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In Silico Evaluation of Molecular Binding Affinity, Physicochemical Properties, and ADMET Profile of Nicotine Derivatives Targeting *Plasmodium falciparum* DHFR and LDH

Évaluation in silico de l'affinité de liaison moléculaire, des propriétés physicochimiques et du profil ADMET de dérivés de nicotine ciblant la DHFR et la LDH de Plasmodium falciparum.

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ABSTRACT

The discovery of new drug candidates increasingly relies on computational approaches that enable the rapid assessment of their efficacy and safety. In this study, six nicotine derivatives (C1-C6) were evaluated through molecular docking against two validated antimalarial targets, Plasmodium falciparum dihydrofolate reductase (PfDHFR) and Plasmodium falciparum lactate dehydrogenase (PfLDH). Their physicochemical characteristics and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles were also investigated using in silico prediction tools. The docking results demonstrated that all investigated derivatives exhibited stronger binding affinities than the parent nicotine molecule toward both protein targets. Compounds C1 and C2 exhibited the most favorable binding affinities, together with promising pharmacokinetic profiles. Moreover, all investigated compounds satisfied the major drug-likeness criteria, suggesting good oral bioavailability and favorable physicochemical properties. Overall, these findings suggest that nicotine derivatives, particularly compounds C1 and C2, represent promising lead compounds for the development of novel antimalarial agents. Nevertheless, further in vitro and in vivo investigations are required to validate their biological activity and safety.

Mots clés : Molecular docking; Plasmodium falciparum; PfDHFR; PfLDH; nicotine derivatives; ADMET; drug discovery.

RESUME :

La découverte de nouveaux candidats médicaments repose de plus en plus sur des approches computationnelles permettant une évaluation rapide de leur efficacité et de leur innocuité. Dans cette étude, six dérivés de la nicotine (C1-C6) ont été évalués par amarrage moléculaire sur deux cibles antipaludiques validées : la dihydrofolate réductase de Plasmodium falciparum (PfDHFR) et la lactate déshydrogénase de Plasmodium falciparum (PfLDH). Leurs caractéristiques physico-chimiques et leurs profils ADMET (absorption, distribution, métabolisme, excrétion et toxicité) ont également été étudiés à l'aide d'outils de prédiction in silico. Les résultats de l'amarrage ont démontré que tous les dérivés étudiés présentaient des affinités de liaison plus fortes que la molécule de nicotine d'origine pour les deux cibles protéiques. Les composés C1 et C2 ont présenté les affinités de liaison les plus favorables, ainsi que des profils pharmacocinétiques prometteurs. De plus, tous les composés étudiés satisfaisaient aux principaux critères de « drug-likeness », suggérant une bonne biodisponibilité orale et des propriétés physico-chimiques favorables. Globalement, ces résultats suggèrent que les dérivés de la nicotine, notamment les composés C1 et C2, constituent des molécules de tête prometteuses pour le développement de nouveaux agents antipaludiques. Toutefois, des études complémentaires in vitro et in vivo sont nécessaires pour valider leur activité biologique et leur innocuité.

Keywords: Amarrage moléculaire ; Plasmodium falciparum ; PfDHFR ; PfLDH ; dérivés de la nicotine ; ADMET ; découverte de médicaments.

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I. INTRODUCTION

Malaria remains one of the world's most devastating infectious diseases, accounting for a substantial number of cases and deaths each year, particularly in tropical and subtropical regions. Plasmodium falciparum is the most virulent human malaria parasite and is responsible for the majority of severe malaria cases and fatalities, especially among children under five years of age and other vulnerable populations [1,2].

Current antimalarial therapy is primarily based on artemisinin-based combination therapies (ACTs), which combine artemisinin derivatives with partner drugs such as mefloquine and amodiaquine. Quinoline-based antimalarial agents exert their activity mainly by inhibiting heme polymerization, thereby promoting the accumulation of toxic ferriprotoporphyrin IX released during hemoglobin degradation within the parasite [3]. Other antifolate agents,

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including proguanil and pyrimethamine, inhibit the tetrahydrofolate biosynthetic pathway, preventing DNA synthesis and parasite proliferation.

Despite the remarkable clinical success of ACTs, the continuous emergence and spread of drug-resistant *Plasmodium* strains have become a major challenge to malaria control and eradication efforts worldwide [4]. Consequently, the identification of novel antimalarial compounds with improved efficacy and favorable pharmacological properties remains a global research priority [5]. Synthetic artemisinin analogs have shown encouraging therapeutic potential and illustrate the importance of developing new classes of antimalarial agents [6,7]**.**

Modern drug discovery increasingly relies on computer-aided drug design (CADD), which enables the rapid identification and optimization of potential therapeutic candidates. Molecular docking has become an indispensable computational approach for predicting ligand-protein interactions, estimating binding affinity, and prioritizing compounds before experimental validation, thereby reducing both the cost and time required for drug development [8-12].

