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MOLECULAR DOCKING STUDIES OF SOME NOVEL HYBRID TETRAOXAQUINES & DISPIROTETRAOXANES AS ANTIMALARIAL AGENTS

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Key words:

Molecular Docking Studies, dispirotetraoxanes, hybrid tetraoxaquines, falcipain-3 protein, Antimalarial Agents

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ABSTRACT: In the present study, total fifteen compounds of 1,2,4,5-tetraoxane derivatives were docked. Two series of 1,2,4,5-tetraoxane derivatives were taken for molecular docking studies, one tetraoxaquines, a hybrid of two pharmacophores such as 4-aminoquinoline & 1,2,4,5-tetraoxane, and other dispirotetraoxanes. The docking studies were performed into the binding pocket of a falcipain-3 protein (pdb: 3bwk – hydrolase) by using the Ligand fit module within docking server. The results showed a better binding affinity of hybrid tetraoxaquines compared to dispirotetraoxanes at the active site of falcipain-3 because of very low binding energies for falcipain-3 protein (pdb: 3bwk – hydrolase). Therefore, hybrid tetraoxaquines are better Cysteine proteases (falcipains) inhibitors. They would be potent antimalarial agents. So the proposed inhibitors in the future could be more effective to treat malaria.

INTRODUCTION: Malaria is a life-threatening parasitic disease transmitted by mosquitoes. Malaria is caused by four parasite species of the genus Plasmodium within the phylum *Apicomplexa,* class *Sporozoa* and Suborder *haemosporina; P. vivax, P. malariae, P. ovale and P. falciparum,* the most deadly of these being *P. falciparum* [1, 2]. Today, approximately 40% of the world's population, mostly those living in the world's poorest countries, is at risk of malaria. In India, over the past two decades, malaria incidence has been fluctuating between 2 to 3 million cases per year.

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India contributes 40% of all cases outside Africa. The prevention of malaria is complicated by the spread of the antimalarial drug resistant strains of the plasmodium species [3, 4].

The severity of the disease caused by *P. falciparum* results primarily from its ability to modify the surface of infected red blood cells by inserting parasite proteins. The enzymes in parasite digestive vacuole (cysteine and aspartic proteinases) break down hemoglobin into amino-acids and heme. While all amino-acid contents is used for building parasite proteins, only a small portion of heme is incorporated into parasite hemoproteins; the rest of heme is detoxified (polymerized) caused by parasite enzymes. A number of drugs have been investigated for their efficacy in the treatment of malaria; however, the appearance of resistant strains of *P. falciparum* to some of those drugs has made necessary further investigation of new classes of compounds which might have effective action

against them. Also, computational (molecular docking) and quantitative structure-activity relationship (QSAR) studies of any of those drugs have been done aiming to unravel its mechanisms of action and guidelines for the syntheses of new derivatives with improved efficiency [5].

The molecular docking simulation process allows for faster and cheaper identification of promising subsequently, *in vitro* test can be performed to further evaluate the screening is founded on the principle that computationally obtaining the three-dimensional structure of protein and ligand complexes is feasible. With regard to biologically inspired logarithms (BIAs), molecular docking simulation is a computational problem that may benefit from such methodologies. In molecular docking simulations, the main goal is to find the fittest solution (pose) using a fitness function (scoring function). The many docking programs currently in use are DOCK, AUTODOCK, GOLD, FLEXX, ZDOCKMCDOCK, GLIDE, GEMDOCK and MOLDOCK etc [6,7].

Cysteine proteases (falcipains), a papain-family of enzymes of *Plasmodium falciparum*, are responsible for haemoglobin degradation and thus necessary for its survival during asexual life cycle phase inside the human red blood cells while remaining non-functional for the human body. The falcipains (FP) comprised four peptidases- FP-1, FP-2, FP-2' and FP-3. FP-1 was reported as not essential to the erythrocytic stage of *P. falciparum*. FP-2 and FP-2' are ~96% identical; share ~68% identity with FP-3. The ratio of concentration of falcipain-II is 1.8 times higher than falcipain-III concentration in trophozoites stage. The cleaving capacity of falcipain-III is nearly twice as falcipain-II for haemoglobin. Therefore, FP-2 & FP-3 are proteins may be ideal targets for antimalarial therapy using new approaches in rational drug design.

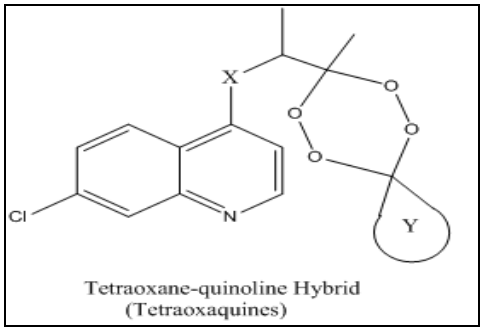
The objective of the present work was to design novel antimalarial derivatives by generating key interaction site and receptor based pharmacophore for 1,2,4,5-tetraoxane in order to generate its derivatives leading to better inhibitors for deadly disease malaria.

MATERIALS AND METHODS:

Chemistry:

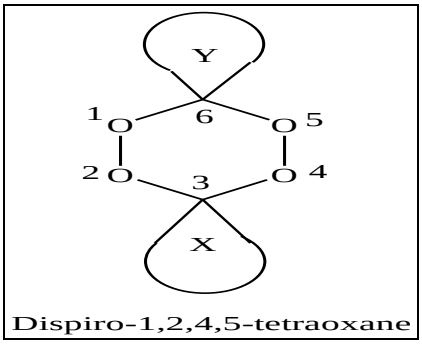
Design of ligands:

Series-A



Tetraoxane-quinoline Hybrid
(Tetraoxaquines)

