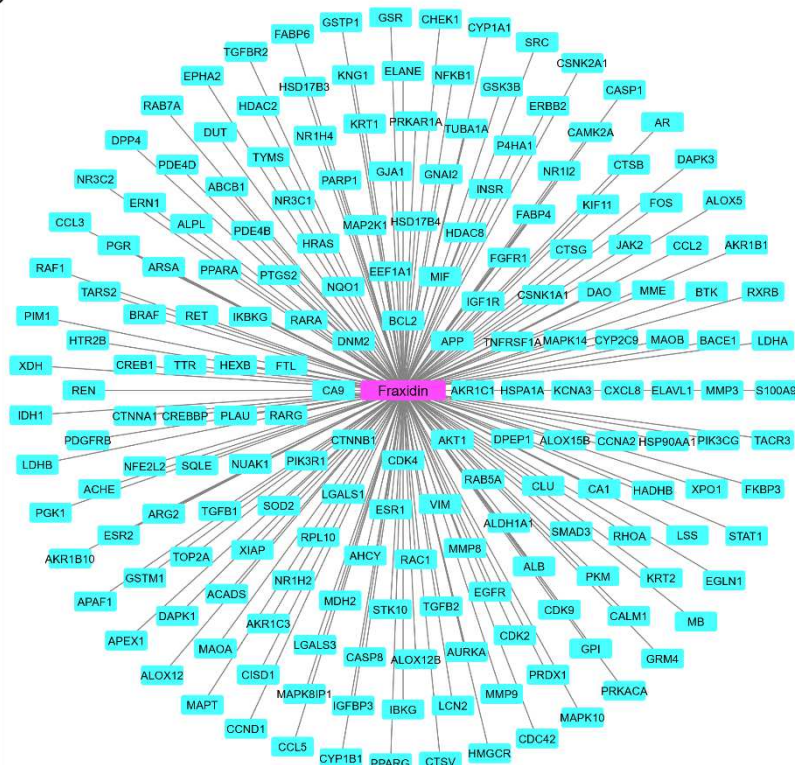
Table 2. Docking Scores and Interaction Profiles of *S. divaricata* Compounds Against Alzheimer’s-Related Targets

Summary of S-scores, binding energies, RMSD values, and key interacting residues for each ligand–target pair. Lower (more negative) S-scores indicate stronger predicted binding affinity. Highlighted values represent the strongest interactions observed for deltoin–PTGS2, panaxydol–MTOR, anomalin–INS, and 5-O-methylvisamminol–MTOR.

a)

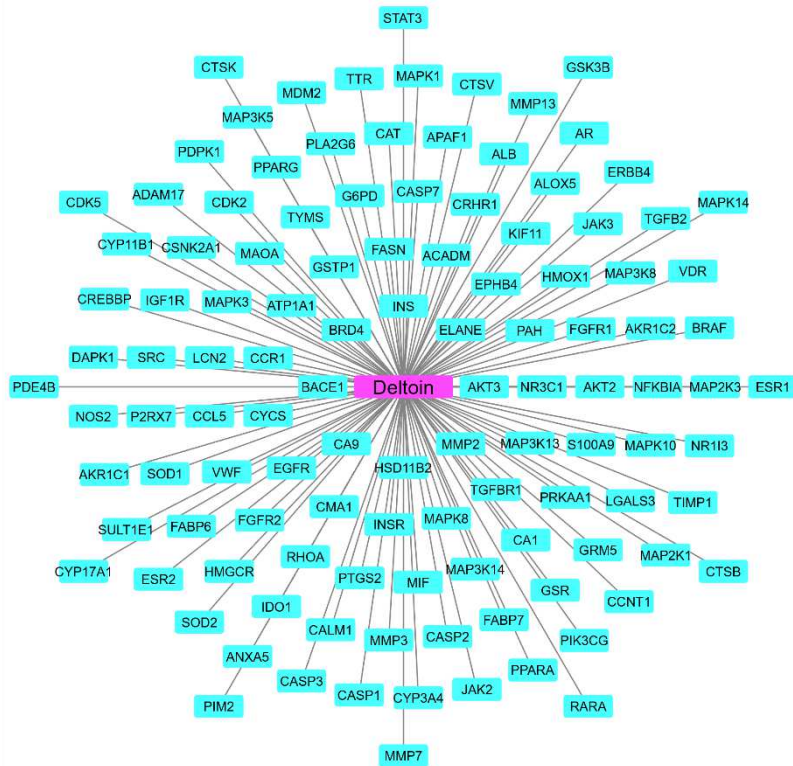


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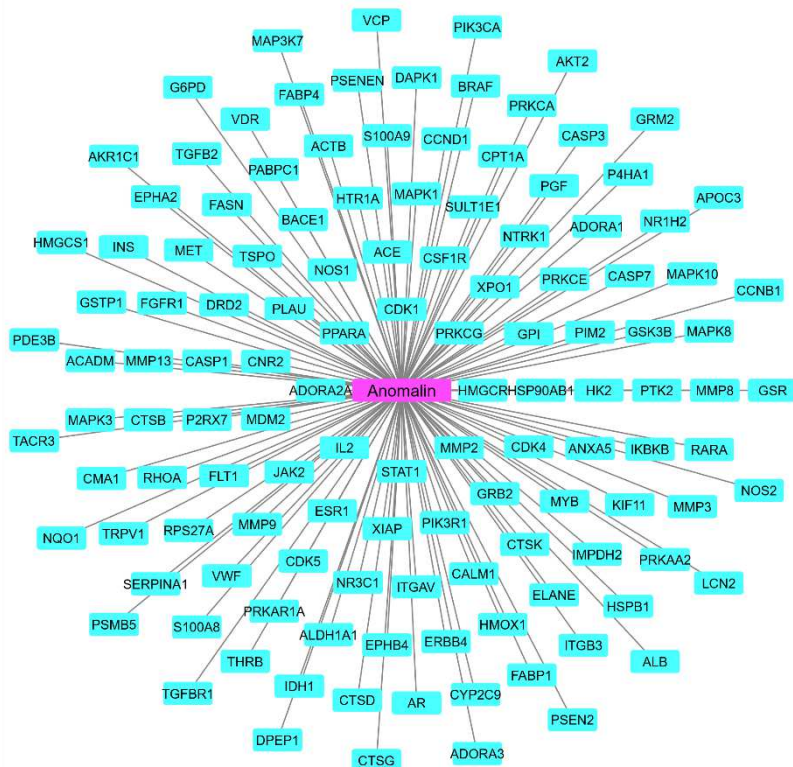


[illegible][illegible]

e)



f)



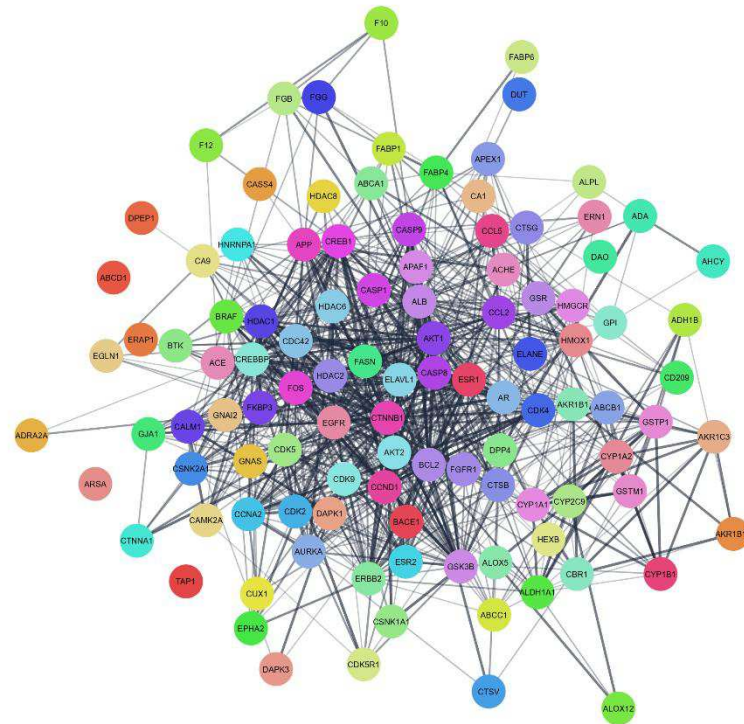
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Figure 1. Compound–Target Network of Coumarins and Terpenoids from *Saposhnikovia divaricata*

This network visualizes the interactions between eight bioactive compounds: a) scopoletin, b) fraxidin, c) isofraxidin, d) 5-O-methylvisamminol, e) deltoin, f) anomalin, g) α -pinene and h) panaxydol and their predicted human protein targets. Nodes representing compounds are shown as central hubs, while surrounding nodes represent target proteins. Edge connections denote predicted compound–target interactions generated from PharmMapper, SEA, and SwissTargetPrediction.

a)

c)



d)

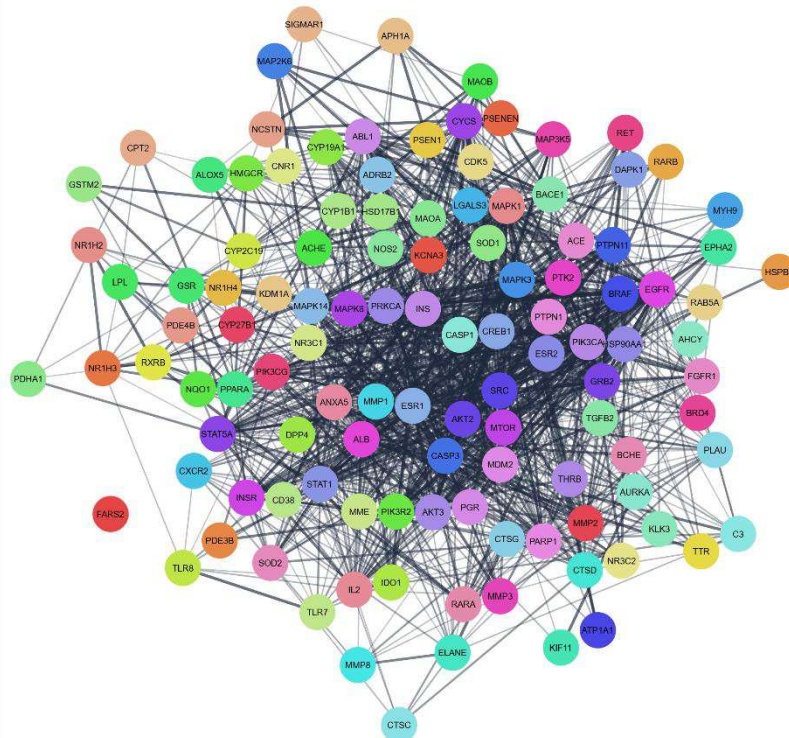
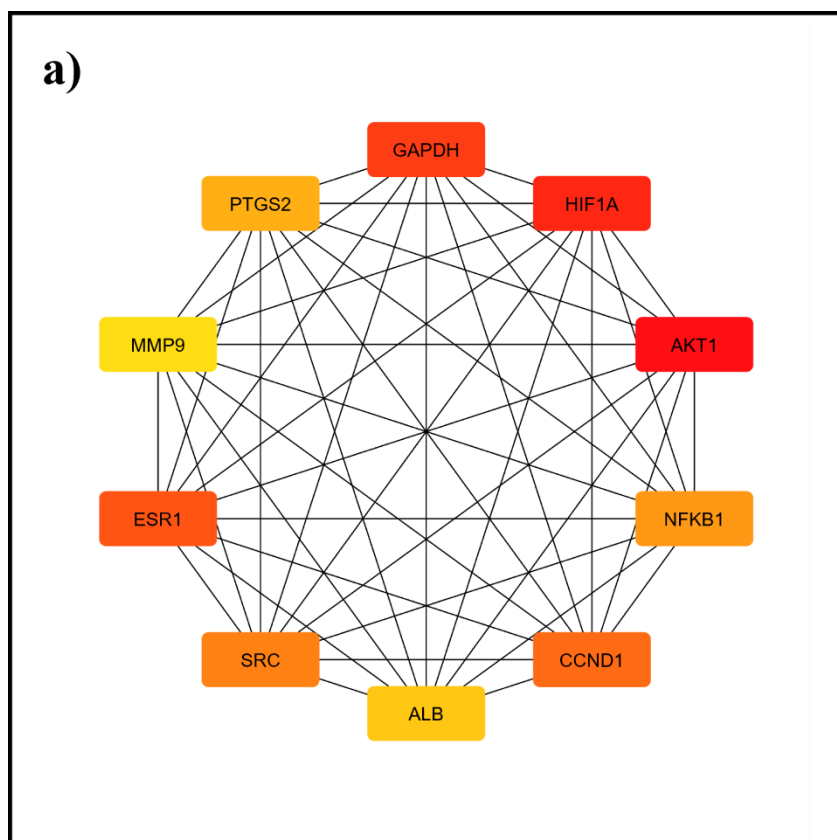
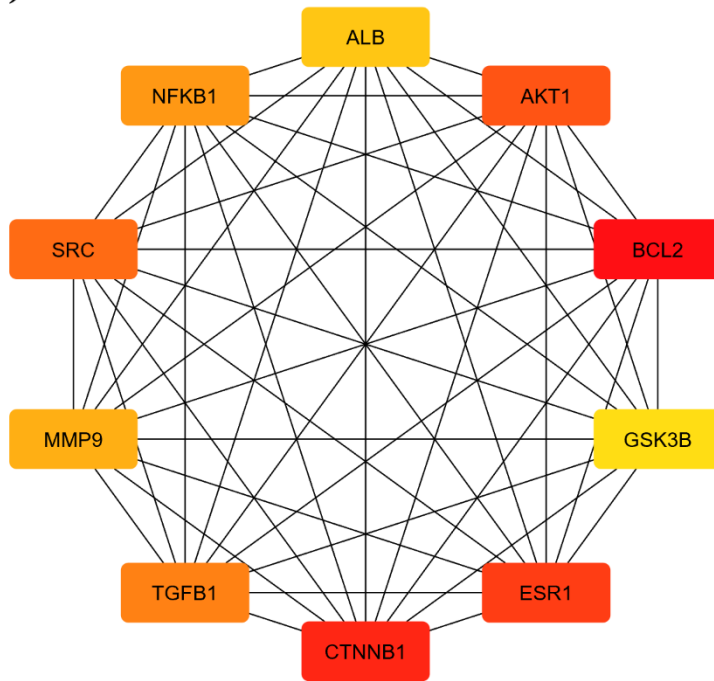


Figure 2. Protein–Protein Interaction (PPI) Network of Multi-Mechanism Common Targets

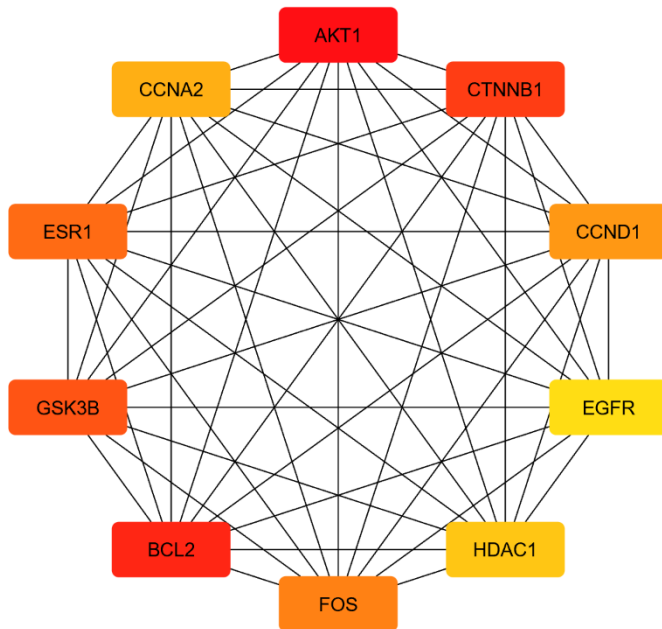
STRING-derived PPI network constructed from common targets shared across all eight Alzheimer's disease mechanisms for each compound: a) scopoletin, b) fraxidin, c) isofraxidin, d) 5-O-methylvisamminol, e) deltoin, f) anomalin, g) α -pinene and h) panaxydol. Nodes represent proteins, and edges represent high-confidence interactions.



