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IN SILICO DOCKING STUDIES OF CYANURIC CHLORIDE DERIVATIVES AS INHIBITORS OF *PLASMODIUM FALCIPARUM* HEXOSE TRANSPORTER 1

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ABSTRACT

Malaria is the leading cause of worldwide mortality with high resistance to existing drugs available in market. The *Plasmodium falciparum* hexose transporter 1 (PfHT1) is a promising target for antimalarial drug discovery due to its critical role in glucose uptake, which is essential for the survival of the malaria parasite during its blood stage. Thus, there is a need for safe and potent *Plasmodium falciparum* hexose transporter 1 (PfHT1) inhibitors which can pave the way for designing new drug molecules for malarial treatments. The present work describes the docking study of few Cyanuric chloride derivatives as *Plasmodium falciparum* hexose transporter 1 (PfHT1) receptor inhibitors. The designed derivatives show comparable dock scores with Primaquine and Chloroquine. The docking study reveals that the binding of Cyanuric Chloride derivatives and amino acids in the binding pocket of the *Plasmodium falciparum* hexose transporter 1 (PfHT1) inhibitors. The predicted ADME properties of the designed compounds are in an acceptable range.

KEYWORDS: Molecular docking, ADME study, Cyanuric Chloride, Malaria, *Plasmodium falciparum.*

INTRODUCTION

Malaria is a life-threatening parasitic disease transmitted to humans through the bite of infected female *Anopheles* mosquitoes; it is generally caused by *Plasmodium falciparum* and *P. vivax*, and presents with fever, chills, anaemia and, in severe cases, multi-organ failure and cerebral complications.[1,2] Despite decades of control efforts, the global malaria burden remains substantial: recent WHO reporting indicates hundreds of millions of cases annually and on the order of 0.6 million deaths per year, with the highest mortality concentrated among children under five in sub-Saharan Africa region. These figures reflect a worrying plateau, and in some years a small rise—in cases and deaths that threatens to reverse earlier gains.[1] A major challenge to malaria control is the emergence and spread of parasite resistance to frontline therapies. Partial resistance to artemisinin derivatives—manifested as delayed parasite clearance—and growing failures of some artemisinin-combination therapies have been documented, eroding the effectiveness of current treatment regimens and increasing the risk of treatment failure. In parallel, insecticide resistance in mosquito vectors is also one of the reason.[3] Altogether, the clinical and operational impacts of resistance mean there is an urgent need for new antimalarial drugs with novel mechanisms of action, improved safety profiles, and formulations suitable for vulnerable populations. Drug discovery efforts are therefore diversifying to validate new parasite targets (for example, the *Plasmodium falciparum* hexose transporter PfHT1) and to develop chemotypes capable of overcoming existing resistance mechanisms; these approaches are central to sustaining progress toward malaria control and eventual elimination.[4]

Heterocyclic compounds have broad range of synthetic applicability and pharmacological activity. Cyanuric Chloride is not used directly as a marketed drug, the 1,3,5-triazine derivatives are widely studied as potential medicinal agents due to their structural tunability and ability to interact with cellular target. Functionalized triazines synthesized from cyanuric chloride were found to have a versatile range of pharmacological activities, including antibacterial[5], anticancer[6], antifungal[7], antimalarial[8], antiviral, anti -Alzheimer's Disease[9] and enzyme inhibitory properties.[10] Recent reviews and experimental investigations emphasize that strategic substitution at the triazine ring can notably modulate efficacy, selectivity, and pharmacokinetic properties. Advances in computational modelling, structure–activity relationship (SAR) analysis, and ADMET prediction have further reinforced the value of cyanuric chloride–derived triazines as **potential drug leads**, particularly in antimicrobial and antifungal research.[11]

Owing to the synthetic and biological values of Cyanuric chloride derivatives, we aimed to design a series of Cyanuric chloride derivatives for their in silico docking study and drug likeness properties.

2. Experimental

Ligands were docked to the respective proteins using AutoDock Vina (Integrated with PyRx) assisted by AutoDock Vina (Version 1.2.3) which has advanced scoring functions, improved docking speed and accuracy, supports flexible ligand and receptor modelling, multicore processing capabilities for protein preparation and docking. AutoDock Vina is frequently used for virtual screening of large libraries of compounds to identify potential antimalarial agents. The docking process was validated by re-docking the native ligand to the respective protein and checking the root mean square deviation (RMSD) values (RMSD score was required to be less than 2) and interactions of the native ligand with active site residues. OpenBabel (Version 3.1.1.4) with UFF Force Field was used for ligand preparation. The free energy of binding (kcal/mol) of ligands to the respective protein was noted. The 2D and 3D interaction of the complex was visualized in Discovery Studio Visualizer (version 2025). In order to investigate the most likely binding mechanism, the derivatives were positioned within *Plasmodium falciparum* Hexose Transporter 1 (PfHT1) with (PDB ID 6M2L). The Plasmodium falciparum hexose transporter 1 (PfHT1) is a promising target for antimalarial drug discovery due to its critical role in glucose uptake, which is essential for the survival of the malaria parasite during its blood stage. The transporter facilitates the uptake of glucose, the primary energy source for the parasite, making it a strategic point for therapeutic intervention. Inhibiting PfHT1 can effectively starve the parasite, offering a novel approach to combat malaria, especially in the face of rising drug resistance.

Ten docking postures were created for each ligand, and the best docked confirmation was taken into consideration for further hydrogen bonding research.

