iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 3 **Issue:** VII **Month of publication:** July 2015

DOI:

www.ijraset.com

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)

Homology Model of *Leishmania Donovani* Udp-Galactopyranose Mutase Binds Antifungal Compounds *in Silico*

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Abstract- UDP-galactopyranose mutase (UGM) is a critical enzyme required for cell wall synthesis and a component of Lipophosphoglycan (LPG) and Glycoinositolphospholipids (GIPL), well known virulent molecules. Absence of UGM in human makes it an ideal drug target for structure based drug design against Leishmania. Since there is no crystal structure record has been found with this protein, a homology modeling was performed in order to create three dimensional structure of L. donovani UGM using SWISS-MODEL server. Further quality of structure was validated using PROCHECK and ERRAT programs which confirms that the structure is reliable. Further the topological analysis was done for the presence of pockets on the surface of proposed homology model of protein using the RaptorX server. Molecular docking was performed with two antifungal compounds 2-(methylthio)-5-[(5-nitro-1,3-thiazol-2-yl)thio]-1,3,4-thiadiazole) and 2-nitro-5-(4-nitroStyryl)furan. Our homology model of L. donovani UGM shows the interaction with antifungal compounds. The predicted binding models of both the compounds show that these bind at the FAD and UDP biding site, which could interfere with the functional aspects of L. donovani UGM enzyme and may subsequently lead to loss of virulence of Leishmania parasites. These observations would provide useful information for the drug designing studies.

Key words: UGM, drug target, homology modeling, Leishmania, docking

I. INTRODUCTION

UDP-galactopyranose mutase (UGM) (E.C.5.4.99.9) is a flavo-dependent enzyme. It catalyzes the conversion of UDP-Galactopyranose to UDP-Galactofuranose. UGM has been identified in several pathogenic microorganisms including *M. Tuberculosis, L. major, T. cruzi* and *A. fumigates* [1]. UGM is the only source for the biosynthesis of a sugar Galactofuranose (Gal*f)* and it is not present in mammalian host [2] which makes it an ideal drug target against parasitic diseases like Leishmaniasis, Tuberculosis and Chagas disease. UGM shows a very high sequence identity among other *Leishmania* species while shows less similarity with other trypanosomes such as *T. cruzi*. Gal*f* is a five membered ring form of galactose and a component of cell wall, glycolipids, glycoproteins on cell surface of many human pathogens including bacteria, fungi and parasites. [3-6]. In *Leishmania .spp* Gal*f* is found in promasticotes. Gal*f* play a vital role in growth of many pathogenic prokaryotes and lower eukaryotes including *Leishmania* spp. In *Leishmania* Gal*f* is found on cell surface and involved in the pathogenesis of disease by facilitating host- parasite interactions [7]. It was found that Gal*f* is found in Lipophosphoglycan (LPG), a recognized virulent molecule and GIPL (glycoinositolphospholipids) [8]. It has been observed that for host parasite interactions, cell surface plays a crucial role in recognition of hostand evading the immune system. The importance of LPG and GIPL are well studied and observed that these molecules facilitates host specific cell recognition, growth of parasite and subsequent pathogenesis. Thus blocking the integration of Gal*f* residues into cell wall could be a novel therapy against Leishmaniasis.

A. Reaction

Galactofuranose (Gal*f*) residues are formed from Galactopyranose (Gal*p*) residues after a polymerization reaction, catalysed by UGM. The reaction starts from uridine 5' diphosphate (UDP)-galactopyranose which isolmerizes into uridine 5' diphosphate (UDP)-galactofuranose. The biosynthesis of Gal*f* is as follows