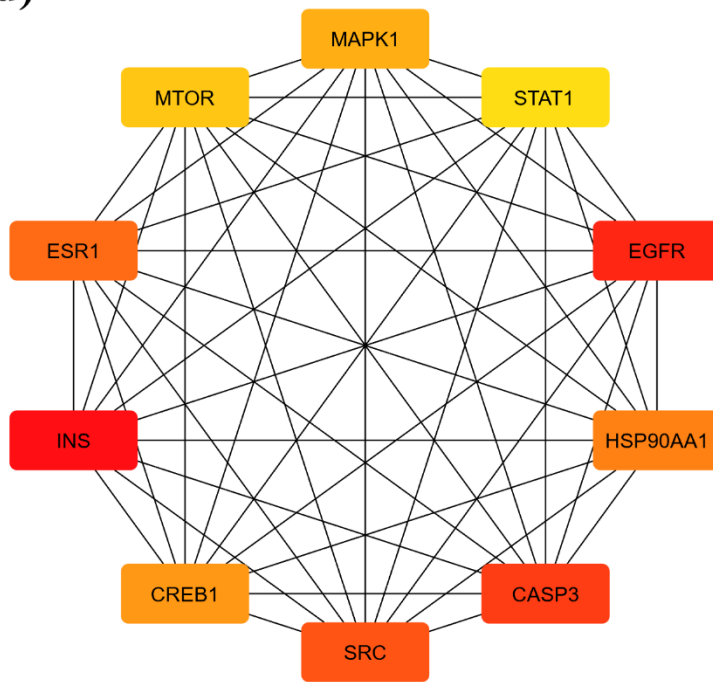
b)



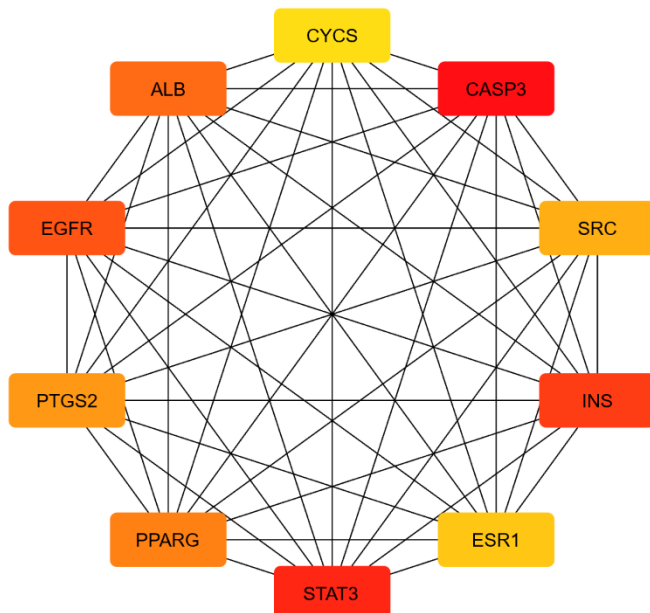
c)



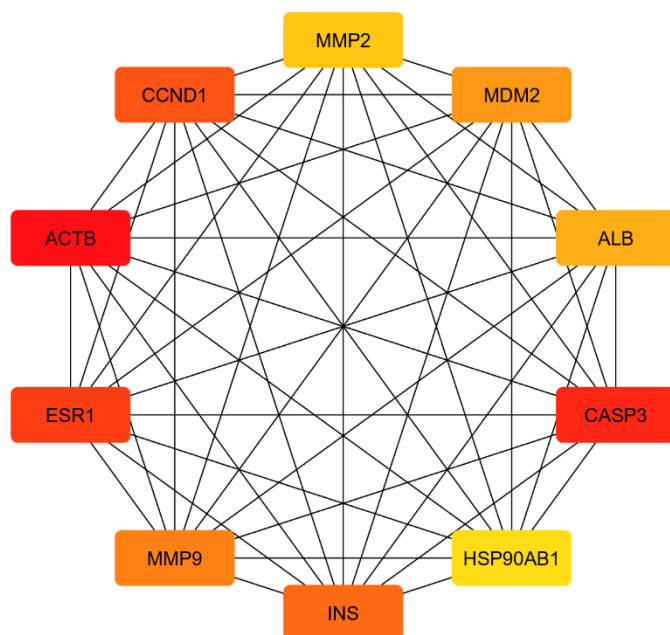
d)



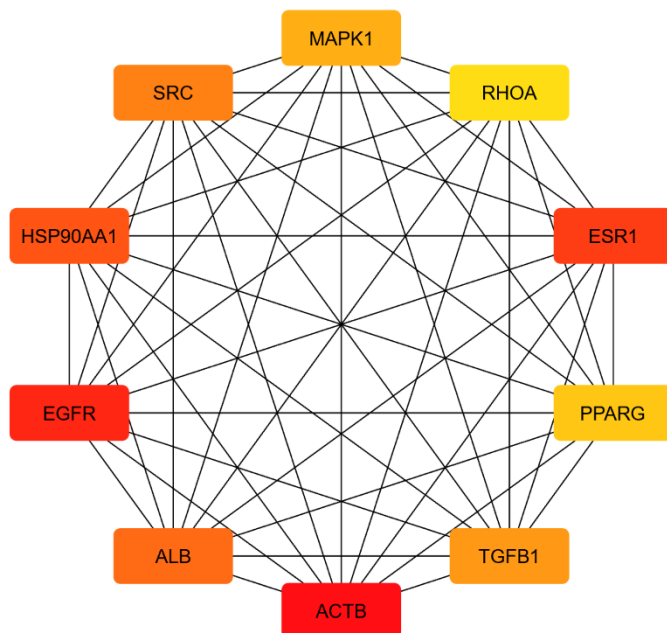
e)



f)



g)



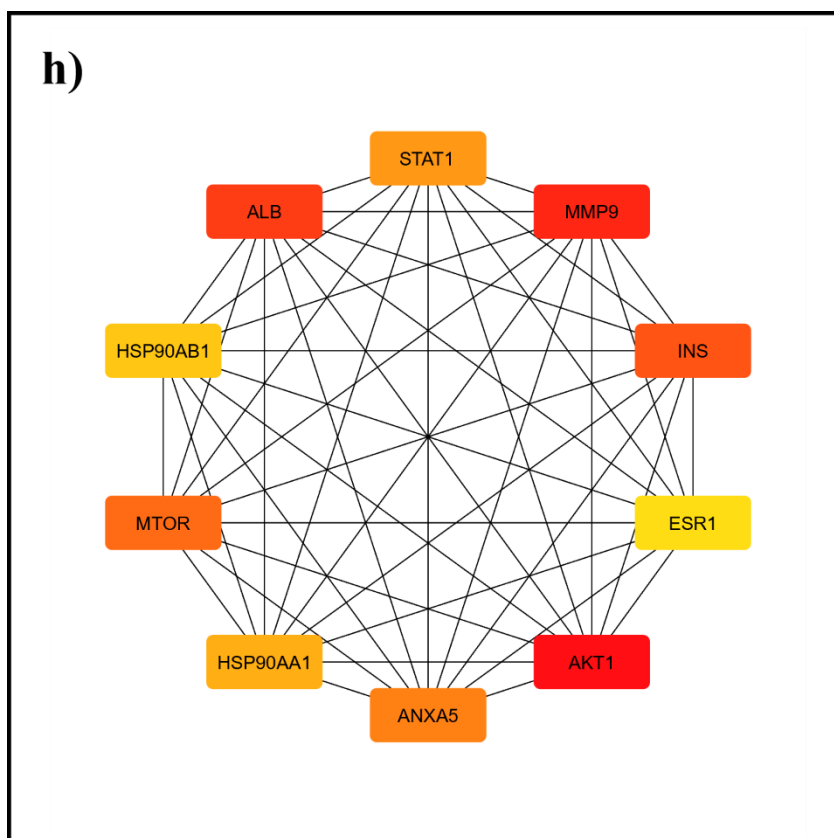


Figure 3. Hub Gene Network Identified by CytoHubba MCC Ranking

Top 10 hub genes for each compound: a) scopoletin, b) fraxidin, c) isofraxidin, d) 5-O-methylvisamminol, e) deltoin, f) anomalin, g) α -pinene and h) panaxydol, identified using the Maximal Clique Centrality (MCC) algorithm in Cytoscape. Red coloration denotes the highest-ranked hubs.

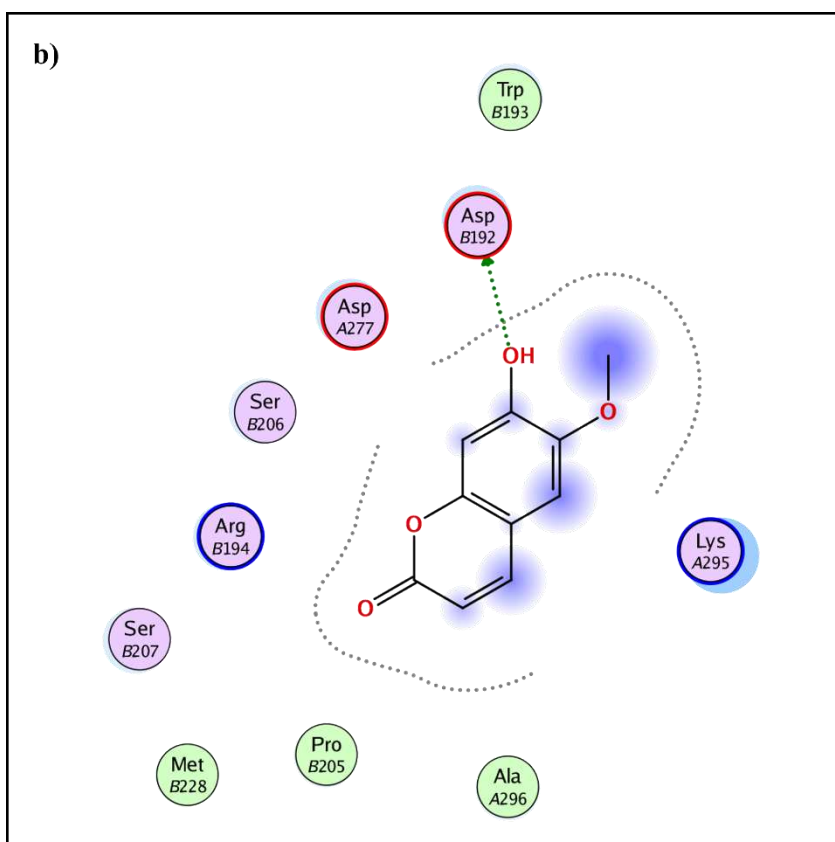
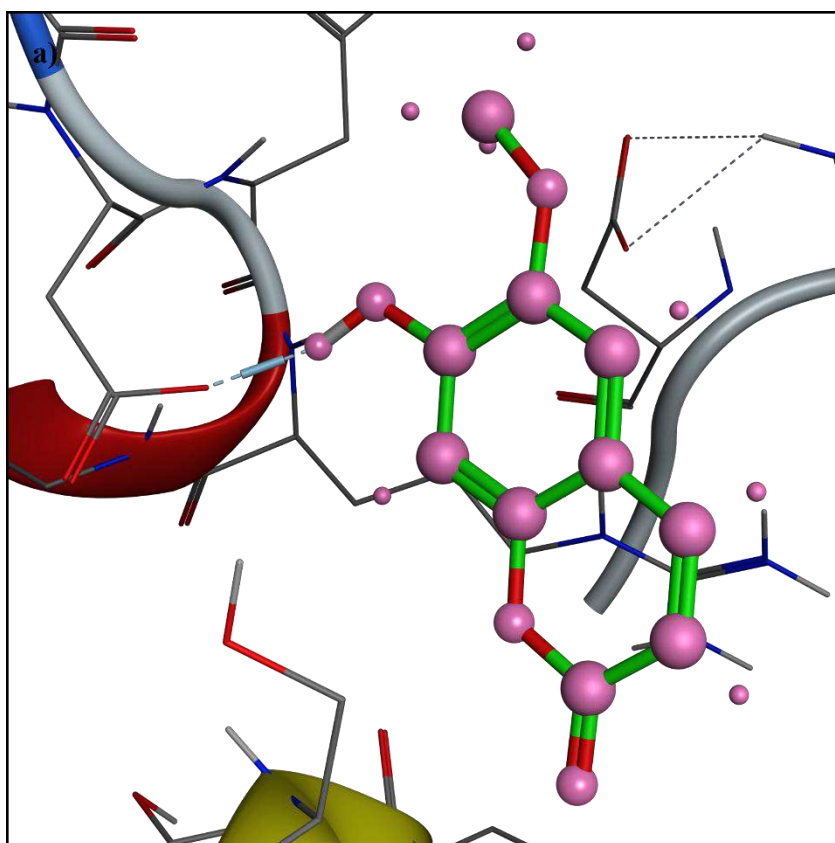
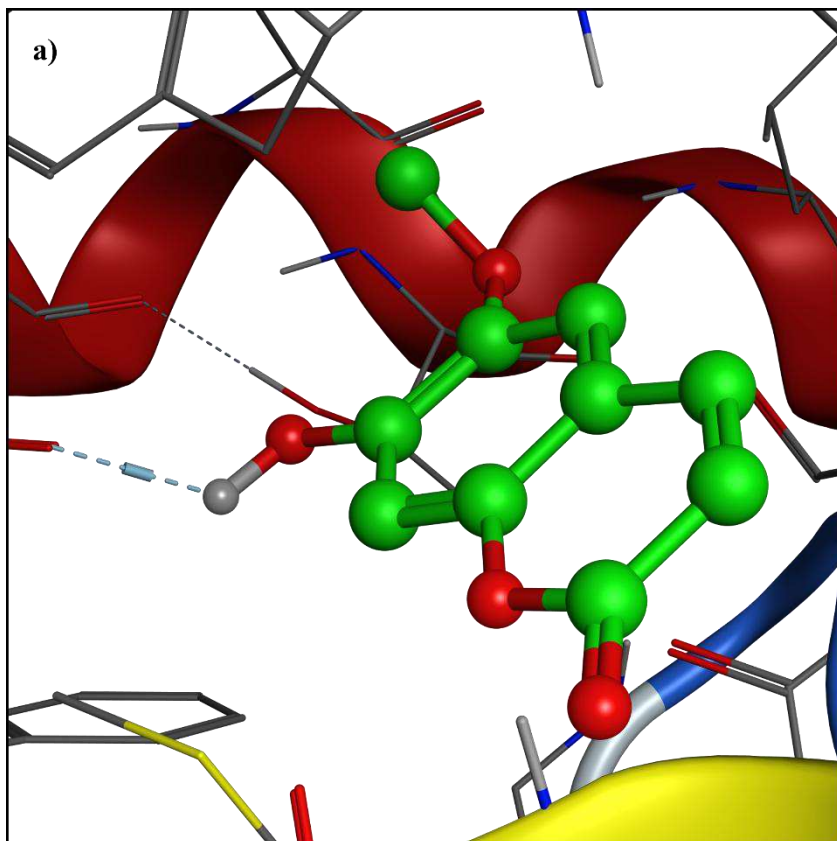