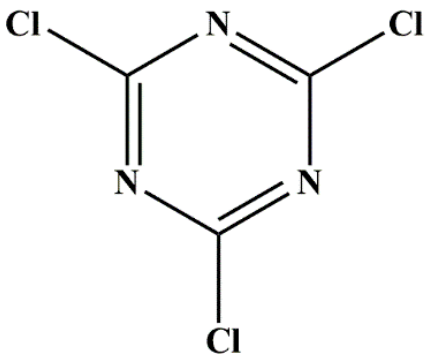
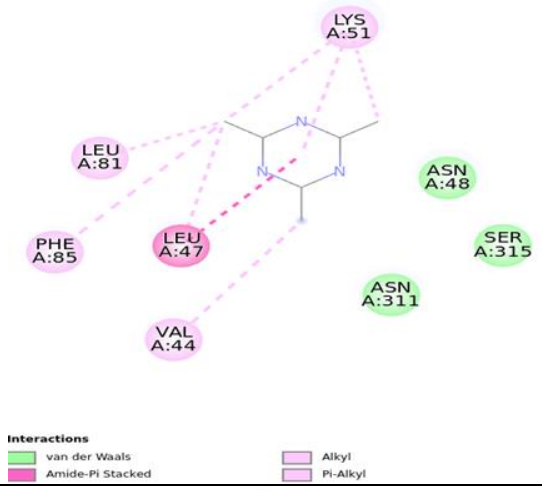
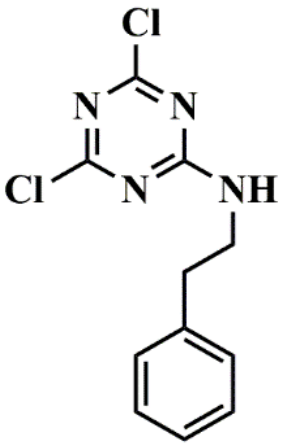
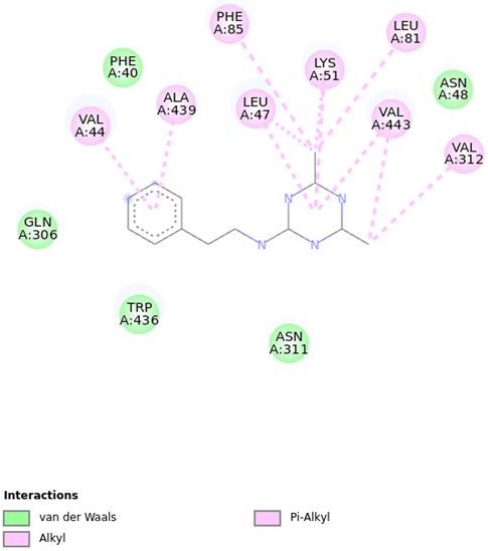
SwissADME(Daina et al., 2017) was used for computing ADME properties. ADME properties, which involve parameters such as solubility, blood brain barrier permeability, number of rotatable bonds, H-bond acceptor, H-bond donor, GI-absorption, P-gp substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2D6 inhibitors, CYP3A4 inhibitor, etc. The molecules were analysed for drug-likeness by assessing their physicochemical properties.

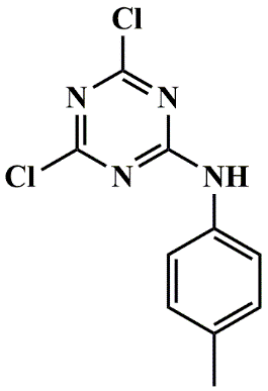
According to the Lipinski rule, it is necessary that the molecule should satisfy the conditions like Molecular Weight < 500, Lipophilicity (log P) < 5, Hydrogen Bond Donors ≤ 5 (Sum of NH and OH), Hydrogen Bond Acceptors ≤ 10 (sum of N and O), number of rotatable bonds 10, etc. A compound is considered a feasible drug candidate when it adheres to the criteria specified above.

3. RESULTS AND DISCUSSION

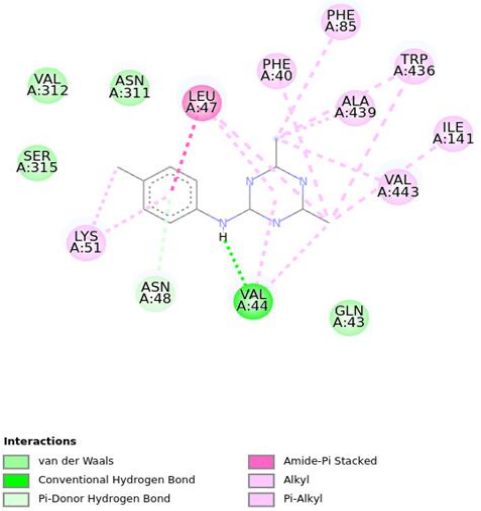
Cyanuric chloride and all designed Cyanuric chloride molecules were supplied to the docking software to determine the active binding sites and binding affinity. The computational results obtained were compared with the standard drugs **Chloroquine, Quinine, Primaquine, Mefloquine Lumefantrine** which are given in tables below.

Table 1: 2D docking poses of the compounds (1- 7) d.