Series-B



Dispiro-1,2,4,5-tetraoxane

TABLE 1: LIST OF THE DESIGNED COMPOUNDS

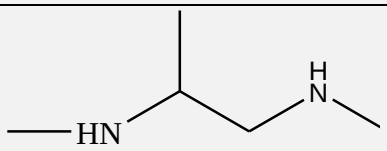
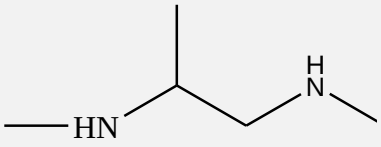
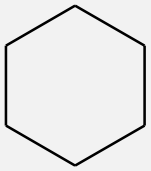
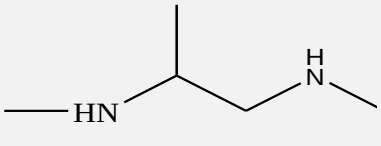
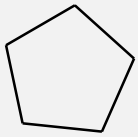
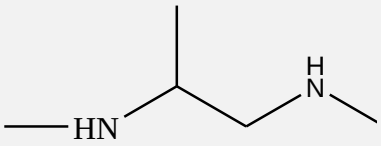
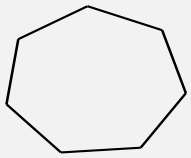
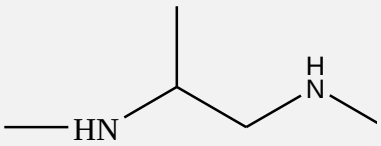
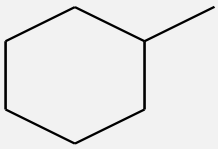
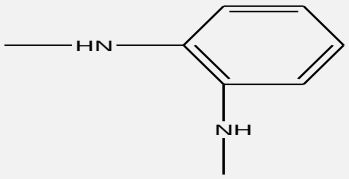
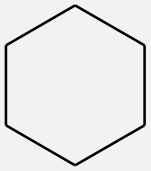
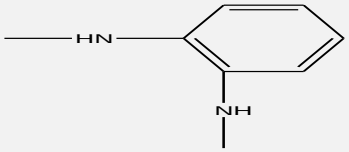
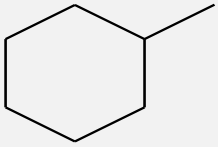
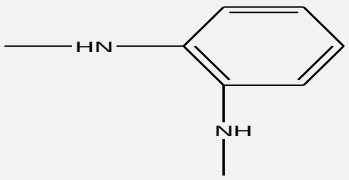
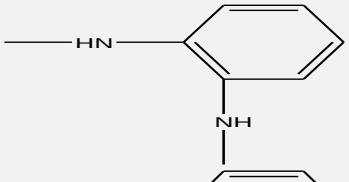
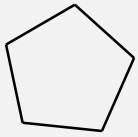
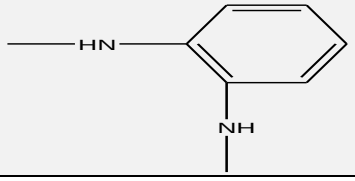
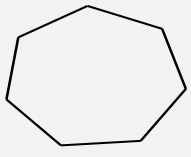
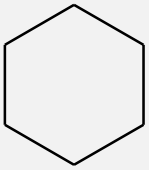
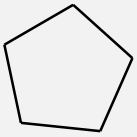
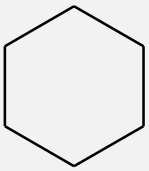
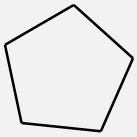
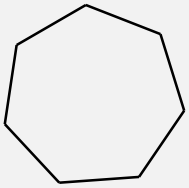
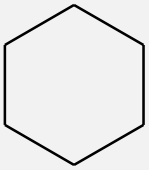
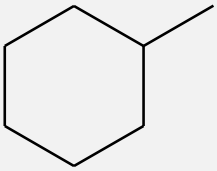
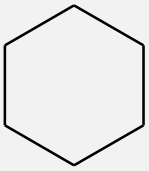
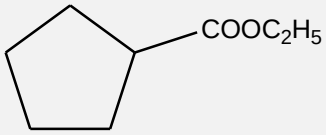
S.No.	Comp. Code	Name of Compound / Ligand	X	Y
1.	A1	N2-(7-chloroquinolin-4-yl)-N1-(1-(3,6,6-trimethyl-1,2,4,5-tetraoxan-3-yl)ethyl)propane-1,2-diamine		R_1= -CH_3 R_2 = -CH_3
2.	A2	N2-(7-chloroquinolin-4-yl)-N1-(1-(3-methyl-1,2,4,5-tetraoxaspiro[5.5]undecan-3-yl)ethyl)propane-1,2-diamine		
3.	A3	N2-(7-chloroquinolin-4-yl)-N1-(1-(8-methyl-6,7,9,10-tetraoxaspiro[4.5]decan-8-yl)ethyl)propane-1,2-diamine		
4.	A4	N2-(7-chloroquinolin-4-yl)-N1-(1-(3-methyl-1,2,4,5-tetraoxaspiro[5.6]dodecan-3-yl)ethyl)propane-1,2-diamine		
5.	A5	N2-(7-chloroquinolin-4-yl)-N1-(1-(3,7-dimethyl-1,2,4,5-tetraoxaspiro[5.5]undecan-3-yl)ethyl)propane-1,2-diamine		
6.	A6	N1-(7-chloroquinolin-4-yl)-N2-(1-(3-methyl-1,2,4,5-tetraoxaspiro[5.5]undecan-3-yl)ethyl)benzene-1,2-diamine		
7.	A7	N1-(7-chloroquinolin-4-yl)-N2-(1-(3,7-dimethyl-1,2,4,5-tetraoxaspiro[5.5]undecan-3-yl)ethyl)benzene-1,2-diamine		
8.	A8	N1-(7-chloroquinolin-4-yl)-N2-(1-(3,6,6-trimethyl-1,2,4,5-tetraoxan-3-yl)ethyl)benzene-1,2-diamine		R_1= -CH_3 R_2 = -CH_3
9.	A9	N1-(7-chloroquinolin-4-yl)-N2-(1-(8-methyl-6,7,9,10-tetraoxaspiro[4.5]decan-8-yl)ethyl)benzene-1,2-diamine		
10.	A10	N1-(7-chloroquinolin-4-yl)-N2-(1-(3-methyl-1,2,4,5-tetraoxaspiro[5.6]dodecan-3-yl)ethyl)benzene-1,2-diamine		

TABLE 2: LIST OF THE DESIGNED COMPOUNDS

S. No.	Comp. Code	Name of Compound / Ligand	X	Y
1.	B1	6,7,14,15-tetraoxa-dispiro[4.2.5.2]pentadecane		
2.	B2	7,8,16,17-tetraoxa-dispiro[5.2.6.2]heptadecane		
3.	B3	6,7,15,16-tetraoxa-dispiro[4.2.6.2]hexadecane		
4.	B4	1-methyl-7,8,15,16-tetraoxadispiro[5.2.5.2]hexadecane		
5.	B5	ethyl-6,7,14,15-tetraoxadispiro[4.2.5.2]pentadecane-1-carboxylate		

Molecular Docking Studies:

The 3D X-ray crystal structure of falcipain-3 protein (pdb: *3bwk* – hydrolase) was used as the starting model for this study [8, 9]. The protein was prepared, docked and the molecular dynamics simulation carried out. All computational analysis was carried out using docking server (www.dockingserver.com).

