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STRUCTURE BASED VIRTUAL SCREENING IN SEARCH OF POTENTIAL INHIBITORS AGAINST HGPRT AS TARGET FOR *PLASMODIUM FALCIPARUM*

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Keywords:

PFHGPRT, HSHGPRT, Docking, Malaria, Virtual screening.

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ABSTRACT: Malaria is a parasitic infectious disease transmitted through the bite of female Anopheles mosquitos. Every year, approximately 210 million Peoples are suffering from this dangerous disease, and around 440,000 individuals pass from this infectious disease. Recently, the Indonesia Ministry of Health declared that the malaria pre-elimination stage should be reached by 2020 and be free of malaria transmission by 2030 to achieve the goal of an Asia-Pacific free of malaria by 2030. So, this study focused on the discovery of novel anti-malarial and medication targets against malaria. The three-dimensional (3D) structures of PFHGPRT, HSHGPRT, and TCHGPRT were used for comparative docking study, while two inhibitors 6-(2, 2-Dichloro-acetamido) chrysene and GMP-2', 3'-dialdehyde were used as a lead for designing and discovery of potential inhibitor of PFHGPRT with the help of various software. The three-dimensional structure (3D) of pfHGPRT (3OZF) and (4RAO) PfHGPRT was isolated from its intricate structure and was utilized for docking study, and comparably, HsHGPRT was isolated from its perplexing structure, and it also utilized for docking study. (3OZF) and (4RAO) hsHGPRT (3GEP) and (3GGJ) increasingly solid official and in this manner, it will offer better PFHGPRT hindrance for bringing wellness among the sufferer of Plasmodium-infected individuals. After binding energy calculation, this study emphasizes the need of the synthesis of PFHGPRT lead molecule against malaria and then preclinical/clinical studies of such PFHGPRT inhibitors could help in controlling malaria more effectively in the future.

INTRODUCTION: Malaria disease is a dangerous blood illness transported by different types of protozoan parasite *Plasmodium* such as *Plasmodium falciparum, Plasmodium vivex, Plasmodium malari, Plasmodium ovale,* and *Plasmodium knowelsi*.

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Once an infected mosquito bites a human and then transmits the parasite, the parasite multiplication in the host's liver cell before infecting and destroying red blood cells (RBCs).

Progress of resistance against usually used anti-malarial necessitates the search for novel chemotherapeutic targets and drugs against this disease. The disease can be controlled and treated if the person is diagnosed as soon as possible. Unfortunately, this disease may also not be possible in some areas of the world because lacking of medical facilities, where malaria outbreaks can occur.

Therefore, many researchers are also working hard day by day for the improving the prevention of malarial infection, early diagnosis and treatment [1]. Among all malaria parasite *Plasmodium falciparum* is dangerous species and most troublesome form of human malaria, infected 200-300 million individuals per year worldwide [2]. The clinical manifestations of *Plasmodium falciparum* infection are induced by the asexual stages of the parasite that develop inside RBCs. Malaria researchers have won multiple Nobel Prizes for their achievements, although the disease continues to afflict some 200 million patients each year. Because of its high rate of resistance outbreaks, there is a constant need for the discovery of novel anti-malarial and drug targets [3]. The field of structure-based drug design is a rapidly growing area in which many successes have occurred in recent years. The explosion of genomic, proteomic, and structural information has provided hundreds of new targets and opportunities for future drug lead discovery [4].

Hypoxanthine guanine phosphor-ribosyl transferase (HGPRT) is essential for purine nucleotide as it catalyses the conversion of 6-oxopurine bases to their respective nucleotides [hypoxanthine to inosine mono-phosphate (IMP) and guanine to guano sine monophosphate (GMP) from the purine bases hypoxanthine and guanine respectively, utilizing 5' - phosphoribosyl - 1-pyrophosphate (PRPP) as a Co-substrate] and hence nucleic acid synthesis in *Plasmodium falciparum* as well as in human [5]. Purines are essential molecules for all living organisms. Purine-containing nucleotides are the building blocks of nucleic acids (DNA and RNA) and purine bases are constituents of enzyme cofactors (*e.g.* NAD+, FAD), sources of chemical energy (*e.g.* ATP, GTP) or signalling molecules (*e.g.*, cAMP). Thus, selective inhibition of the enzymes HGPRT of a human *vs.* parasite is likely to be required as a novel approach for the treatment of malaria. In the present study, designing and virtual screening of PFHGPRT Inhibitors could help in guiding medicinal chemists to improve target specificity [6].

MATERIALS AND METHODS:

Retrieval and Preparation of Molecules: Schrodinger software was used for the calculation of principal descriptors and prediction of the structure of protein-ligand [7].

The three-dimensional structure of pfHGPRT (3OZF) and (4RAO) hsHGPRT (3GEP) and (3GGJ) were retrieved from the Protein Data Bank (www.rcsb.org). Protein preparation wizard (Schrodinger). By assign bond order, add hydrogen atom, assign charge, fill missing residues and optimize the side chain for hydrogen bond network, energy minimization.

Similarly, ligand preparation (ligprep) with the help of Schrodinger. PfHGPRT was separated from its complex structure and was used for docking study, and similarly, HsHGPRT was separated from its complex structure and was used for docking study. To perform the docking with Glide, you need to perform:

- Protein Preparation
- Grid Generation
- Ligand Preparation
- Ligand Docking (Screening)

Protein Preparation: It likewise gives items in different research territories, including little particle demonstrating and reproductions, macromolecular displaying and re-enactments, lead revelation, lead enhancement and representation and mechanization [8]. Protein preparation of protein pfHGPRT (3OZF) and (4RAO) hsHGPRT (3GEP) and (3GGJ) was done by protein preparation wizard using selected amino acid residues of the protein.

