

Research Article

Computational Insights into the Antimalarial Potential of Geranylated Chalcone from *Terminalia brownii*: A Multi-target Approach Against *Plasmodium Falciparum* Enzymes

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Abstract

The emergence of resistance to existing antimalarial therapies has escalated the urgency for novel compounds that effectively inhibit *Plasmodium falciparum*. This comprehensive study explores the antimalarial potential of Geranylated Chalcone, a bioactive compound extracted from *Terminalia brownii*. The molecular structure of Geranylated Chalcone was generated and optimized using ChemDraw and Spartan14 software, respectively, and evaluated its theoretical bioavailability and toxicity profiles through the SwissADME web platform and ProTox 3.0 tool. Molecular docking studies was performed with AutoDock Vina to assess binding interactions with critical enzymes, including Falcipain-2, Falcipain-3, Plasmepsin-2, and Aminopeptidase. Geranylated Chalcone displayed notable binding affinities ranging from -6.4 to -7.3 kcal/mol, indicating substantial interactions facilitated by hydrogen bonds, van der Waals forces, and pi interactions. Furthermore, the compound demonstrated a favorable drug-likeness profile, adhering to Lipinski's rule of five and exhibiting low toxicity (LD₅₀: 2652mg/kg). These findings substantiate that Geranylated Chalcone serves as a promising candidate for antimalarial drug development, possessing advantageous binding affinities and a multi-target profile. Elucidation of its therapeutic efficacy, in vitro and in vivo studies are essential to validate its potentiality as a groundbreaking antimalarial agent. This research contributes valuable insights into the multifaceted role of natural compounds in combating malaria and the pressing challenge of drug resistance.

Keywords

Geranylated Chalcone, *Terminalia brownii*, Antimalarial Agents, Molecular Docking, *Plasmodium falciparum*, Drug-likeness

1. Introduction

Malaria remains one of the most significant global health challenges, responsible for approximately 263 million cases and over 597, 000 deaths worldwide in 2023 [1]. The increasing resistance of *Plasmodium falciparum*, the most lethal

malaria parasite, to current antimalarial drugs has prompted urgent calls for the discovery and development of novel therapeutic agents [1]. Among the various natural products being explored for their therapeutic potential, flavonoids have

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emerged as a promising class due to their diverse biological activities, including antimalarial properties [2].

Chalcones, a subclass of flavonoids, are characterized by their open-chain structure and have demonstrated significant pharmacological potential, including anti-inflammatory, antioxidant, and anticancer activities [3]. The geranylated chalcone derived from *Terminalia brownii*, a plant traditionally used in various cultures for medicinal purposes, has recently gained attention for its bioactive properties [2]. However, the specific mechanisms by which geranylated chalcone exerts its antimalarial effects remain largely unexplored.

In this study, we aimed to investigate the antimalarial potential of geranylated chalcone from *Terminalia brownii* through a comprehensive in silico approach. We employed molecular docking studies to evaluate the binding interactions of geranylated chalcone with key proteolytic enzymes of *P. falciparum*, including Falcipain-2, Falcipain-3, Plasmepsin-2, and Aminopeptidase. These enzymes play critical roles in the parasite's life cycle and are validated targets for drug development [4]. This research focuses not only on the binding affinities of the compound but also assesses its bioavailability and toxicity profiles using computational tools.

By elucidating the interactions between geranylated chalcone and these enzymes, this study aims to contribute valuable insights into the potential of this natural compound as a multi-target antimalarial agent. This effort aligns with the broader goal of discovering novel therapeutic strategies to combat malaria and address the pressing issue of drug resistance.

2. Material and Method

2.1. Generation and Optimization of Molecular Structures

The two-dimensional (2D) structures of bioactive compound (Geranylated Chalcone) isolated from *Terminalia brownii* [2], were constructed using ChemDraw software to ensure accurate molecular depiction. These structures were then subjected to three-dimensional (3D) optimization using Spartan14 software. Energy minimization was performed to stabilize the molecular conformations, preparing them for subsequent computational studies.