Figure 4. MOE-based docking visualization of Scopoletin within the GAPDH binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed

and hydrogen bonding depicted as dashed lines.
(b) **2D interaction diagram** showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.



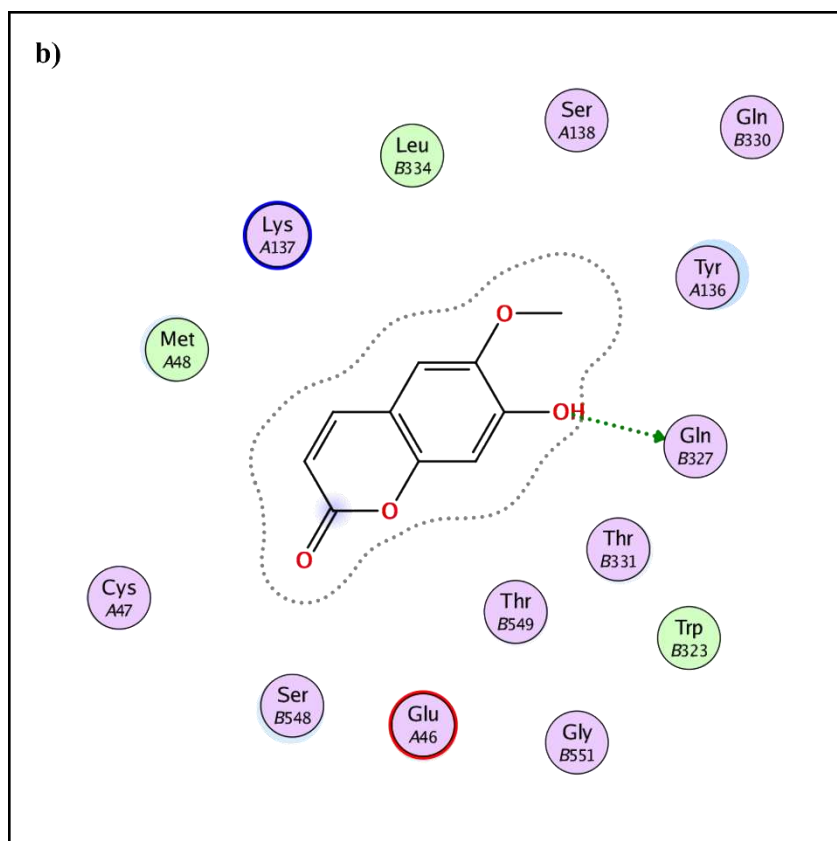


Figure 5. MOE-based docking visualization of Scopoletin within the PTGS2 binding pocket.

(a) **3D binding pose** highlighting the spatial orientation with key interacting residues displayed and hydrogen bonding depicted as dashed lines.

(b) **2D interaction diagram** showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.

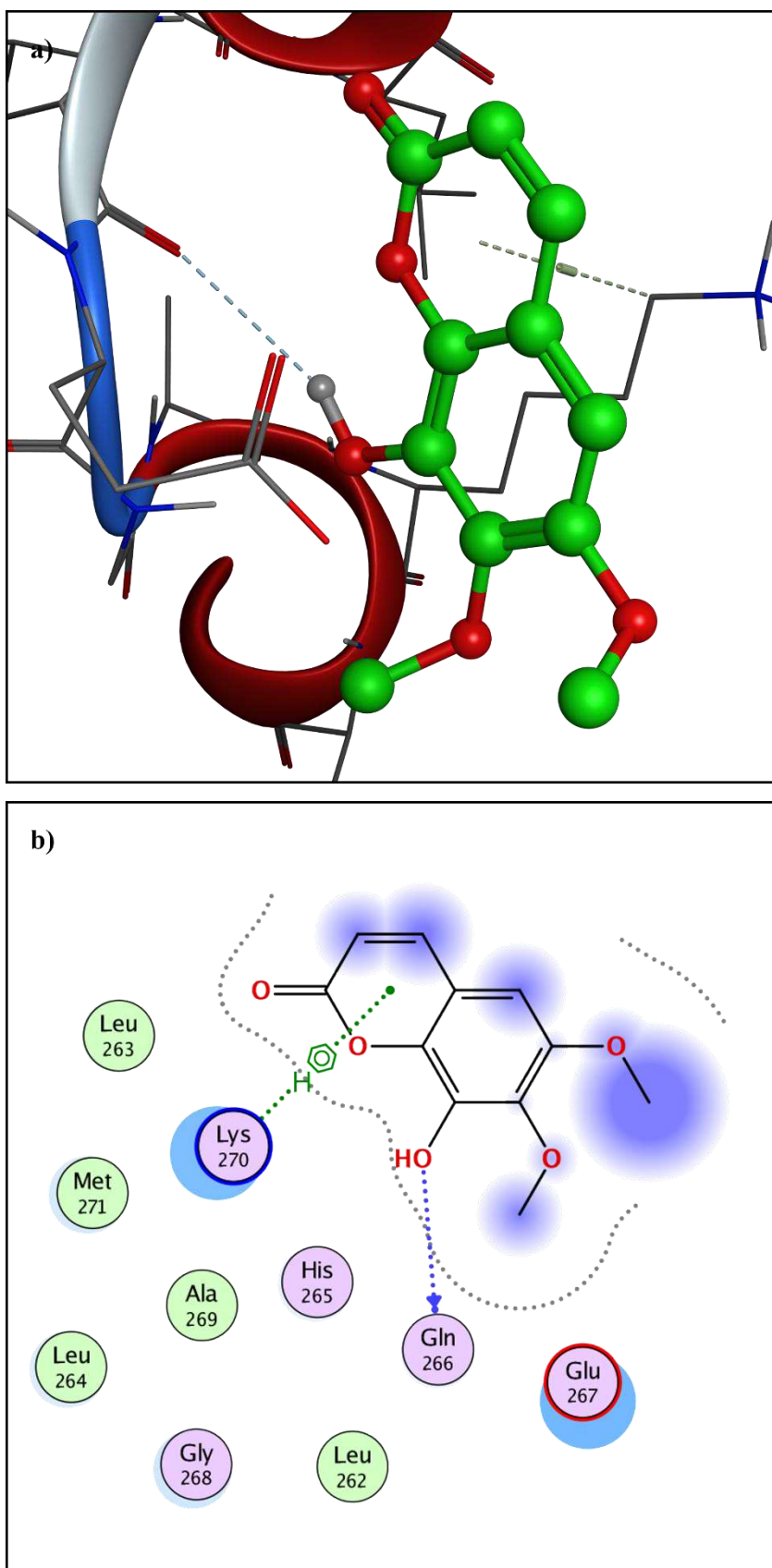
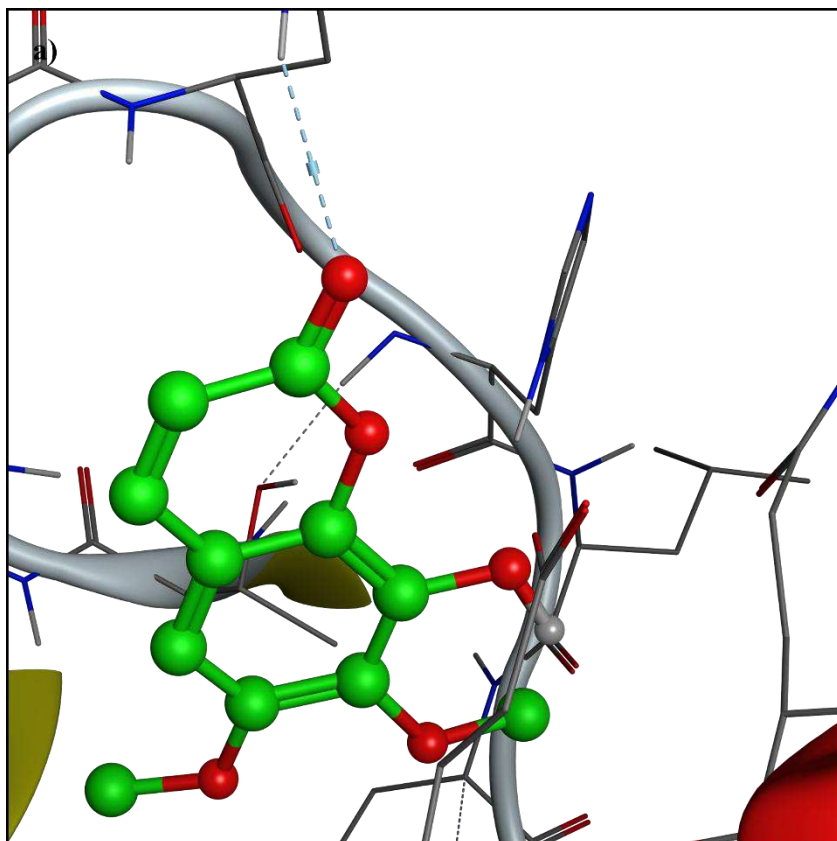


Figure 6. MOE-based docking visualization of Fraxidin within the CTNNB1 binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed

and hydrogen bonding depicted as dashed lines.
(b) **2D interaction diagram** showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.



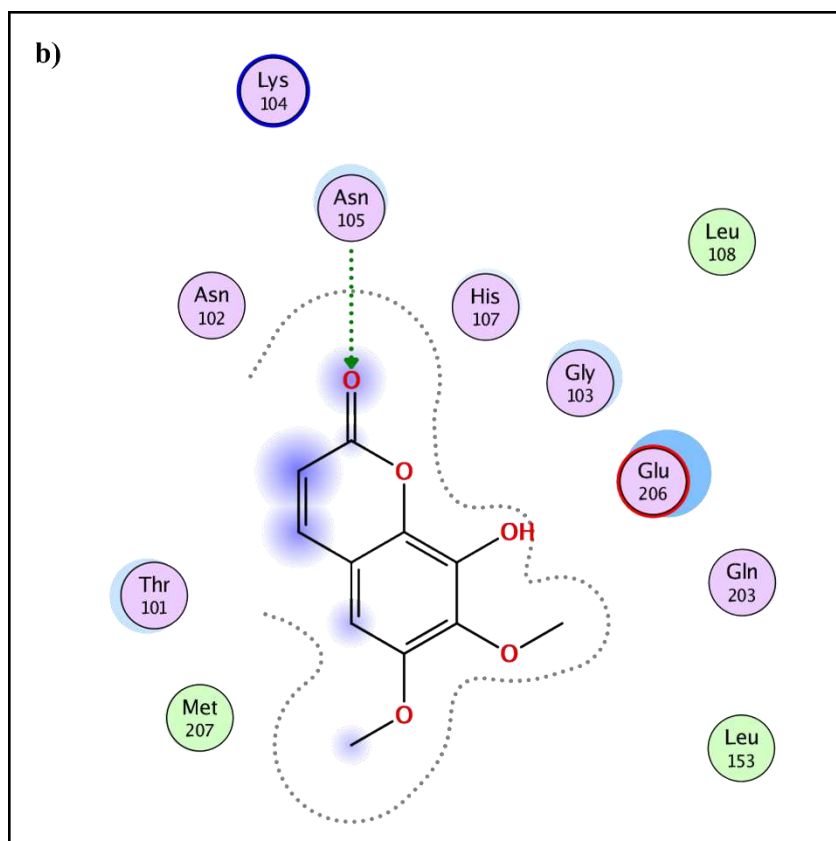


Figure 7. MOE-based docking visualization of Fraxidin within the NFKB1 binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed and hydrogen bonding depicted as dashed lines.

(b) 2D interaction diagram showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.

