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Article

Molecular Docking and ADMET Profiling of Bioactive Compounds from *Ricinodendron heudelotii* Seeds as Potential Antimalarial Agents Targeting PfGST (1OKT)

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Abstract. Malaria remains a major global health problem, particularly in tropical regions, and increasing resistance of *Plasmodium falciparum* to antimalarial drugs necessitates the discovery of new therapeutic candidates. This study aimed to identify potential PfGST inhibitors among 26 compounds from R.*heudelotii* seeds and evaluate their druglikeness and pharmacokinetic profiles. Molecular docking against PfGST (PDB ID: 1OKT) was performed using Molecular Operating Environment (MOE) 2022.02, followed by ADMET prediction using pkCSM. All compounds showed negative binding energies, indicating favorable interactions with PfGST. The primary candidate was selected by considering binding affinity, RMSD, Lipinski's Rule of Five, pharmacokinetic properties, and toxicity.5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one showed a binding energy of –9.5780 kcal/mol and an RMSD of 1.2172 Å. The compounds complied with Lipinski's criteria and was predicted to have no Ames toxicity or hepatotoxicity, indicating a more balanced druglike profile. Therefore, this compound was identified as the most promising candidate for further investigation as a potential PfGST targeted antimalarial agent. These findings support the use of an integrated docking and ADMET approach to prioritize natural compunds before experimental antimalarial evaluation in vitro.

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1. Introduction

Malaria remains a major global health problem, particularly in tropical and subtropical regions, with *Plasmodium falciparum* being a major cause of severe malaria. Although artemisinin based combination therapies remain an important treatment option, the emergence and spread of antimalarial drug resistance threaten their effectiveness. Therefore, the discovery of new antimalarial candidates with novel molecular targets and mechanisms of action is urgently needed [1].

Natural products are important sources of structually diverse compounds with potential biological activities. Recent studies have continued to explore plat derived compounds as potential antimalarial agents through experimental and computational approaches [2]. *Ricinodendron heudelotii* seeds contain diverse phytoconstituents, and recent GC-MS analysis identified 26 compounds, including monoterpenes, fatty acids, and phytosterols. The seed extracts also demonstrated antimalarial activity against *P.falciparum,* supporting further investigation of their individual constituents [3].

Glutathione S-transferase from *Plasmodium falciparum* (PfGST) is a potential molecular target involved in parasite detoxification and protection against oxidative stress. Recent studies have demonstrated the potential of PfGST as a target for natural product derived antimalarial compounds [4-5]. In particular, the PfGST structure with PDB: ID 1OKT has been used in recent computational studies to investigate ligand interactions and target stability [4]. These findings support the use of PfGST as a relevant target for screening phytoconstituents from *R.heudelotii* seeds.

The development of new drugs using conventional experimental approaches is time consuming and resource intensive. Therefore, computational approaches such as molecular docking have become important tools in early stage drug discovery because they can predict ligand protein interactions and assist in identifying potential drug candidates [2]. In addition, pharmacokinetic evaluation through absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis is essential for assesing the druglikeness and safety of compounds before further development [6-7]. Integrating molecular docking and ADMET evaluation can therefore provide a more comprehensive basis for prioritizing natural product candidates.

Although 26 compounds from *R.heudelotii* seeds have been identified by GC-MS and the seeds extracts have demonstrated antimalarial activity, the individual constituents have not been comprehensively evaluated against PfGST. In particular, their binding interactions with PfGST and predicted pharmacokinetic and toxicity profiles remain insufficiently characterized [3-5]. This represents an important research gap because extract level activity does not establish the molecular target or identify the most promising individual constituent. Therefore, this study evaluated 26 compounds identified by GC- MS from *Ricinodendron heudelotii* seed extract against PfGST (PDB ID: 1OKT) using molecular docking and ADMET predicition to identify candidates with favorable binding interactions and balanced druglike properties.