Among the validated molecular targets in *P. falciparum*, dihydrofolate reductase (*Pf*DHFR) is one of the most extensively investigated enzymes because of its essential role in folate metabolism, nucleotide biosynthesis, and parasite DNA replication [13]. *Pf*DHFR catalyzes the reduction of dihydrofolate (DHF) to tetrahydrofolate (THF) according to the following reaction:

$$\mathbf{DHF + NADPH + H^{+} \rightarrow THF + NADP^{+}}$$

Antifolate drugs such as pyrimethamine and cycloguanil, the active metabolite of proguanil, inhibit this enzyme, ultimately disrupting DNA synthesis and parasite survival.

Another promising therapeutic target is *P. falciparum* lactate dehydrogenase (*Pf*LDH), a key glycolytic enzyme responsible for catalyzing the conversion of pyruvate into lactate [14]:

$$\mathbf{Pyruvate + NADH + H^{+} \rightarrow Lactate + NAD^{+}}$$

Because the malaria parasite relies almost exclusively on glycolysis for ATP production during its erythrocytic stage, *Pf*LDH is indispensable for parasite survival. Moreover, structural differences between the parasite and human LDH enzymes provide an opportunity to develop highly selective inhibitors with reduced host toxicity.

In the present study, six structurally modified nicotine derivatives were investigated to evaluate their potential as antimalarial candidates. Molecular docking simulations were performed against *Pf*DHFR and *Pf*LDH, followed by comprehensive analyses of their physicochemical characteristics and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties. This integrated computational strategy aims to identify promising lead compounds while minimizing the risk of failure during the early stages of drug discovery [15].

II. MATERIALS AND METHODS

II.1. Selection and preparation of ligands

Nicotine (C0), Figure 1, and six structurally modified nicotine derivatives were selected for this study. These compounds, designated C1-C6, were generated through the condensation of nicotine with selected halogenated derivatives. The six compounds consist of three pairs of enantiomers (C1/C2, C3/C4, and C5/C6), as illustrated in Table 1.

Before molecular docking, the chemical structures of all ligands were prepared and optimized to ensure appropriate molecular geometries suitable for computational analysis.

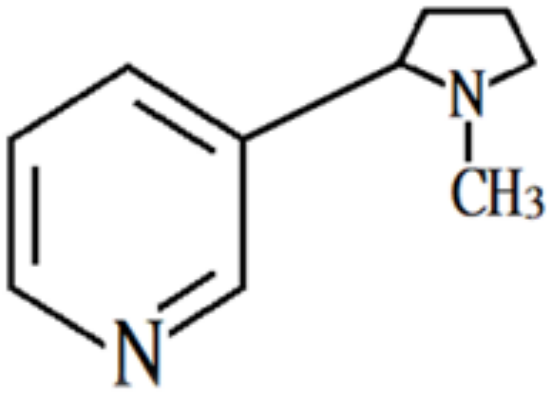

Figure 1. Chemical structure of nicotine.

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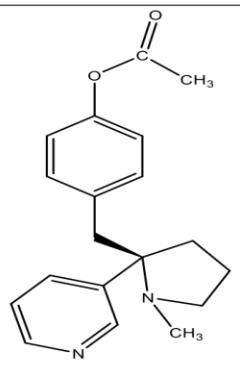
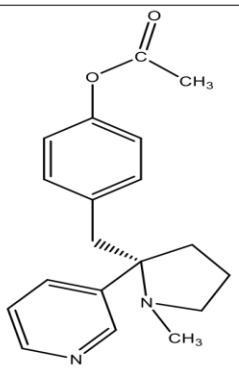
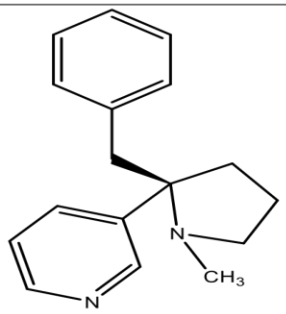
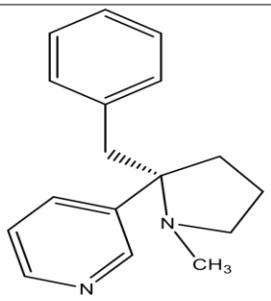
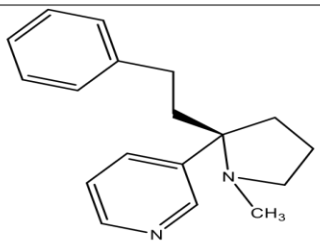
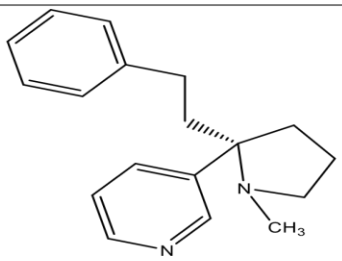
Table 1. Chemical structures of the investigated nicotine derivatives.