(i) Preparation of Protein:

Protein structures were uploaded from a file or download them from the Protein Data Bank using docking server by providing the entry code or by text search. The protein chain, heteroatom and ligands were selected present in the protein *pdb* file that important in docking calculation in the process of protein setup. Known binding sites selected through a co-crystallized ligand. Then the center of mass of the box center was selected. These coordinates of the box center were selected. Amino acid residues were selected that define the binding site. Molecular docking server calculated necessary map files for each atom type and prepares the input files for docking calculations.

(ii) Preparation of Ligand: The ligand drawn using Java applet and uploaded it. The chemical structure drawn by Marvin Sketch. A ligand uploaded in MDL MOL, PDB, or SMILES format. Various parameters were set up during the simulation such as described pH, structure optimization and partial charge calculation using molecular mechanics or semi empirical quantum chemical methods. Rotable bonds and atoms were set up automatically or modify manually. Downloaded the attached file formats including mol, pdb, mol2, and pdbqt. The ligand organized into self-defines folder. This way the ligands saved for later docking calculation.

(iii) Setup ligand protein docking calculations: A protein and a ligand selected from the library. The advanced parameters modified during the

simulation, such as number of runs, number of evaluations etc.

(iv) Computational Methods: Docking calculations were carried out using Docking Server [10]. The MMFF94 force field[11] was used for energy minimization of ligand molecule using Docking Server. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. Docking calculations were carried out on falcipain-3 (pdb: *3bwk* – hydrolase) protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools [12]. Affinity (grid) maps of 20×20×20 Å grid points and 0.375 Å spacing were generated using the Autogrid program[13]. AutoDock parameter set and distance dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method[14]. Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250000 energy evaluations [15]. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

RESULTS AND DISCUSSION:

1,2,4,5-tetraoxanes were proved to inhibit the growth of the malaria parasite via inhibition of falcipains, which considered as a critical step in the survival of the parasite. Hence, it was worthwhile to perform the docking study of targeted 1,2,4,5-tetraoxane derivatives developed in the present study with the falcipain-3 binding pocket residues. The present study was carried out to explain the inhibitory activity of 1,2,4,5-tetraoxanes on the basis of molecular interactions established with falcipain-3. The molecular docking server was used to perform docking experiments, where top ranking posses of ligand selected according to their scoring functions. The docked complexes of ligands were visually and analyzed for hydrophobic interactions, which leads to the stability of ligands in the active site for effective inhibition.

The docking studies of the target compounds were performed into the binding pocket of an falcipain-3 (pdb: *3bwk* – hydrolase). The docking results and docked conformations of the ligands in the active site were illustrated in **Table3** and **Fig. 1 &2, Fig. 3 & 4, Fig. 5 & 6, Fig. 7 & 8.**

These results showed that the targeted molecules were snugly fitted into the active pose with considerable and diverse binding affinities towards the falcipain-3 (pdb: *3bwk* – hydrolase) along with the formation of numerous hydrophobic, hydrogen, halogen, polar and other interactions.

The hybrid tetraoxaquines found to have hydrophobic interactions with CYS51, HIS183, ALA184, TRP215, TYR93, ALA180, PRO181, ALA61, ALA166, TRP52 and ALA161 of S1, S1' and S2 site of the binding pocket. Particularly, compound A10, engages ALA161, ALA166, TRP215 via hydrophobic interaction (**Fig. 1 & Fig. 2**) with lowest binding energy -9.46 Kcal/mol & K_i 116.72 µM. In the case of A5, hydrophobic interactions (**Fig. 3 & Fig. 4**) CYS51, ALA61, ALA166, TRP215, TRP215 of S1, S1' and S2 site of the binding pocket increased but binding energy also increased as -6.11 Kcal/mol with K_i 33.28 µM.

Dispirotetraoxanes found to have hydrophobic interactions with CYS51, TYR93, ILE94, TRP52, PRO181 and ALA184 of S1, S1' and S2 site of the binding pocket. Compound B4, engages CYS51,TRP52, TYR93, ILE94 & ALA184 via hydrophobic interaction (**Fig. 5 & Fig. 6**) with lowest binding energy in the series -6.68 Kcal/mol & K_i 12.62 µM. In the case of B5, hydrophobic interactions (**Fig. 7 & Fig. 8**) found to be very minimum only with ILE94 of S2 site of the binding pocket and binding energy highest among the series as -5.62 Kcal/mol with K_i 75.62 µM. As depicted from **Table 3**, these ligands effectively engages vital catalytic residues and deeply buried in the S1', S1, S2 and S3 pocket of the active site via formation of numerous interactions.

The results disclosed that hybrid tetraoxaquines (binding energies -9.46 to -6.11 Kcal/mol) compared dispirotetraoxanes (binding energies -6.68 to -5.62 Kcal/mol) will exhibit high antimalarial activity because of very low binding

energies for falcipain-3 protein (3bwk.pdb). Among all 15 ligands, all tetraoxaquines except A5 and two dispirotetraoxanes as B2, B4, showed very good interaction to protein with minimum binding energies. These results corroborate the idea that the creation of hydrophobic interactions is the main predictor for the activity of the ligands. Finally, the native ligands were allowed to dock into the active site of falcipain-3 protein (3bwk.pdb) for the validation of the docking protocol.

TABLE 3: DOCKING INTERACTION AND SCORING OF COMPOUNDS IN FALCIPAIN-3 (PDB: 3BWK) BINDING SITE[#]