2.2. Assessment of Bioavailability and Toxicity

Theoretical bioavailability was evaluated using the SwissADME web platform (<http://www.swissadme.ch/index.php>), which provided data on absorption, distribution, metabolism, and excretion (ADME) properties, as well as drug-likeness and medicinal chemistry suitability [5]. Toxicity profiles were

predicted with the ProTox 3.0 online tool (<https://comptox.charite.de/protox3/>), which analyzed potential toxicological risks by assessing various molecular features of the compounds.

2.3. Preparation of Ligands and Target Enzymes

For molecular docking, protein structures of Falcipain2 [PDB ID: 6JW9] [6], Falcipain3 [PDB ID: 3BWK] [7], Plasmepsin [PDB ID: 1LF3] [8] and Aminopeptidase [PDB ID: 5Y1K] [9] were retrieved from the Protein Data Bank (PDB). Following established protocols [10], the enzymes were prepared by adding hydrogen atoms, removing water molecules, and assigning appropriate charges to optimize docking accuracy. Binding sites were precisely defined to improve the reliability of the simulations.

2.4. Molecular Docking Studies

Docking simulations were conducted using AutoDock Vina, adhering to validated procedures [11]. This tool evaluated the binding affinities and orientations of the isolated compounds with the target enzymes. Grid-box parameters for Falcipain-2, Falcipain-3, Plasmepsin-2, and Aminopeptidase were carefully set (Table 1) to comprehensively explore the active sites and identify optimal ligand-enzyme interactions.

2.5. Analysis of Docking Results

Post-docking analysis was performed using Biovia Discovery Studio to assess binding scores, interaction modes, and key molecular contacts between ligands and enzymes. Specific interactions, such as hydrogen bonds and hydrophobic contacts, were scrutinized to elucidate the determinants of binding strength. These analyses offered valuable insights into the inhibitory potential of the compounds against Falcipain-2, Falcipain-3, Plasmepsin-2, and Aminopeptidase in the context of malaria.

Table 1. Grid-box parameters for the enzymes.

Enzyme	Gridbox Size			Center		
	X	Y	Z	X	Y	Z
FP-2	27	25	22	-8.889	15.368	-38.694
FP-3	18	17	14	5.96	-22.35	50.07
Plm-2	13	26	20	16.22	6.85	27.61
AP	18	16	30	14.164	11.384	12.55

3. Results and Discussion

Table 2. Chemical description of isolated compound from *Terminalia brownii*.

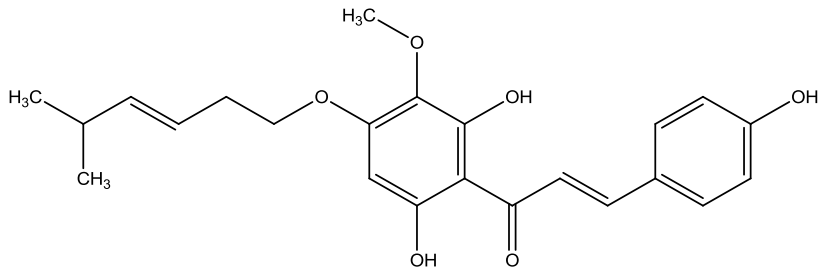
2D- Representation	IUPAC Name
	2',6',4-trihydroxy-3'-methoxy-4-O-prenyloxy chalcone

Table 3. Showing analysis of theoretical oral bioavailability of compound (Geranylated Chalcone) isolated from *Terminalia brownii* based on Lipinski's rule of five, GI absorption and Toxicity evaluation.

Compound Code	Lipinski's rule of five ^b					Inference	Predicted LD50	Toxicity Class
	Mol.Wt ^a	HbA	HbD	MLogP	GI			
T4	398.45	6	3	2.25	High	Pass	2652mg/kg	5

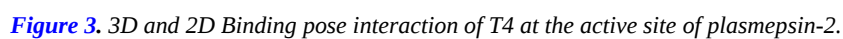
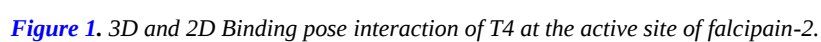
(a) Molecular weight in g/mol, (b) Lipinski *et al.*, 2001 (Mwt≤500, MLogP≤4.15, N or O≤10, NH or OH≤5 and number of rotatable bonds≤10), T4= Geranylated Chalcone

Table 4. Binding Energies of the isolated compound T4 and respective co-crystallized ligands.