2. Experimental Section

2.1. Materials

The tools used in this in silico study were a computer with an Intel Core i5 processor running Windows 11 (64-bit). The software utilized included Molecular Operating Environment (MOE) 2022.02, the Protein Data Bank (PDB), PubChem, and pkCSM. MOE 2022.02 was used to perform molecular docking simulations, including ligand preparation, energy minimization, and analysis of ligand–protein interactions.The Protein Data Bank (PDB) was used to obtain the three-dimensional structure of the target protein Plasmodium falciparum glutathione S-transferase (PfGST) with PDB ID: 1OKT. PubChem was used to retrieve and verify the chemical structures of the ligands. Meanwhile, pkCSM was used to predict pharmacokinetic and toxicity properties. The ligands used in this study were 26 compounds identified from gas chromatography–mass spectrometry (GC–MS) analysis of Ricinodendron heudelotii seed extract.

2.2. Protein and Ligand Preparation

The three-dimensional structure of PfGST (PDB ID: 1OKT) was obtained from the Protein Data Bank. Protein preparation was perfomed using MOE 2022.02 by removing water molecules, adding hydrogen atoms, correcting structural errors, and minimizing energy to obtain a stable protein structure. The active site was determined based on the position of the native ligand in the crystal structure. The ligands consisted of 26 compounds reported in previous literature as chemical constituents of *Ricinodendron heudelotii* seeds [3]. The chemical structures of the selected compounds were obtained from PubChem in SMILES notation and converted into three-dimensional structures. Each ligand was subsequently optimized through energy minimization and stored in Molecular Operating Environment (.mdb) format for further molecular docking analysis.

2.3 Molecular Docking

Molecular docking simulations were performed using the Dock feature in MOE 2022.02 software. The docking process was initiated by placing the ligand into the active site of PfGST based on the position of the native ligand in the crystal structure (PDB ID: 1OKT). The docking site was defined using a grid box centered on the active site coordinates determined from the native ligand position and covering the surrounding residues of the active pocket. The Triangle Matcher algorithm with the London dG scoring function was used for ligan placement, followed by pose refinement using the GBVI/WSA dG scoring function. The docking protocol was validated by redocking the native ligand into the active site of PfGST, resulting in an RMSD value of 1.30 Å. The docking resulte were evaluated based on binding affinity and RMSD values, and the molecular interactions between the selected ligands of PfGST were visualized using MOE.

2.4 Lipinski's Rule of Five Prediction

The druglikeness of the selected compounds was evaluated using the SwissADME web server (https://www.swissadme.ch/index.php) based on Lipinski's Rule of Five. The evaluation considered four criteria, molecular weight <500g/mol, hydrogen bond donors <5, hydrogen bond acceptors <10, and log P value <5.

2.5 Pharmacokinetic Study

The pharmacokinetic properties of the ligands were analyzed using pkCSM (https://biosig.lab.uq.edu.au/pkcsm/) by inputting the SMILES notation of each compound. The parameters evaluated included absorption, distribution, metabolism, excretion, and toxicity (ADMET). This analysis was used to assess the potential of the compounds as drug candidates.



Figure 1. Flowchart of Research

3. Results and Discussion

Docking validation was performed through the redocking of the native ligand into the active site of PfGST (PDB ID: 1OKT), which demonstrated that the ligand was able to reoccupy the same binding position. This indicates that the docking parameters applied were capable of accurately representing the physicochemical environment of the protein active site. The RMSD value below 2 Å (1.30 Å) suggests minimal deviation in ligand positioning, confirming that the orientation and conformation of the ligand were reliably reproduced [8].

From a mechanistic perspective, a low RMSD reflects strong geometric complementarity between the ligand and the active site, allowing the lowest energy binding conformation to be consistently achieved [9]. However, docking validation is not solely dependent on positional agreement, but also on the method's ability to capture relevant chemical interactions within the binding pocket [10]. Therefore, the analysis of native ligand interactions is essential to ensure that the docking model realistically represents the binding mechanism.