 (*R*)-4-((1-methyl-2-(pyridin-3-yl)pyrrolidin-2-yl)methyl)phenyl acetate CN(CCC1)[C@@]1(C2=CC=CN=C2)CC3=CC=C(OC(C)=O)C=C3	 (*S*)-4-((1-methyl-2-(pyridin-3-yl)pyrrolidin-2-yl)methyl)phenyl acetate CN(CCC1)[C@]1(C2=CC=CN=C2)CC3=CC=C(OC(C)=O)C=C3
C1	C2
 (*R*)-3-(2-benzyl-1-methylpyrrolidin-2-yl)pyridine CN(CCC1)[C@@]1(C2=CC=CN=C2)CC3=CC=CC=C3	 (*S*)-3-(2-benzyl-1-methylpyrrolidin-2-yl)pyridine CN(CCC1)[C@]1(C2=CC=CN=C2)CC3=CC=CC=C3
C3	C4
 (*S*)-3-(1-methyl-2-phenethylpyrrolidin-2-yl)pyridine CN(CCC1)[C@@]1(C2=CC=CN=C2)CCC3=CC=CC=C3	 (*R*)-3-(1-methyl-2-phenethylpyrrolidin-2-yl)pyridine CN(CCC1)[C@]1(C2=CC=CN=C2)CCC3=CC=CC=C3
C5	C6

II.2. Selction and preparation of biological targets

Two validated therapeutic targets from *Plasmodium falciparum* were selected for molecular docking analysis: dihydrofolate reductase (*Pf*DHFR) and lactate dehydrogenase (*Pf*LDH). The crystal structures of the enzyme *Pf*LDH (PDB ID: 1T2C) in complex with NADH (https://www.rcsb.org/structure/1T2C) and *Pf*DHFR (PDB ID: 7F3Y) complexed with methotrexate (MTX), NADPH and dUM (https://www.rcsb.org/structure/7F3Y), were retrieved from the Protein Data Bank (PDB), and shown in Figure 2 (left), and also visualized using the GaussView graphical interface (right). There These enzymes play essential roles in parasite survival and metabolism and are therefore considered attractive targets for antimalarial drug discovery. The molecular structures of both protein targets are presented in Figure 2.

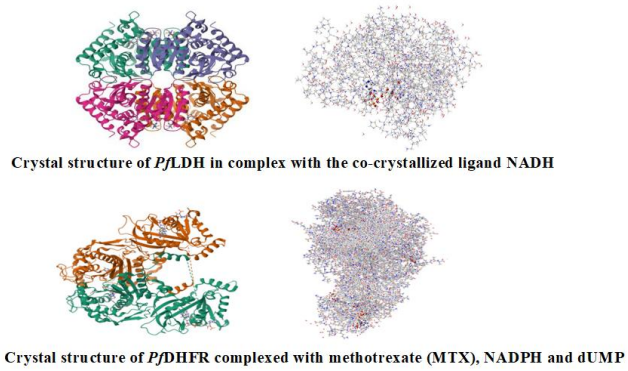


Figure 2. Three-dimensional structures of the selected biological targets (*Pf*DHFR and *Pf*LDH).

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II.3. Molecular docking analysis

Molecular docking simulations were performed to evaluate the binding affinity of the selected nicotine derivatives toward *Pf*DHFR and *Pf*LDH biological targets. In parallel, physicochemical properties were predicted using the SwissADME web platform, while pharmacokinetic parameters were assessed using complementary *in silico* tools.

The stability of each ligand-protein complex was estimated from its binding free energy (ΔG). More negative ΔG values indicate stronger molecular interactions and greater stability of the corresponding ligand-receptor complex.

II.4. ADMET prediction

The pharmacokinetic and toxicological profiles of the investigated compounds were predicted using the pkCSM web server [16]. The evaluated parameters included absorption, distribution, metabolism, excretion, and toxicity (ADMET), providing an early assessment of the drug-likeness and safety profiles of the proposed antimalarial candidates.