Compound	Dock pose
 1d	
 2d	


Cl
N
N
Cl
N
NH

3d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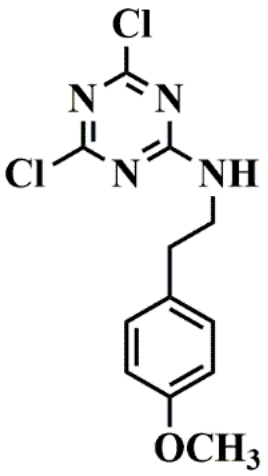
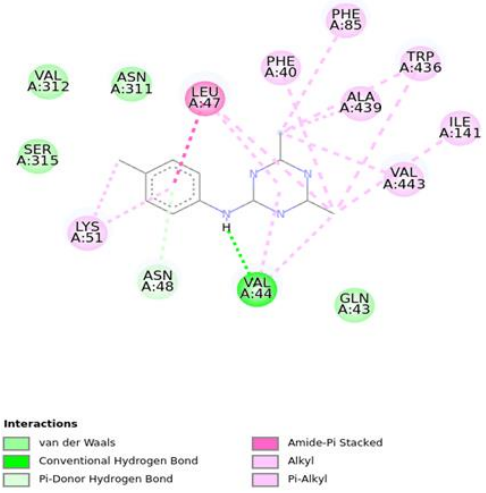
PHE A:40
TRP A:436
VAL A:312
ASN A:311
LEU A:47
ALA A:439
ILE A:141
SER A:315
VAL A:443
LYS A:51
ASN A:48
VAL A:44
GLN A:43
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Donor Hydrogen Bond
Amide-Pi Stacked
Alkyl
Pi-Alkyl


Cl
N
N
Cl
N
NH
OCH3

4d


PHE A:85
PHE A:40
TRP A:436
VAL A:312
ASN A:311
LEU A:47
ALA A:439
ILE A:141
SER A:315
VAL A:443
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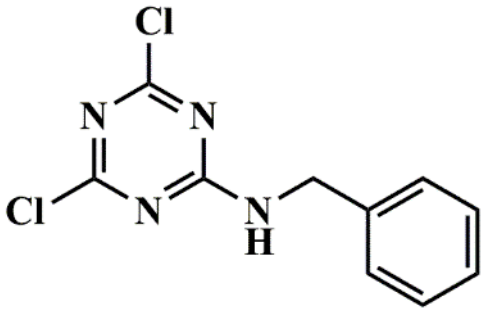
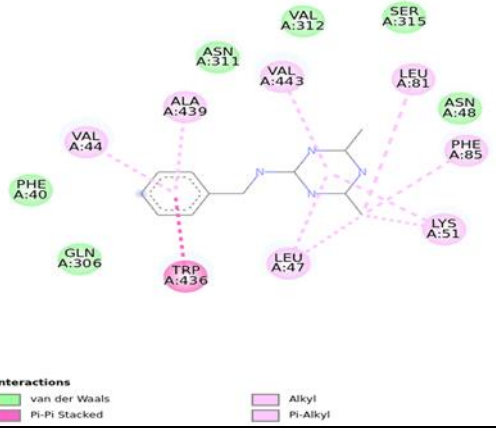
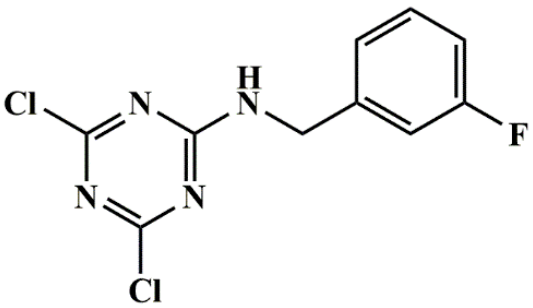
Pi-Alkyl

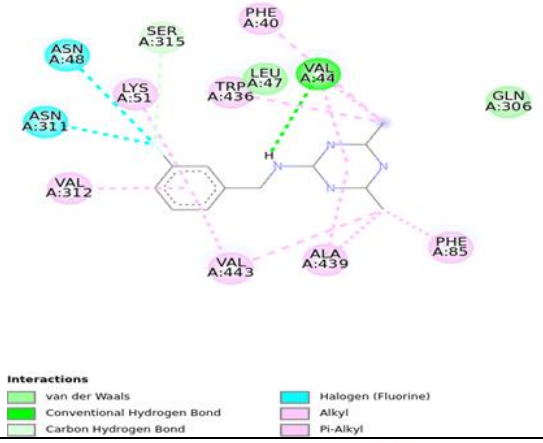

Cl
N
N
Cl
N
N
H

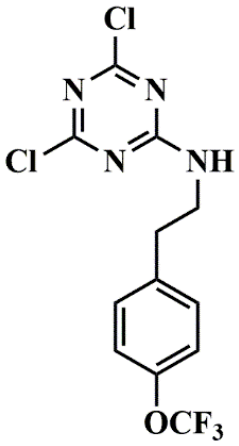
5d


VAL A:312
SER A:315
ASN A:311
VAL A:443
LEU A:81
ALA A:439
ASN A:48
VAL A:44
PHE A:85
PHE A:40
LYS A:51
GLN A:306
TRP A:436
LEU A:47
Interactions
van der Waals
Pi-Pi Stacked
Alkyl
Pi-Alkyl