S. N.	Comp Code	Hydro-phobic	Hydrogen bonds	Halogen bond	Polar	Pi-Pi	Other	Est. Free Energy of Binding (kcal/mol)	Est. Inhibition Constant Ki (µM)	vdW+ Hbond+desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Total Intermol. Energy (kcal/mol)	Inter-action Surface
1	A1	None	TYR90, TYR93	GLY92	none	TYR93	TYR93	-6.51	16.81	-5.65	-1.02	-6.67	672.616
2	A2	CYS51, HIS183, ALA184, TRP215	ASN182, CYS51	GLU243	GLN45, HIS183	none	GLN45, CYS51, ASN182, TRP215	-7.69	2.30	-8.91	-0.92	-9.83	824.224
3	A3	HIS183, ALA184, CYS51, TRP215	ASN182, CYS51, ASN182	GLU243	ASN182	none	ILE94, GLN45, ASN182, HIS183	-6.99	7.50	-8.09	-1.08	-9.17	758.604
4	A4	TYR93, ALA180, PRO181, ALA184	PRO181	ASN182	GLU243	none	TYR93, SER158, PRO181, ASN182, GLU243	-7.39	3.80	-7.49	-0.89	-8.38	694.581
5	A5	CYS51, ALA61, ALA166, TRP215, TRP215	none	LEU47	TRP215	TYR90	GLN45, TYR90, ASN182, TRP215	-6.11	33.28	-7.58	-0.67	-8.24	755.809
6	A6	None	ASN182	SER162	none	none	ALA161, ASN182, TRP215	-8.86	323.00	-8.45	+0.02	-8.42	789.636
7	A7	CYS51, ALA161, TRP215	GLY92, ASN182	GLU243	ASN182	TRP52	GLN45, CYS51, ASN182, HIS183	-9.11	209.41	-9.24	-0.03	-9.28	807.97
8	A8	HIS183, TRP215	none	ALA46	ASN182	none	GLN45, LEU47, ASN182, TRP215	-6.94	8.14	-6.59	-0.01	-6.59	629.604
9	A9	CYS51, TRP52, PRO181	PRO181	none	none	none	CYS51, TYR93, SER158, ASN182, GLU243	-9.09	218.33	-8.15	-0.04	-8.18	691.518
10	A10	ALA161, ALA166, TRP215	none	ALA166	GLN45, ASN182, TRP215	TRP215	GLN45, ALA166, ASN182, HIS183, TRP215	-9.46	116.72	-8.55	+0.03	-8.51	737.96
11	B1	TRP52, ILE94, PRO181, ALA184	none	none	GLU243	none	TYR93, SER158, PRO181, GLU243	-6.27	25.49	-6.28	+0.01	-6.27	472.071
12	B2	CYS51, TRP52, TYR93	none	none	GLU243	none	TYR93, SER158, PRO181,	-6.62	14.02	-6.64	+0.02	-6.62	510.494

		ILE94, ALA184					GLU243						
13	B3	CYS51, TRP52, TYR93, ILE94, ALA184	none	none	GLU 243	none	TYR93, SER158, PRO181, GLU243	-6.45	18.62	-6.48	+0.02	-6.45	492.619
14	B4	CYS51,TRP52, TYR93, ILE94, ALA184	none	none	none	none	TYR93, SER158,PRO181, GLU243	-6.68	12.62	-6.66	-0.02	-6.68	510.034
15	B5	ILE94	none	none	none	none	CYS51, SER158, GLU243	-5.62	75.62	-6.49	+0.01	-6.47	588.745

Where # is
Binding Site: S1, S1', S2, S3 pockets
S1 subsite: CYS51, CYS 84, ALA61, ALA166, TYR 83,
S1' subsite: ALA 156, ALA161, ALA180, ALA184, TYR161, TYR93
S2 subsite: PRO174, PRO181, ASN 175, GLU 236, LEU 86, ILE 87
S3 subsite: ASN 81, LYS 80

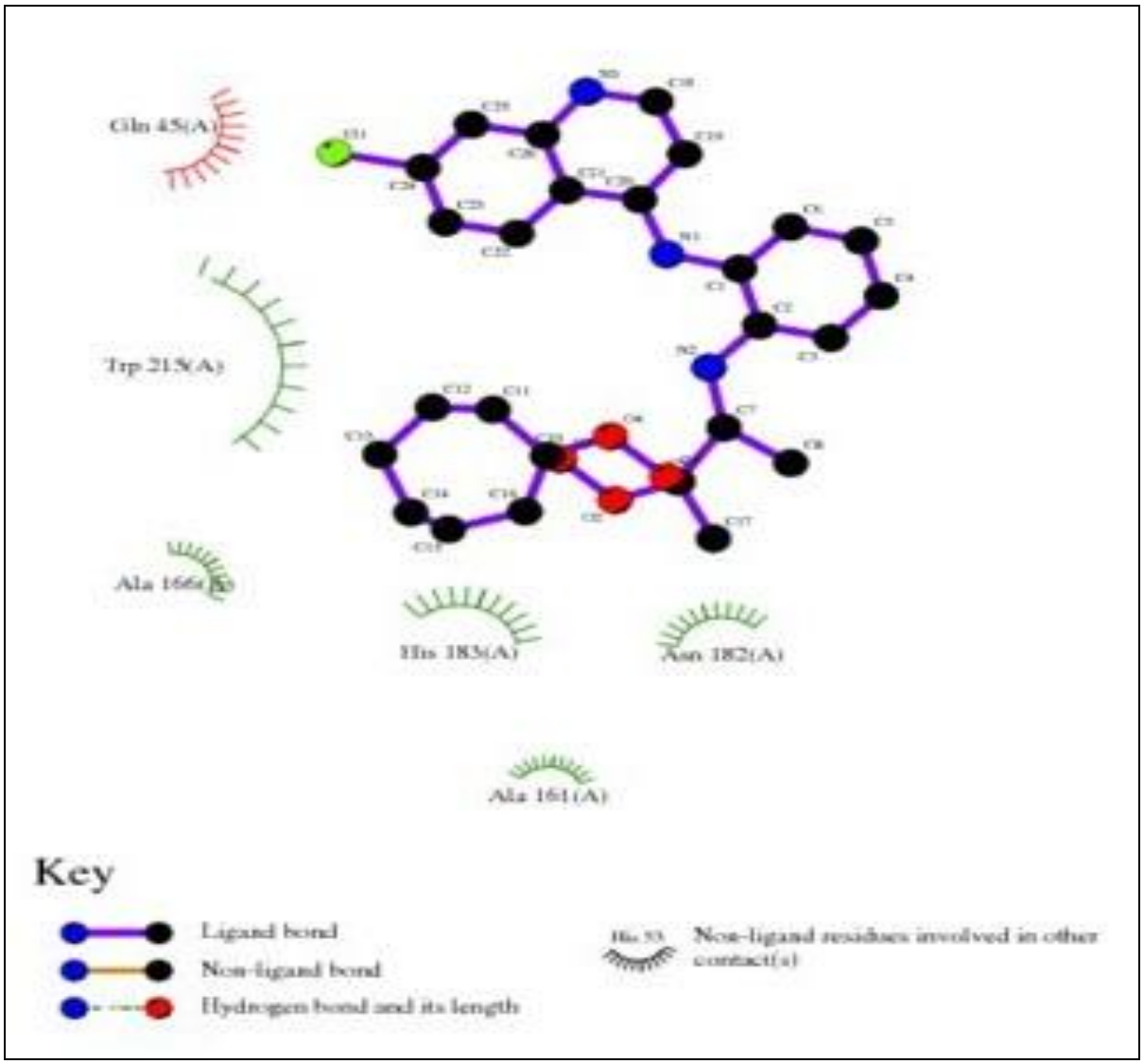


FIG. 1: DOCKED COMPLEX OF COMPOUND A10 IN THE BINDING POCKET OF FALCIPAIN-3 PROTEIN (PDB: *3BWK* – HYDROLASE) IN 2D.

