IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
June 2020 Vol.:18, Issue:3

Structure Based Virtual Screening in Search of Potential Inhibitors against HGPRT as Target for *Plasmodium falciparum*

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ISSN 2349-7203
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Submission: 25 May 2020
Accepted: 02 June 2020
Published: 30 June 2020

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: PFHGPRT, HSHGPRT, Docking, Malaria, Virtual screening

ABSTRACT

Intestinal sickness is an ailment brought about by a parasite. The parasite is transmitted to people through the nibbles of tainted mosquitoes. Individuals who have intestinal sickness for the most part feel exceptionally wiped out, with a high fever and shaking chills. Every year, roughly 210 million individuals are tainted with jungle fever, and around 440,000 individuals pass on from the sickness. A large portion of the individuals who pass on from the ailment are little youngsters in Africa. With the goal that it requirement for the disclosure of novel antimalarials and medication targets. The three-dimensional structures of PFHGPRT, HSHGPRT and TCHGPRT were utilized for near docking study, at that point for all intents and purposes screened against the objective PFHGPRT and based on Moledock scoring The three-dimensional structure of pfHGPRT (3OZF) and (4RAO) hsHGPRT (3GEP) and (3GGJ) were recovered from the Protein Data Bank (www.rcsb.org). Protein readiness wizard (Schrodinger). By allocate bond request, include hydrogen particle, dole out charge, fill missing buildups, streamline the side chain for hydrogen bond organize, vitality minimization. Similarly ligand arrangement (ligprep) with the assistance of Schrodinger. PfHGPRT was isolated from its intricate structure and was utilized for docking study and comparably HsHGPRT was isolated from its perplexing structure and was utilized for docking study. (3OZF) and (4RAO) hsHGPRT (3GEP) and (3GGJ) increasingly solid official and in this manner will offer better PFHGPRT hindrance. Thus, further synthesis, preclinical/clinical studies of such PFHGPRT inhibitors could help in controlling malaria more effectively.

1. INTRODUCTION

Malaria fever is a perilous blood illness brought about by different types of protozoan parasite Plasmodium such as *Plasmodium falciparum, Plasmodium vivax, Plasmodium malari, Plasmodium praise,* and *Plasmodium knowlesi* which is transmitted to people through the nibble of the Anopheles mosquito. Once a tainted mosquito chomps a human and transmits the parasite, the parasites duplicate in the host's liver before contaminating and obliterating red platelets (RBCs). Advancement of opposition against usually utilized antimalarial requires the quest for novel chemotherapeutic targets and medications against the ailment. The infection can be controlled and treated whenever analyzed at an opportune time. Lamentably, this may likewise not be conceivable in certain zones of the world ailing in therapeutic offices, where intestinal sickness episodes can happen. Along these lines, specialists are additionally buckling down on improving the aversion of malarial disease, early conclusion and treatment [1]. Among all malaria parasite, *Plasmodium falciparum* is dangerous species and most burdensome form of human malaria, affecting 200–300 million individuals per year worldwide [2]. Clinical indications of *Plasmodium falciparum* contamination are initiated by the abiogenetic phases of the parasite that create inside RBCs. Malaria analysts have won various Nobel Prizes for their accomplishments, in spite of the fact that the illness keeps on distressing around 200 million patients every year. As a result of its high pace of obstruction episodes, there is a consistent requirement for the disclosure of novel antimalarial and medication targets [3]. The field of structure-based medication configuration is a quickly developing region wherein numerous triumphs have happened as of late. The blast of genomic, proteomic, and basic data has given many new targets and open doors for future medication lead disclosure [4]. Hypoxanthine guanine phosphoribosyl transferase (HGPRT) is fundamental for purine nucleotide as it catalyze the transformation of 6-oxopurine bases to their individual nucleotides [hypoxanthine to inosine monophosphate (IMP) and guanine to guanosine monophosphate (GMP) from the purine bases hypoxanthine and guanine separately, using 5'- phosphoribosyl-1-pyrophosphate (PRPP) as a Co-substrate] and henceforth nucleic corrosive amalgamation in Plasmodium falciparum just as in human [5]. Purines are basic atoms for every single living being. Purine containing nucleotides are the structure squares of nucleic acids (DNA and RNA) and purine bases are constituents of chemical cofactors (for example NAD+, FAD), wellsprings of concoction vitality (for example ATP, GTP) or flagging atoms (for example cAMP). Along these lines, particular restraint of the chemicals HGPRT of a human versus parasite are probably going to be

required as a novel methodology for treatment of intestinal sickness. In the present investigation, structuring and virtual screening of PFHGPRT Inhibitors could help in managing restorative scientific experts to improve target particularity [6].