PDB ID	Ligands	Binding affinity (kcal/mol)	Residues involved in bonded interaction
6JW9	E64	-5.7	Conventional H-Bond: GLN36, CYS42, GLY83, HIS174, ASN81 Pi-Donor H-Bond: TYR78 Pi-Alkyl: LEU84 Van der Waals: GLY82, GLY40, SER41, TRP43, ASN173, ALA175, ILE85, SER149, LEU172
			Conventional H-Bond: GLY83 Carbon H-Bond: TRP43, HIS174
	T4	-6.4	Pi-Sulfur: CYS42 Alkyl: LEU84, LEU172, ILE85 Van der Waals: PHE236, SER149, ASP234, ALA175, ASN173, GLN36, GLY40, ASN81, GLN171, PHE236
			Conventional H-Bond: GLN45, TRP215, GLY92, ASN182 Carbon H-Bond: TRP52, GLY91, GLY49, TYR90 Pi-Alkyl: TYR93, ALA161
3BWK	C1P	-7.0	Amide-Pi Stacked: GLY91 Pi-Sulfur: TRP215 Van der Waals: ASN87, PRO181, SER158, ILE94, ALA184, ALA166, HIS183, CYS51, CYS89

PDB ID	Ligands	Binding affinity (kcal/mol)	Residues involved in bonded interaction
1LF3	T4	-6.5	Carbon H-Bond: ASN182 Unfavorable Acceptor-Acceptor: GLY49 Pi-Sulfur: CYS51 Alkyl: ALA184 Pi-Alkyl: HIS183, TRP215, CYS51, ALA184 Van der Waals: ALA166, GLN45, TRP52, ILE94, SER158, GLU243, TYR93, GLY92, GLY91, TYR90 Conventional H-Bond: VAL78, SER79, SER218, GLY216, ASP34, ASP214 Carbon H-Bond: GLY36, ILE14, GLY216, Alkyl: VAL78, ILE290, PHE294 Pi-Sigma: VAL78
	EH5	-10.1	Pi-Donor H-Bond: TYR192 Pi-Alkyl: ILE32, ILE123 Pi-Pi T-shaped: TYR77 Pi-Sulfur: MET15 Van der Waals: LEU29, ILE300, PHE111, THR114, PHE120, SER37, LEU131, MET75, ASN76, ILE212, ALA219, THR217 Conventional H-Bond: THR217, ASP214, Carbon H-Bond: GLY216 Alkyl: VAL78, ILE32, ILE123
	T4	-7.3	Pi-Anion: ASP214 Pi-Alkyl: TYR77, PHE120, VAL78, LEU292 Van der Waals: PRO295, ASP34, MET15, PHE11, SER79, THR114, GLY36, TYR192, ILE212, ILE300, PHE294 Conventional H-Bond: ALA320, TYR580, ALA461, GLU463, GLU497 Carbon H-Bond: GLU319, ALA461 Pi-Sigma: MET1034
	B1B	-8.5	Pi-Pi Stacked: TYR575 Pi-Alkyl: TYR575, TYR580 Alkyl: ALA320, MET1034, VAL459 Van der Waals: GLU519, HIS490, HIS500, MET462, PHE457, GLN317, GLU572, GLY460 Conventional H-Bond: GLU526 Carbon H-Bond: VAL493, GLU526 Pi-Cation: ARG489
5Y1K	T4	-8.1	Pi-Pi T-shaped: HIS496, TYR580 Alkyl: VAL523 Pi-Alkyl: TYR580, VAL459 Van der Waals: GLU319, ALA461, GLU497, ASP581, THR577, LEU546, GLY460, TYR575, GLU519, HIS500, GLU463, GLN317, MET462