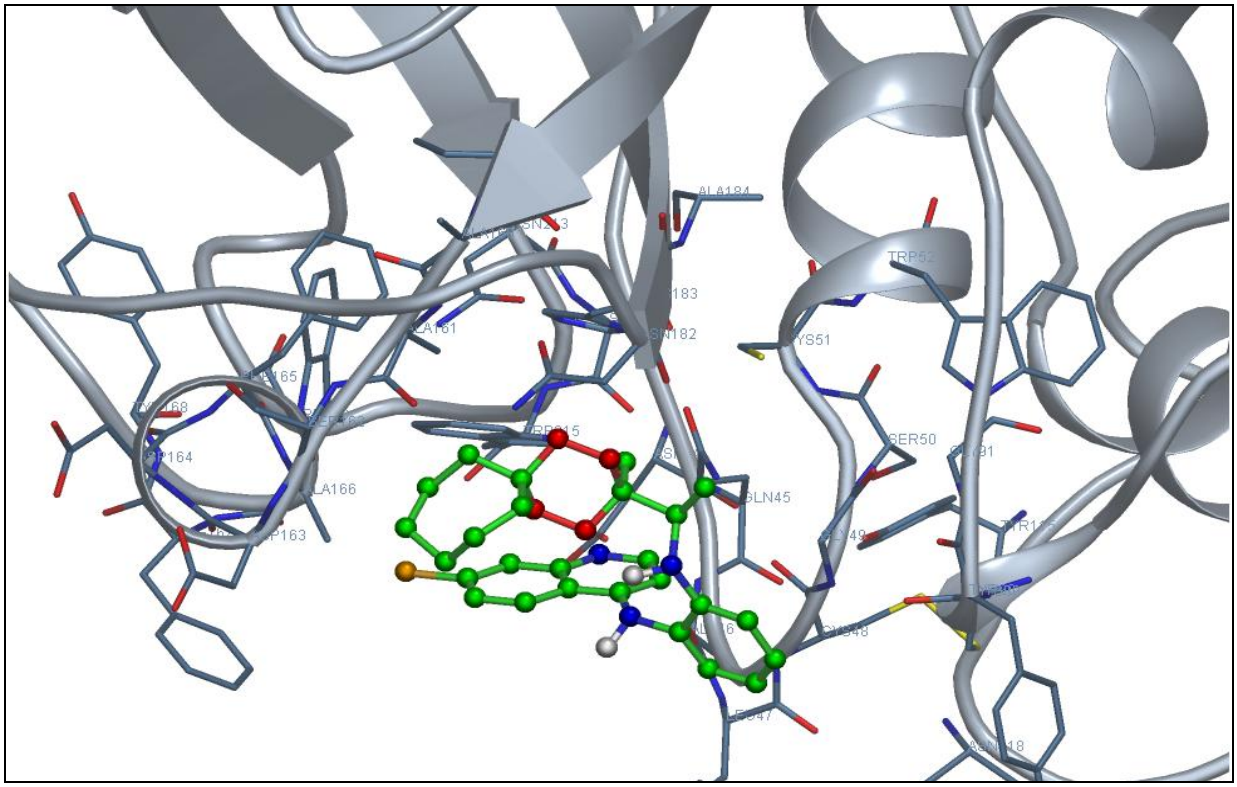


FIG. 2: DOCKED COMPLEX OF COMPOUND A10 IN THE BINDING POCKET OF FALCIPAIN-3 PROTEIN (PDB: *3BWK* – HYDROLASE) IN 3D

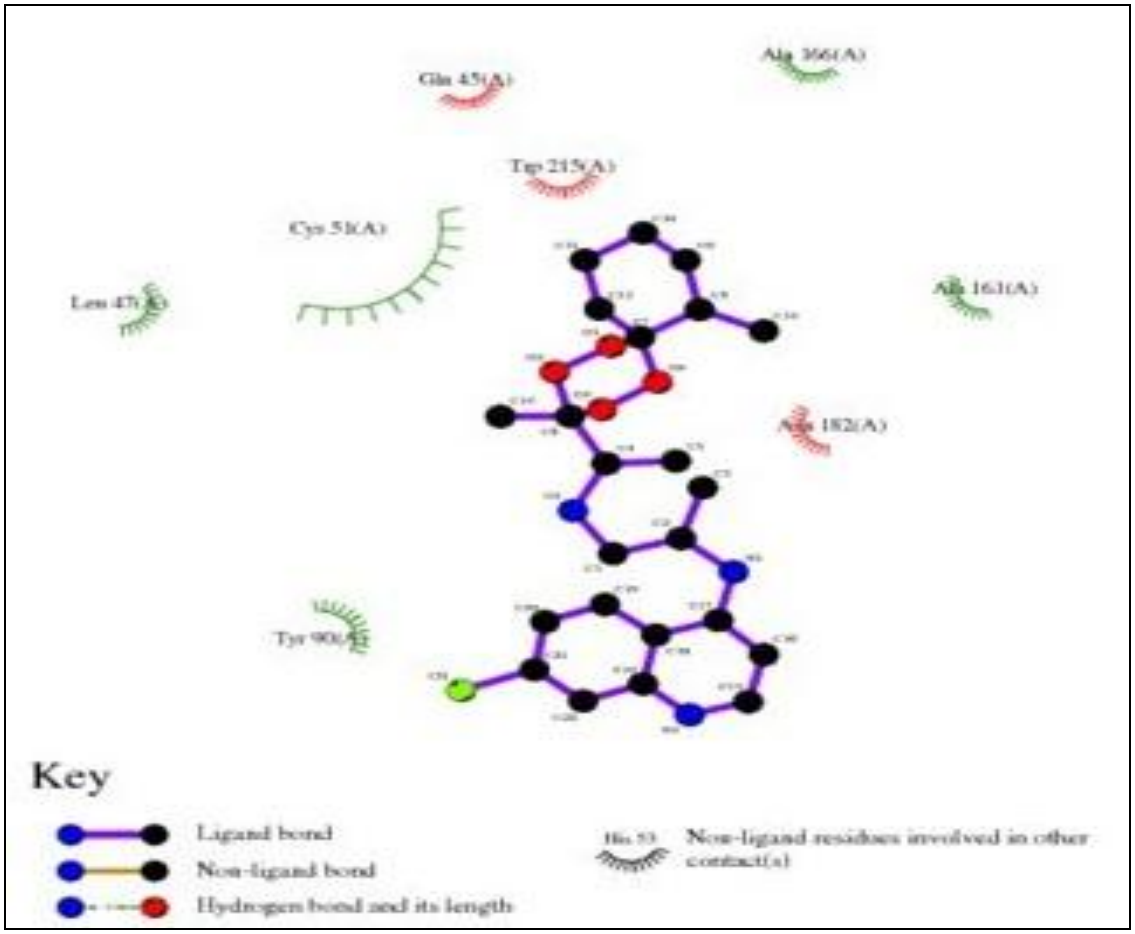


FIG. 3: DOCKED COMPLEX OF COMPOUND