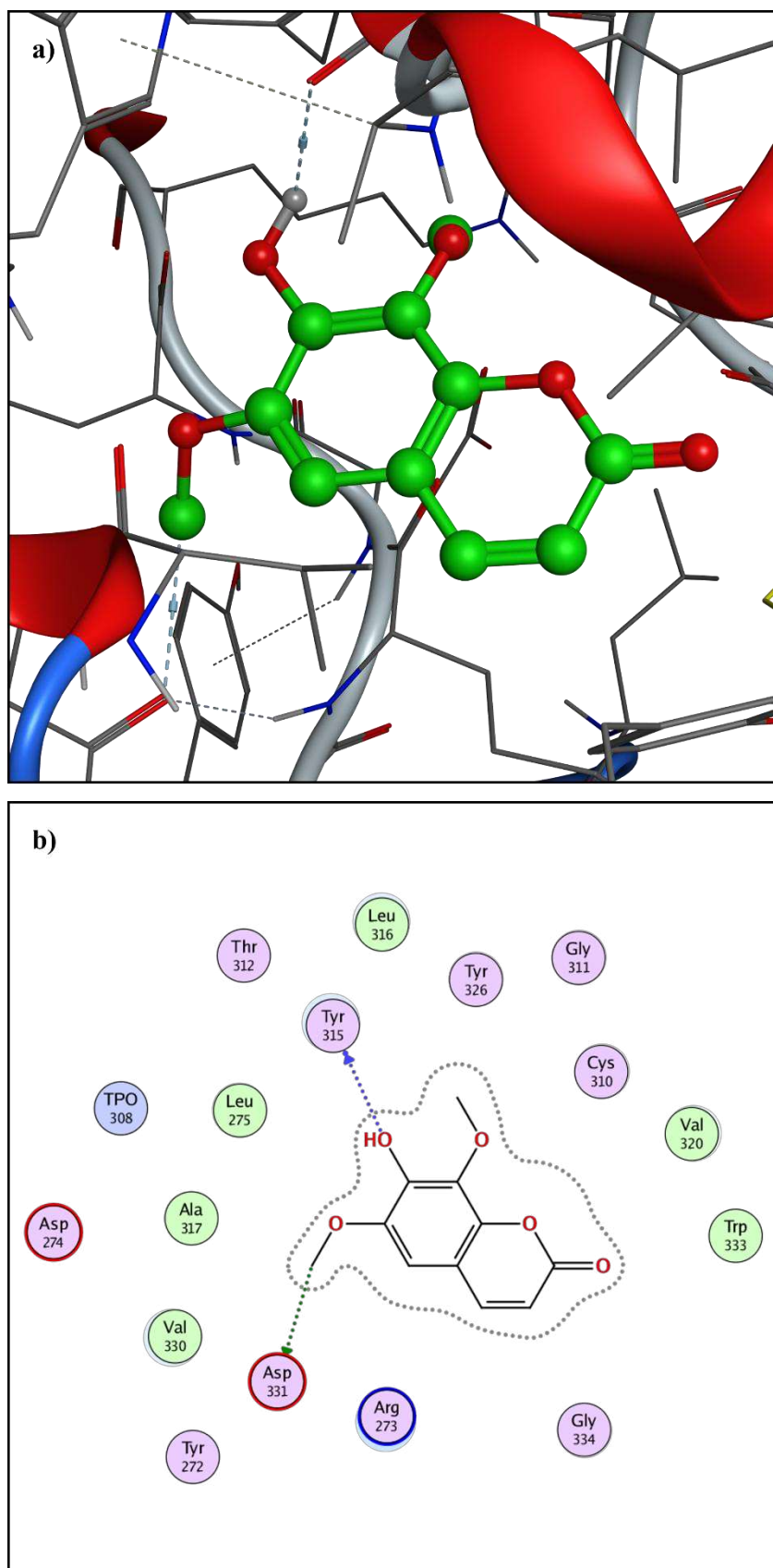
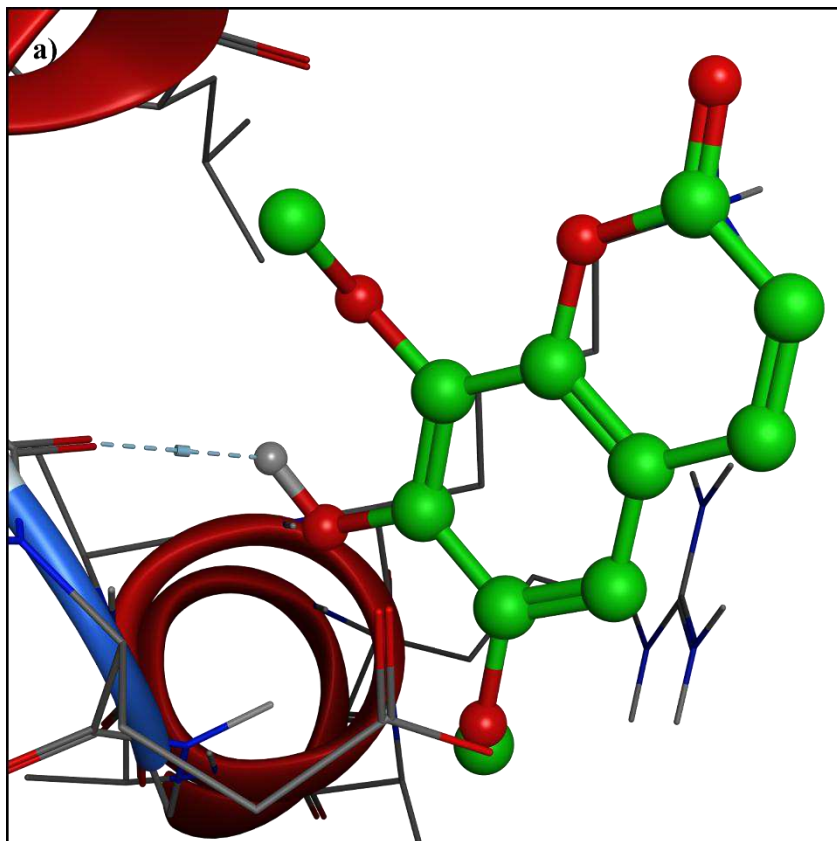


Figure 8. MOE-based docking visualization of Isofraxidin within the AKT1 binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed and hydrogen bonding depicted as dashed lines.

(b) 2D interaction diagram showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.



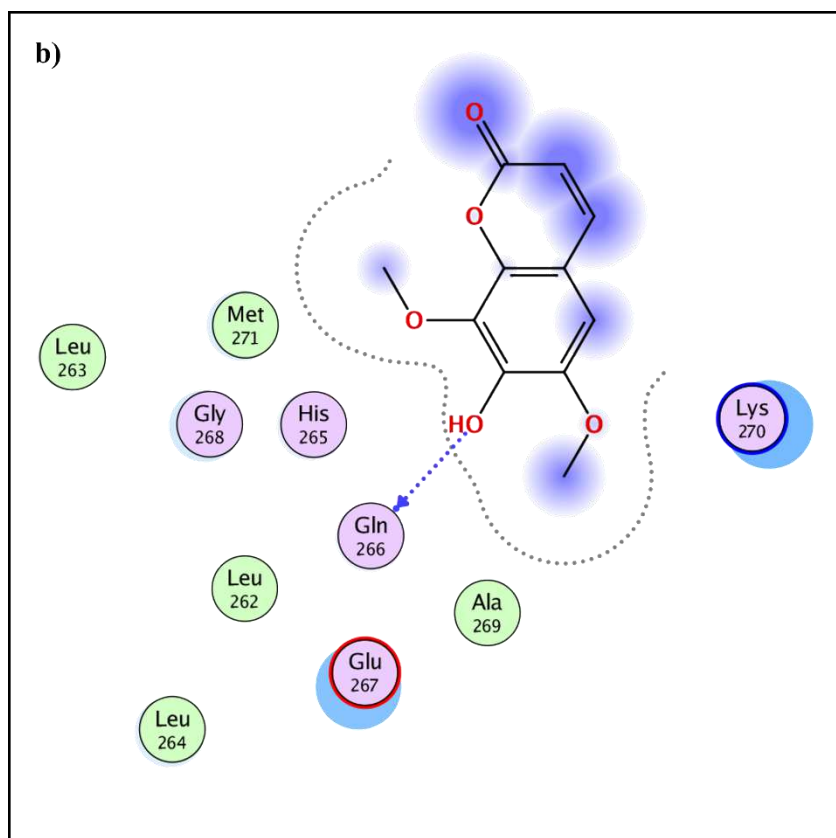


Figure 9. MOE-based docking visualization of Isofraxidin within the CTNNB1 binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed and hydrogen bonding depicted as dashed lines.

(b) 2D interaction diagram showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.

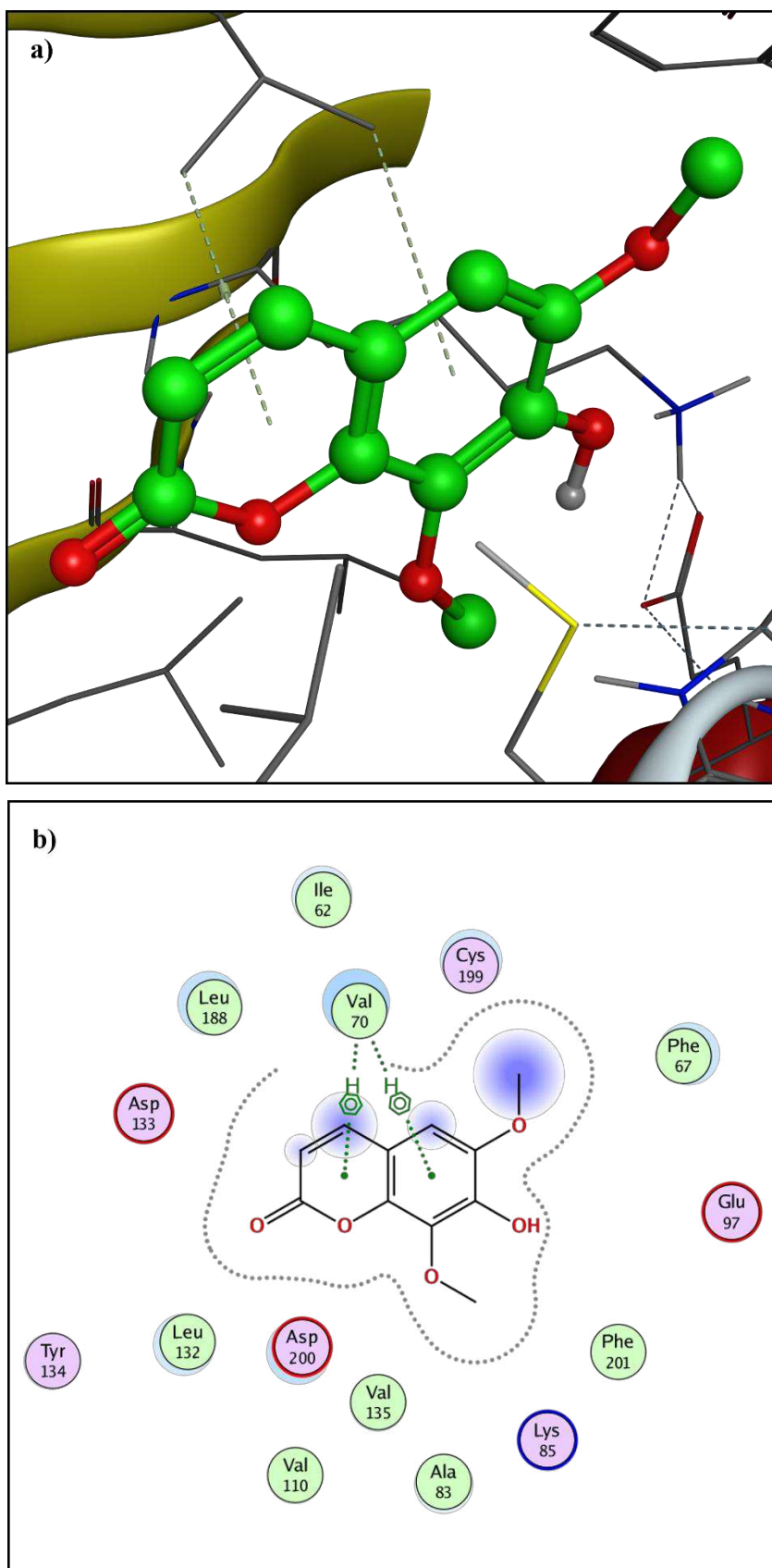
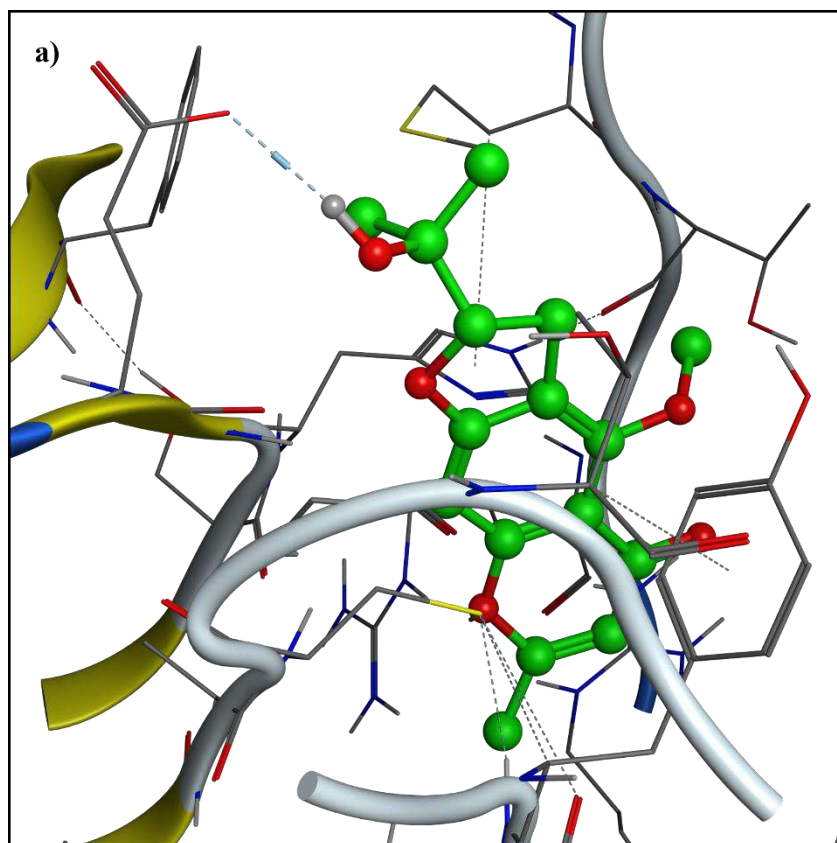


Figure 10. MOE-based docking visualization of Isofraxidin within the GSK3b binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed

and hydrogen bonding depicted as dashed lines.
(b) **2D interaction diagram** showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.