2. MATERIALS AND METHODS

2.1 Retrieval and Preparation of Molecules

Schrodinger software was used for calculation of principal descriptors and prediction of 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, 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:

1) Protein Preparation

2) Grid Generation

3) Ligand Preparation

4) Ligand Docking (Screening)

2.2 Protein preparation

It likewise gives items in different research territories, including little particle demonstrating and reproductions, macromolecular displaying and reenactments, 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 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 buildups, improve the side chain for hydrogen bond organize, energy minimization protein were 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 depended on less exacting conflicts. RC plot can be seen and thought about when enhancement.

2.3 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 (Find it by opening Strasbourg-Chemoinformatics-Docking-Training.prjzip if you have not prepared the protein).

2.4 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 protein basic 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 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.

2.5 Ligand Docking (Screening)

Float is a ligand docking program for anticipating protein-ligand restricting modes and positioning ligands by means of high-throughput virtual screeningLigand protein docking was finished utilizing Glide using binding [9]. GOLD is foreseeing ligand protein-docking. It is 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. 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.

2.6 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 QikSimmodules. ADME prediction was performed utilizing QikFit module which uses 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].

2.7 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 distinguishing between binders and nonbinders or active and inactive compounds [12].

3 RESULTS AND DISCUSSION

3.1 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 an unbending protein receptor geometry. This unit presents conventions for adaptable ligand docking with Glide, alternatively including ligand imperatives or ligand sub-atomic similitudes [13]. Ligand docking has turned into an undeniably significant apparatus for the computational investigation of restricting communications among proteins and ligands. By foreseeing the most good 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. Docking simulation study was

carried out to recognize the inhibiting potential against HGPRT enzyme. Docking study was performed by (Gold) and Glide software. 3OZF protein (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 No. 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 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 83.32Kcal/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.

3.1.1 Redocking

Table No. 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

3.1.2 Crossdocking

Table No. 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

Similaly docking with GLIDE OF PFHGPRT and HSHGPRT

3.1.3 Docking

Table No. 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

3.1.4 Crossdocking

Table No. 5: Crossdocking 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	

3.2 Validation of targets

3.2.1 Post prediction

Glide and Gold its visualizer were used for interaction site analysis. Dataset prepared according to institution based, making a group according to institution based 4RAO is

selective inhibitor, docking of Institution based with 4RAO (ligand and protein). Docking of Known inhibitor by Glide and also docking of Decoys with same software. After docking study mixing of known inhibitors and decoys for enrichment study [15].

3.2.2 Decoys

Wallach and Lilien tended to impediments inalienable in the DUD set: spanning a little artificially plausible subset of little molecule space, limited physicochemical similitude between active and fakes, by and large, confined number of imitations, and benchmark bias. 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 overfitting. 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].

3.2.3 Enrichment study

ROC (Receiver operating characteristics) is discriminate active vs inactives molecules. Selection of dataset according to institute (science of Czech Republic and The University of Queensland. Database (CHEMBL database) is used. Combine of active molecules and decoys for enrichment study and there activity range between7.5-6.5, if target is between this activity range then target is validated for study. 3GEP decoys was 994and 10 active molecules.3GGJ decoys was 995 and 11 active molecules of HSHGPRT inhibitor. Similarly, for PFHGPRT inhibitor 3OZF having decoys 771 and 11 active molecules.

