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Synthesis of Pyranoquinoline Derivatives and *In-Silico* Anti-Malarial Activity Using Docking Studies

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ABSTRACT

Novel pyrano quinolone derivatives were synthesized by the treatment of *p*-methyl acetanilide upon treatment with DMF and $POCL_3$ at 0^0 C it undergone cyclization reaction which gives 2-chloro-6-methyl quinolone-3-carbaldehyde and further treated the reaction with 4M HCL gives 2-hydroxy-6methyl quinolone-3-carbaldehyde is formed. The above reaction further treated with ethyl aceto acetate and piperidine by using grind stone technique with the elimination of ethanol and water gives 3-acetyl-7-methyl-2H- Pyrano[2,3-b] quinolone-2-one. The above reaction was further treated with 40% KOH and ethanol with different substituted aldehyde to give novel pyrano quinoline derivatives. Compounds which are synthesized are identified by MP and TLC as well as characterized by IR, ^{1}HNMR and MASS spectroscopy. Docking studies were performed for anti-malarial activity using *Plasmodium falciparum* lactate dehydrogenase for a selected compounds shows good binding energy when compared to Chloroquine which is used as standard.

Keywords: Vilsmeier Hacck reagent, pyrano quinolones, docking.

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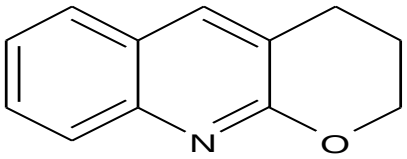
INTRODUCTION

Pyranoquinolines constitute the parent ring structure of the pyranoquinoline alkaloids, which occur in the plant family *Rutaceae*[1,2]. Pyranoquinolines are important class of quinolones in which pyran ring is fused to the b bond of quinolone ring. Pyranoquinoline derivatives are found to be a wide range of spectrum of biological activities. The preparation of pyranoquinolines has received significant attention in previous years because of the broad spectrum of their biological properties[3,4]. These derivatives are one of the important classes of heterocycles. Pyranoquinolines are also reported to possess anti-microbial and anti-leishmanial activity. Some of them are used to treat viral and neoplastic diseases and also used for inducing cytokine biosynthesis in animals. There are number of synthetic procedures are used for preparing pyranoquinoline derivatives.

Pharmacological activities of pyranoquinolines include

- Anti-allergenic activity
- Psychotropic activity
- Anti-inflammatory activity
- Estrogenic activity



Introduction to Docking

Various views of compounds are known by three dimensional structure of a compound. Superimpose of a three dimensional structure of compound on it's possible target site by using complex molecular mechanics program whih is automated is called **DOCKING**[5].

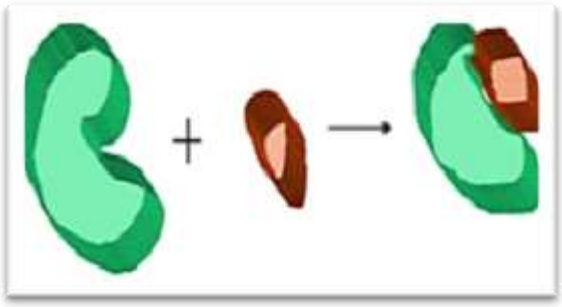


Figure 1: Docking of Ligand and Receptor

Molecular docking is useful for knowing intermolecular interactions between the compound and target site.

Compound which binds to target site is called **ligand**

The place where ligand binds is called **target site**. It is a part of protein structure.

Molecular modeling tells about strength of binding, interaction between ligand& binding site.

Molecular docking includes 2 parts:

- Search algorithm
- Scoring function
- **Search algorithm**: It is useful for knowing optimum no. of configuration of binding site.

Various types of algorithms are

a. Molecular dynamics
b. Monte Carlo method
c. Genetic algorithm
d. Fragment based method
e. Point complimentary method
f. Distance geometry method
g. Systematic searches

- **Scoring function**: It is useful for knowing binding affinity after docking.