A5 IN THE BINDING POCKET OF FALCIPAIN-3 PROTEIN (PDB: *3BWK* – HYDROLASE) IN 2D

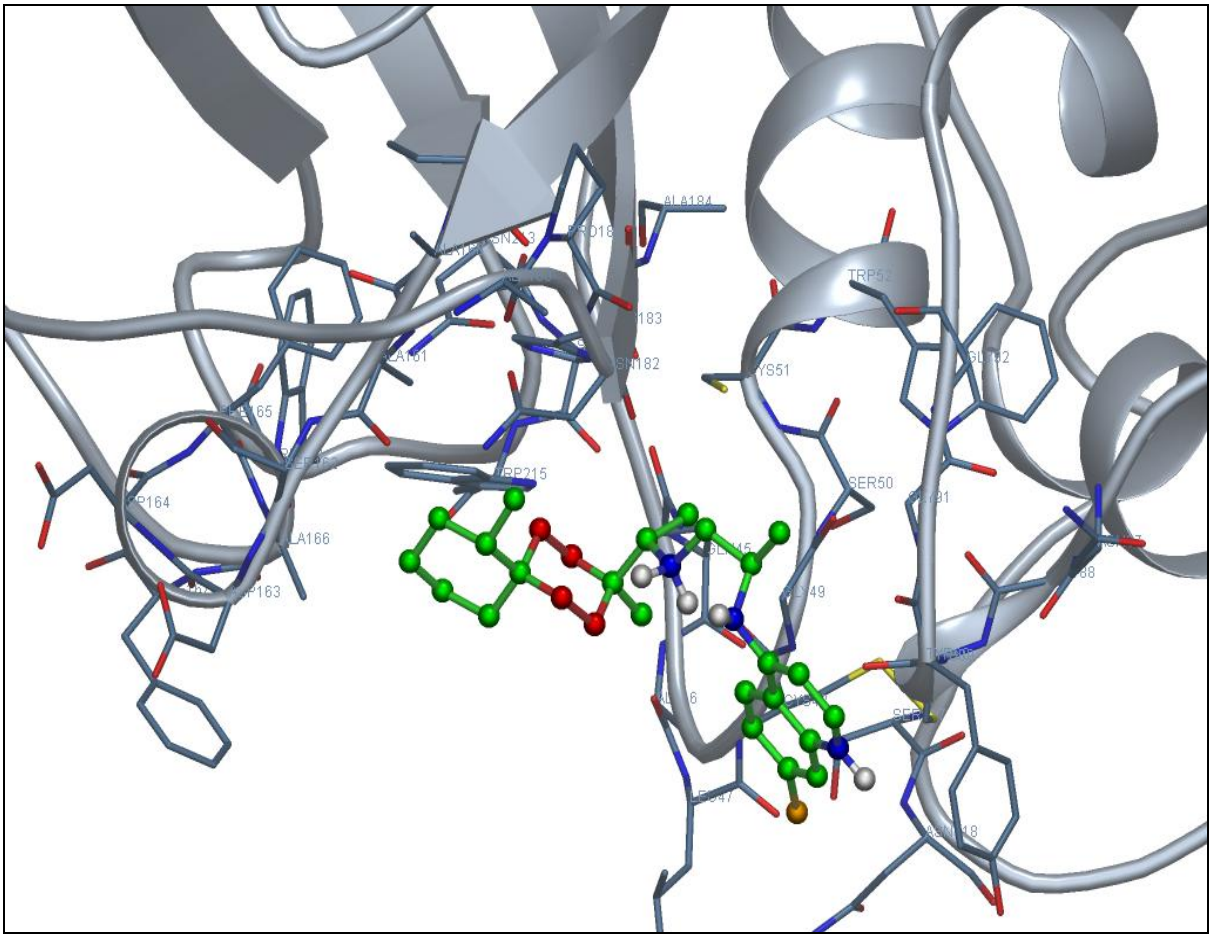


FIG. 4: DOCKED COMPLEX OF COMPOUND A5 IN THE BINDING POCKET OF FALCIPAIN-3 PROTEIN (PDB: *3BWK* – HYDROLASE) IN 3D.