Record is imported in prep wizard and handled at that point bond order, by relegate bond request, include hydrogen particle, dole out charge, fill missing build-ups, improve the side chain for hydrogen bond organize, energy minimization protein was chosen for docking in the wake of evacuating water atoms at PH 7.0-3.0. Amino acids associated with flip were bolted. Groups are dependent on less exacting conflicts. RC plot can be seen and thought about when enhancement.

Grid Generation: To perform all the more effectively the docking counts, Glide does not work with the structure itself but rather with a framework speaking to the properties of the structure (for example, electrostatic potential created on every lattice focuses, van der Waals, and so forth). We will therefore produce such a framework from the readied structure. Include in your workspace the second entry called 3EML-Prepared-No-Waters

(you can find it by opening Strasbourg Chem-informatics-Docking-Training if you have not prepared the protein).

Ligand Preparation: Computational techniques, including virtual screening, could possibly be utilized to find new biomolecular focuses for an individual particle of intrigue (MOI). Notwithstanding, existing scoring capacities may not precisely separate proteins to which the particle ties from a bigger arrangement of macromolecules in a basic protein database. It gives items going from general atomic demonstrating projects to a full suite of synthetic reproduction and medication plan programming, including ligand and structure-based techniques. Ligand readiness was finished by the Ligprep module of Schrodinger maestro. During ligand planning, atom range was set from 1 to 300 particles and 1-50 rotatable bonds for figuring scoring capacity.

Ligand Docking (Screening): Float is a ligand docking program for anticipating protein-ligand restricting modes and positioning ligands by means of high-throughput virtual screening. Ligand protein docking was finished utilizing Glide using binding [9]. GOLD is foreseeing ligand protein-docking. It is a standard device in sub-atomic modelling. HGPRT focused by pfHGPRT (3OZF) and (4RAO), hsHGPRT (3GEP), and (3GGJ) one posture was chosen out of 10,000 stances according to one docking run. A vitality edge of 0.5 kcal/mol was taken for dismissing limited posture. Every one of the stances was created underneath this vitality edge for producing 10,000 stances [10]. The analysis of docking results was done using XP visualizer Glide.

ADME was Predicted by QikProp: Schrodinger programming (QikProp v3.3) was utilized for computation of head descriptors and expectation of ADMET. ADMET was anticipated by QikProp v3.3 device using fast Processing Mode. Its yield can be utilized as information for the QikFit and Qik Simmodules. ADME prediction was performed utilizing QikFit module, which uses the linear regression technique for tentatively decided sub-atomic properties and predicts the properties of designed derivatives given as information auxiliary information file position (SDF). The subsequent relapse conditions is then be coordinated again into QikProp and used to anticipate the exploratory property of basically comparative atoms. QikProp can be run either from the Maestro GUI or from the command line [11].

Scoring Functions: It has now been shown in many studies that most well-validated docking programs are generally capable of producing "correct" binding modes, thus signifying an acceptable solution to the sampling problem. However, the ranking problem, that of correctly identifying such modes or effectively disting uishing between binders and non-binders or active and inactive compounds [12].

RESULTS AND DISCUSSION:

Docking Simulation Study: Float is a ligand docking program for foreseeing protein-ligand restricting modes and positioning ligands by means of high-throughput virtual screening. Skim uses two diverse scoring capacities, SP and XP Glide Score, to rank-request mixes. Three methods of inspecting ligand conformational and positional degrees of opportunity are accessible to decide the ideal ligand direction with respect to unbending protein receptor geometry.

This unit presents conventions for adaptable ligand docking with Glide, alternatively including ligand imperatives or ligand sub-atomic similitude's [13]. Ligand docking has turned into an undeniably significant apparatus for the computational investigation of restricting communications among proteins and ligands. By foreseeing the best position (present) of a ligand in a protein restricting site, docking is equipped for uncovering pivotal protein/ligand associations at the sub-atomic level [14]. Gold was used for flexible docking study.

Gold requires a 3D structure of both protein and ligand. A docking simulation study was carried out to recognize the inhibiting potential against HGPRT enzyme. Docking study was performed by (Gold) and Glide software. 3OZFprotein (pf) RMSD (root mean square deviation) was 2.3051Å, docking score found to be 85.65 and 4RAO protein RMSD was 2.0221 Å (pf), and docking score was found to be 83.32 similarly for human protein 3GEP (Hs) RMSD was 1.3562 Å docking score found to be 50.02, and 3GGJ RMSD was 1.7812 Å, docking score found to be 106.45 **Table 1.**

TABLE 1: RESIDUES COUNT AND RESOLUTION OF PFHGPRT AND HSHGPRT PROTEIN BY GOLD

Protein	Residues Count	Resolution
30ZF	250	1.94
4RAO	217	1.87
3GEP	217	2.7
3GGJ	217	2.6

GOLD was used for docking and redocking study, redocking used for further validation. 3OZF and 4RAO is PFHGPRT protein and 3GEP and 3GGJ is HSHGPRT protein. (2.3051 Å and 2.0221Å) RMSD with docking score (85.65Kcal/mol and 83.32 Kcal/mol) of 3OZF, 4RAO, similarly (1.3562 Å, 1.7812 Å) RMSD with docking score (50.02 and 106.45Kcal / mol) of 3GEP, 3GGJ is shown in **Table 2.**