Empirical scoring function of Igemdock:

Fitness = vdW + Hbond + Elec

Binding Energy:

ΔG bind = ΔGvdw + ΔGhbond + ΔGelect + ΔGconform + ΔG tor + ΔG sol

Steps involved in molecular docking

- Building of Receptor
- Finding of Active Site
- Preparation of Ligand
- Molecular Docking

Building of Receptor[6]

Receptor's 3D structure was taken and is modified by elimination of water molecules from the pockets of receptor. Charges are stabilized and missing residues are filled. Some other parameters are available are added to it, finally it become stable and biologically active.

Finding of Active Site

Active site for binding of ligand was identified on the receptor. Various no. of active sites are available on receptor but proper site was fixed which is suitable for binding of ligand.

Preparation of Ligand

Ligands were obtained from Chemdraw, Chemsketch etc. In this ligand preparation LIPINSKI'S rule was applied. By using this, we got proper pharmacologically active compounds.

Lipinski's Rule

a. Hydrogen bond donors should be below 5
b. Hydrogen bond acceptors should be below 10
c. Log P value below 5
d. Molecular weight of compound below 500 Da

- **Molecular Docking:** This is the final step of molecular docking. Here ligand was docked on the target site of receptor. Interactions are noted. Search algorithm and scoring function gives the values of interaction[7].
- **Programming of Docking**

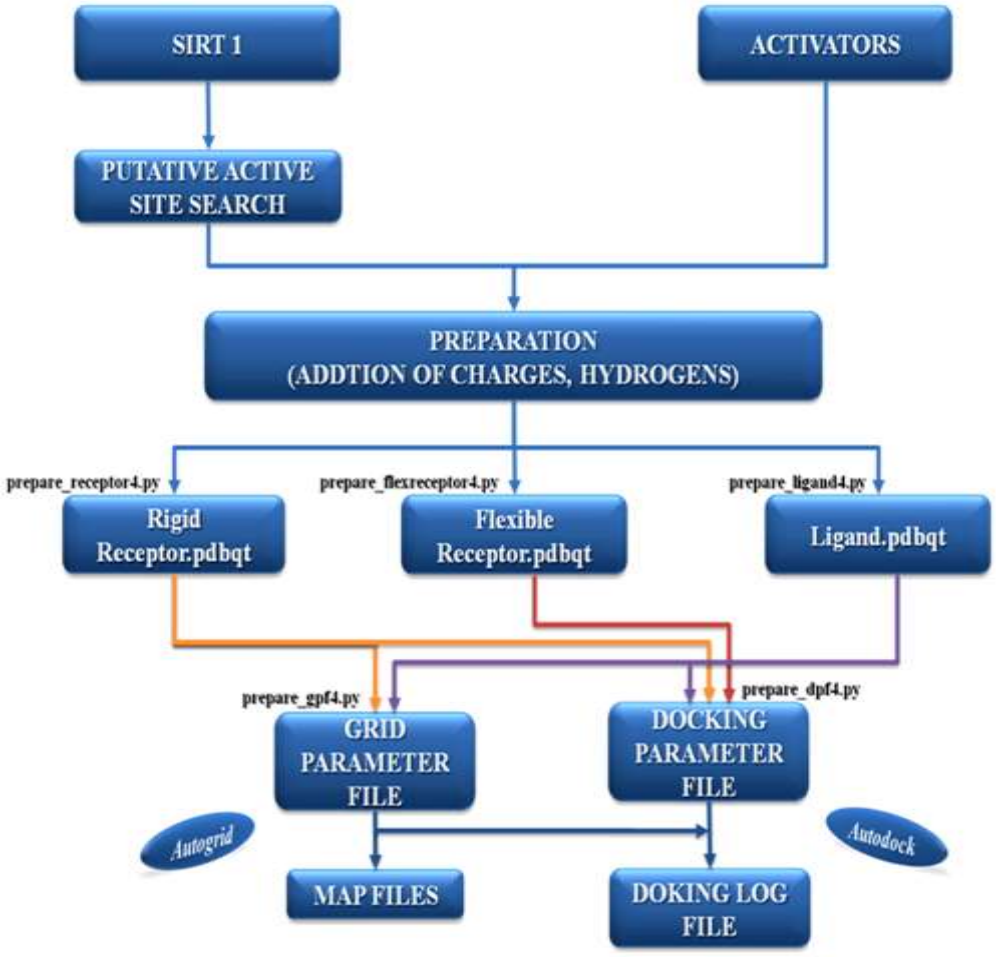


Figure 2: Docking program working flow chart

Software available for Molecular Docking[8]