III. RESULTATS

III.1. Binding affinity of nicotine derivatives toward *Pf*DHFR and *Pf*LDH

The molecular docking results (Table 2) demonstrated that all six nicotine derivatives exhibited stronger binding affinities toward both Plasmodium falciparum dihydrofolate reductase (*Pf*DHFR) and lactate dehydrogenase (*Pf*LDH) than the parent nicotine molecule, indicating that structural modification of nicotine significantly enhanced its interaction with these therapeutic targets.

Table 2. Binding energy (kcal/mol) after molecular docking

Compound	Target 1 (*Pf*DHFR)		Target 2 (*Pf*LDH)	
	Binding energy	Residues (H-bonds)	Binding energy	Residues (H-bonds)
Nicotine	-5.8	HIS 195	-5.2	ILE 164, TYR 170
Compound 1	-8.3	-	-7.5	ASN140
Compound 2	-8.1	-	-7.2	ASN140, THR97
Composé 3	-7.4	-	-6.5	-
Compound 4	-8.0	-	-6.5	THR97
Compound 5	-7.5	-	-7.1	-
Compound 6	-8.0	-	-6.8	THR97

For *Pf*DHFR, the calculated binding energies ranged from -7.4 to -8.3 kcal/mol, whereas nicotine exhibited a binding energy of -5.8 kcal/mol. Among the investigated compounds, C1 displayed the highest binding affinity (-8.3 kcal/mol), followed by C2 (-8.1 kcal/mol) and compounds C4 and C6 (both -8.0 kcal/mol). These findings indicate that the introduction of halogenated substituents considerably improves ligand-protein interactions compared with the parent nicotine scaffold.

The observed differences between the R and S stereoisomers further suggest that stereochemistry influences binding affinity, although this effect varies depending on the chemical substitution pattern.

A similar trend was observed for *Pf*LDH. Compound C1 achieved the best binding score (-7.5 kcal/mol), followed by C2 (-7.2 kcal/mol) and C5 (-7.1 kcal/mol), whereas nicotine showed a substantially weaker affinity (-5.2 kcal/mol). These results are consistent with previous molecular docking studies reporting binding energies close to -7.7 kcal/mol for quinoline-based inhibitors against *Pf*LDH [17].

Because more negative binding free energy (ΔG) values generally reflect stronger ligand–protein interactions and greater complex stability [18], compounds C1 and C2 appear to be the most promising candidates among the investigated series. Their favorable docking scores against both molecular targets suggest a higher probability of biological activity compared with the remaining derivatives.

Interestingly, C1 and C2 correspond to the two stereoisomers of the same acetylated nicotine derivative. Since both compounds exhibited very similar docking performances, the need for stereoisomeric separation during future synthesis and biological evaluation may be reduced, thereby simplifying the experimental development process.

Analysis of the ligand–protein interaction maps (Figures 3 and 4) revealed that these compounds established several stabilizing interactions within the active sites of *Pf*DHFR and *Pf*LDH, including hydrophobic contacts, π-alkyl interactions, π-sulfur interactions, van der Waals contacts, and, in some cases, hydrogen bonds with key catalytic residues. These interactions collectively contribute to the enhanced stability of the docked complexes. Comparison of Figures 3 and 4 reveals that the six ligands establish a greater number of strong conventional hydrogen-bond interactions with the *Pf*LDH target than with *Pf*DHFR, where non-conventional hydrogen bonds predominate (Table 1). Nevertheless, the ligands–*Pf*DHFR complexes, which are primarily stabilized