Redocking:

TABLE 2: DOCKING SCORE AND RMSD OF PFHGPRT AND HSHGPRT BY GOLD

Protein	RMSD	Docking Score
3OZF	2.3051	85.65
4RAO	2.0221	83.32
3GEP	1.3562	50.02
3GGJ	1.7812+	106.45

Cross Docking:

TABLE 3: CROSSDOCKING SCORE OF PFHGPRT AND HSHGPRT

Protein	3GEP	3GGJ	3OZF	4RAO
3OZF	42.39	42.42	50.32	41.71
4RAO	104.66	108.58	129.37	137.49
3GEP	88.56	86.50	95.06	95.23
3GGJ	82.92	84.10	98.71	87.86

Similarly, docking with GLIDE OF PFHGPRT and HSHGPRT

Docking:

TABLE 4: DOCKING OF PFHGPRT AND HSHGPRT BY GLIDE

Protein	RMSD	Glide Score
3OZF	1.0219	-4.876
4RAO	6.8351	-16.505
3GEP	1.4687	-13.638
3GGJ	1.2456	-13.078

Cross Docking:

TABLE 5: CROSS DOCKING OF PFHGPRT AND HSHGPRT BY GLIDE

Protein	3GEP	3GGJ	3OZF	4RAO	Ligand
3GEP	-13.638	-11.997	-6.411	-11.289	
3GGJ	-13.529	-13.078	-6.4181	-13.900	
3OZF	-14.218	-10.084	-7.759	-16.950	
4RAO	-11.509	-11.952	-5.989	-16.505	

Validation of Targets:

Post Prediction: Glide and Gold its visualizer, was used for interaction site analysis. Dataset prepared according to institution based making a group according to institution based 4RAO is a selective inhibitor, docking of Institution-based with 4RAO (ligand and protein). Docking of Known inhibitor by Glide and also docking of Decoys with the same software. After docking study mixing of known inhibitors and decoys for enrichment study [15].

Decoys: Decoys are essentially a codename for a way of evaluating how well your docking program has done on a target (or a set of targets). Decoys refer to a set of molecules that (probably) won't bind to your target. They suggested that a virtual, as opposed to artificially feasible, nature of imitations would have a few focal points: feasibility for any dynamic, coordinating of physicochemical properties between actives and distractions, on-the-fly age of baits and multiple decoy sets to diminish over fitting. To accomplish these objectives, they presented a virtual fake set that is artificially conceivable but not fundamentally artificially practical also built up a strategy for normalizing docking scores utilizing virtual fake sets with coordinated physical properties. They demonstrated that, by analyzing docking scores of library atoms thought about with the docking scores of their essentially produced property-matched decoys, it is conceivable to benchmark scoring capacities and judge their points of interest, confinements, and unwavering quality [16].

Enrichment Study: ROC (Receiver operating characteristics) is discriminate against active *vs.* inactive molecules. Selection of dataset according to institute (the science of Czech Republic and The University of Queensland. Database (CHEMBL database) is used. Combine active molecules and decoys for enrichment study and their activity range between 7.5-6.5; if the target is between this activity range, then the target is validated for study [17.] 3GEP decoys were 994 and 10 active molecules. 3GGJ decoys were 995 and 11 active molecules of HSHGPRT inhibitor. Similarly, for PFHGPRT inhibitor 3OZF having decoys 771 and 11 active molecules [18-21].

Enrichment Study of 3GEP Decoys and Active Molecules:

TABLE 6: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF DECOYS RESULT

% Decoys	1%	5%	10%
# of actives	10	10	10

TABLE 7: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF RESULTS

% Result	1%	5%	10%
# of actives	9	10	10

TABLE 8: ENRICHMENT FACTORS WITH RESPECT TO N% SAMPLE SIZE

% Sample	1%	5%	10%
EF	9	10	10

Enrichment Study of 3GGJ Decoys and Active Molecules:

TABLE 9: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF DECOYS RESULT

% Decoys	1%	5%	10%
# of actives	10	10	10

TABLE 10: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF RESULTS

% Result	1%	5%	10%
# of actives	9	10	10

TABLE 11: ENRICHMENT FACTORS WITH RESPECT TO N% SAMPLE SIZE

% Sample	1%	5%	10%
EF	90	20	10

Enrichment Study of 3OZF Decoys and Active Molecules:

TABLE 12: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF DECOYS RESULT

% Decoys	1%	5%	10%
# of actives	9	9	9

TABLE 13: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF RESULTS

% Result	1%	5%	10%
# of actives	5	9	9

TABLE 14: ENRICHMENT FACTORS WITH RESPECT TO N% SAMPLE SIZE

% Sample	1%	5%	10%
EF	58	18	9

ADME Analysis: ADME properties were calculated for inhibitors by QikProp software. ADME was anticipated by QikProp v3.3 device utilizing quick Processing Mode. Its yield can be utilized as a contribution for the QikFit TM and QikSim TM modules. ADME forecast was performed utilizing the QikFit module, which uses a straight relapse strategy for tentatively decided atomic properties and predicts the properties of planned subordinates given as information auxiliary information file design (SDF) [22, 23]. The subsequent relapse conditions are then be coordinated once more into QikProp and used to anticipate the test property of fundamentally comparable atoms. QikProp can be run either from the Maestro GUI or from order line [17].

Monte Carlo measurable mechanics re-enactments anticipate configurational midpoints for various descriptors, including hydrogen bond tallies and dissolvable available surface zone (SASA) on natural solutes in intermittent boxes of unequivocal water atom pursued by similar examination virtually screening virtual screening of particles have finished with different database ASINEX, IBS, SPECS, NCI, Ligand info, ZINC [24, 25].