Table 1: Software available for Molecular Docking

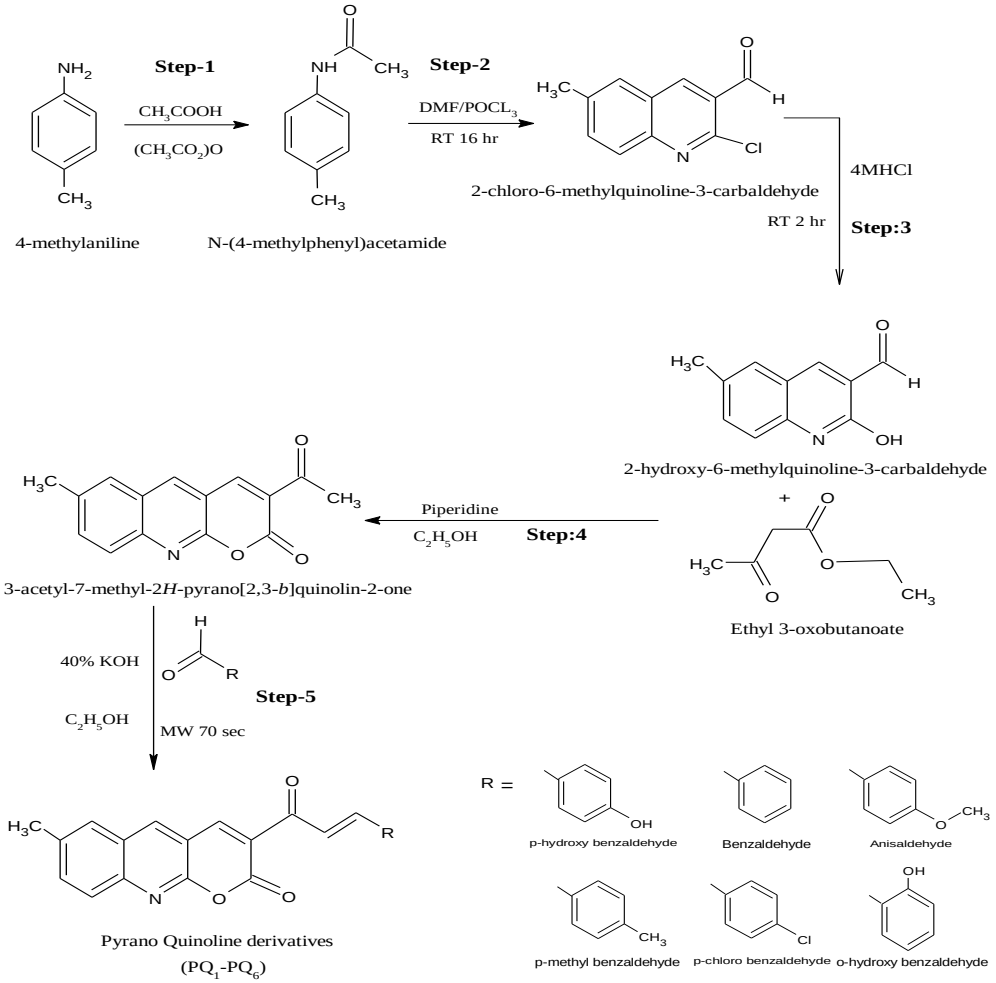
Program	Country of Origin	Year Published
AADS	India	2011
ADAM	Japan	1994
AutoDock	USA	1990
AutoDockVina	USA	2010
BetaDock	South Korea	2011
DARWIN	USA	2000
DIVALI	USA	1995
DOCK	USA	1988
DockVision	Canada	1992
EADock	Switzerland	2007
eHiTS	UK	2006
EUDOC	USA	2001
FDS	UK	2003
FlexE	Germany	2001
FlexX	Germany	1996
FLIPDock	USA	2007
FLOG	USA	1994
FRED	UK	2003
FTDOCK	UK	1997
GEMDOCK	Taiwan	2004
Glide	USA	2004
GOLD	UK	1995
Hammerhead	USA	1996
ICM-Dock	USA	1997
Lead finder	Canada	2008
LigandFit	USA	2003
SOFTDocking	USA	1991
Surflex	USA	2003
SYSDOC	USA	1994
VoteDock	Poland	2011
YUCCA	USA	2005
ProPose	Germany	2004
PSI-DOCK	China	2006
PSO@AUTODOCK	Germany	2007
PythDock	South Korea	2011
Q-Dock	USA	2008
rDock	UK	2013