6d





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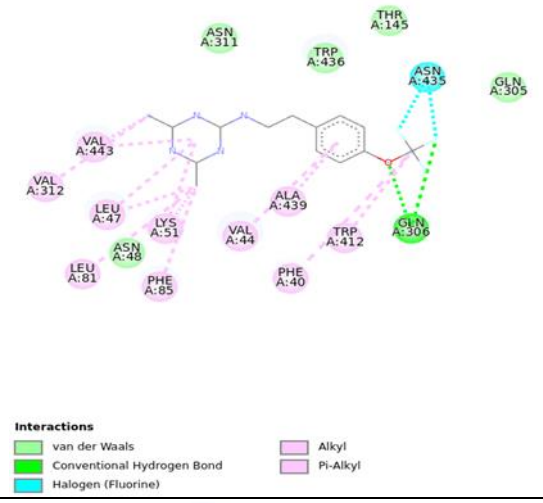
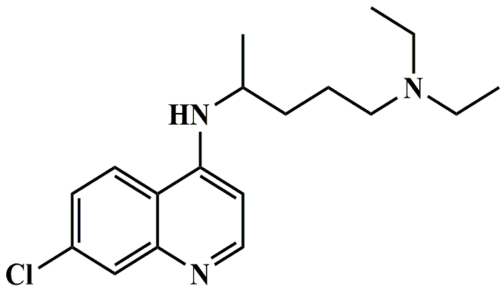
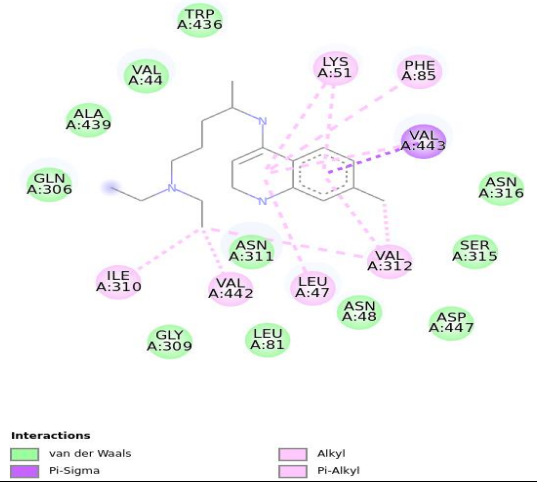
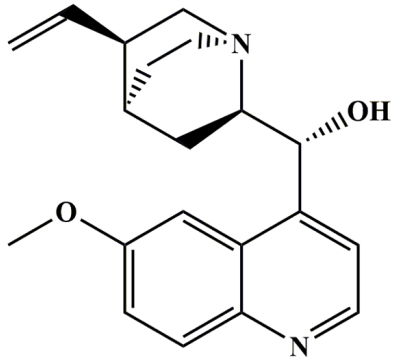