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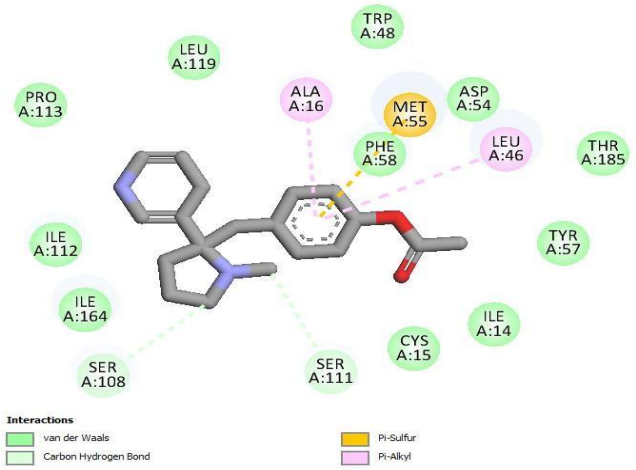
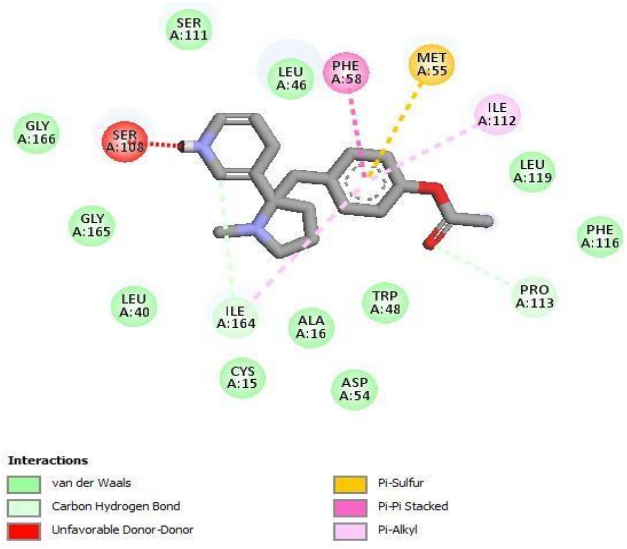
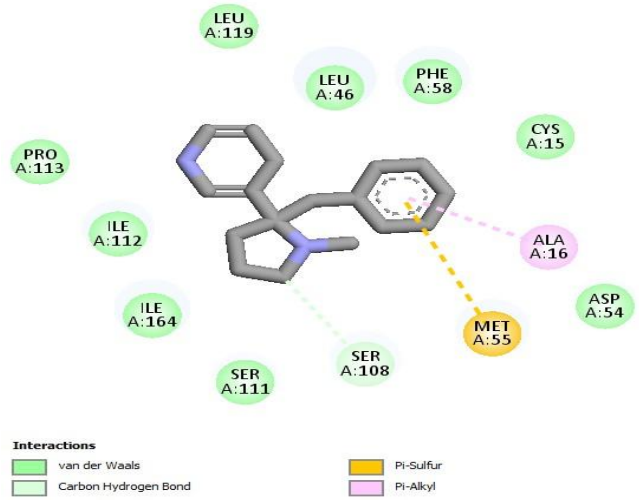
by dispersion interactions, exhibit stronger overall binding than the corresponding ligands–*Pf*LDH complexes. These findings are consistent with previous reports by Tunga *et al.* [19] and Kasende *et al.* [20].