*E64, C1P, EH5 and B1B are the co-crystallized ligands for the respective enzyme



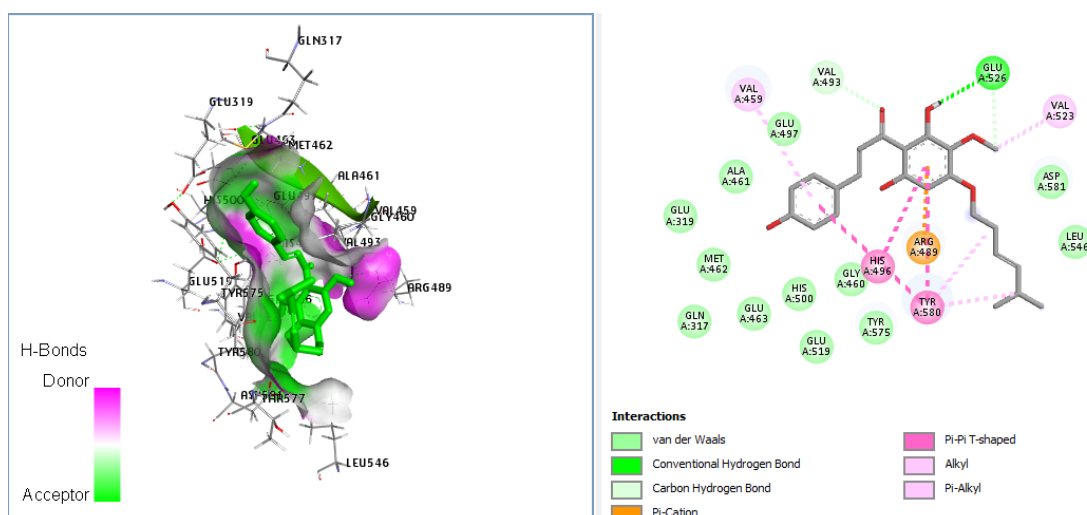


Figure 4. 3D and 2D Binding pose interaction of T4 at the active site of Amino Peptidase.

3.1. Docking Parameters and Methodology

Molecular docking of T4 against FP-2, FP-3, Plm-2, and AP utilized tailored grid-box parameters (Table 1), with FP-2's $27 \times 25 \times 22$ Å grid centered at (-8.889, 15.368, -38.694) and AP's extended 30 Å Z-dimension reflecting active site diversity. These settings, optimized via AutoDock Vina [11], ensured precise binding predictions, underpinning the reliability of our *in-silico* findings.

3.2. Drug-likeness of T4

T4, a Geranylated Chalcone from *Terminalia brownii* 2',6',4-trihydroxy-3'-methoxy-4-O-prenyloxy chalcone (Table 2), adheres to Lipinski's rule of five [12], with a molecular weight of 398.45g/mol, 6 hydrogen bond acceptors, 3 donors, and an MLogP of 2.25 (Table 3). Its high GI absorption and low toxicity (LD₅₀: 2652mg/kg, Class 5) align with the favorable profiles of *Terminalia*-derived leads [13], positioning T4 as a bioavailable antimalarial candidate.

3.3. Binding Interactions and Affinities

T4 exhibited binding affinities of -6.4 to -7.3 kcal/mol across the four *Plasmodium falciparum* enzymes (Table 4), competitive with co-crystallized ligands (-5.7 to -10.1 kcal/mol).

Falcipain-2 (FP-2, PDB: 6JW9): T4's -6.4 kcal/mol outstripped E64's -5.7 kcal/mol, driven by hydrogen bonds (GLY83), carbon hydrogen bonds (TRP43, HIS174), and a pi-sulfur interaction with catalytic CYS42 (Figure 1). Hydrophobic contacts (LEU84, LEU172, ILE85) and van der Waals forces (PHE236, ASP234) enhance stability, suggesting T4's potential as a cysteine protease inhibitor [4, 14].

Falcipain-3 (FP-3, PDB: 3BWK): At -6.5 kcal/mol, T4 trailed CIP's -7.0 kcal/mol, forming a carbon hydrogen bond

(ASN182), pi-sulfur (CYS51), and pi-alkyl (HIS183, TRP215) interactions (Figure 2). An unfavorable acceptor-acceptor clash with GLY49 may weaken binding relative to CIP's polar network [7, 14], highlighting a need for polar optimization.