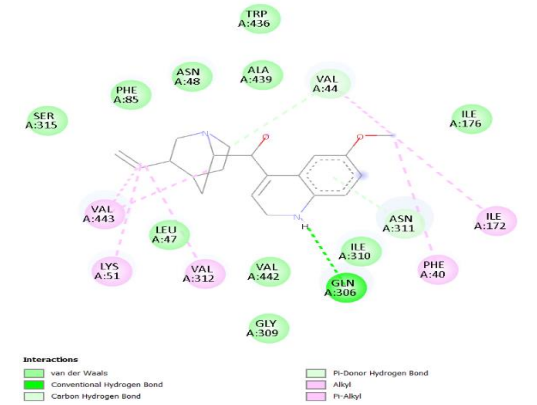


Chloroquine





Quinine



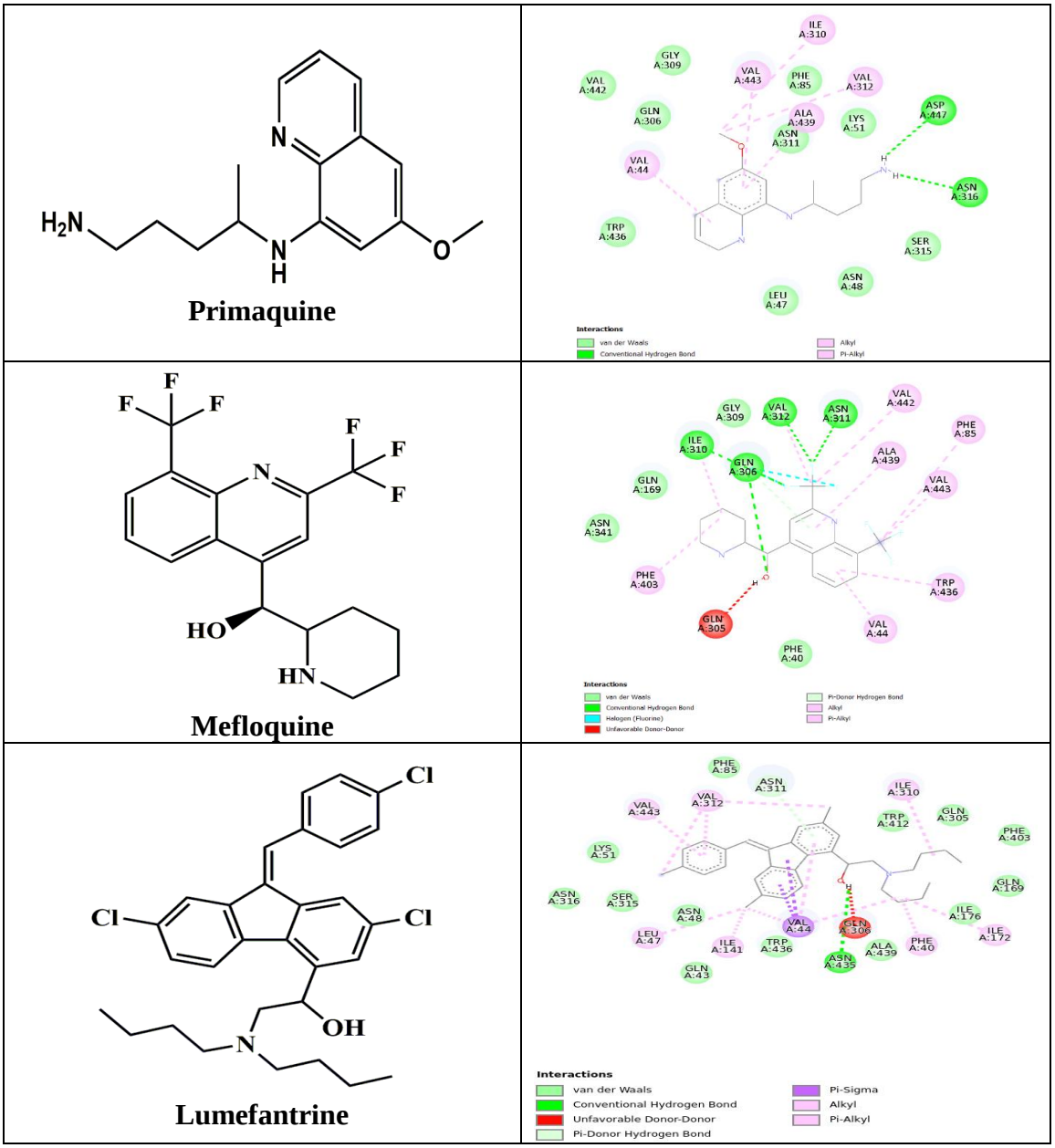
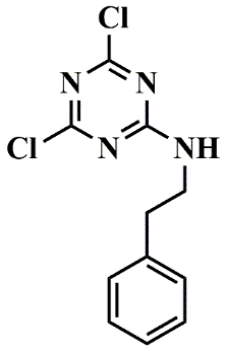
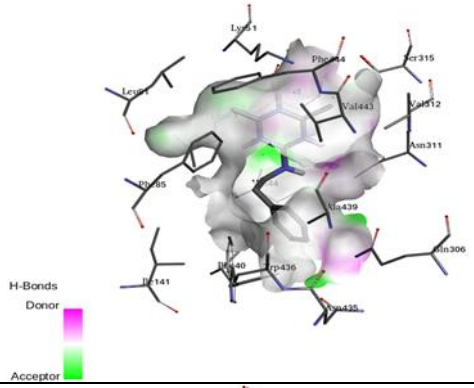
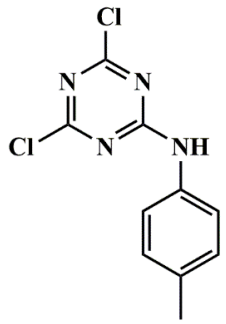
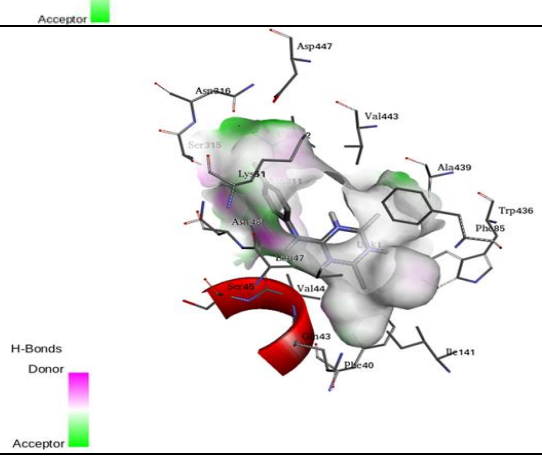
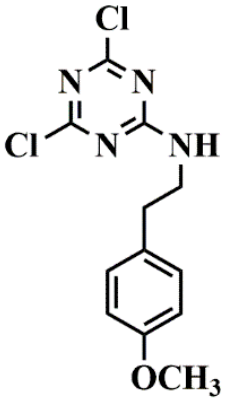
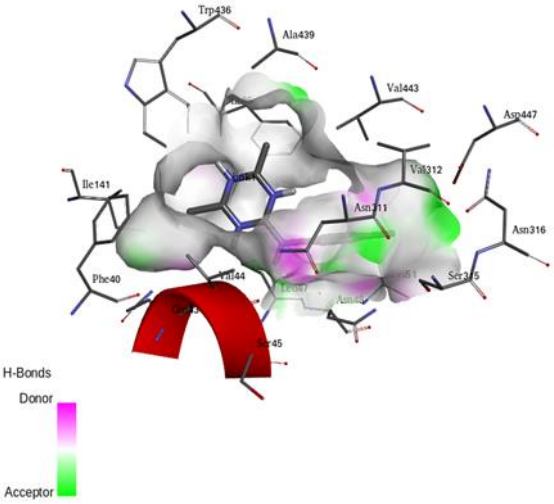
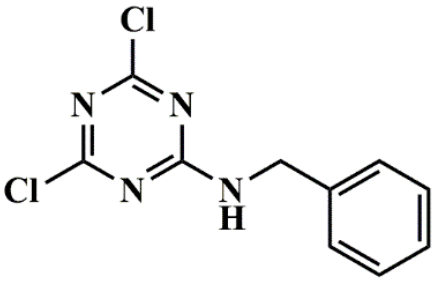
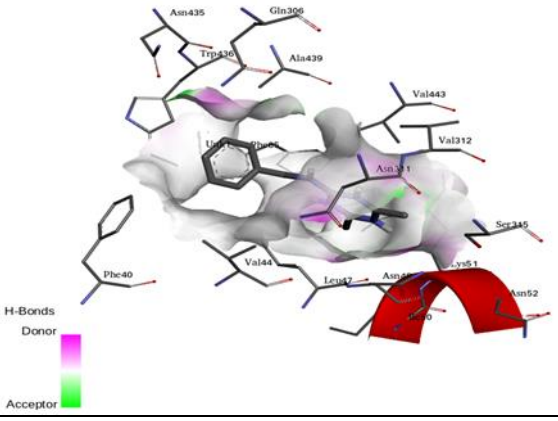
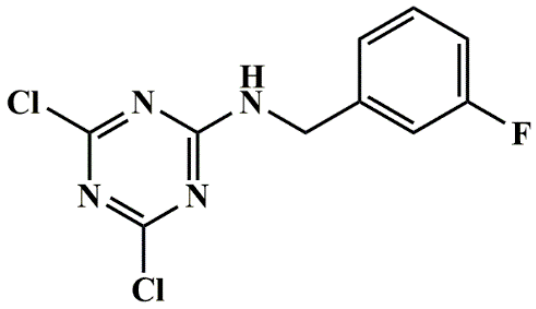