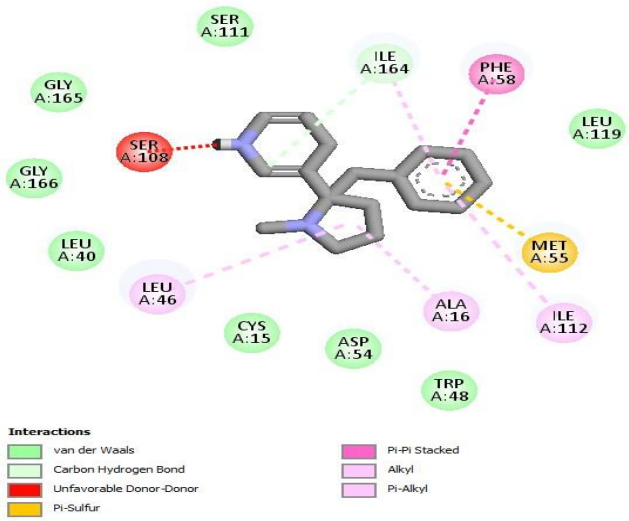
C1



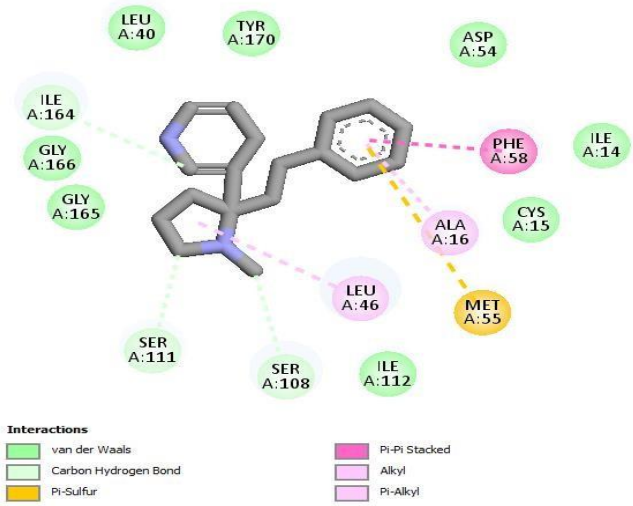
C2



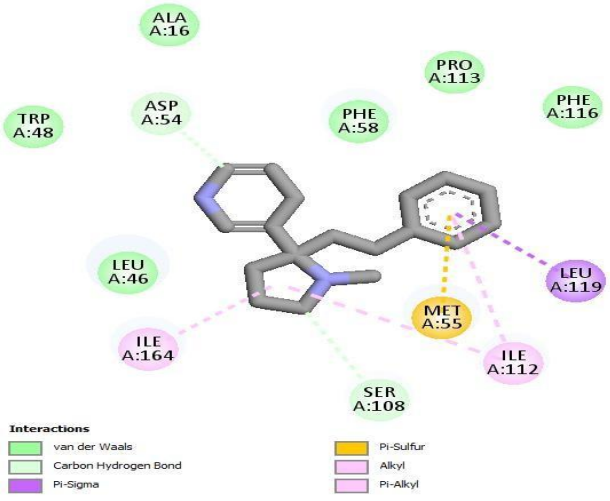
C3



C4



C5



C6

Figure 3. 2D representation of interactions between *Pf*DHFR and ligands

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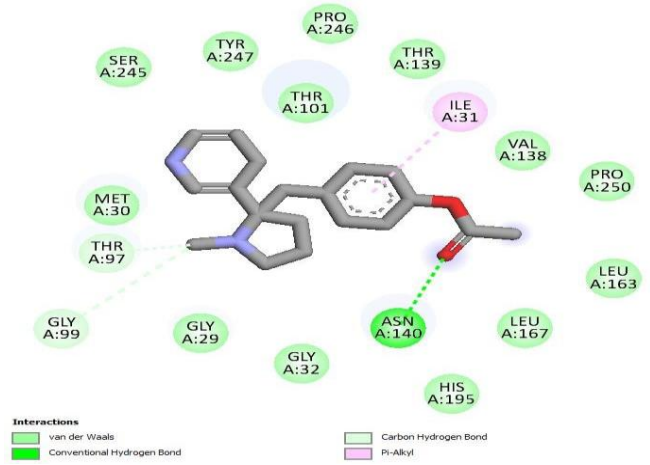
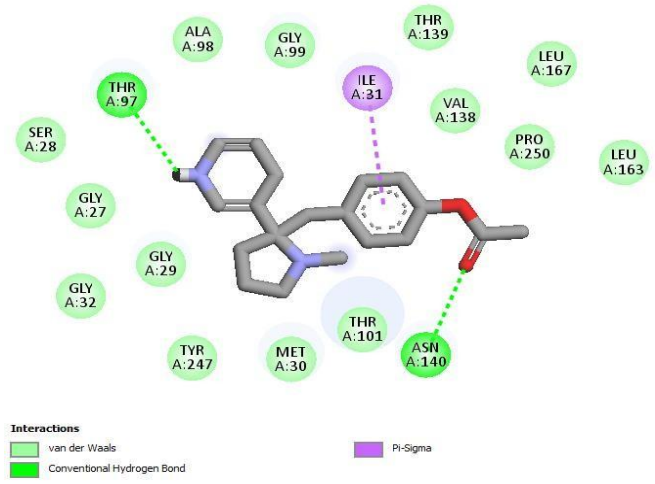
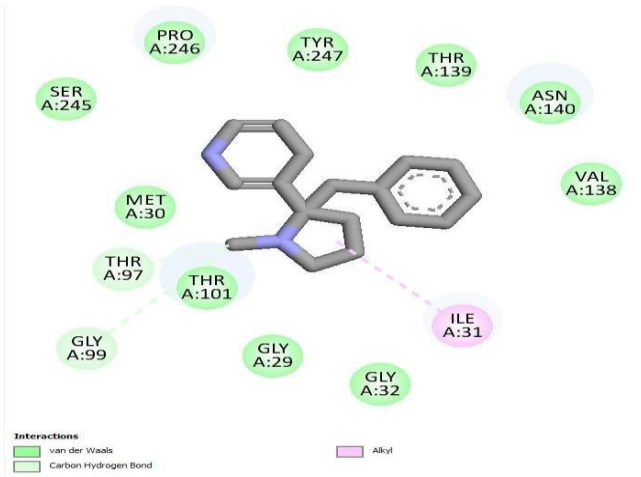
Overall, the molecular docking results indicate that structural modification of nicotine constitutes an effective strategy for improving binding affinity toward validated antimalarial targets. Consequently, compounds C1 and C2 emerge as promising lead molecules for further optimization and experimental validation as potential antimalarial agents.