Enrichment Study of 3GEP Decoys and Active Molecules:

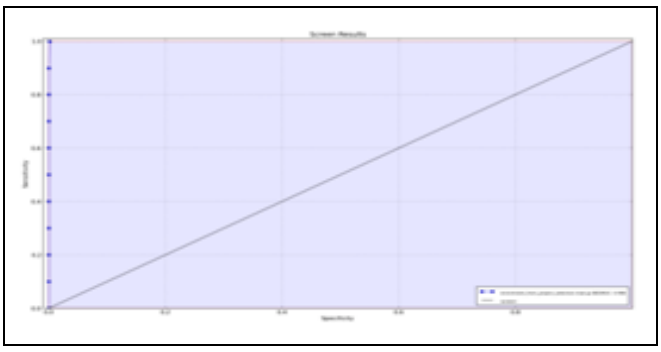

FIG. 1: 3GEP PERCENT ACTIVES FOUND

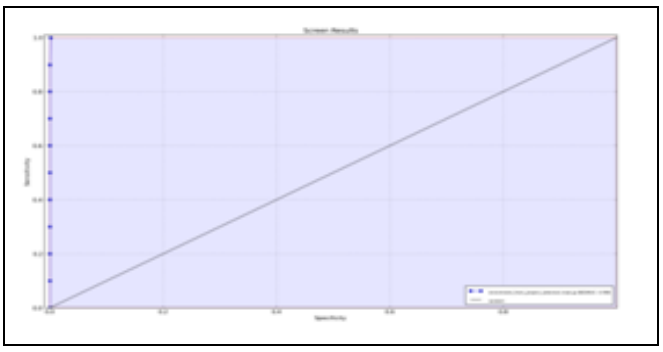

FIG. 2: 3GEP ROC PLOT

TABLE 15: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF DECOYS RESULT

% Decoys	1%	5%	10%
# of actives	10	10	10

TABLE 16: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF RESULTS

% Result	1%	5%	10%
# of actives	9	10	10

TABLE 17: ENRICHMENT FACTORS WITH RESPECT TO N% SAMPLE SIZE

% Sample	1%	5%	10%
EF	9	10	10

TABLE 18: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF DECOYS RESULT

% Decoys	1%	5%	10%
# of actives	10	10	10

Enrichment Study of 4RAO Decoys and Active Molecules:

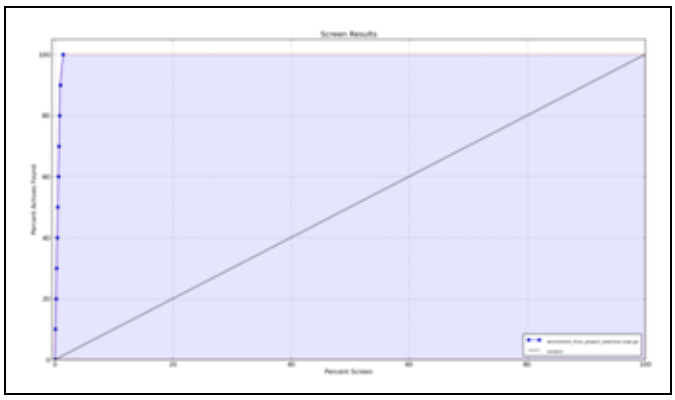

FIG. 3: 4RAO PERCENT ACTIVES FOUND

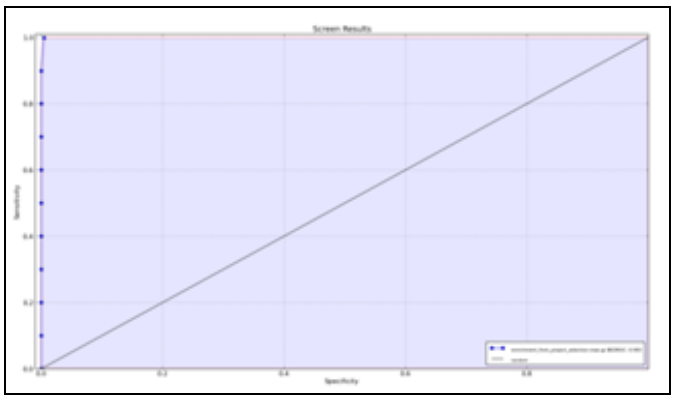

FIG. 4: 4RAO ROC PLOT

TABLE 19: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF RESULTS

% Result	1%	5%	10%
# of actives	9	10	10

TABLE 20: ENRICHMENT FACTORS WITH RESPECT TO N% SAMPLE SIZE

% Sample	1%	5%	10%
EF	90	20	10

Enrichment Study of 3OZF Decoys and Active Molecules:

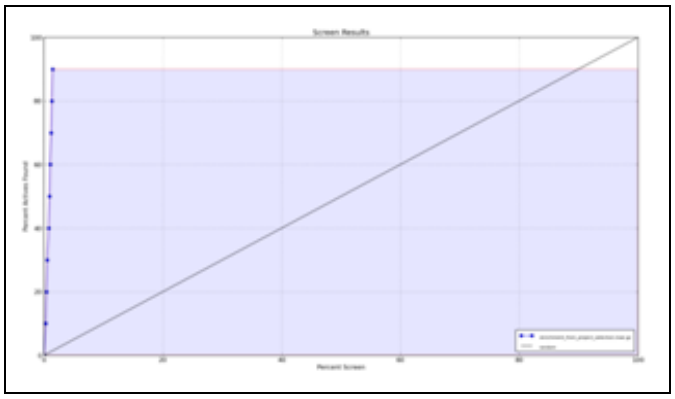

FIG. 5: 3OZF PERCENT ACTIVES FOUND

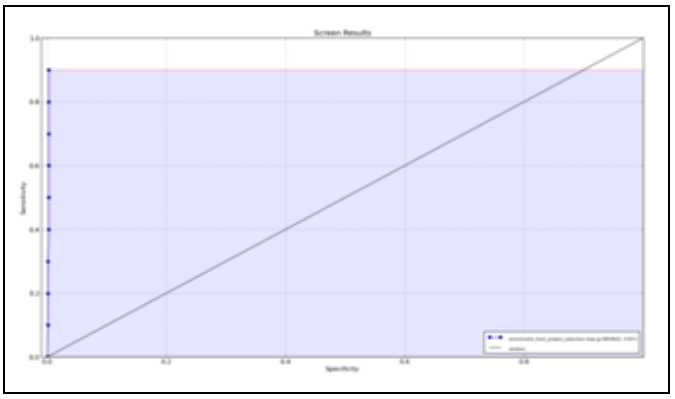

FIG. 6: 3OZF NROC PLOT

TABLE 21: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF DECOYS RESULT

% Decoys	1%	5%	10%
# of actives	9	9	9

TABLE 22: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF RESULTS

% Result	1%	5%	10%
# of actives	5	9	9

TABLE 23: ENRICHMENT FACTORS WITH RESPECT TO N% SAMPLE SIZE

% Sample	1%	5%	10%
EF	58	18	9

TABLE 24: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF DECOYS RESULT

% Decoys	1%	5%	10%
# of actives	11	11	11

TABLE 25: COUNT AND PERCENTAGE OF ACTIVES IN TOP N% OF RESULTS

% Result	1%	5%	10%
# of actives	10	11	11

TABLE 26: ENRICHMENT FACTORS WITH RESPECT TO N% SAMPLE SIZE

% Sample	1%	5%	10%
EF	84	18	9.2

Enrichment Study of 3GGJ Decoys and Active Molecules:

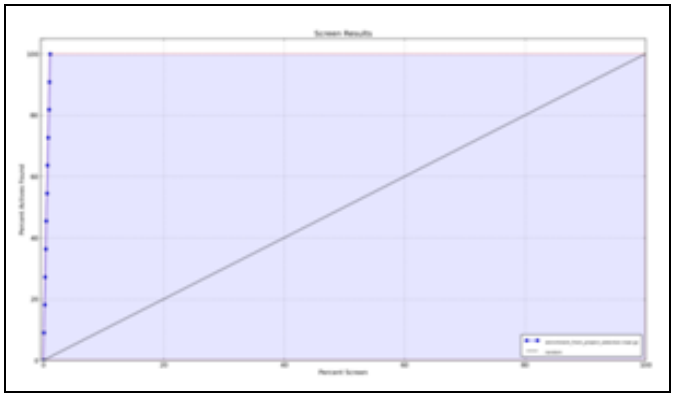

FIG. 7: 3GGJ PERCENT ACTIVES FOUND

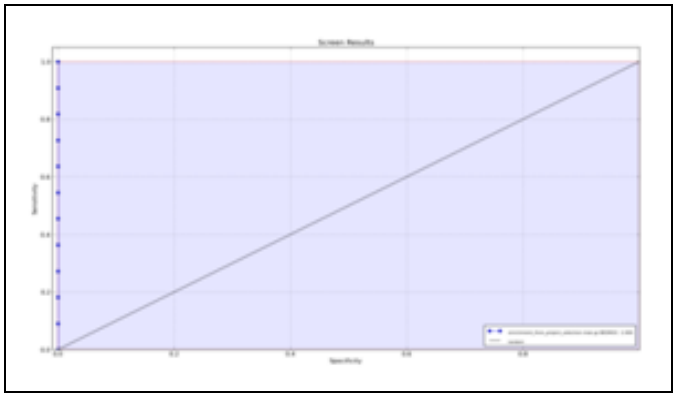

FIG. 8: 3GGJ ROC PLOT

Virtual Screening Workflow
Drug Like / Lead like Filter:
Shape-Based Virtual Screening:

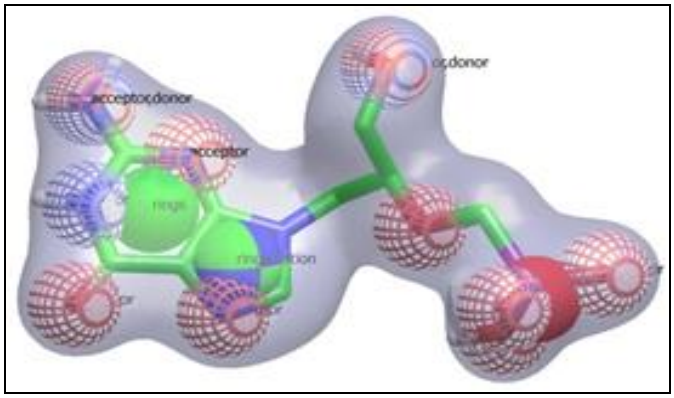

FIG. 9: 3GEP_SHAPE_BASED_QUERY

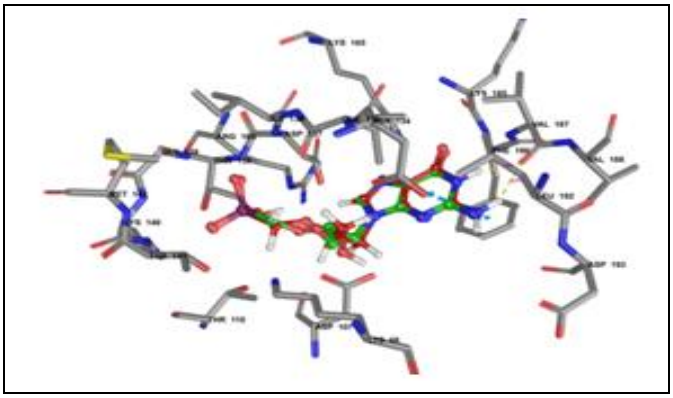

FIG. 10: 3GEP_SUPERIMPOSITION

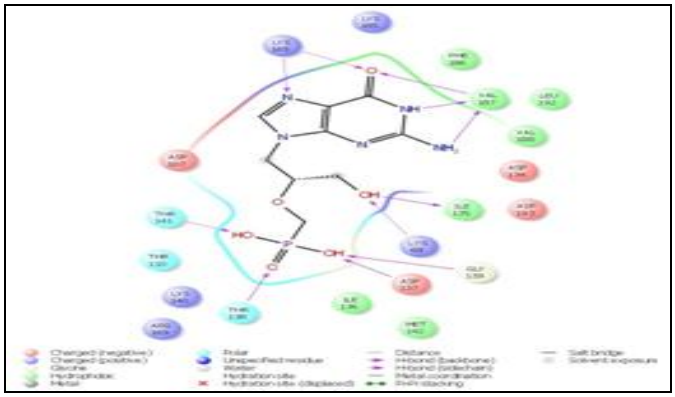

FIG. 11: 3GEP_SUPERIMPOSITION_2D

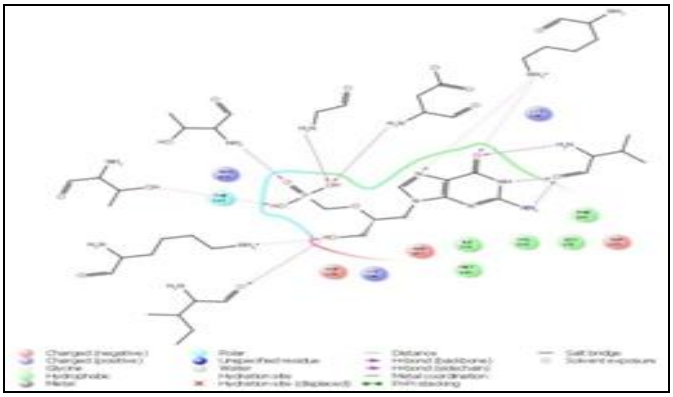

FIG. 12: 3GEP_SUPERIMPOSITION_2D_1

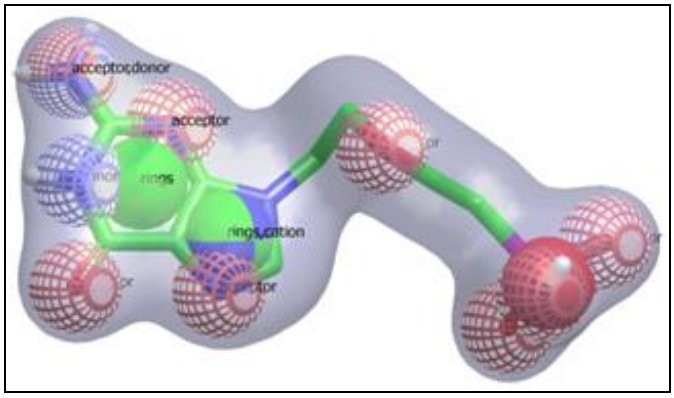

FIG. 13: 3GGJ_SHAPE_BASED_QUERY

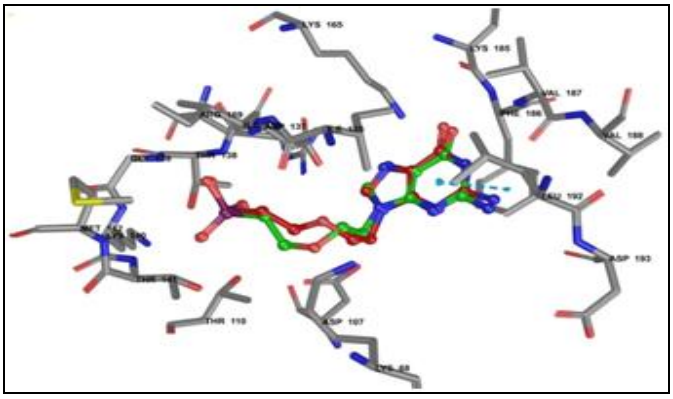

FIG. 14: 3GGJ_SUPERIMPOSITION

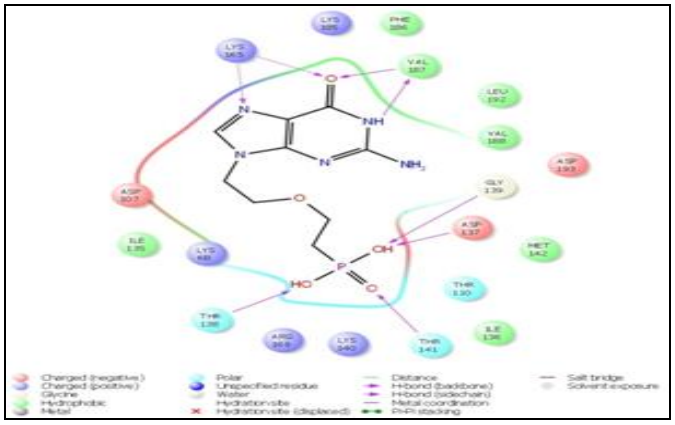

FIG. 15: 3GGJ_SUPERIMPOSITION_2D_1

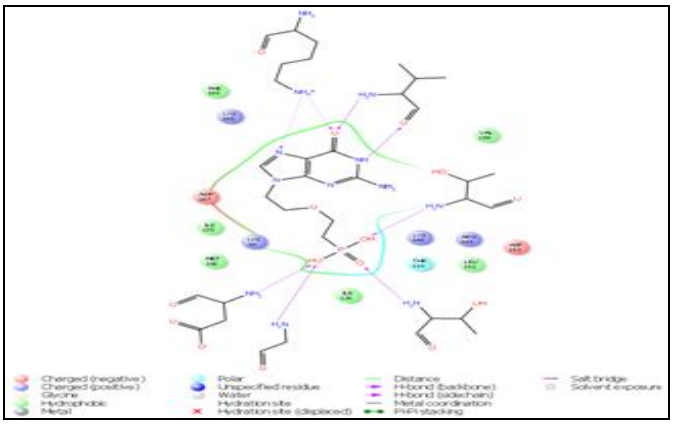

FIG. 16: 3GGJ_SUPERIMPOSITION_2D_1

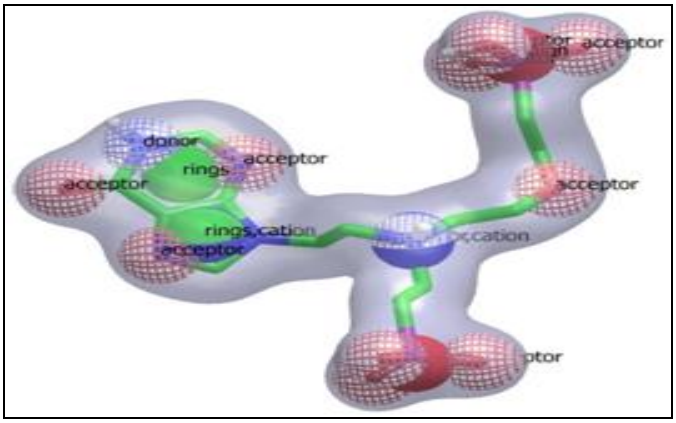

FIG. 17: 4RAO_SHAPED_BASED_QUERY

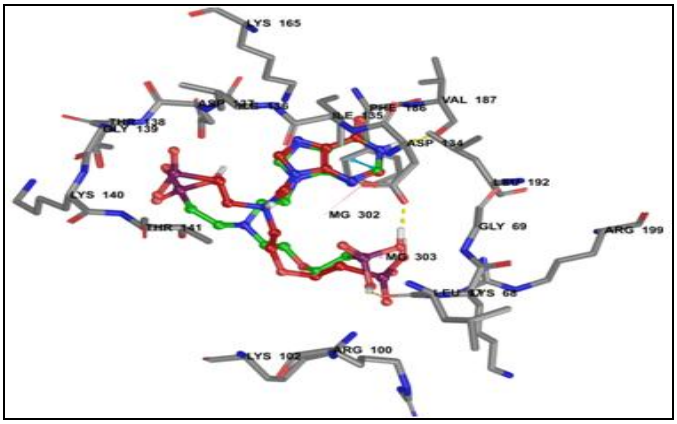

FIG. 18: 4RAO_SUPERIMPOSITION

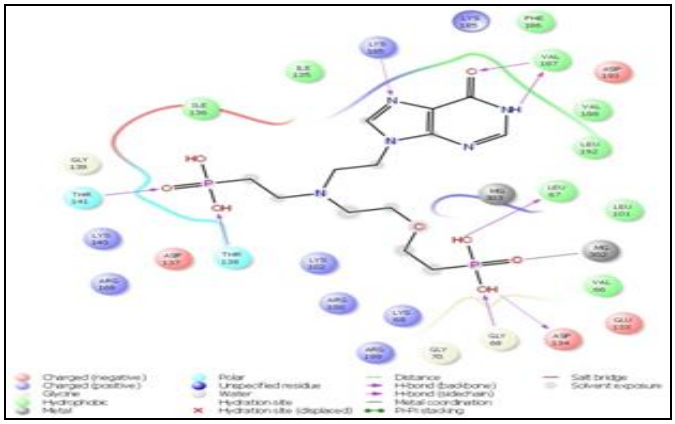

FIG. 19: 4RAO_SUPERIMPOSITION_2D