Table 2: 3D docking poses of the compounds (1- 7) d.

Compound	Dock pose
1d	H-Bonds Donor Acceptor

 **2d**	
 **3d**	
 **4d**	
 **5d**	



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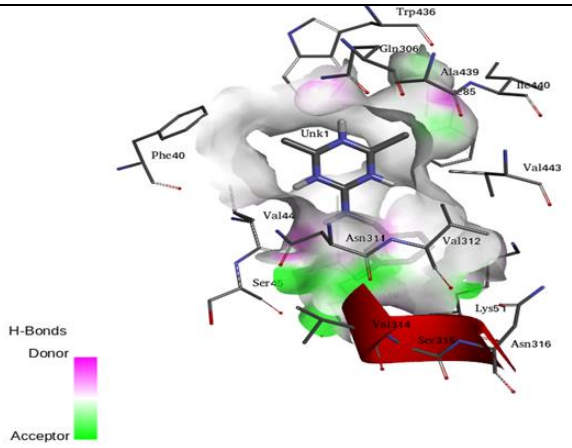

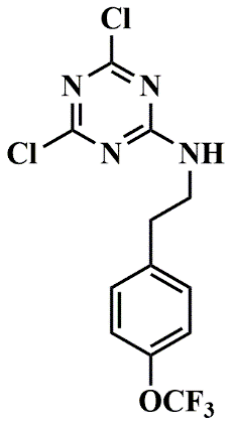

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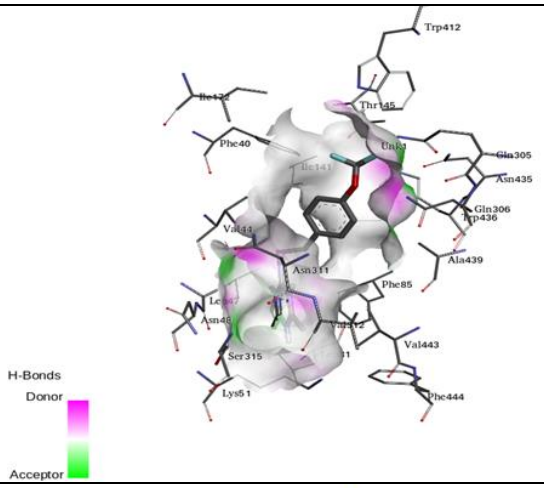
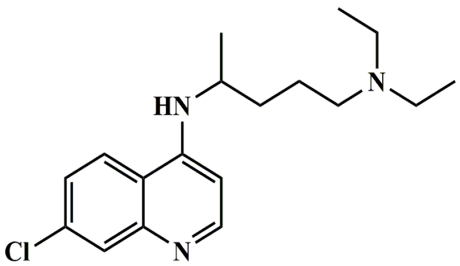
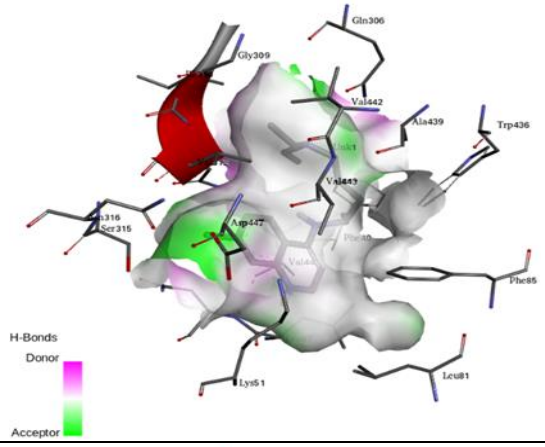
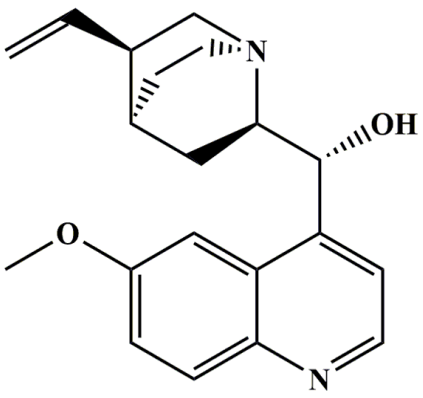