MATERIALS AND METHOD

All the chemicals used were of analytical grade and purchased from SD Fine. Melting points of all the synthesized compounds were determined by open capillary tube method. The compounds are

identified by TLC and spots was visualized using Uv chamber.

Experimental work



General procedure for synthesis of novel derivatives (1 to 6)

Step 1: Synthesis of 2-chloro-6-methyl quinolone -3-carbaldehyde

DMF (0.125mol, 48.25ml) was cooled to 0^0c then add $pocl_3$ (0.35mol, 161ml) in a drop wise manner with stirring. To this solution add 4-methyl acetanilide (0.05mol 37 g) was added & after 5 min the solution was heated under reflux for 16hrs at 85-90^0C. The reaction mixture was cooled & poured into ice water, filtered, dried & recrystallized from ethyl acetate. Completion of reaction was monitored by using TLC

Step 2: synthesis of 2-hydroxy-6-methyl quinolone-3-carbaldehyde

To a mixture of 2-chloro-6-methyl quinolone-3-carbaldehyde (0.01 mol, 9.5gms) add 4M HCL (35ml) was heated under reflux for 1 hr then allow to cool at room temperature, The mixture was poured into crushed ice filter, dried and recrystallized with acetic acid. Completion of reaction was monitored by using TLC.

Step 3: synthesis of 3-acetyl-7-methyl-2H-pyrano [2, 3 -b] quinolone -2-one

To a mixture of 2-hydroxy-6-methyl quinolone-3-carbaldehyde (0.1 mol, 9.3 gms) add ethyl acetoacetate (0.1 mol, 6.3 ml), few drops of piperidine the mixture was grinded for 5min at room temperature without any solvent reaction was neutralized with 1M HCL and finally product was isolated by filtration. Completion of reaction was monitored by using TLC.

Step 4: synthesis of pyranoquinoline derivatives: (1 to 6)

Above mixture (0.005 mol, 1.26 gms) was dissolved in ethanol (15ml) , add 15ml of 40% KOH then treated with various substituted aldehydes to give corresponding pyranoquinoline derivatives and finally product was filtered and dried. Completion of reaction was monitored by using TLC. Purification of derivatives was done by recrystallization using ethanol.

RESULTS AND DISCUSSION

Selected derivatives were docked by AUTO DOCK 4.2 version for theoretical prediction of antimalarial activity using "Plasmodium falciparum lactate dehydrogenase" as a target site, chloroquine as a standard. Inhibitory activity of the most potent derivatives was explained by hydrogen bonding interactions, dipole-dipole interactions. Provide binding energy to the protein-ligand complex, the significance of a particular hydrogen bond to a particular protein-ligand complex was dependent on the geometry and distance of the bond, partial charges on the donor (or) acceptors. All the selected compounds PQ1, PQ4-6 were found to possess greater antimalarial activity on the target, "Plasmodium falciparum lactate dehydrogenase" due to the more no. of hydrogen bonding interactions.