3.2.3.1 Enrichment study of 3GEP decoys and active molecules

Table No. 6: Count and percentage of actives in top N% of decoys result

% decoys	1%	5%	10%
# of actives	10	10	10

Table No. 7: Count and percentage of actives in top N% of results

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

Table No. 8: Enrichment factors with respect to N% sample size

% sample	1%	5%	10%
EF	9	10	10

3.2.3.2 Enrichment study of 3GGJ decoys and active molecules

Table No. 9: Count and percentage of actives in top N% of decoys result

% decoys	1%	5%	10%
# of actives	10	10	10

Table No. 10: Count and percentage of actives in top N% of results

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

Table No. 11: Enrichment factors with respect to N% sample size

% sample	1%	5%	10%
EF	90	20	10

3.2.3.3 Enrichment study of 3OZF decoys and active molecules

Table No. 12: Count and percentage of actives in top N% of decoys result

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

Table No. 13: Count and percentage of actives in top N% of results

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

Table No. 14: Enrichment factors with respect to N% sample size

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

3.3 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 contribution for the QikFitTM and QikSimTM modules. ADME forecast was performed utilizing QikFit module which uses straight relapse strategy for tentatively decided atomic properties and predicts the properties of planned subordinates given as information auxiliary information file design (SDF). The subsequent relapse conditions is 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 the order line [17]. Monte Carlo measurable mechanics reenactments 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.