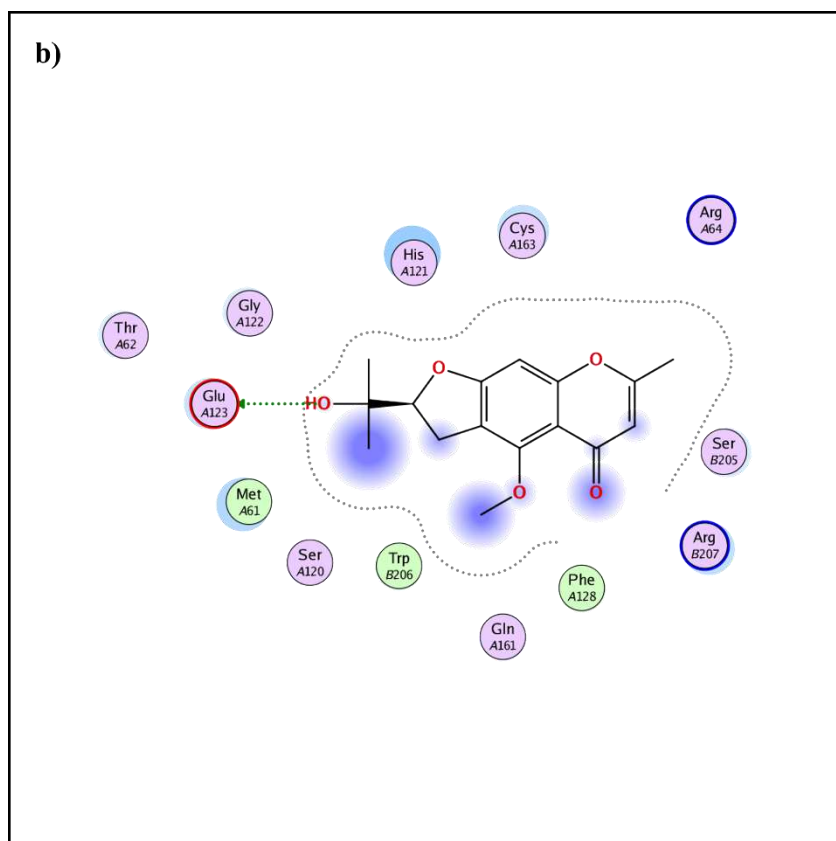


Figure 11. MOE-based docking visualization of 5-*O*-methylvisamminol within the CASP3 binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed and hydrogen bonding depicted as dashed lines.

(b) 2D interaction diagram showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.

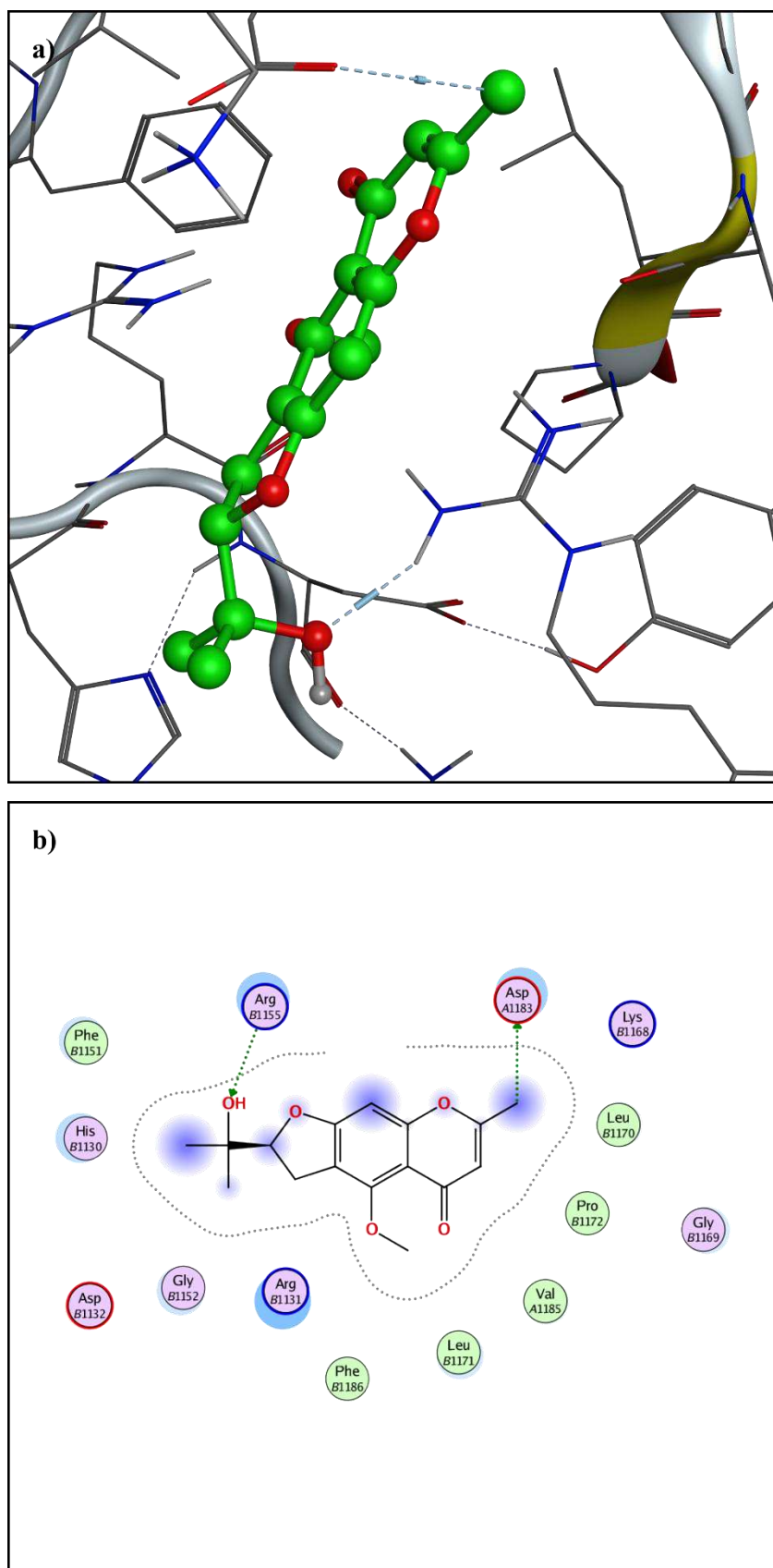
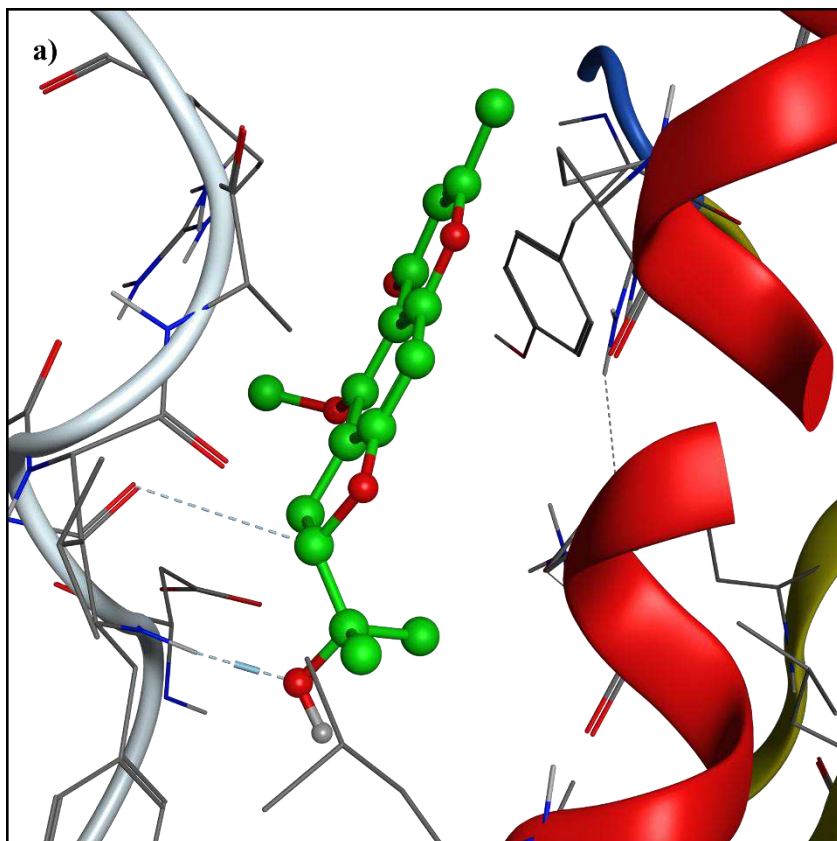


Figure 12. MOE-based docking visualization of 5-O-methylvisamminol within the INS binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed

and hydrogen bonding depicted as dashed lines.

(b) **2D interaction diagram** showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.



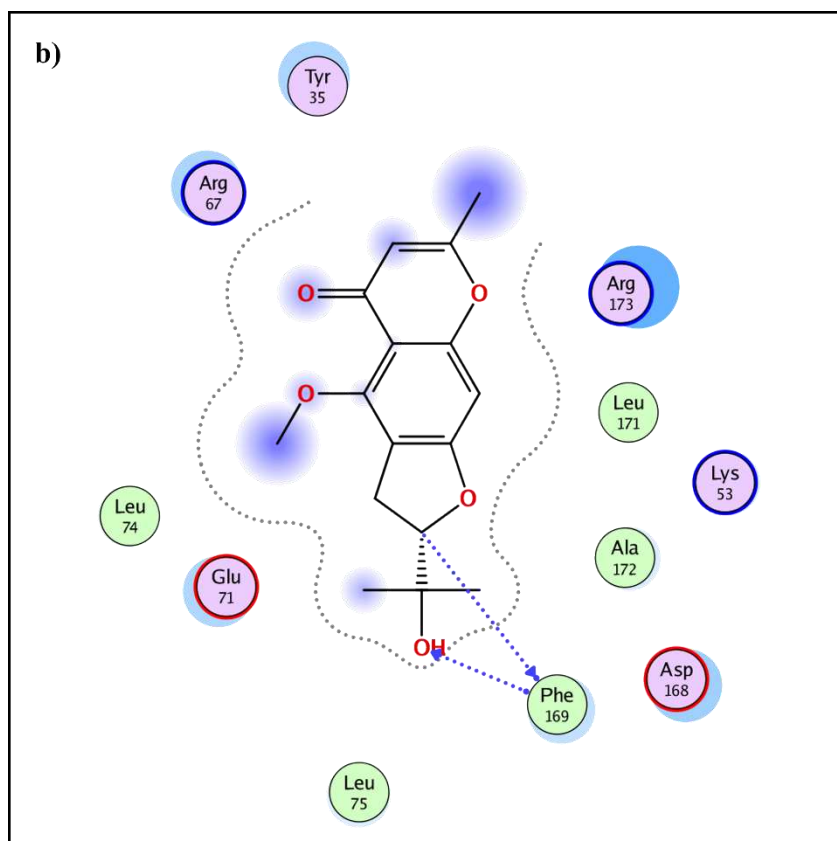


Figure 13. MOE-based docking visualization of 5-*O*-methylvisamminol within the MAPK1 binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed and hydrogen bonding depicted as dashed lines.

(b) 2D interaction diagram showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.