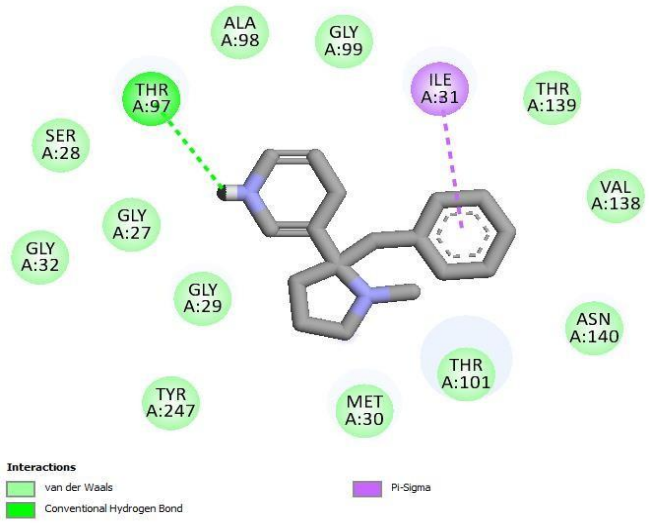
C1



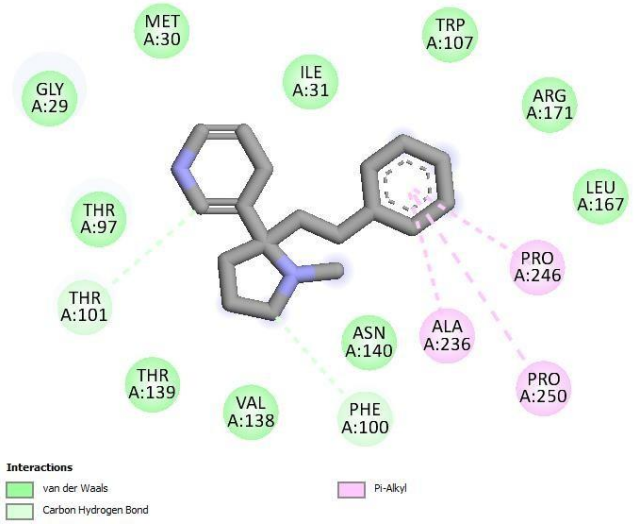
C2



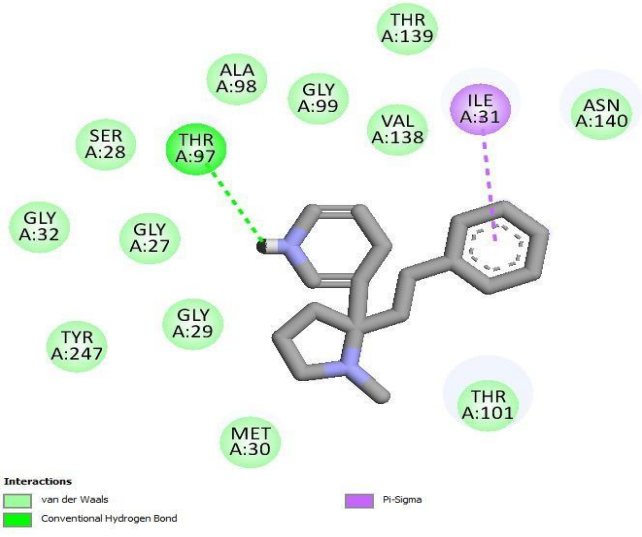
C3



C4



C5



C6

Figure 4. 2D representation of interactions between *Pf*LDH and ligands

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II.2. Physicochemical properties

The physicochemical properties of the investigated nicotine derivatives are summarized in Table 5. Their molecular weights ranged from 252.35 to 310.39 g/mol, remaining well below the 500 g/mol threshold recommended by Lipinski's Rule of Five [21]. This characteristic suggests favorable molecular size for oral drug candidates.

The predicted LogP values (3.17-3.64) indicate moderate lipophilicity, which is considered suitable for passive membrane diffusion while maintaining an appropriate balance between aqueous solubility and permeability [22]. Furthermore, the topological polar surface area (TPSA) values were all below 140 Å², suggesting good intestinal absorption and satisfactory oral bioavailability.

In addition, all compounds complied with the principal drug-likeness criteria, including acceptable numbers of hydrogen bond donors and acceptors, rotatable bonds, and molecular flexibility. Collectively, these findings indicate that the six nicotine derivatives possess physicochemical characteristics compatible with the requirements of orally administered drug candidates.