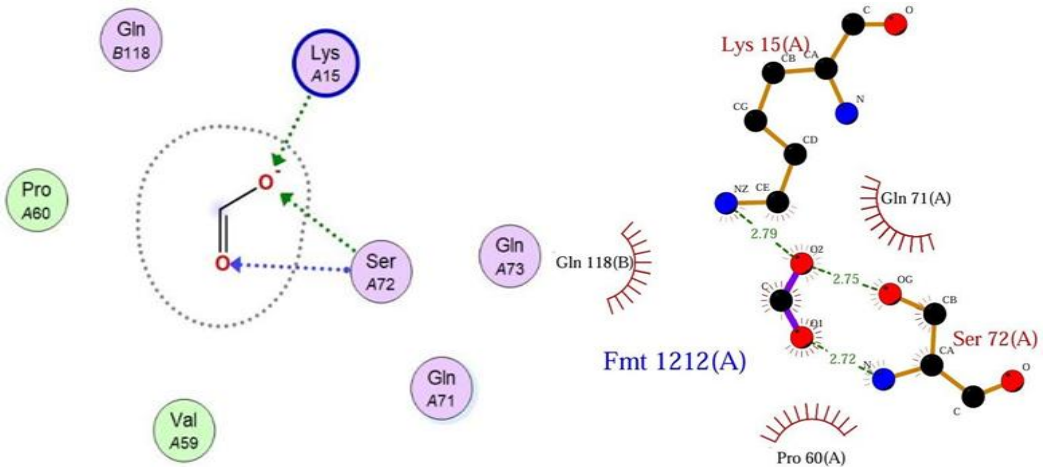


Figure 2. PfGST protein interaction with native ligand

Interaction analysis revealed that the native ligand binds to key residues through a combination of hydrogen bonding and hydrophobic interactions. Hydrogen bonds contribute to binding specificity by directing ligand orientation through electrostatic interactions between donor and acceptor groups, whereas hydrophobic interactions enhance the overall stability of the complex by increasing nonpolar contact within the binding pocket [11].

The coexistence of these interactions indicates that the native ligand exhibits well balanced structural compatibility with the PfGST active site. This is particularly important because ligands that exhibit similar interaction patterns with key residues are generally more likely to exhibit favorable binding characteristics [12]. Therefore, the validated redocking results and the interaction profile of the native ligand provide a reliable reference for evaluating the binding behavior of the tested ligands and for understanding the underlying binding mechanism.

Molecular docking was performed to evaluate the strength and stability of interactions between ligands and the PfGST target protein based on binding affinity and the PfGST target protein based on binding affinity and Root Mean Square Deviation (RMSD) parameters. Binding affinity represents the free binding energy (ΔG) ,where more negative values indicate stronger and more stable interactions between the ligand and the protein [8-10].

Table 1. Molecular docking results of bioactive compounds from *Ricinodendron heudelotii* seed extract against PfGST protein

No	Ligand	Binding Energy (kcal/mol)	RMSD (A)	Residue involeved
1.	hexadecanoic acid	-9.1892	1.1465	Tyr7,Phe6Leu54, Gln69
2.	diethyl bis(trimethylsilyl) silicate	-8.9755	1.3666	Tyr7, Phe36, Val55, Gln69
3.	pentyl octadecanoate	-8.3582	1.3986	Tyr7, Phe36, Leu54, Asp100
4.	(2R)-2,7,8-trimethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol	-12.0432	2.5482	Tyr7, Phe36, Leu54, Val55, Gln69, Asp100
5.	(Z)-octadec-9-enoic acid	-10.0493	1.0401	Tyr7, Phe36, Leu54, Val55, Gln69, Asp100