3.4.1 Enrichment study of 3GEP decoys and active molecules

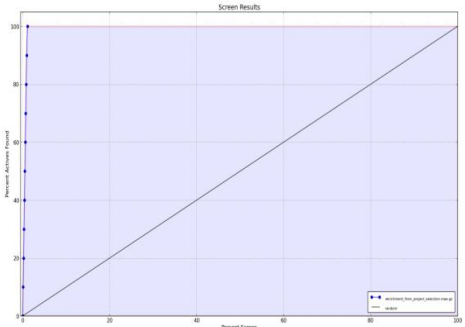

Figure No. 1: 3GEP_Percent_Actives_Found

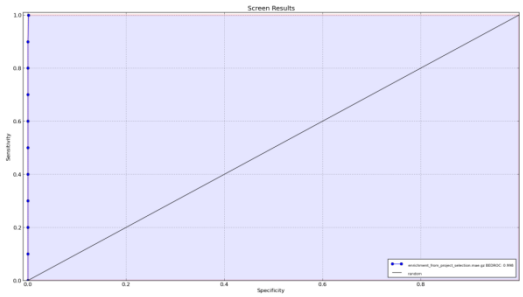

Figure No. 2: 3GEP_ROC_PLOT

Table No. 15: Count and percentage of actives in top N% of decoys result

% decoys	1%	5%	10%
# of actives	10	10	10

Table No. 16: Count and percentage of actives in top N% of results

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

Table No. 17: Enrichment factors with respect to N% sample size

% sample	1%	5%	10%
EF	9	10	10

3.4.2 Enrichment study of 4RAO decoys and active molecules

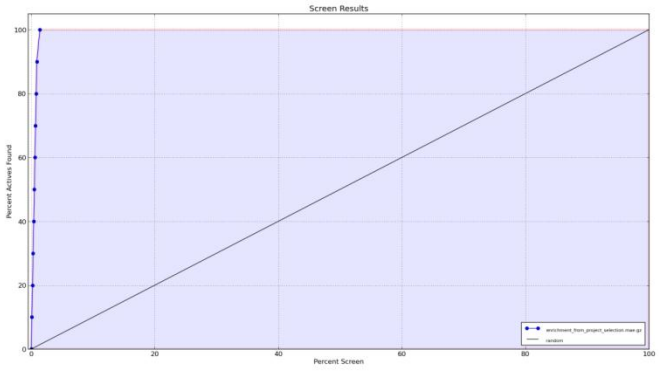

Figure No. 3: 4RAO_Percent_Actives_Found

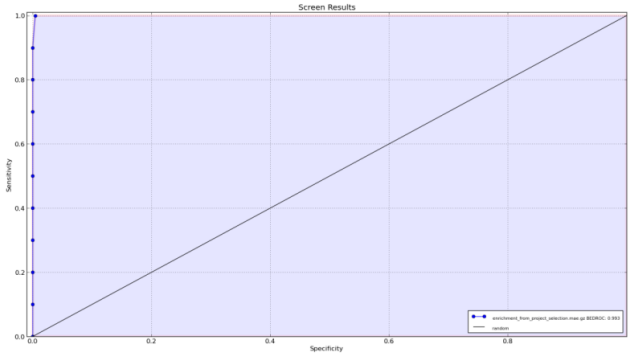

Figure No. 4: 4RAO_ROC_PLOT

Table No. 18: Count and percentage of actives in top N% of decoys result

% decoys	1%	5%	10%
# of actives	10	10	10

Table No. 19: Count and percentage of actives in top N% of results

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