Table 2: Characteristic analytical data of intermediates

Iupac name	Molecular formula	Molecular weight	Solubility	State	Melting point	% yield	Rf value
2-chloro-6-methylquinoline-3-carbaldehyde	$C_{11}H_8NOCl$	205.5	Chloroform	solid	136	64.8	0.32
2-hydroxy-6-methylquinoline-3-carbaldehyde	$C_{11}H_9NO_2$	187	Chloroform	solid	210	82.8	0.39
3-acetyl-7-metyl-2H-pyrano[2.3-b]quinoline-2-one	$C_{15}H_{11}NO_3$	252	Chloroform	solid	180	75.2	0.23

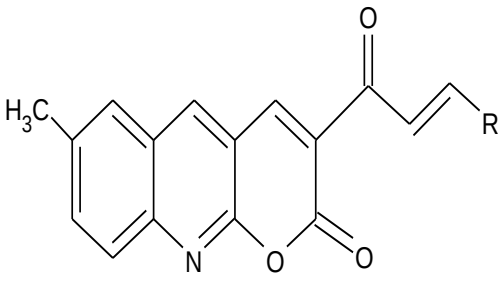
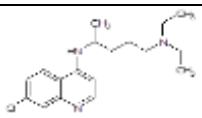
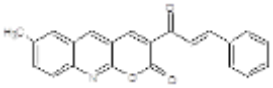
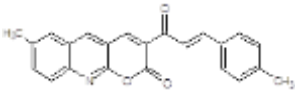
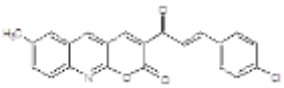
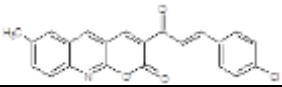


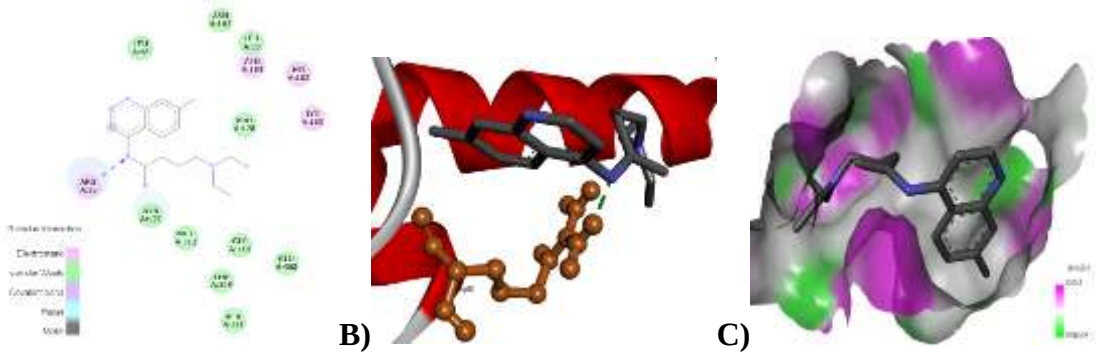
Table 3: Characteristic analytical data of pyranoquinoline derivatives

S. No	Compound Code	M.P. ^{0}C	%Yield	Mol. Form.	M. Wt.	Calculated %		
						C	H	N
1	PQ1	156	64.70	$C_{22}H_{15}NO_3$	341.35	77.41	4.43	4.10
2	PQ2	171	59.45	$C_{23}H_{17}NO_4$	371.38	74.38	4.61	3.77
3	PQ3	163	67.41	$C_{22}H_{15}NO_4$	357.35	73.94	4.23	3.92
4	PQ4	187	62.14	$C_{23}H_{17}NO_3$	355.38	77.73	4.82	3.94
5	PQ5	175	67.41	$C_{22}H_{14}ClNO_3$	375.8	70.31	3.75	3.73
6	PQ6	164	61.79	$C_{22}H_{15}NO_4$	357.35	73.94	4.23	3.92

Table 4: Docking studies

S. No.	Drug target	Compound Name	Compound Structure	Binding Energy in Kcal/mol
1	Plasmodium falciparum Lactate dehydrogenase	Chloroquine		-6.14
2		PQ-1		-8.54
3		PQ-4		-8.77
4		PQ-5		-8.88
5		PQ-6		-8.82