6.	trimethyl-(2-trimethylsilylphenyl)silane	-8.3695	0.9552	Tyr7, Phe36, Leu54, Gln69
7.	pentadec-14-enoic acid	-9.9248	2.2971	Tyr7, Phe36, Val55, Gln69
8.	5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one	-9.5780	1.2172	Tyr7, Phe36, Leu54, Gln69
9.	methyl heptadeca-5,8,11-trienoate	-8.5200	1.1741	Tyr7, Phe36, Leu54, Asp100
10.	8-(2-octylcyclopropyl)octanal	-9.6723	3.3145	Phe36, Leu54, Val55, Gln69
11.	N-(4-trimethylsilylphenyl)acetamide	-7.8055	1.8104	Tyr7, Phe36, Leu54
12.	pentyl hexadecanoate	-9.5814	1.6559	Tyr7, Phe36, Leu54, Asp100
13.	Propan-2-yl 6-(4-ethoxyphenyl)-3-methyl-4-oxo-1,5,6,7-tetrahydroindole-2-carboxylate	-9.7202	3.9409	Tyr7, Phe36, Val55, Gln69
14	(9E,12E)-octadeca-9,12-dienoic acid	-9.7572	1.3378	Tyr7, Phe36, Leu54, Gln69
15.	(2E,4E)-nona-2,4-dienal	-6.7227	1.3747	Phe36, Leu54
16.	(8E,12E)-octadeca-8,12-dienoic acid	-9.9504	1.3586	Tyr7, Phe36, Leu54, Asp100, Gln69
17.	Methyl (9Z,12Z,15Z)-octadeca-9,12,15-trienoate	-8.6269	1.1750	Tyr7, Phe36, Leu54
18.	ethyl (9E,12E)-octadeca-9,12-dienoate	-8.9484	1.9162	Phe36, Leu54, Asp100
19.	butyl hexyl sulfite	-8.9138	3.6607	Phe36, Leu54, Val55
20.	butyl (9Z,12Z)-octadeca-9,12-dienoate	-84896	0.9553	Tyr7, Phe36, Leu54, Gln69
21.	((9Z,12Z)-11-hydroxyoctadeca-9,12-dienoic acid	-10.8630	1.4592	Tyr7, Phe36, Leu54, Asp100, Gln69
22.	methyl heptadeca-8,11,14-trienoate	-9.3683	1.5884	Phe36, Leu54, Val55, Asp100
23.	N-[tert-butyl(dimethyl)silyl]-1,2-benzothiazol-3-amine	-8.9926	1.3465	Tyr7, Phe36, Gln69
24.	tris[tert-butyl(dimethyl)silyl] arsorite	-98884	2.3480	Tyr7, Phe36, Leu54, Gln69, Asp100
25.	1-cyclopenta-1,4-dien-1-ylcyclohepta-1,3,5-triene;vanadium	-8.4490	1.3457	Gln69, Asp100

Based on the data in Table 1, all compounds exhibited negative binding affinity values, indicating that ligand protein interaction occur spontaneously. The variation in energy values reflects differences in interaction strength influenced by the chemical structures of each compound [8-13].

The compound with the lowest binding affinity was (2R)-2,7,8-trimethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol with a value of -12.0432 kcal/mol, followed by (9Z,12Z)-11-hydroxyoctadeca-9,12-dienoic acid with a value of -10.8630 kcal/mol. These results indicate that both compounds exhibit strong binding affinity toward the PfGST active site.

The very low binding energy of the chromanol derivative can be attributed to the presence of an aromatic ring system combined with a hydrophobic side chain. This structural feature enables both hydrophobic interactions and π–π interactions with residues such as Tyr7 and Phe36, thereby enchancing the stability of the ligan protein complex through a combination of surface contact and interaction specificity [14].

Similarly, the low binding energy observed in (9Z,12Z)-11-hydroxyoctadeca-9,12-dienoic acid can be explained by its long hydrophobic hydrocarbon chain, which facilitates extensive hydrophobic interactions with nonpolar residues such as Tyr7, Phe36, and Leu54. Hydrophobic contacts significantly contribute to lowering the binding energy by increasing the ligan protein contact surface [15]. However, these interactions are generally non specific and lack directional constraints compared to hydrogen bonding [8].

Despite exhibiting lower binding energies, both the chromanol derivative and the fatty acid compound are highly lipophilic, which may limit their pharmacokinetic performance, particularly in terms of aqueous solubility and binding selctivity [16]. Therefore, binding affinity alone is insufficient to determine the best candidate compound, and further evaluation considering interaction specificity and pharmacokinetic properties is required.

In this context, 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one emerges as a more promising candidate despite having a slightly higher binding affinity value. This is attributed to its heterocyclic structure containing hydroxyl (-OH) and carbonyl (C=O) functional groups, which facilitate hydrogen bond formation with residues within the PfGST active site. The combination of hydrophobic interactions and hydrogen bonding provides a balance between binding strength and interaction specificity, thereby contributing to the stability of the ligand within the binding pocket [14].