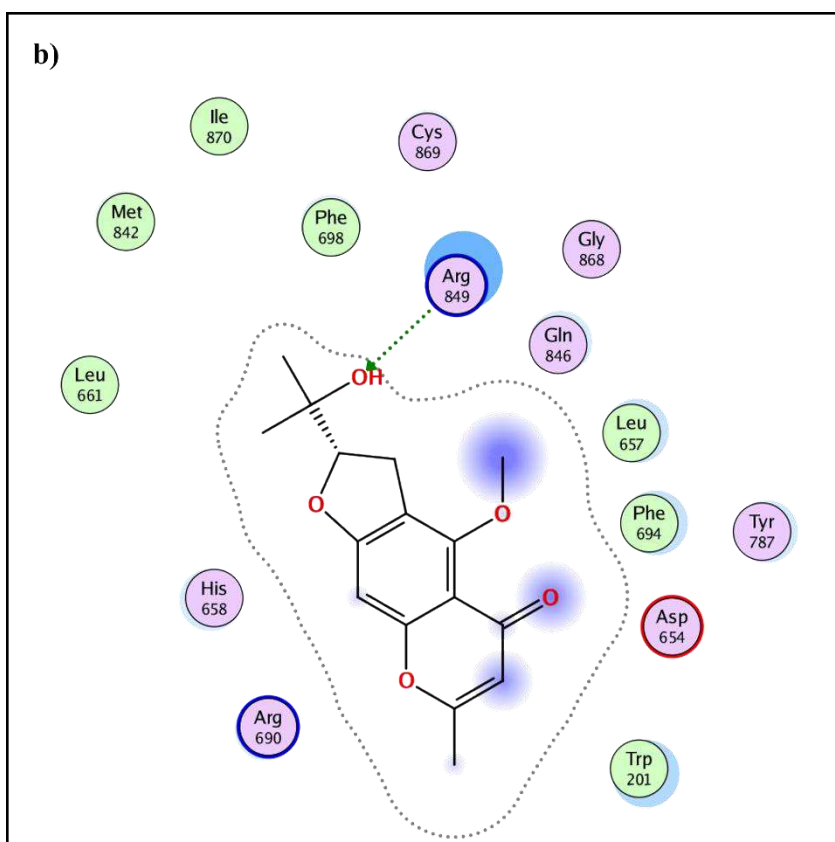
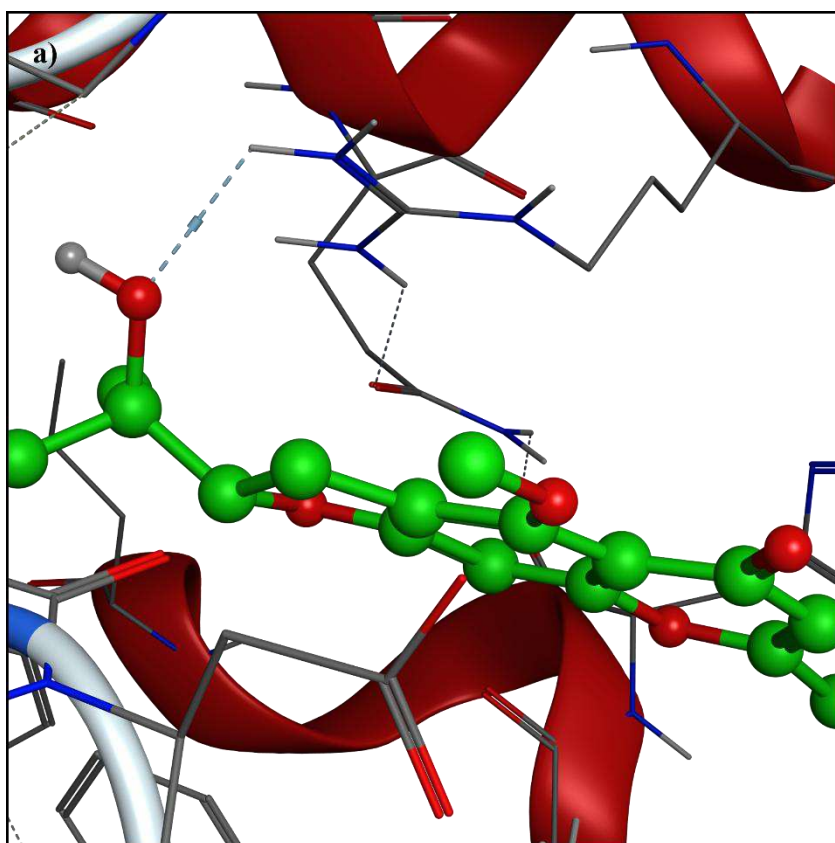
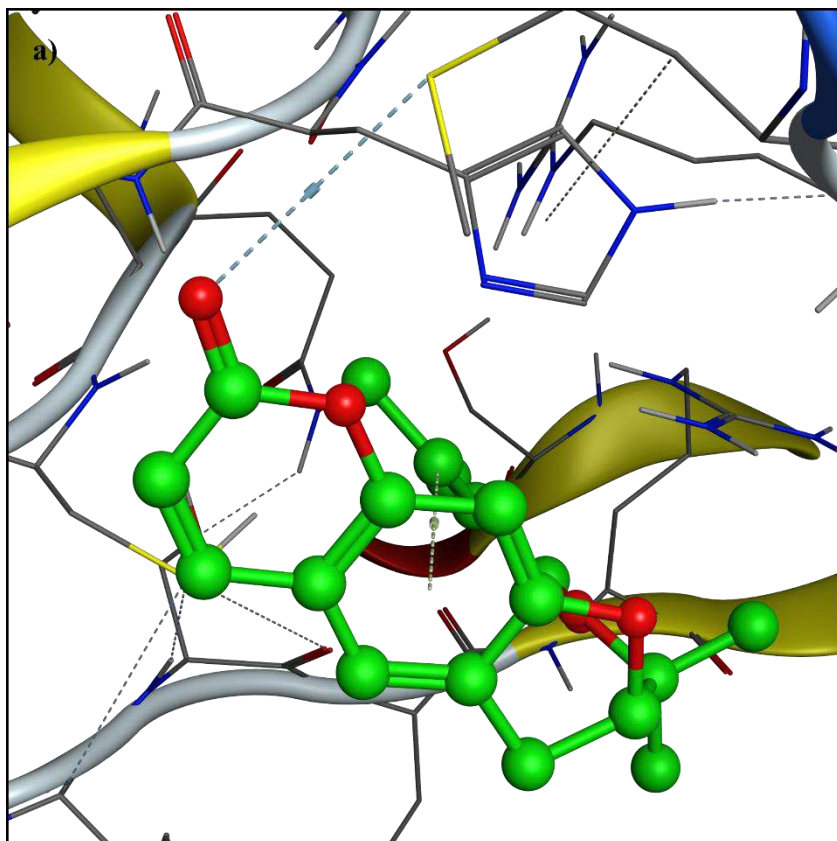


Figure 14. MOE-based docking visualization of 5-*O*-methylvisamminol within the MTOR binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed

and hydrogen bonding depicted as dashed lines.

(b) **2D interaction diagram** showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.



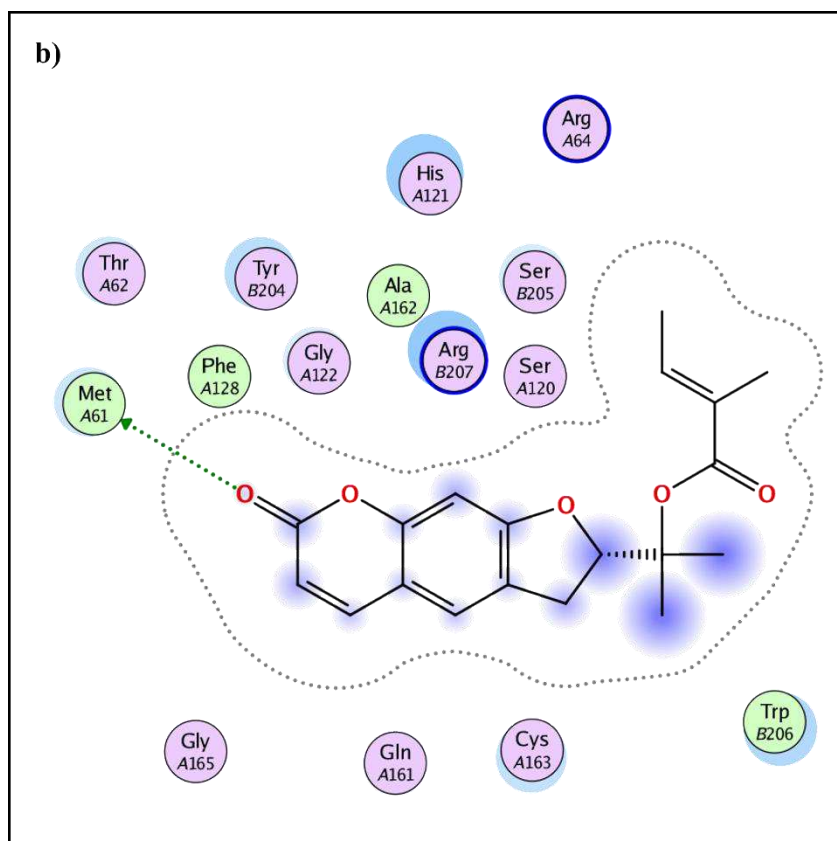


Figure 15. MOE-based docking visualization of Deltoin within the CASP3 binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed and hydrogen bonding depicted as dashed lines.

(b) 2D interaction diagram showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.

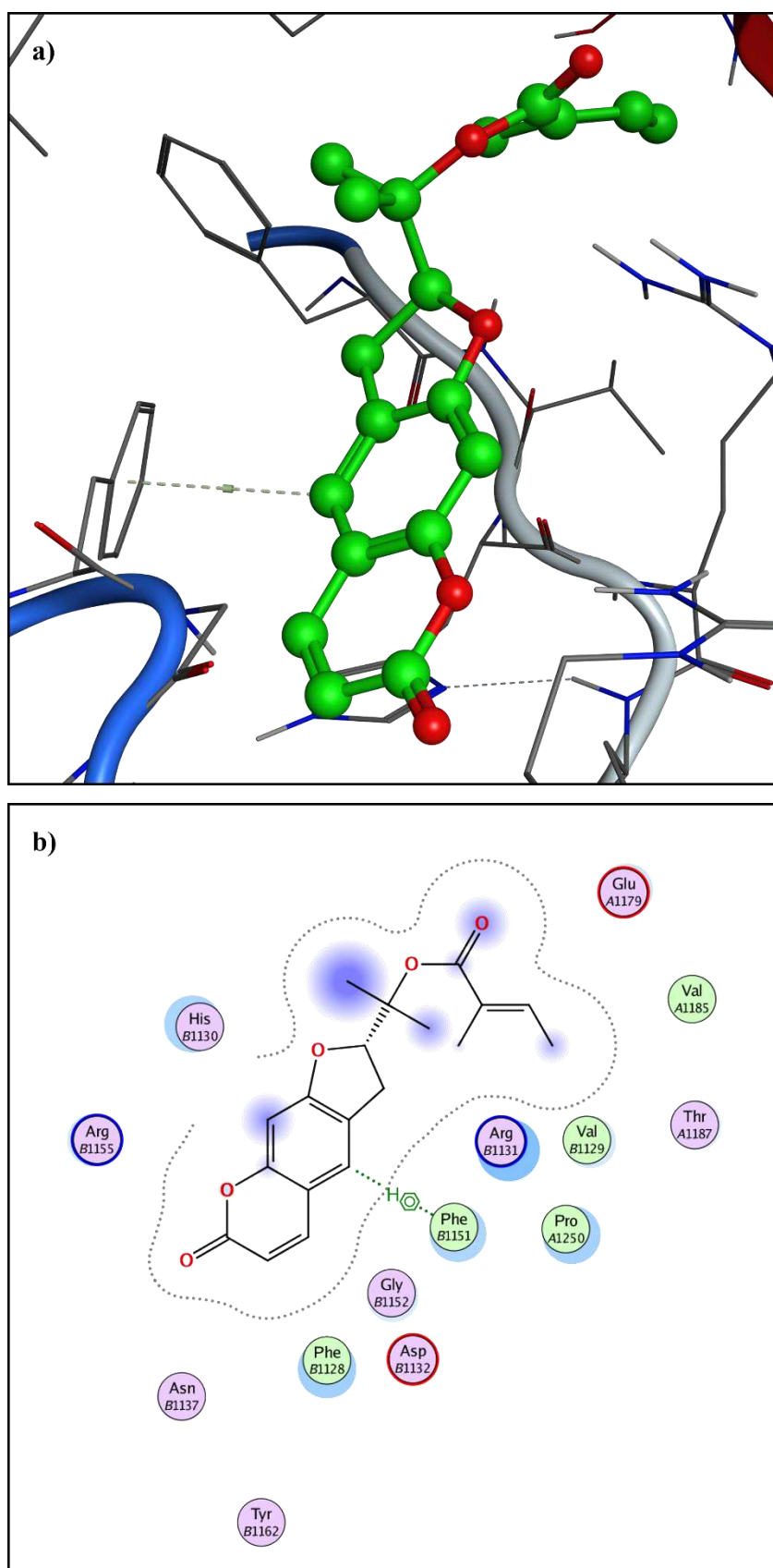
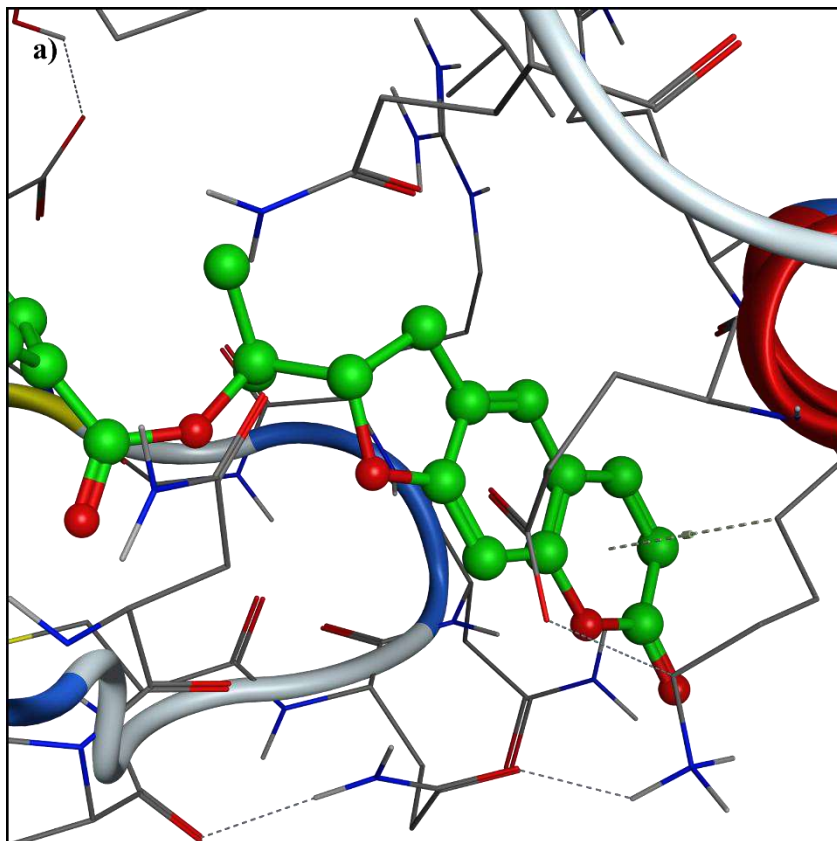


Figure 16. MOE-based docking visualization of Deltoin within the INS binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed and hydrogen bonding depicted as dashed lines.

(b) 2D interaction diagram showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.



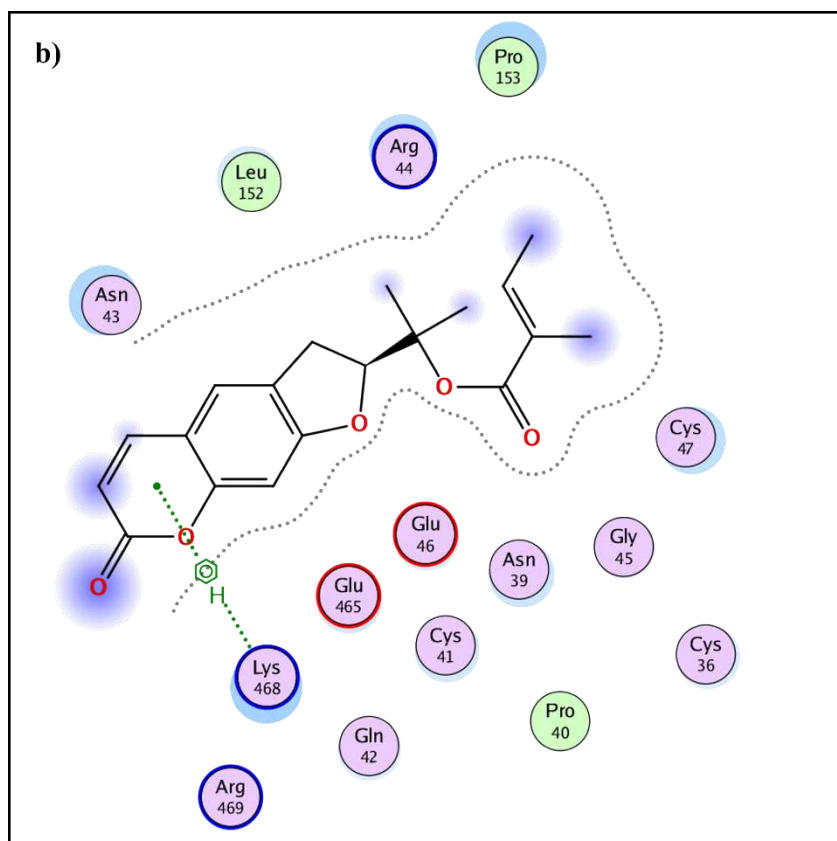


Figure 17. MOE-based docking visualization of Deltoin within the PTGS2 binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed and hydrogen bonding depicted as dashed lines.