The predicted blood-brain barrier (BBB) permeability values ranged from 0.41 to 0.59, suggesting moderate penetration into the central nervous system. Although BBB permeability is not a prerequisite for antimalarial drugs, this characteristic may be advantageous for the treatment of cerebral malaria caused by *P. falciparum.*

Regarding metabolism, all compounds were predicted to be substrates of CYP2D6 but not CYP3A4, suggesting that CYP2D6 may play a major role in their biotransformation [23]. This information is relevant for anticipating possible drug-drug interactions during future pharmacological development.

The predicted total clearance values indicated acceptable elimination profiles for all compounds. Likewise, all molecules were identified as potential substrates of the renal organic cation transporter OCT2.

From a toxicological perspective, compounds C1-C4 were predicted to be non-mutagenic according to the Ames test, whereas C5 and C6 showed a potential risk of mutagenicity. Nevertheless, all investigated compounds were predicted to exhibit potential hepatotoxicity, highlighting the need for further experimental toxicological assessment. Therefore, although the computational predictions are encouraging, comprehensive *in vitro* and *in vivo* toxicity studies remain essential before any pharmacological application.

Table 3. Physicochemical properties of the investigated nicotine derivatives

Compounds	MW (g.mol^{-1})	LogP	nHA	nHD	nRot	nRig	Fx	MR	TPSA (Å²)
C1	310.39	3.17	4	0	5	18	0.29	93.80	42.43
C2	310.39	3.17	4	0	5	18	0. 29	93.80	42.43
C3	252.35	3.25	2	0	3	17	0.18	82.30	16.13
C4	252.35	3.25	2	0	3	17	0.18	82.30	16.13
C5	266.38	3.64	2	0	4	17	0.24	87.11	16.13
C6	266.38	3.64	2	0	4	17	0.24	87.11	16.13

III.3. ADMET profile

The predicted ADMET properties are presented in Table 4. All investigated compounds exhibited excellent human intestinal absorption (HIA), with predicted absorption values exceeding 94%, indicating a high probability of efficient oral uptake.

Table 4. ADMET properties of ligands

Parameters	C1	C2	C3	C4	C5	C6
Absorption & Distribution						
IA (%)	96.17	96.17	95.32	95.32	94.72	94.72
Water solubility	-3.17	-3.17	-2.89	-2.89	-3.23	-3.23
BBB	0.41	0.41	0.55	0.55	0.59	0.59
VDss	0.87	0.87	1.13	1.13	1.24	1.24
Metabolism						
CYP2D6	Oui	Oui	Oui	Oui	Oui	Oui
CYP3A4	Non	Non	Non	Non	Non	Non
Excretion						
Total clearance	0.88	0.88	0.97	0.97	1.03	1.03
Renal OCT2 substrate	Oui	Oui	Oui	Oui	Oui	Oui
Toxicity						
Ames test	Non	Non	Non	Non	Oui	Oui
Hepatotoxicity	Oui	Oui	Oui	Oui	Oui	Oui
TO (LD50)	2.74	2.74	2.75	2.75	2.73	2.73
MTD	-0.19	-0.19	-0.18	-0.18	-0.03	-0.03

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III.4. Identification of the most promising lead compounds

Among the six investigated nicotine derivatives, compound C1 emerged as the most promising lead candidate. It exhibited the strongest binding affinity toward both *Pf*DHFR (-8.3 kcal/mol) and *Pf*LDH (-7.5 kcal/mol), combined with excellent intestinal absorption, compliance with Lipinski's Rule of Five, and the absence of predicted mutagenicity.

Compound C2 also demonstrated a highly favorable pharmacological profile, with docking scores and ADMET properties closely comparable to those of C1. Considering their overall biological, physicochemical, and pharmacokinetic characteristics, compounds C1 and C2 represent the most promising candidates for further experimental evaluation as potential antimalarial agents.

IV. CONCLUSION

This *in silico* investigation demonstrated that structural modification of nicotine significantly enhances its interaction with two validated antimalarial molecular targets, *Pf*DHFR and *Pf*LDH. All six nicotine derivatives exhibited stronger binding affinities than the parent nicotine molecule while satisfying the main physicochemical requirements for orally active drug candidates.

Among the investigated compounds, C1 and C2 showed the most favorable combination of molecular docking performance, drug-likeness, and pharmacokinetic properties, making them attractive lead compounds for antimalarial drug discovery.

Although these computational findings provide encouraging evidence of their therapeutic potential, further advancing artificial intelligence or machine-learning–based drug discovery techniques, including MD simulations and MM-PBSA calculations; *in vitro* and *in vivo* studies, and eventually clinical investigations will be necessary to confirm their efficacy, selectivity, and safety. Overall, this study highlights nicotine-derived compounds as promising scaffolds for the rational design of novel antimalarial agents.

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