Table No. 20: Enrichment factors with respect to N% sample size

% sample	1%	5%	10%
EF	90	20	10

3.4.3 Enrichment study of 3OZF decoys and active molecules

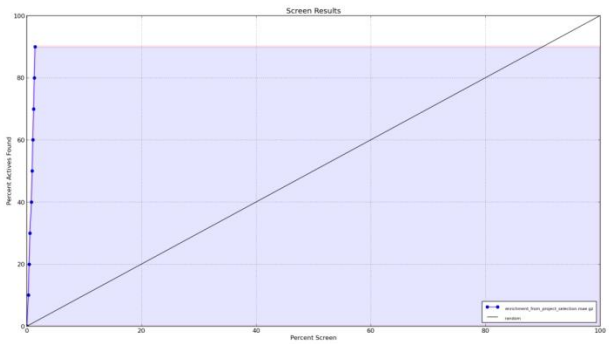

Figure No. 5: 3OZF_Percent_Actives_Found

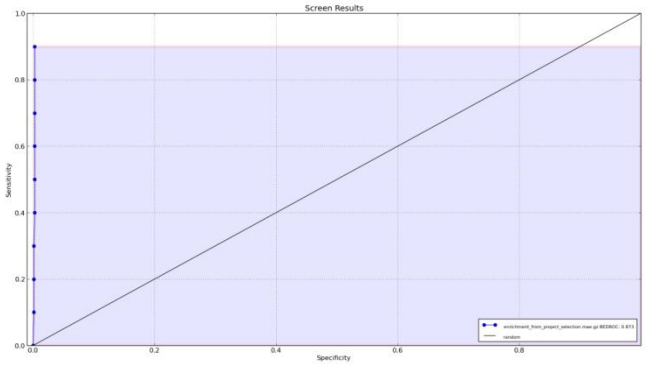

Figure No. 6: 3OZF_ROC_PLOT

Table No. 21: Count and percentage of actives in top N% of decoys result

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

Table No. 22: Count and percentage of actives in top N% of results

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

Table No. 23: Enrichment factors with respect to N% sample size

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

3.4.4 Enrichment study of 3GGJ decoys and active molecules

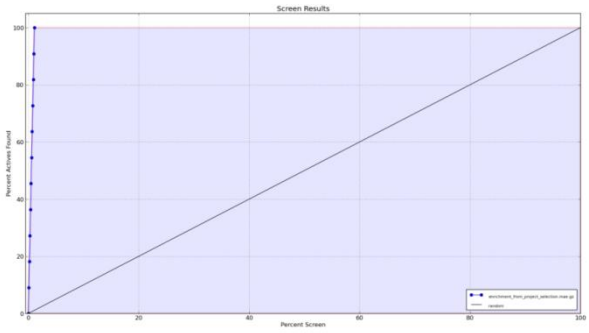

Figure No. 7: 3GGJ_Percent Actives Found

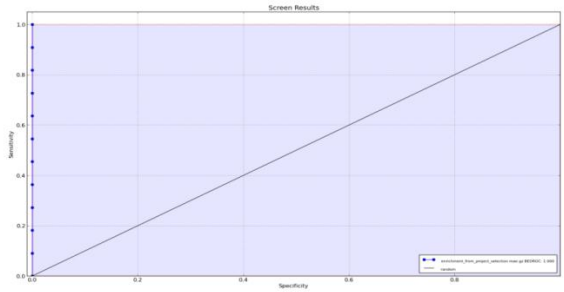

Figure No. 8: 3GGJ_ROC_PLOT

Table No. 24: Count and percentage of actives in top N% of decoys result

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