Chloroquine compound docking interactions with plasmodium falciparum Lactate dehydrogenase for anti-malarial activity



(A) **B)** **C)**

Figure 3: Docking interactions of Chloroquine

PQ-1 compound docking interactions with plasmodium falciparum Lactate dehydrogenase for anti-malarial activity

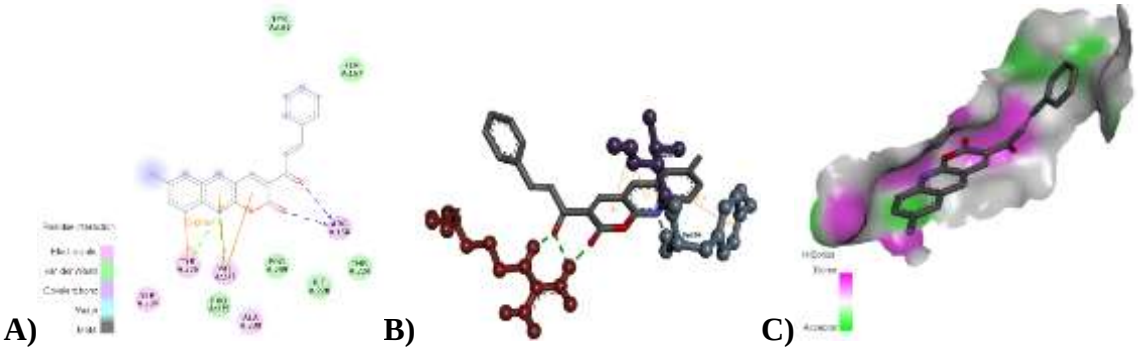


Figure 4: Docking interactions of PQ-1

PQ4 compound docking interactions with plasmodium falciparum Lactate dehydrogenase for anti-malarial activity

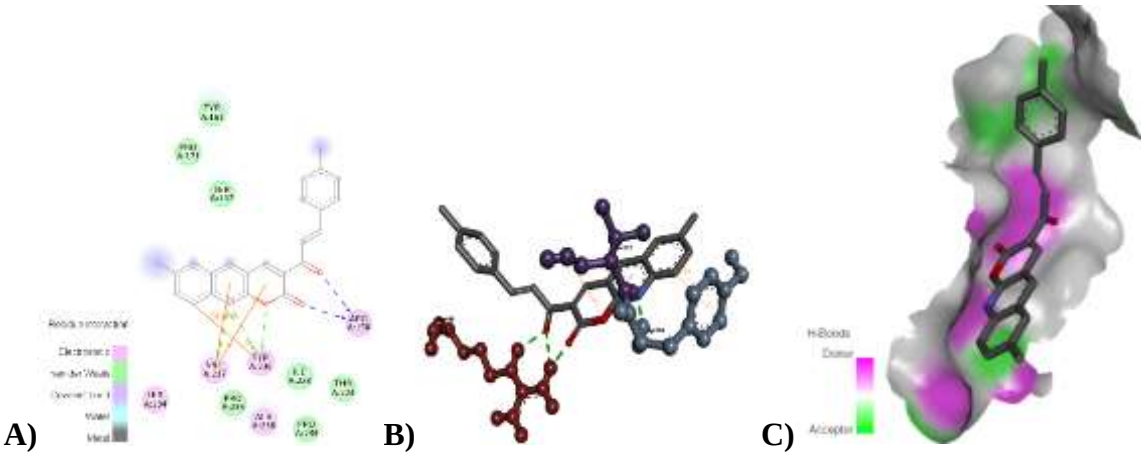


Figure 5:Docking interactions of PQ-4

PQ-5 compound docking interactions with plasmodium falciparum Lactate dehydrogenase for anti-malarial activity