Flavonoid compounds have been reported to generally exhibit binding affinity values in the range of -7 to -10 kcal/mol, with favorable inhibitory activity associated with a combination of hydrophobic interactions and hydrogen bonding [17]. Hydrogen bonding is known to complement hydrophobic interactions and enhance ligand binding selectivity, thereby improving the stability of ligan protein complexes [4]. Furthermore, heterocyclic compounds containing polar functional grups have been shown to provide a balanced contribution between interaction strength and pharmacokinetic properties, making them promising candidates in drug development [5].

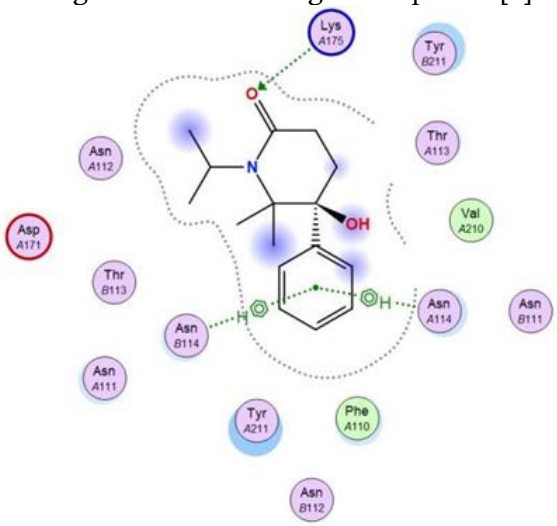


Figure 3. 2D molecular interaction of 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one within the active site of PfGST

The spesific interaction profile of 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one within the PfGST active site is presented in Figure 3. The 2D interaction diagram shows that the compound forms hydrogen bond interactions with residues such as Lys175 and Asn114, as indicated by green dashed lines. These interactions contribute to ligand stabilizarion within the active site due their directional and specific nature[18]. The presence of these hydrogen bonds, together with hydrophobic contacts involving the nonpolar regions of the compound, supports the stability of the ligan protein complex [19]

Therefore, this interaction analysis comfirms that 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one one is the most promising candidate among the evaluated compounds. Its interaction profile demonstrates a favorable balance between binding strength, specificity, and complex stability, indicating that the compound may interact effectively with the PfGST active site [20]. These characteristics provide a basis for further evaluation through pharmacokinetic and druglikeness analyses to assess its potential as a PfGST inhibitor [21].

Following the molecular docking and interaction analysis, the next step was to evaluate the druglikeness properties of the selected compounds using Lipinski's Rule of Five. This analysis is important to predict the oral bioavailability potential of a compound based on its physicochemical

properties, such as molecular weight, lipophilicity (LogP), the number of hydrogen bond donors and acceptors, as well as other related parameters. Compounds that comply with these criteria are generally considered to have a higher probability of being developed as orally active drugs [22].

In addition, Lipinski's rule serves as an initial screening step to identify compounds with favorable pharmacokinetic profiles, particularly in terms of absorption and permeability. Deviations from these criteria may indicate potential limitations, such as poor solubility or low membrane permeability, which can ultimately affect drug effectiveness [23]. Therefore , thus analysis is essential to complement the docking results, ensuring that the selected compound not only exhibits strong interactions with the target protein but also possesses suitable physicochemical properties for further drug development.

Table 2. Lipinski's rule of five evaluation of selected bioactive compounds

Pharmacokinetic Prediction						
Ligand	**Molecular Weight**	**Hydrogen Bond Donors**	**Hydrogen Bond Acceptors**	**Log P**	**Refactory Molar**	**Rotatable Bond**
	<500 g/mol	**<5**	**<10**	**<5**	**40-130**	**<10**
5-Hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one	261.36 g/mol	1	2	2.41	40.54 Å²	2
(Z)-octadec-9-enoic acid	282.46 g/mol	1	2	5.65	37.30 Å²	15
9,12-Octadecadienoic acid, ethyl ester	308.50 g/mol	0	2	6.09	26.30 Å²	16

Table 2 presents the evaluation of Lipinski's Rule of Five for the selected bioactive compounds to assess their physicochemical properties and drug-likeness as considerations for candidate selection. Based on these results, 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one exhibited a more balanced physicochemical profile than the other two compounds. Drug-likeness evaluation is important because the physicochemical properties of a compound can influence absorption, permeability, distribution, and overall ADMET characteristics; therefore, candidate selection should not be based solely on biological activity or binding affinity toward the target [24].