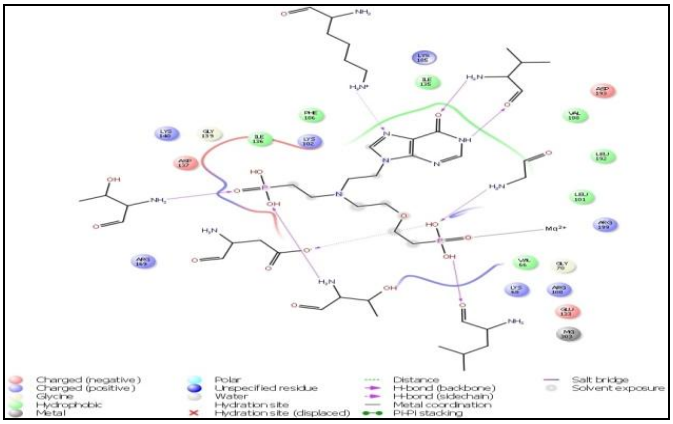

FIG. 20: 4RAO_SUPERIMPOSITION_2D_1

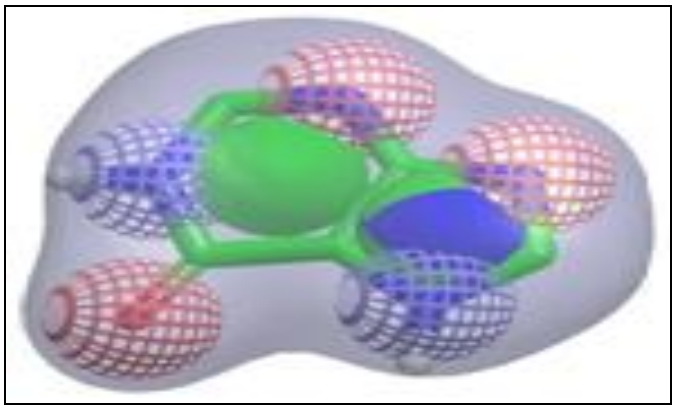

FIG. 21: 3OZF_SHAPE_BASED_QUERY

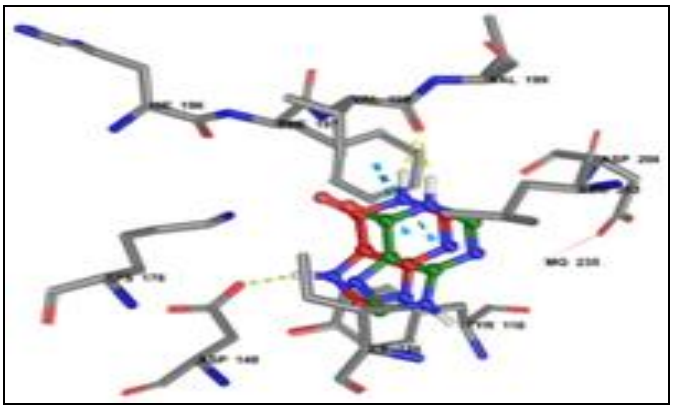

FIG. 22: 3OZF_SUPERIMPOSITION

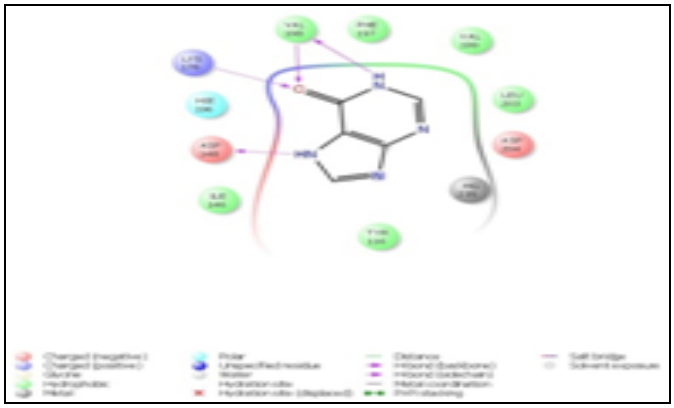

FIG. 23: 3OZF_SUPERIMPOSITION_2D

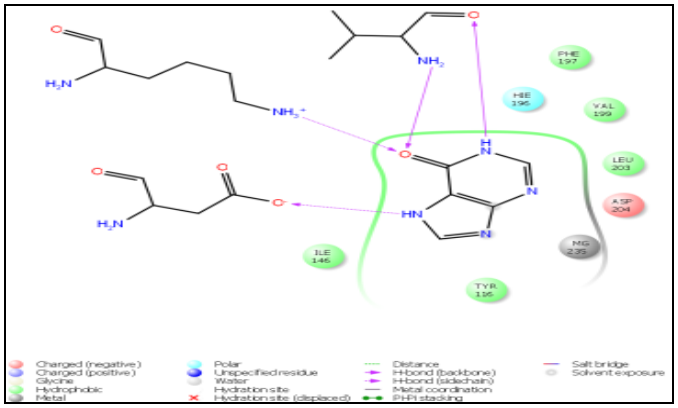

FIG. 24: 3OZF_SUPERIMPOSITION_2D_1

Toxicity Parameter Based Screening:
Standard Precision (SP) Mode Molecular Docking:
Extra Precision (XP) Mode Molecular Docking:
MM-GBSA (Binding Energy Calculation):

CONCLUSION: Docking is a powerful *in-silico* drug-design method. Atomic docking is a protected and simple instrument that aides in researching, translating, clarifying, recognizable proof of sub-atomic properties utilizing 3D structure; sub-atomic docking is attempted to utilize predict the structure of intermolecular complex-shaped between at least two constituent particles. The result of this study showed that the PFHGPRT inhibitor 6-(2, 2 Dichloroacetamido) chrysene it got the best dock score - 94.4 after calculation of binding energy so it would be a better target against malaria.

This study also concludes that the research explores the synthesis of a series of novel Quinoline derivatives having scaffold/ moieties of hetero-cyclic compounds such as pyridine, purine, pyrrole, oxazole, triazole, and thiazolidine scaffolds. The structural information of the above lead molecule will be the better target after *in-vitro* and *in-vivo* study against potential anti-malarial activity in the near future.

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CONFLICTS OF INTEREST: Nil

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