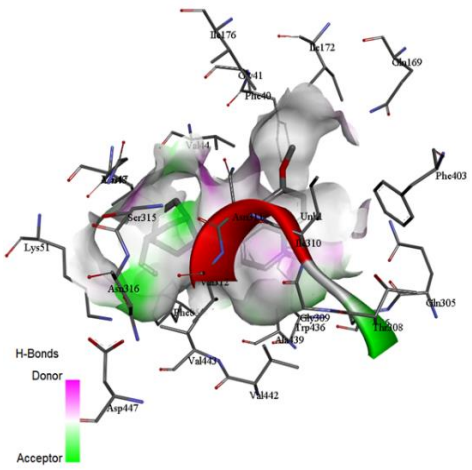


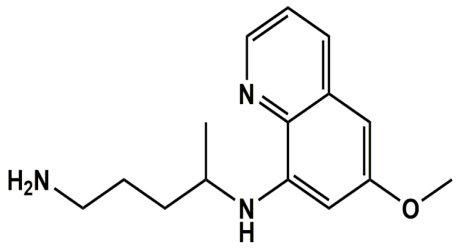
Chloroquine





Quinine





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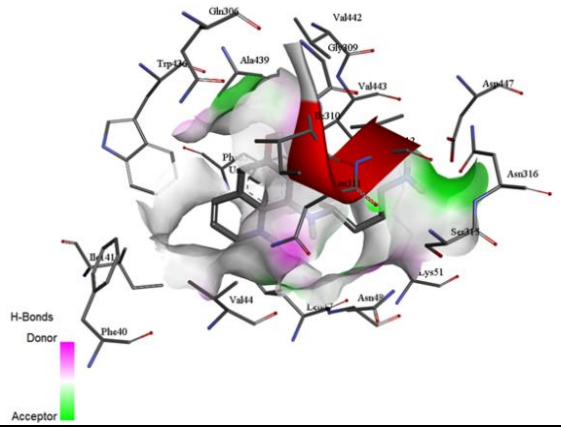
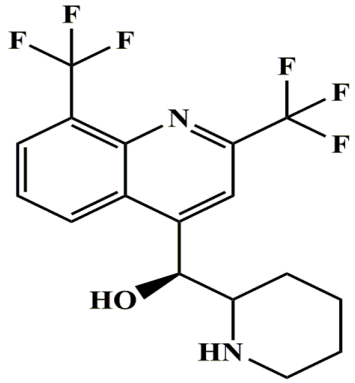
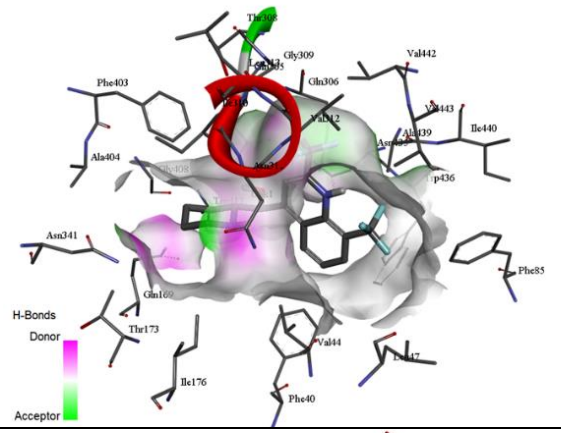
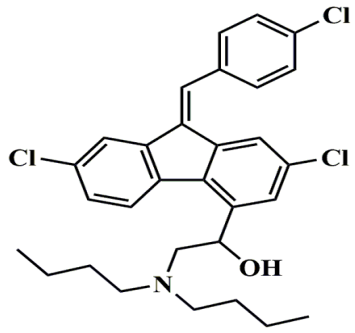


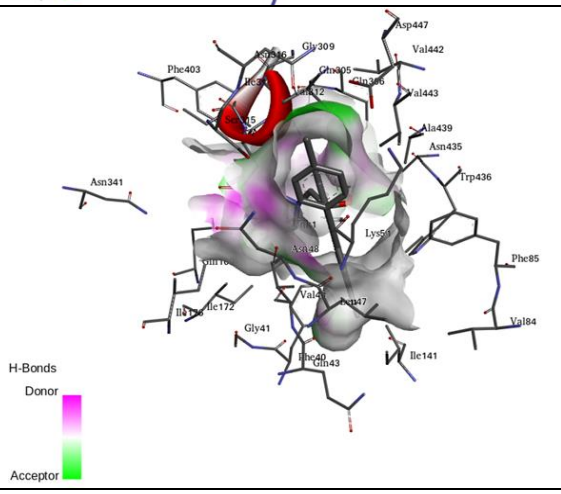


Mefloquine





Lumefantrine



The ligand fits into active sites of protein and due to this higher interaction depend on the binding affinity and hydrogen bonding between amino acids and atoms of ligands. The H-bond induce better drug-likeness property in the molecule due to providing stability in conformation of the complex which was found in 6d and 7d with amino acids **VAL 44, GLN 306**. When the above molecules were docked into the active site of the protein, it was observed that **VAL 44, VAL 443, ALA 439, LEU 47, LYS 51** were the common interacting residues. The binding affinities and interacting residues are depicted in **Table 3**.

Table 3: Binding affinity, interacting residues and H-bond interaction resdues of compounds (1-7) d along with few standards used.