Although (Z)-octadec-9-enoic acid and 9,12-octadecadienoic acid, ethyl ester exhibited lower binding affinity values, both compounds showed Log P values of 5.65 and 6.09, respectively, exceeding the Log P threshold of <5 specified by Lipinski's criteria [25]. A high Log P value indicates greater lipophilicity and may be associated with reduced aqueous solubility, increased plasma protein binding, tissue accumulation, and less favorable ADMET characteristics [26-27]. This is an important consideration because lipophilicity must be appropriately controlled during lead optimization to achieve a balance between target potency and favorable pharmacokinetic properties [26]. Therefore, these two compounds were not prioritized as the main candidates despite their favorable binding affinity, as their lipophilicity profiles were less supportive of desirable drug-like properties.

In addition to Log P, these compounds possessed a relatively high number of rotatable bonds, with 15 and 16, respectively. A high number of rotatable bonds indicates greater molecular flexibility, which may affect conformational properties and the ability of a molecule to adopt a suitable conformation for target interactions [27-28]. Molecular flexibility should also be considered during lead optimization because increased conformational complexity may influence the relationship

between target affinity and physicochemical properties [29-30]. Therefore, the combination of high Log P values and excessive molecular flexibility contributes to the less favorable drug-likeness profiles of these two fatty acid derivatives.

In contrast, 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one has a molecular weight of 261.36 g/mol, one hydrogen-bond donor, two hydrogen-bond acceptors, a Log P value of 2.41, a molar refractivity of 40.54 Å², and only two rotatable bonds. All of these parameters fall within the ranges considered in the drug-likeness evaluation, indicating more favorable physicochemical characteristics than those of the other two compounds [27-31]. Its Log P value of 2.41 also represents a relatively favorable degree of lipophilicity for drug development, as moderate lipophilicity may provide a balance between interactions with lipid environments and the maintenance of adequate aqueous solubility [29-32].

The presence of only two rotatable bonds also indicates lower molecular flexibility compared with the two fatty acid derivatives, suggesting that the structure of 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one is relatively more conformationally restricted. This characteristic may support molecular recognition and more directed interactions with the target, although the number of rotatable bonds is not the sole determinant of biological activity [33]. In addition, the hydroxyl and carbonyl groups in the 5-hydroxy compound provide functional groups capable of acting as hydrogen-bond donors and acceptors, respectively, which may further support interactions with amino acid residues within the target binding site [34].

Following the evaluation of molecular docking and drug-likeness, the three selected compounds were further assessed using ADMET parameters, including absorption, distribution, metabolism, excretion, and toxicity, to compare their pharmacokinetic and safety profiles. The predicted ADMET profiles of the three compounds are presented in Table 3. This evaluation complements the molecular docking and drug-likeness analyses, as favorable binding affinity alone does not necessarily indicate optimal pharmacokinetic and safety characteristics [35-36].

Table 3. ADMET profiles of selected compounds

		Ligands		
	Parameter	**(9Z,12Z)-11-hydroxyoctadeca-9,12-dienoic acid**	**(Z)-octadec-9-enoic acid**	**5- Hydroxy- 1-isopropyl- 6,6-dimethyl- 5-phenyl- piperidin- 2-one**
Absroption	Water solubility (log mol/L)	-5.702	-5.924	-3.071
	$CaCO_2$ Permeability (log Papp 10-6 cm/s)	1.552	1.563	1.722
	Intestinal absorption (% absorbed)	92.368	91.823	94.008
Distribution	VDss (Human, log L/kg)	-0.905	-0.558	0.429
	BBB permeability (logBB)	-0.003	-0.168	0.092