Plasmeprin-2 (Plm-2, PDB 1LF3): T4's -7.3 kcal/mol lagged behind EH5's -10.1 kcal/mol, with hydrogen bonds (THR217, ASP214), pi-alkyl (ASP34, TYR77, PHE120), and a pi-anion interaction with catalytic ASP214 (Figure 3). EH5's extensive hydrogen bonding [8, 14] underscores T4's reliance on hydrophobic contacts, a potential limitation.

Aminopeptidase (AP, PDB: 5Y1K): T4's -6.8 kcal/mol was below B1B's -8.5 kcal/mol, featuring hydrogen bonds (GLU463, TYR580), pi-alkyl (TYR575), and van der Waals (MET1034) interactions (Figure 4). B1B's pi-stacking [9] suggests T4's binding pose could be refined for stronger affinity.

In contextualize T4's activity, a comparative SAR analysis with related chalcones and flavonoids reveals its structural uniqueness. Unlike non-geranylated chalcones, such as lico-chalcone A, which exhibit moderate antimalarial activity (IC₅₀= 2-5 µM against *P. falciparum*) but lack prenylation-driven hydrophobicity, T4's geranyl moiety enhances lipophilicity (MLogP 2.25), likely contributing to its favorable binding to hydrophobic pockets in FP-2 and Plm-2 [15]. Compared to other natural flavonoids like quercetin, which show weaker affinities (-5 to -6 kcal/mol) due to fewer hydrophobic interactions, T4's prenylated chalcone scaffold provides a distinct advantage in targeting hydrophobic enzyme cavities [16]. This geranylation, combined with its multi-target profile, underscores T4's novelty as a lead from *Terminalia brownii*.

3.4. Comparative Insights and Novelty

T4's affinities align with natural inhibitors of FP-2 and FP-3 (-6 to -9 kcal/mol; [4, 7], surpassing E64 against FP-2 a rare feat for a natural compound. Jimoh and his co-researcher

reported 2-pyrazoline carboxamides with superior affinities (e.g., P13: -9.2 kcal/mol for FP-2, -8.7 kcal/mol for FP-3, -8.9 kcal/mol for Plm-2), leveraging polar interactions (e.g., CYS42 in FP-2). T4's chalcone scaffold, however, offers a distinct advantage: its natural origin from *Terminalia brownii* and hydrophobic-driven binding complement synthetic polar inhibitors, broadening the chemical space for antimalarial development. Against Plm-2, T4's -7.3 kcal/mol is competitive among natural leads, though pepstatin analogs (-9 to -11 kcal/mol; [8]) set a higher bar. For AP, T4's -6.8 kcal/mol matches early-stage inhibitors [9], with room for enhancement.

It is critical to note that docking scores, while indicative of binding affinity, do not directly correlate with biological inhibitory potency. Factors such as solubility, cellular uptake, and off-target effects may influence T4's *in vitro* and *in vivo* efficacy, necessitating experimental validation to confirm its antimalarial potential [17, 18]. This study's novelty lies in T4's multi-target profile and its structural divergence from synthetic scaffolds, reinforcing *Terminalia brownii* as an underexplored antimalarial resource.

4. Conclusion

T4, a geranylated chalcone isolated from *Terminalia brownii*, exhibits robust *in silico* affinities (-6.4 to -7.3 kcal/mol) against FP-2, FP-3, Plm-2, and AP, outperforming E64 against FP-2 and aligning with natural inhibitors. Its drug-likeness, low toxicity (LD₅₀: 2652mg/kg), and interactions with catalytic residues underscore its antimalarial promise. Optimization to enhance polar contacts could elevate its potency, with *in-vitro* and *in-vivo* studies now critical to validate this novel chalcone as a multi-target lead.

Abbreviations

AP	Amino peptides
FP	Falci pain
LD	Limit Dose
PDB	Protein Data Bank
2D	Two Dimensional
3D	Three Dimensional
SAR	Structural Activity Relationship

Conflicts of Interest

The authors declare no conflicts of interest.

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