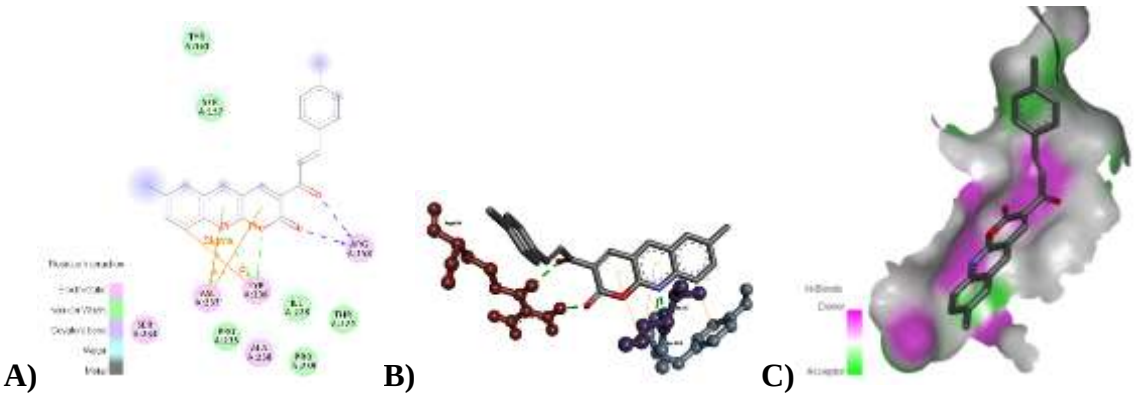


Figure 6: Docking interactions of PQ-5

PQ-6 compound docking interactions with plasmodium falciparum Lactate dehydrogenase for anti-malarial activity

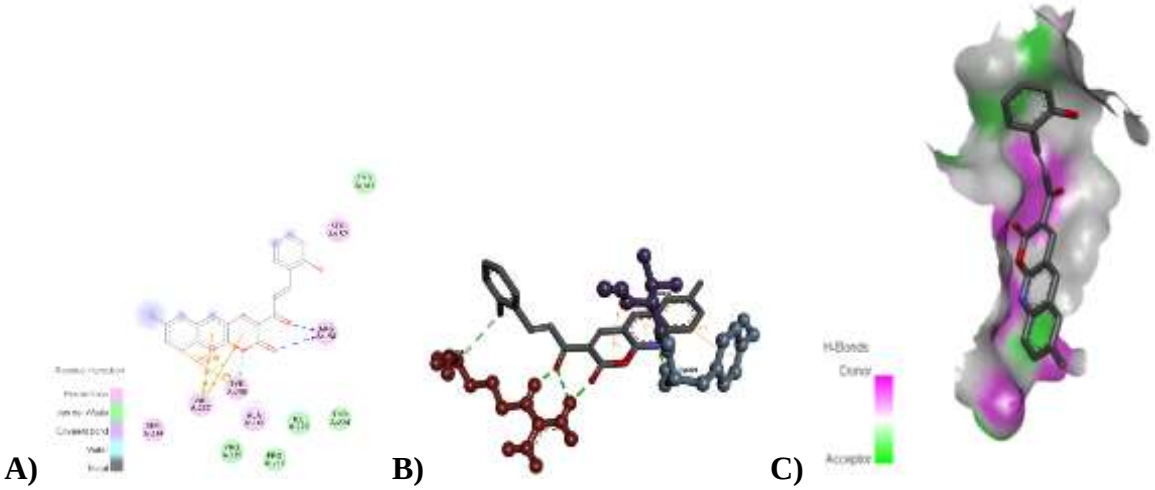


Figure 7: Docking interactions of PQ-6

A) represents 2D interactions of PQ-6, **B)** represents 3D H-bond interaction formed by the PQ-6, whereas **C)** represents Surface area interactions of PQ-6.

CONCLUSION

The docking study of the selected four derivatives (PQ1, PQ4, PQ5, and PQ6) revealed that they were highly potent when compared to chloroquine for antimalarial activity theoretically. The quinoline moiety itself possesses various activities. Various pharmacophore groups on pyranoquinoline moiety may results more potent activities than existing ones. Further research need to be carried out to know the relationship between biological activities and pharmacophore groups.

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