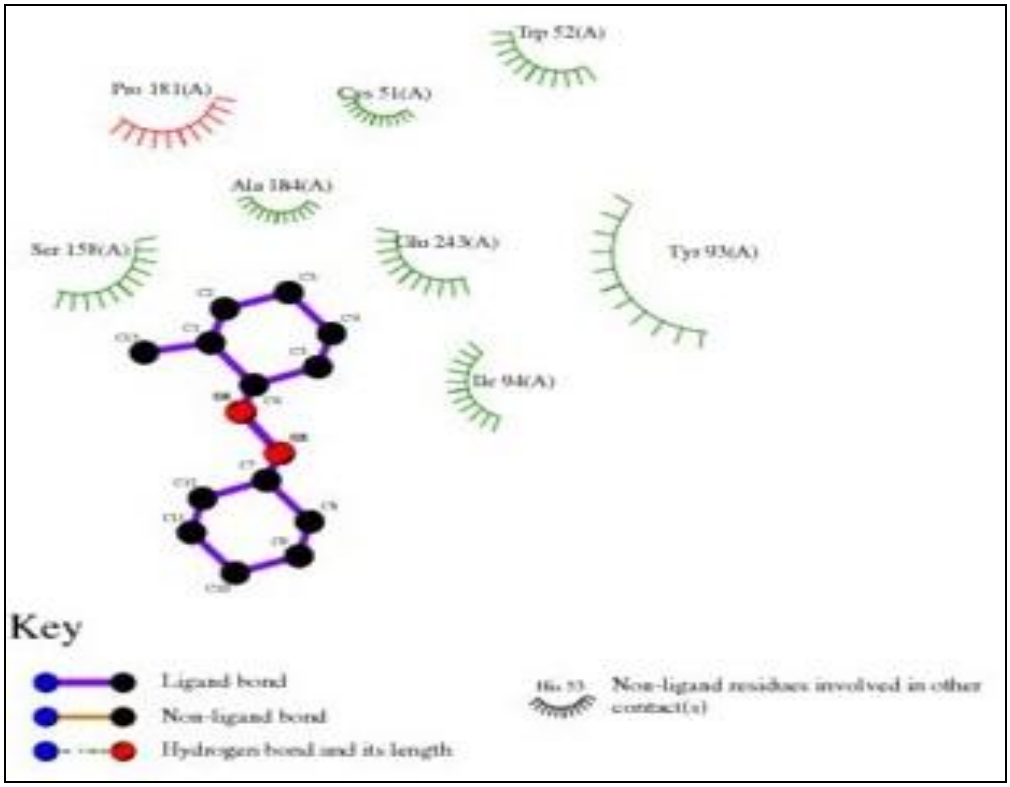


FIG. 5: DOCKED COMPLEX OF COMPOUND B4 IN THE BINDING POCKET OF FALCIPAIN-3 PROTEIN (PDB: *3BWK* – HYDROLASE) IN 2D

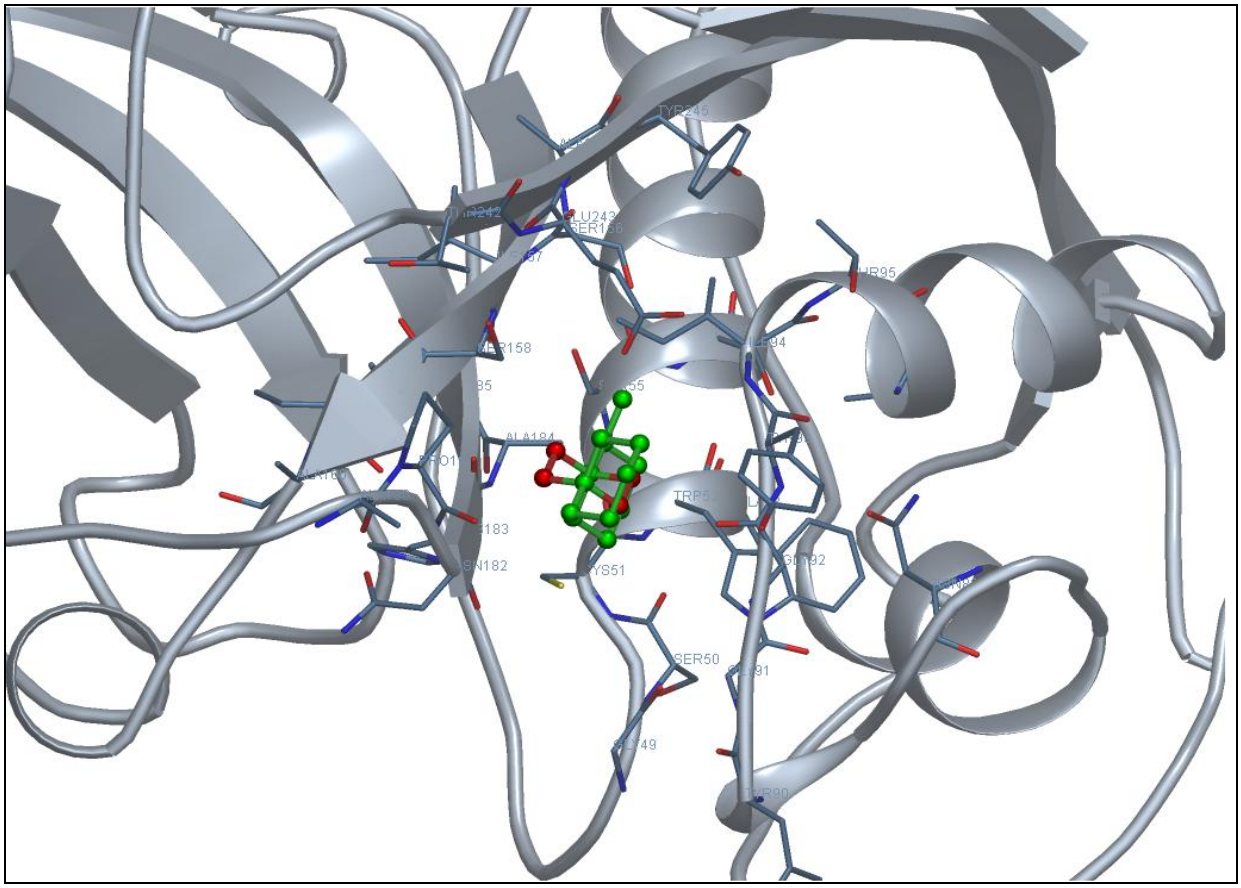


FIG. 6: DOCKED COMPLEX OF COMPOUND B4 IN THE BINDING POCKET OF FALCIPAIN-3 PROTEIN (PDB: *3BWK* – HYDROLASE) IN 3D.