Table No. 25: Count and percentage of actives in top N% of results

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

Table No. 26: Enrichment factors with respect to N% sample size

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

4. Virtual Screening Workflow

4.1 Drug like/Lead like Filter:

4.2 Shape Based virtual screening:

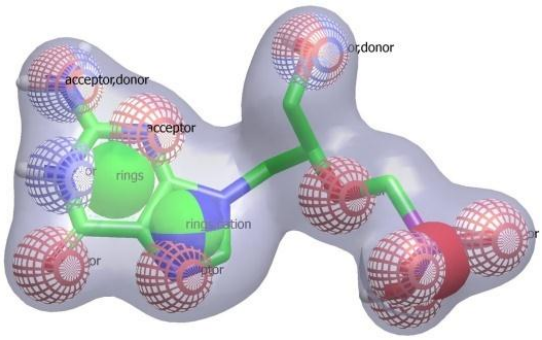

Figure No. 9: 3GEP_SHAPE_BASED_QUERY

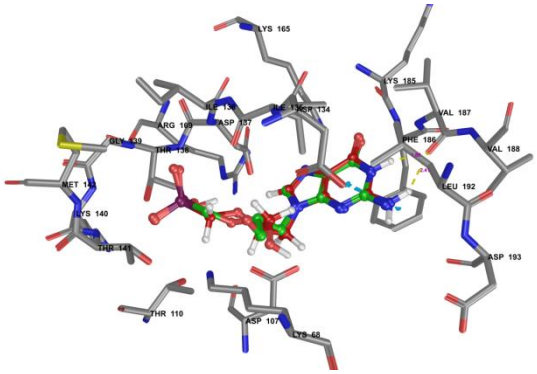

Figure No. 10: 3GEP_SUPERIMPOSITION

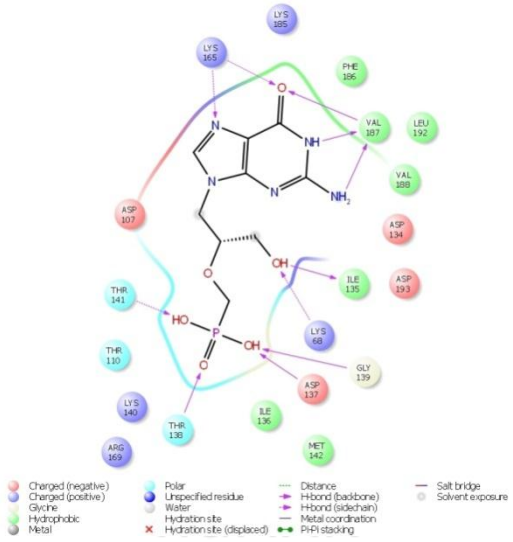

Figure No. 11: 3GEP_SUPERIMPOSITION_2D

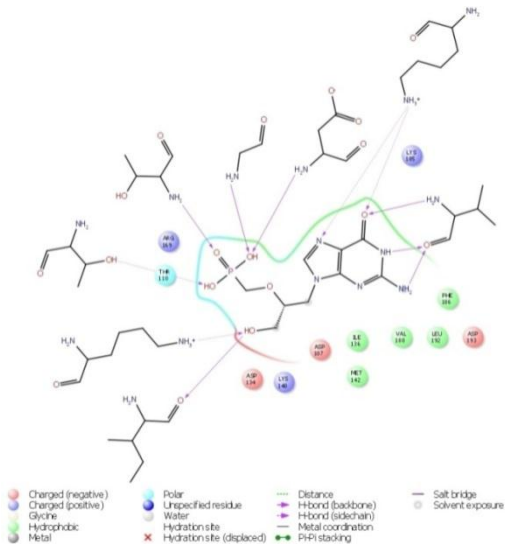

Figure No. 12: 3GEP_SUPERIMPOSITION_2D_1

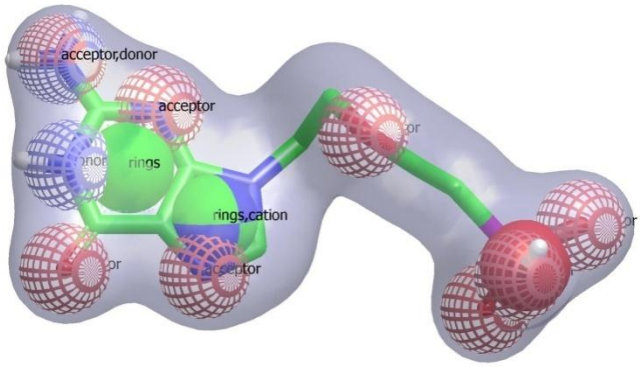

Figure No. 13: 3GGJ_SHAPE_BASED_QUERY

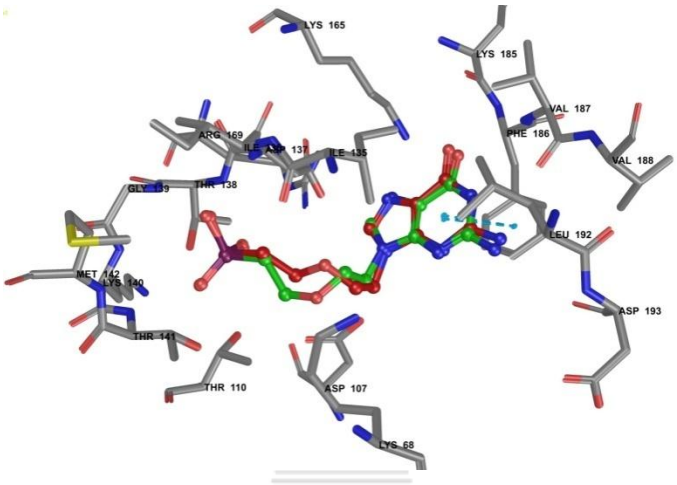

Figure No. 14: 3GGJ_SUPERIMPOSITION

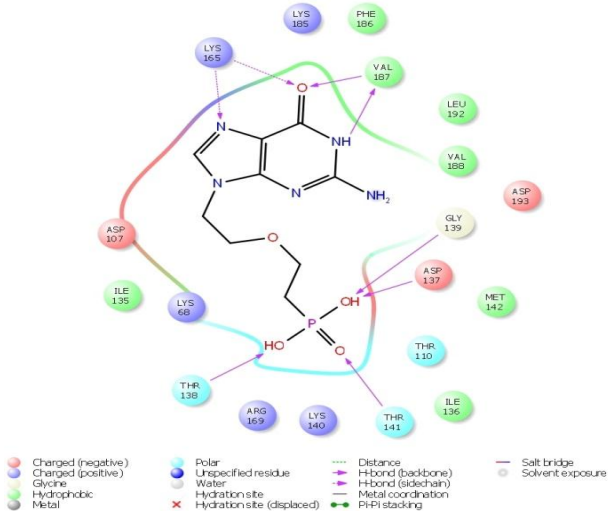

Figure No. 15: 3GGJ_SUPERIMPOSITION_2D_1

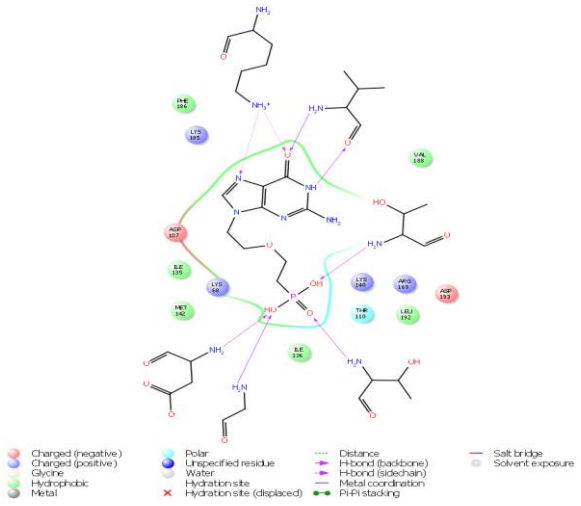

Figure No. 16: 3GGJ_SUPERIMPOSITION_2D_1