Metabolism	CYP1A2 Inhibitor	No	Yes	No
	CYP2C9 Inhibitor	No	No	No
	CYP3A4 Inhibitor	No	No	No
Excretion	Renal OCT2 substrate clearance	No	No	No
	Total clearance (log mL/min/kg	1.965	1.884	1.191
Toxicity	Ames toxicity	No	No	No
	Hepatotoxicit Y	No	No	No
	Rat oral toxicity (LD50) (mol/kg)	1.321	1.417	2.338

Regarding absorption, 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one showed the highest water solubility (−3.071 log mol/L) compared with (9Z,12Z)-11-hydroxyoctadeca-9,12-dienoic acid (−5.702 log mol/L) and (Z)-octadec-9-enoic acid (−5.924 log mol/L). It also exhibited the highest Caco-2 permeability (1.722×10^{-6} cm/s) and intestinal absorption (94.008%). These results indicate a relatively more favorable absorption profile, as adequate solubility and intestinal permeability are important for the systemic availability of orally administered compounds [37]. Although these parameters are predictive, the results suggest that 5-hydroxy has better absorption characteristics than the other two compounds.

For distribution, 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one showed the highest VDss value (0.429 log L/kg), compared with −0.905 and −0.558 log L/kg for (9Z,12Z)-11-hydroxyoctadeca-9,12-dienoic acid and (Z)-octadec-9-enoic acid, respectively. Its logBB value was also the highest (0.092), indicating slightly greater predicted blood–brain barrier permeability than the other compounds (−0.003 and −0.168). These findings suggest a greater tendency for tissue distribution and slightly higher predicted brain penetration of 5-hydroxy, although such predictions require experimental confirmation [38].

Regarding metabolism, all three compounds were predicted not to inhibit CYP2C9 and CYP3A4. However, (Z)-octadec-9-enoic acid was predicted to inhibit CYP1A2, whereas 5-hydroxy and (9Z,12Z)-11-hydroxyoctadeca-9,12-dienoic acid showed no predicted inhibition. The absence of predicted inhibition of CYP1A2, CYP2C9, and CYP3A4 suggests a more favorable metabolic profile for 5-hydroxy, as inhibition of CYP enzymes may contribute to altered drug exposure and potential drug–drug interactions [39].

For excretion, all three compounds were predicted not to be renal OCT2 substrates. The total clearance of 5-hydroxy was the lowest (1.191 log mL/min/kg), compared with 1.965 and 1.884 log mL/min/kg for the other two compounds. This indicates a predicted slower systemic elimination of 5-hydroxy, which may result in longer systemic exposure [40-41]. Regarding toxicity, all three compounds were predicted to be negative for Ames toxicity and hepatotoxicity, while 5-hydroxy showed the highest predicted oral LD50 value (2.338 mol/kg), indicating a relatively more favorable acute toxicity profile [39].

Overall, 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one demonstrated the most balanced ADMET profile among the evaluated compounds. Its higher solubility, Caco-2 permeability,

and intestinal absorption, together with the absence of predicted CYP inhibition and favorable toxicity predictions, further support its selection as the primary candidate. These findings complement the results of the molecular docking and Lipinski evaluations, although experimental studies are still required to validate its pharmacokinetic and safety profiles.

4. Conclusion

Based on the results of this study, the selected compounds show potential as candidate drugs targeting the protein through an in silico approach, with 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one identified as the most promising candidate. This compound demonstrated stable interactions with key amino acid residues in the target protein, although it did not exhibit the lowest binding affinity value, and the docking protocol was validated by a redocking RMSD < 2 Å (1.3 Å), confirming the reliability of the method. Compared to other compounds with lower binding affinity, Lipinski and ADMET evaluations indicated that 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one possesses a more balanced profile, characterized by better solubility, higher Caco-2 permeability and intestinal absorption, absence of predicted inhibition of major CYP enzymes, and lower toxicity (LD50 of 2.338 mol/kg).

In contrast, the other compounds exhibited limitations such as high lipophilicity and excessive molecular flexibility, which may negatively affect their pharmacokinetic properties. Therefore, based on the integrated results of molecular docking, drug-likeness, and ADMET analysis, 5-hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one is considered the most promising candidate for further development, although further experimental validation is required to confirm its pharmacological activity, pharmacokinetic properties, and safety profile.

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