Compound	Binding affinity (Dock score)	Interacting residues
1d	-4.6	LYS 51, LEU 81, PHE 85, LEU 47, VAL 44
2d	-7.1	VAL 44, ALA 439, LEU 47, PHE 85, LYS 51, LEU 81, VAL 443, VAL 312
3d	-7.5	VAL 44, LYS 51, LEU 47, PHE 40, PHE 85, ALA 439, TRP 436, VAL 443, ILE 141, ASN 48
4d	-7.3	VAL 44, ASN 48, LYS 51, LEU 47, PHE 40, PHE 85, ALA 439, TRP 436, ILE 141, VAL 443
5d	-7.0	VAL 44 ALA 439, TRP 436, LEU 47, VAL 443, LYS 51, PHE 85, LEU 81
6d	-7.2	ASN 48, ASN 311, VAL 312, VAL 443, ALA 439, PHE 85, PHE 40, TRP 436, VAL 44, LYS 51
7d	-8.1	VAL 443, VAL 312, LEU 47 , LEU 81, LYS 51, PHE 85, VAL 44, ALA 439, PHE 40, TRP 412, GLN 306, ASN 435
Chloroquine	-7.0	LYS 51, PHE85, VAL443, VAL312, VAL442, LEU47, ILE310
Quinine	-8.1	VAL443, VAL312, LYS51, ASN311, VAL44, GLN306, PHE40, ILE172
Primaquine	-6.4	VAL443, VAL312, VAL44, ILE310, ASN311, ASP447, ASN316
Mefloquine	-9.1	PHE403, VAL442, ALA 439, VAL443, PHE85, TRP436, VAL44, GLN306, ILE310, VAL312, ASN311
Lumefantrine	-8.2	VAL443, VAL312, PHE40, LEU47, ILE141, VAL44, ILE172, ILE310

ADME studies

The pharmacokinetic parameters are summarized in Table 4 and Table 5 and were found to be within the acceptable range.

Table 4: ADME properties of compound (1-4) d calculated by SWISS ADME.

Target molecules	1d	2d	3d	4d
Molecular Formula	$C_4H_4Cl_3N_3$	$C_{12}H_{14}C_{l2}N_4$	$C_{11}H_{12}C_{l2}N_4$	$C_{13}H_{16}C_{l2}N_4O$
Molecular weight	200.45	285.17	271.15	315.2
No. of rotatable bonds	0	4	2	5
H-Bond acceptor	3	3	3	4
H-bond donors	0	1	1	1
SilicosIT Log P	2.31	2.92	2.7	2.94
ESOL Log S	-3.48	-4.62	-4.67	-4.67
Water solubility	Soluble	Moderately soluble	Moderately soluble	Moderately soluble
GI absorption	High	High	High	High
BBB permeant	Yes	Yes	Yes	Yes
P-gp substrate	No	No	No	No
CYP1A2 inhibitor	No	Yes	Yes	Yes
CYP2C19 inhibitor	No	No	No	Yes
CYP2C9 inhibitor	No	No	No	No

CYP2D6 inhibitor	No	Yes	No	Yes
CYP3A4 inhibitor	No	No	No	No
Log Kp (cm/s)	-5.32	-4.91	-4.84	-5.11
Lipinski violations	0	0	0	0
Synthetic Accessibility	1.84	2.02	2.06	2.1
Bioavailability Score	0.55	0.55	0.55	0.55

Table 5: ADME properties of compound (5-7) d calculated by SWISS ADME.

Target molecules	**5d**	**6d**	**7d**
Molecular Formula	$C_{11}H_{12}Cl_2N_4$	$C_{11}H_{11}Cl_2FN_4$	$C_{13}H_{13}Cl_2F_3N_4O$
Molecular weight	271.15	289.14	369.17
No. of rotatable bonds	3	3	6
H-Bond acceptor	3	4	7
H-bond donors	1	1	1
SilicosIT Log P	2.57	2.98	3.52
ESOL Log S	-4.33	-4.48	-5.64
Water solubility	Moderately soluble	Moderately soluble	Moderately soluble
GI absorption	High	High	High
BBB permeant	Yes	Yes	Yes
P-gp substrate	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes
CYP2C19 inhibitor	No	No	Yes
CYP2C9 inhibitor	No	No	No
CYP2D6 inhibitor	No	No	Yes
CYP3A4 inhibitor	No	No	Yes
Log Kp (cm/s)	-5.15	-5.19	-4.58
Lipinski violations	0	0	0
Synthetic Accessibility	1.92	2.03	2.25
Bioavailability Score	0.55	0.55	0.55

CONCLUSION

i. We have virtually analysed Cyanuric Chloride and it's synthesized analogs by subjecting them to molecular docking study with Plasmodium falciparum hexose transport with **PDB ID 6M2L** along with their ADME profiling.

ii. All the analogs exhibited docking results comparable to that of standard drugs Chloroquine, Quinine, and Lumefantrine (Table 3). They surpassed the docking score values of Primaquine and Chloroquine which concluded that the compound dock firmly with the ligand. Highest dock score analog 7d has Dock score **-8.1**(Table 3)

iii. Docking results revealed that virtually designed molecules show good docking values which indicate that some molecules are well docked and reflect the possibilities of antimalarial drug-likeness due to their interactions through hydrogen bonding.

iv. Also, the drug likeness can be supported by ADME properties of molecules which are in acceptable range(Table 4, Table 5) The compounds in this series shows strong potential in early drug discovery.

v. Overall, these compounds provide a blend of good permeability, synthetic tractability, better solubility and also drug like physiochemical properties.

vi. Thus, it can be concluded that the designed molecules are positively interacting with Plasmodium falciparum hexose transporter 1 (PfHT1) and can therefore be considered potential antimalarial drug candidates.; hence can be further processed as potential antimalarial drug candidates.

vii. Results from this study provided a potential lead candidates for future antimalarial drug synthesis with structural modification.

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