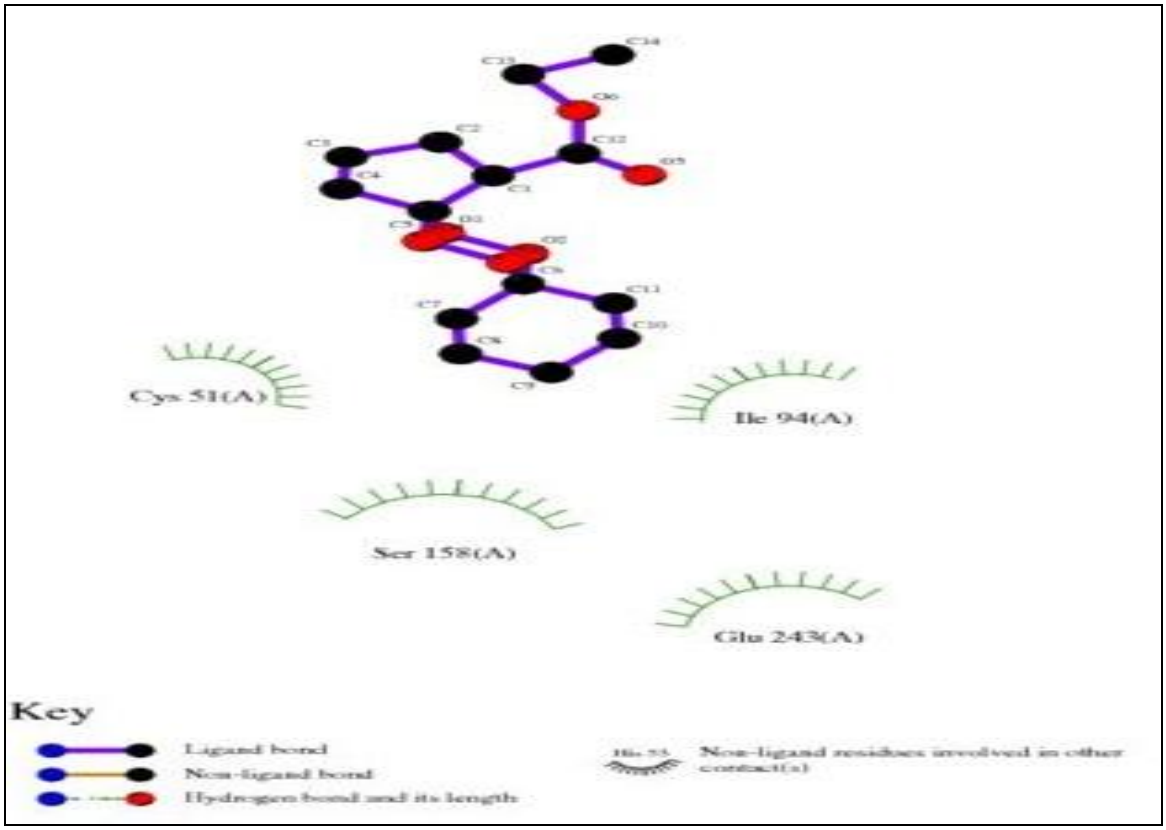


FIG. 7: DOCKED COMPLEX OF COMPOUND B5 IN THE BINDING POCKET OF FALCIPAIN-3 PROTEIN (PDB: *3BWK* – HYDROLASE) IN 2D.

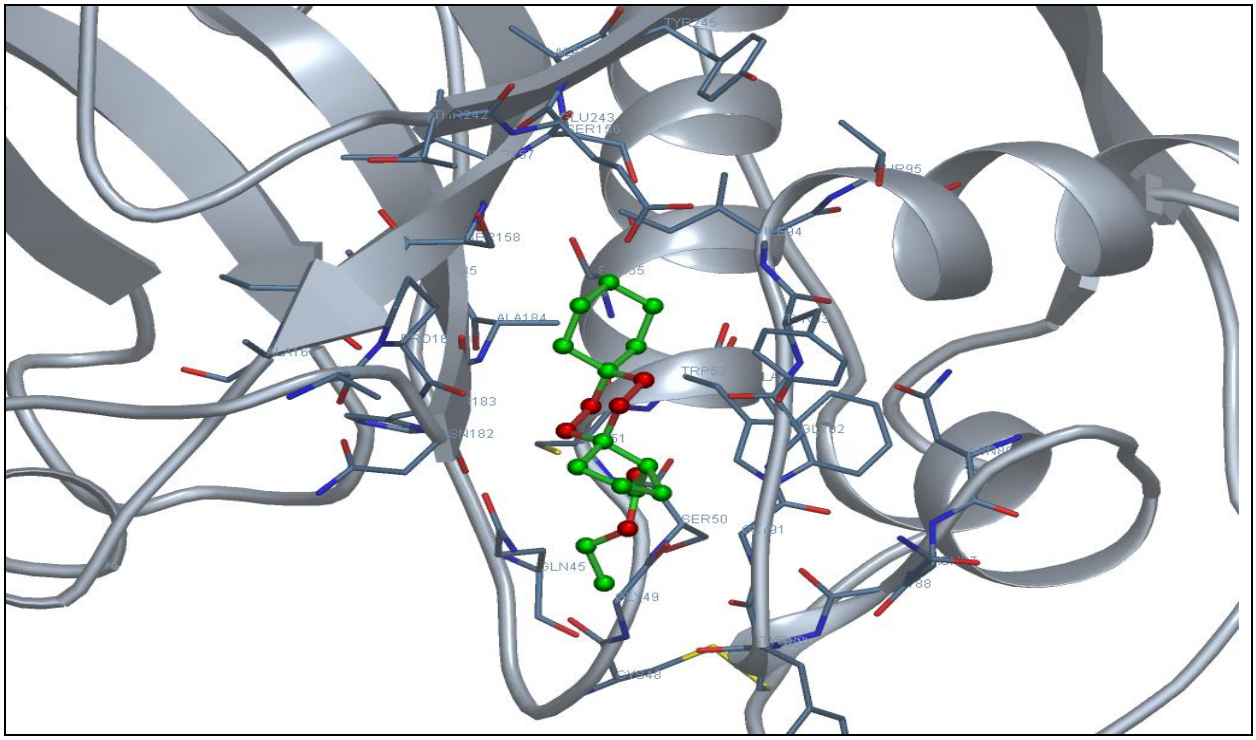


FIG. 8: DOCKED COMPLEX OF COMPOUND B5 IN THE BINDING POCKET OF FALCIPAIN-3 PROTEIN (PDB: *3BWK* – HYDROLASE) IN 3D

CONCLUSION: The docking studies of 15 compounds of 1,2,4,5-tetraoxane derivatives were performed into the binding pocket of a falcipain-3 protein (pdb: *3bwk* – hydrolase) by using the Ligand fit module within docking server. Two series of 1,2,4,5-tetraoxane derivatives were taken for molecular docking studies, one tetraoxaquines, a hybrid of two pharmacophores such as 4-aminoquinoline & 1,2,4,5-tetraoxane, and other dispirotetraoxanes. Among all 15 ligands, all tetraoxaquines except A5 and two dispirotetraoxanes as B2, B4, showed very good interaction with falcipain-3 protein (pdb: *3bwk* – hydrolase) with minimum binding energies. Additional studies to synthesize these potent compounds and evaluate their antimalarial activity may help to the researchers in their effort to make new antimalarial compounds in the future. Authors are also working in the same field and findings will published very soon.

CONFLICTS OF INTEREST: Authors have no any conflicts of interest.

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