(b) 2D interaction diagram showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.

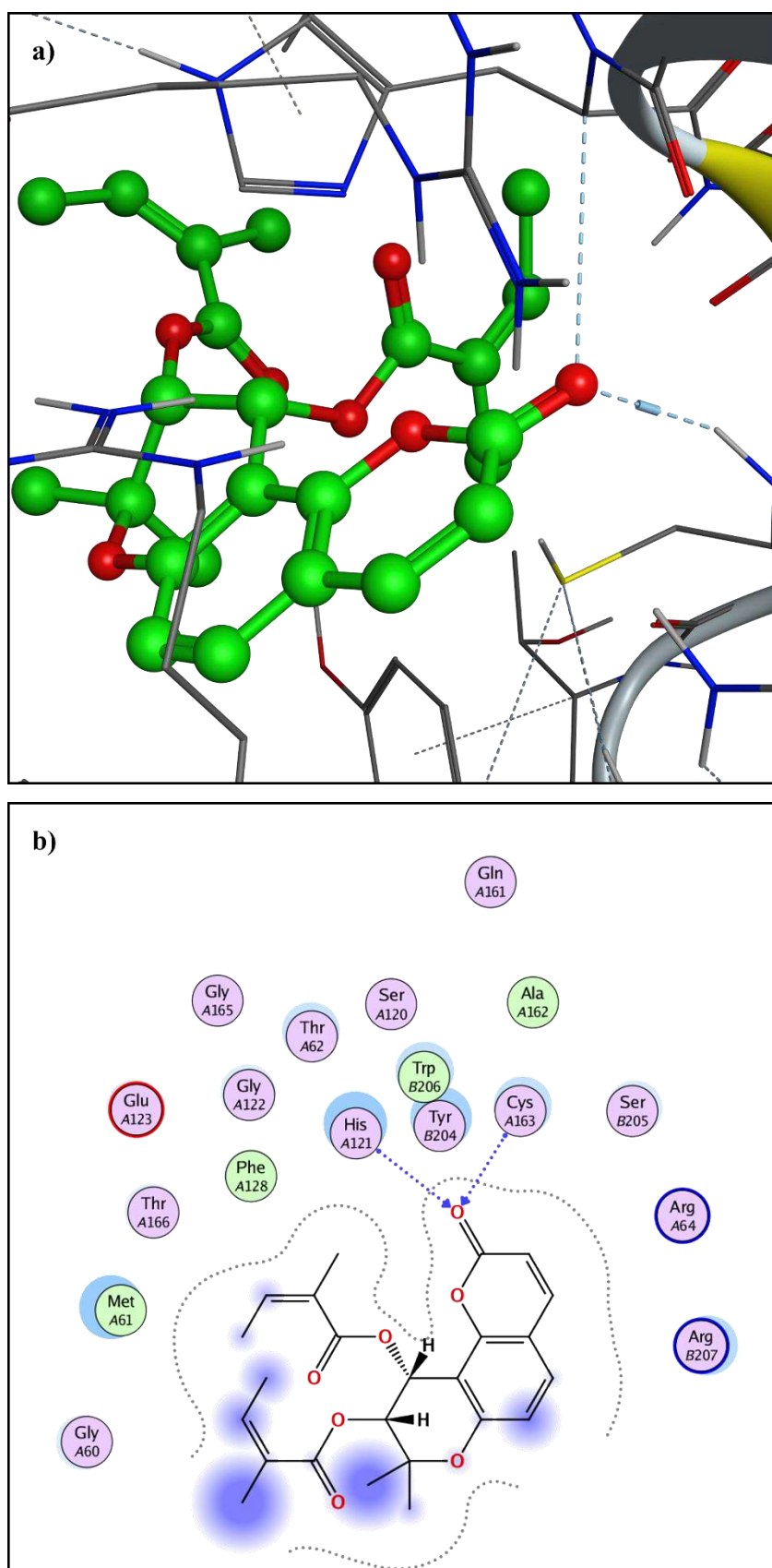
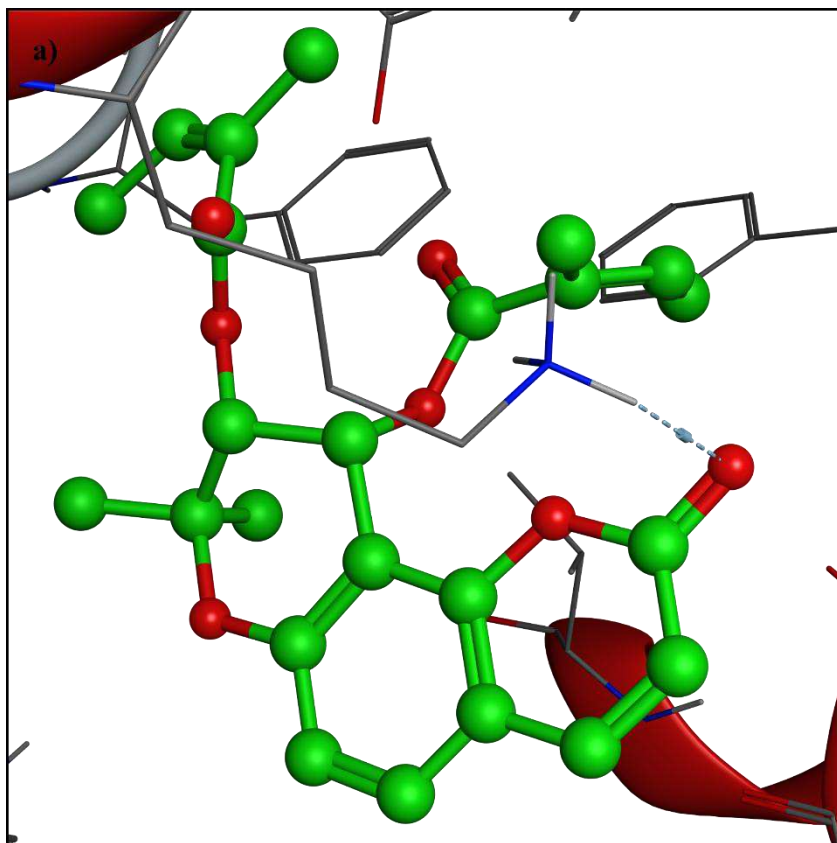


Figure 18. MOE-based docking visualization of Anomalin within the CASP3 binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed

and hydrogen bonding depicted as dashed lines.

(b) **2D interaction diagram** showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.



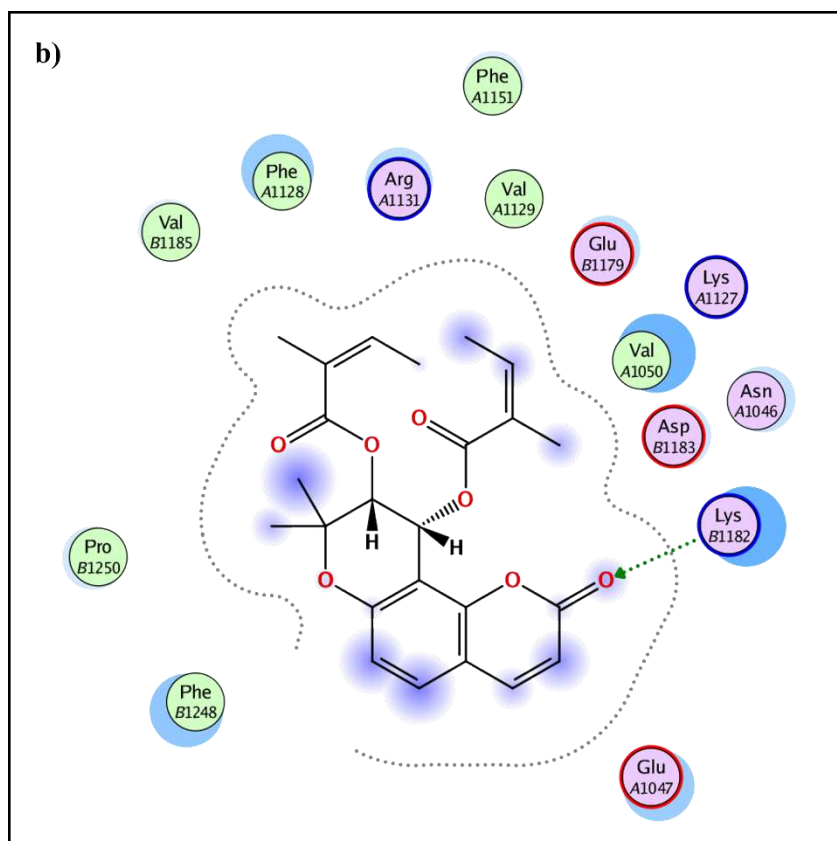


Figure 19. MOE-based docking visualization of Anomalin within the INS binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed and hydrogen bonding depicted as dashed lines.

(b) 2D interaction diagram showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.

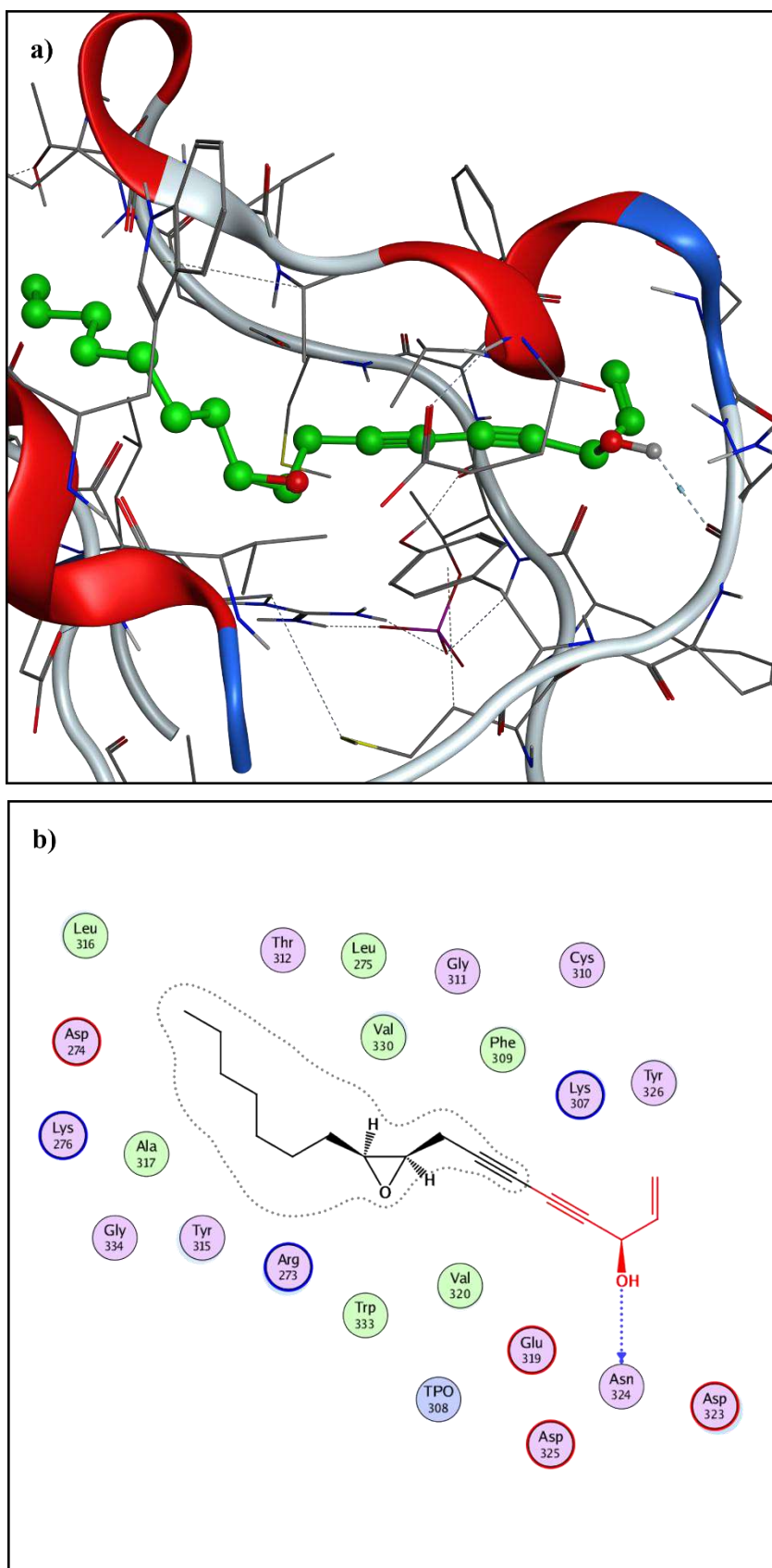
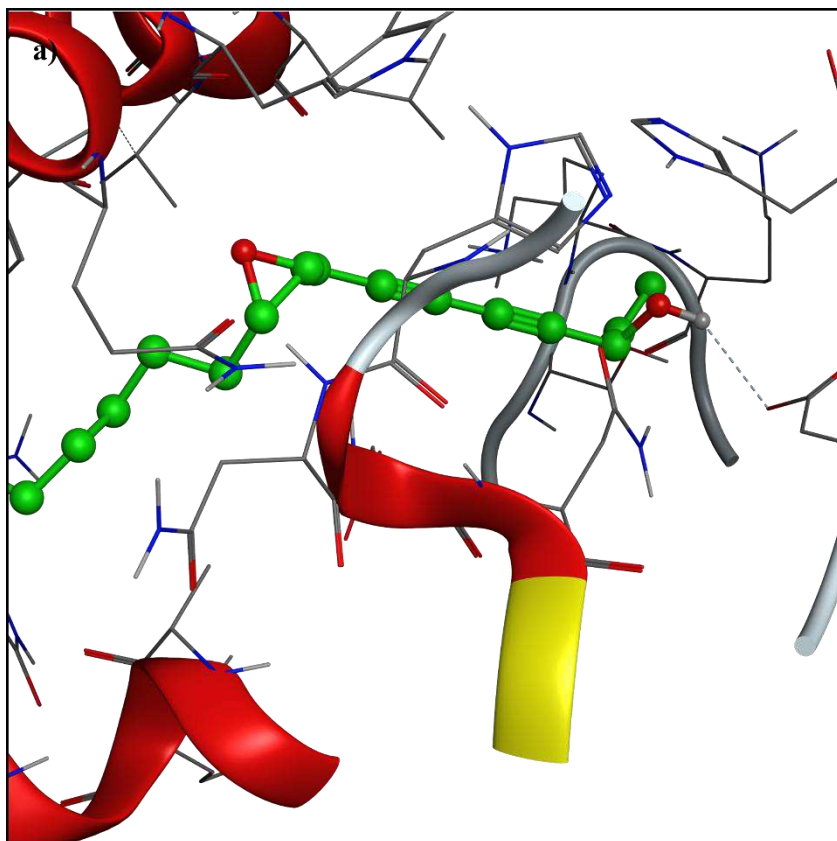


Figure 20. MOE-based docking visualization of Panaxydol within the AKT1 binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed

and hydrogen bonding depicted as dashed lines.