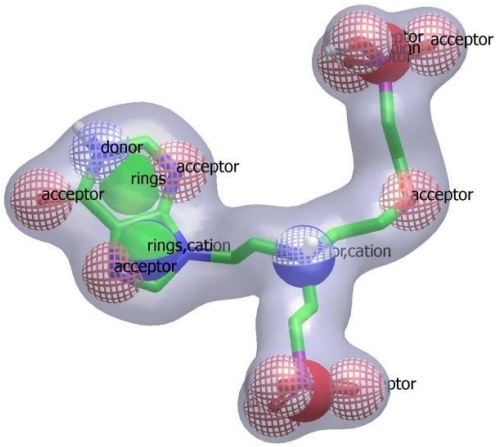

Figure No. 17: 4RAO_SHAPED_BASED_QUERY

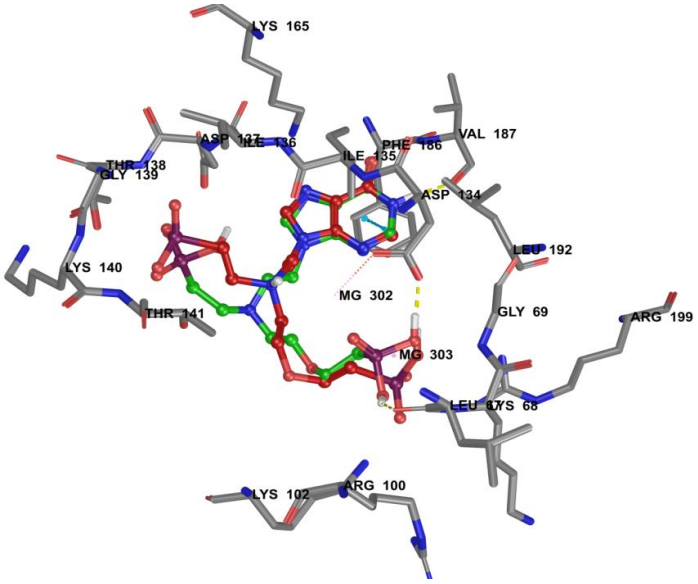

Figure No. 18: 4RAO_SUPERIMPOSITION

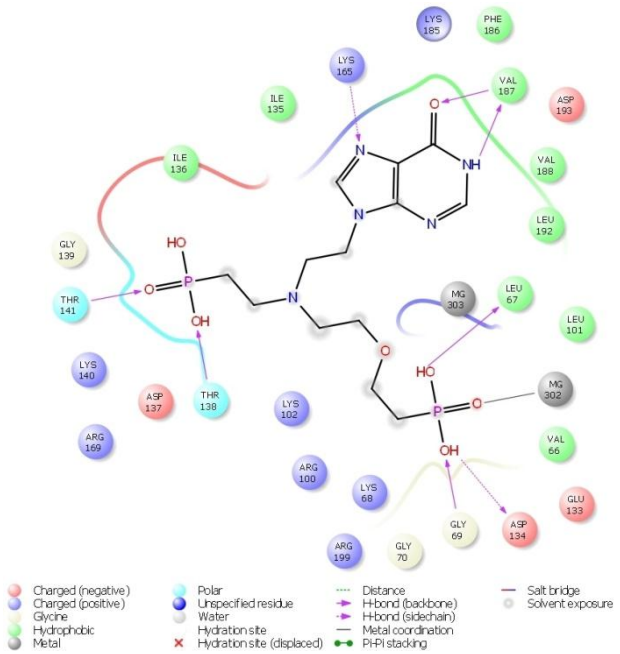

Figure No. 19: 4RAO_SUPERIMPOSITION_2D

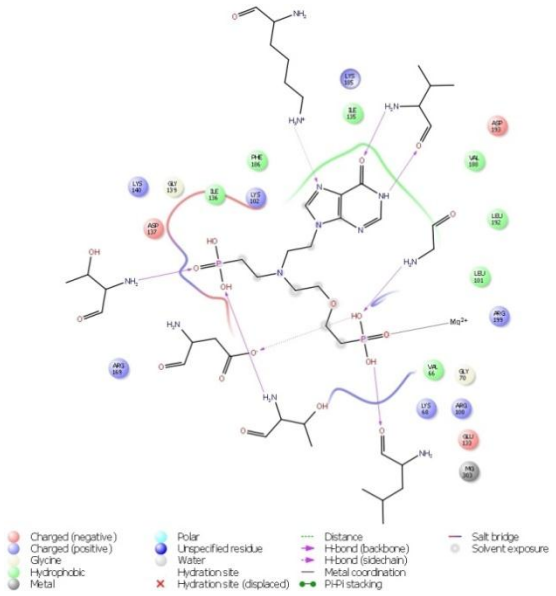

Figure No. 20 4RAO_SUPERIMPOSITION_2D_1

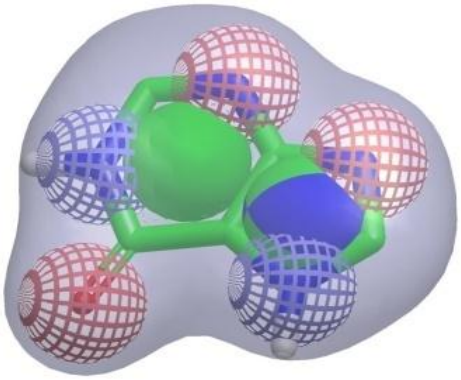

Figure No. 21. 3OZF_SHAPE_BASED_QUERY

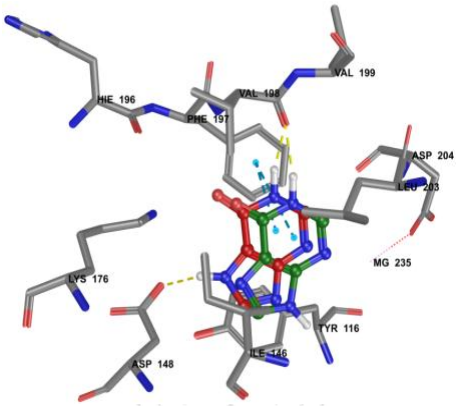

Figure No. 22: 3OZF_SUPERIMPOSITION

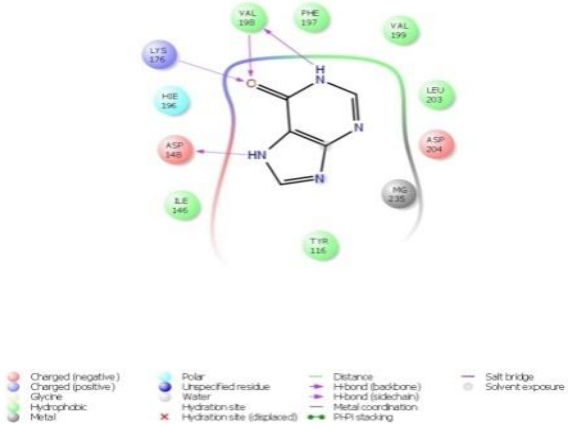

Figure No. 23: 3OZF_SUPERIMPOSITION_2D

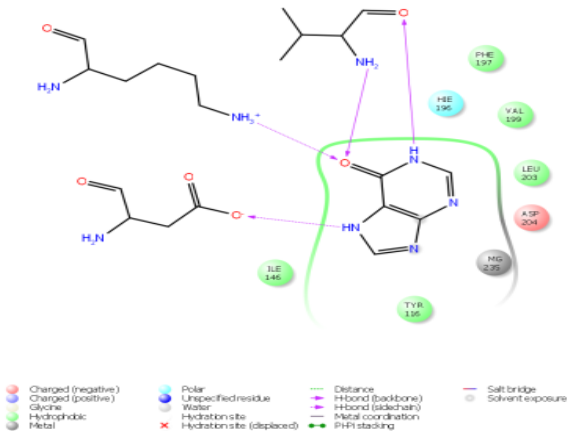

Figure No. 24: 3OZF_SUPERIMPOSITION_2D_1

CONCLUSION

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 attempts to utilize foresee the structure of intermolecular complex shaped between at least two constituent particles. *Plasmodium falciparum* HGPRT (PFHGPRT) is an appealing objective site contender for hostile to malarial medication disclosure and the homology displaying method stands apart as a superb and ground-breaking choice to foresee a solid 3-D structure of the protein. We got best dock score - 94.4, in the wake of docking of potential PFHGPRT inhibitor 6-(2,2 Dichloroacetamido) chrysene with both for example *Plasmodium falciparum* and human, showed that it better focused on jungle fever parasite as contrast with human, shows accomplishment in accomplishing chemoprevention and a stage ahead towards the Global specialized procedure of WHO for intestinal sickness 2016–2030 sets the most ambitious focuses for decreases in intestinal sickness cases. Protein-Ligand cooperation assumes a huge job in basic based medication planning. In future research, toxicological profile of these mixes could be tried in wet lab and research could be continuing for preclinical/clinical preliminary. The structural information of our given model will pave the way for further laboratory experiments to design potential anti-malarial drug in near future.

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