(b) **2D interaction diagram** showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.



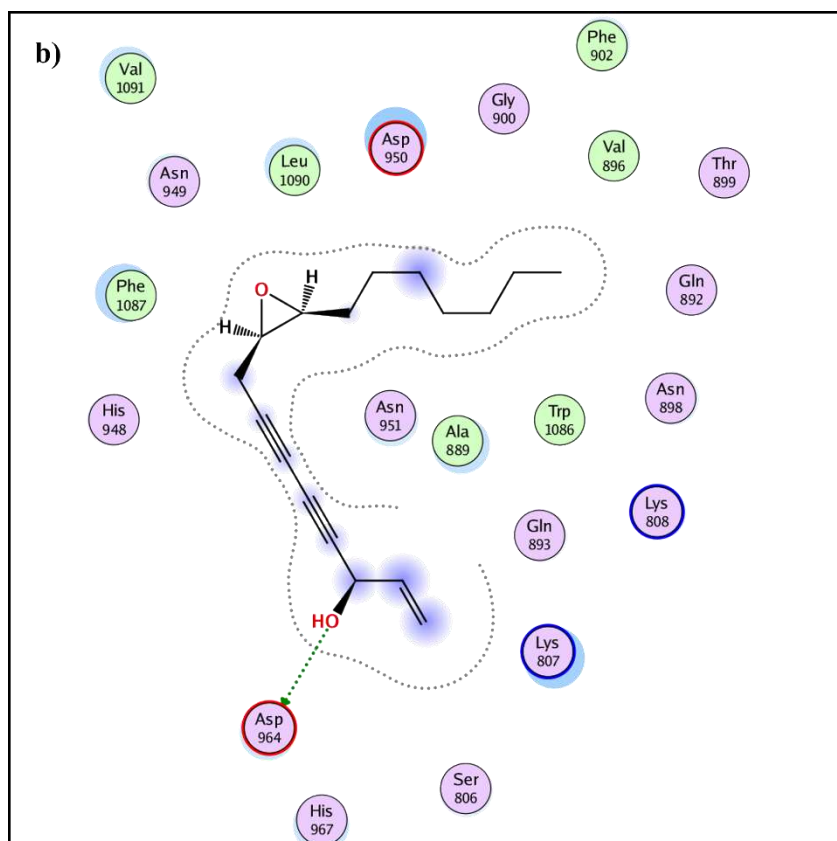


Figure 21. MOE-based docking visualization of Panaxydol within the MTOR binding pocket.

(a) 3D binding pose highlighting the spatial orientation with key interacting residues displayed and hydrogen bonding depicted as dashed lines.

(b) 2D interaction diagram showing detailed ligand–residue contacts, including hydrogen bonds, hydrophobic interactions, and the surrounding pocket environment represented by mapped residue annotations.

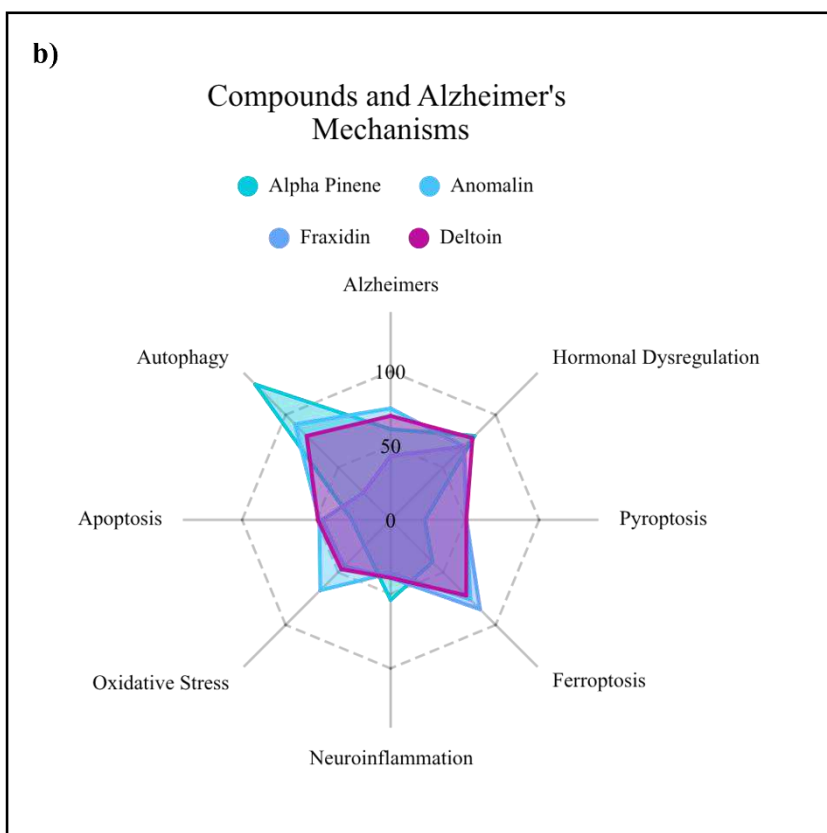
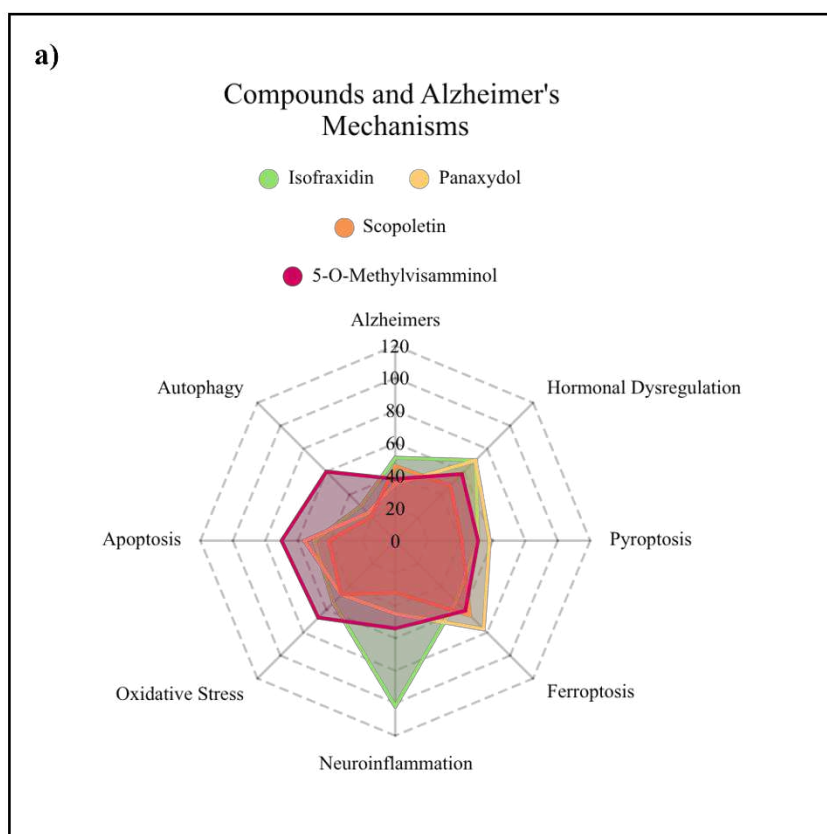


Figure 22. Radar Plot Comparing Compound Activity Across Eight Alzheimer's Disease Mechanisms

Radar graph illustrating the relative strength of each compound across eight pathological mechanisms: Alzheimer's core genes, hormonal dysregulation, pyroptosis, ferroptosis, neuroinflammation, oxidative stress, apoptosis and autophagy. Larger polygon areas indicate broader mechanistic coverage, with fraxidin, panaxydol, deltoin and 5-O-methylvisamminol displaying the strongest multi-mechanistic engagement.

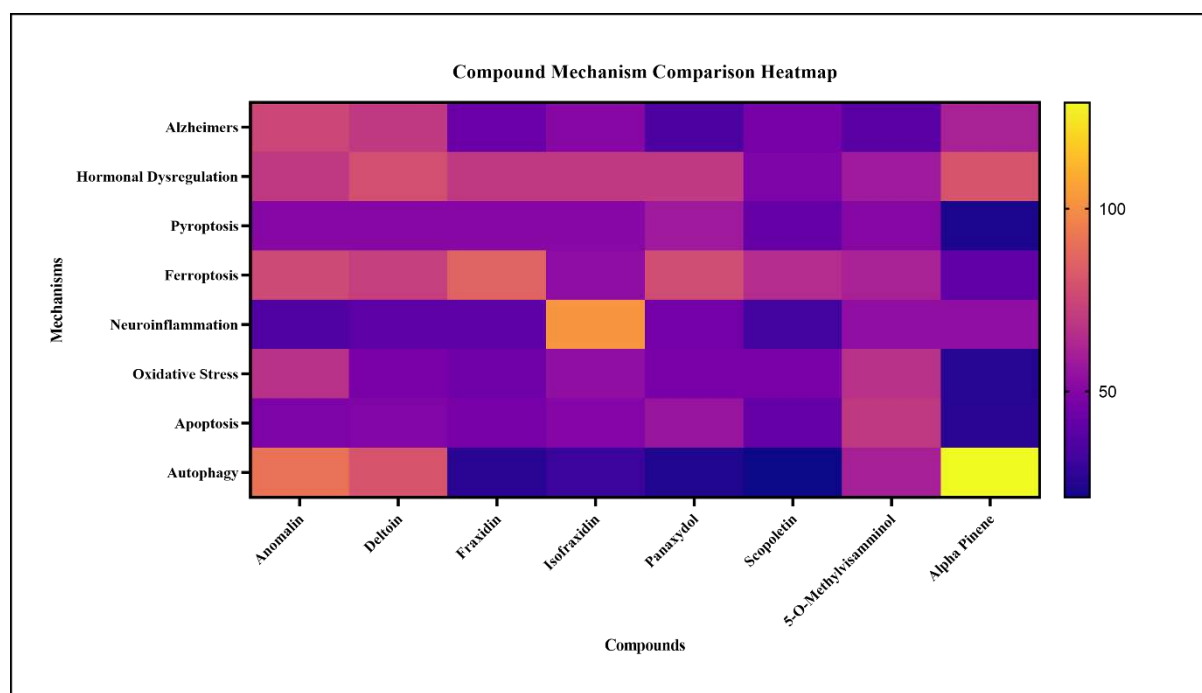


Figure 23. Heatmap of Compound–Mechanism Interactions in Alzheimer’s Disease

Heatmap depicting the intensity of overlap between each compound and the eight Alzheimer’s-related mechanisms. Higher colour intensity corresponds to a greater number of shared targets. The heatmap visually identifies compounds with stronger or more selective effects across mechanistic axes.

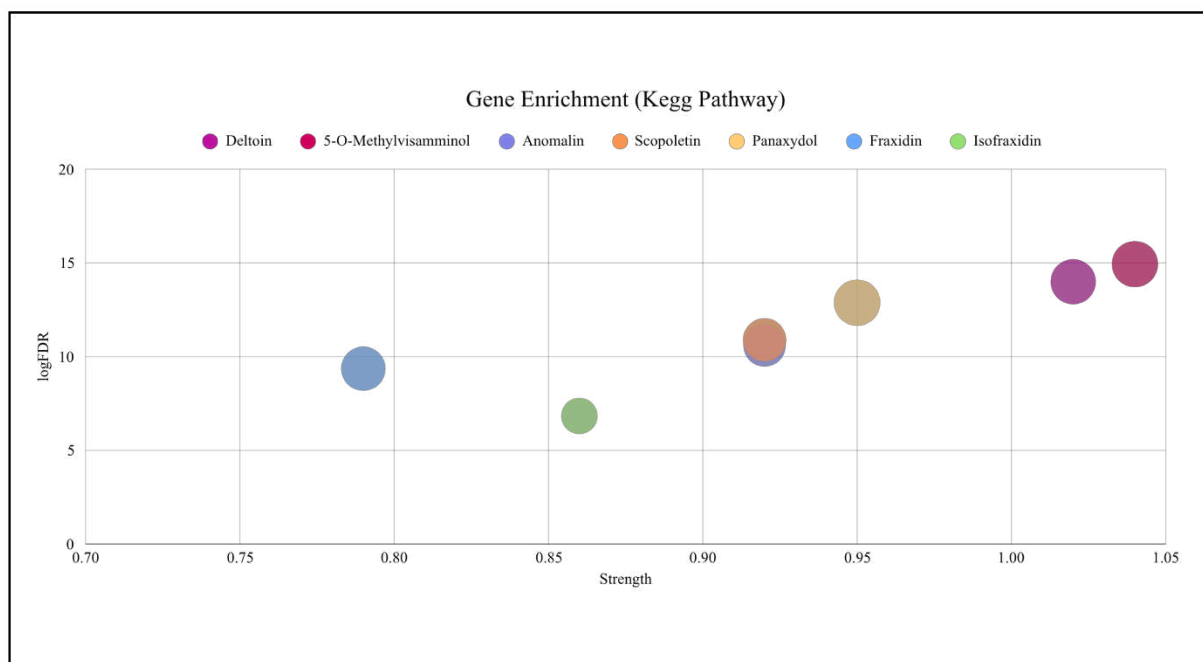


Figure 24. Bubble Plot of KEGG Pathway Enrichment Showing Log FDR, Enrichment Strength and Gene Count

Bubble chart representing KEGG enrichment for all compounds combined. Bubble size corresponds to the number of enriched genes per pathway, bubble colour indicates log FDR values and the horizontal axis shows enrichment strength. Pathways positioned toward the right with larger bubbles and deeper colours represent the most significant and densely targeted biological routes in Alzheimer's disease.