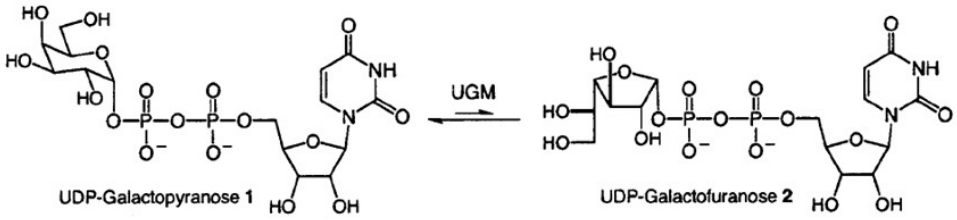


FIGURE 1. THE BIOSYNTHETIC REACTION OF GAL*F* RESIDUES FROM GAL*P* CATALYZED BY UGM

LPG deletion in *L. major* suggests that this glycosylated structure is important for resistance to oxidative stress and immune response [9]. Additionally Gal*f* containing GIPLs shows its role in establishing the infection [7, 10]. According to a study on UGM gene, it was observed that in *L. major*, on deletion of UGM gene, this enzyme plays a crucial role in disease pathogenesis [11]. In this study it was shown that mice infected with *L. major* (lacking Gal*f*) was attenuated. Moreover, the UGM catalyzed reaction requires the flavin cofactor (FAD) to be in reduced form [12, 13]. The parasitic protozoa *L. donovani* belong to the order kinetoplastida. This zoonotic organism is the causative agent of deadly *Leishmania*sis, also known as Kala-azar. The Leishmaniasis is a wide spectrum of vector born disease with great epidemiological and clinical diversity. It is caused by more than 20 species of protozoan parasite [14]. Transmission occurs by the bite of insect vector, sandfly and around 30 species of sand fly are known to be vector for *Leishmania.* The annual global prevalence of all forms (i.e. cutaneous, mucocutaneous and visceral) of Leishmaniasis is nearly 10 million and approximately 350 million people are at risk [15]. Additionally, in the developing countries like India, cases are often being reported from newer (non-endemic) areas and disease is occupying pandemic status due to population migration to non endemic regions though current statistical data are lacking [16]. However, there is a gross under reporting of the cases from endemic regions and these figures may go up [17]. Treatment options for visceral *Leishmania*sis include chemotherapy, which is not found satisfactory. The main reason for this failure is long drug course, high drug toxicity and parasitic resistance to drug such as antimonial drugs. Since the disease belongs to poor thus high cost of drugs make it unavailable in affected rural areas [18]. Vaccine development has been still far from reality due to intricate mechanisms has developed for evading from immune system of host by different species of *Leishmania*. Fortunately the cell biology of *Leishmania* is very unusual and become a subject for interrogation in order to achieve effective remedy for VL. As far as drug development is concerned, several drug targets have been identified for Leishmaniasis. Moreover advanced discoveries in Bioinformatics have made the drug designing a bit easier. Additionally with the help of several databases as well as softwares, protein structure prediction and ligand interaction understandings has been evolved. Since no crystal structure is available for *Leishmania donovani* UGM, a homology modeling is needed to understand the structural and functional features of this protein. The structural modeling using bioinformatics tools provides us about each and every aspects of secondary and tertiary structure of protein along with its functional role in cell biology process such as, ligand binding, which could be beneficial in drug targeting against Leishmaniasis.

II. MATERIAL AND METHODS

A. Template selection

The protein sequence of *L.donovani* UGM was obtained from NCBI (http://www.ncbi.nlm.nih.gov/) having a length of 492 amino acids. For selection of templates, based on sequence similarity and identity, a BLAST search was executed using this sequence.

B. Sequence alignment

Based on the sequence similarity and identity, UGM sequence of various species of *Leishmania* along with *Trypanosoma* was aligned to observe the conservation and variations. This was performed using CLUSTALX2 software.

C. Homology Modeling

A three dimensional structure of the target sequence i.e *L. donovani* UGM was built using online server SWISS-MODEL, by Template based method [19-23]. Briefly, FASTA Sequence of *L.donovani* UGM (query) was put on the server and the SWISS-MODEL template library (SMTL version 2015-05-13, PDB release 2015-05-08) was searched with Blast [24] and HHBlits [25] for evolutionary related structures matching the target sequence. For each identified template, the template's quality has been predicted from features of the target-template alignment. The templates with the highest percentage of sequence similarity have then been

selected for model building. The FASTA sequence of *T cruzi* UGM (best template) was aligned with *L donovani* on Bioedit software. This alignment file was put on server and program was run for homology modeling of UGM. The three dimensional structure of UGM was downloaded and viewed using PyMol software [26]. Analysis of structure was done on Chimera [27].

D. Validation Of Homology Model

The three dimensional protein model was constructed by homology modeling technique could be prone to errors and thus imprecise. Therefore validating the quality of overall structure is important. It needs a careful investigation of the stereo chemical parameters and accuracy of folds at different levels. The structure generated by Swiss Model, was evaluated using various programs such as PROCHECK and ERRAT using online server SAVES (http://nihserver.mbi.ucla.edu/SAVES/). PROCHECK checks the stereochemical quality of protein structure by analyzing residue-by-residue geometry and overall geometry and a Ramachandran plot is produced [28]. ERRAT is used for statistical analysis of non-bonded interactions between different atom types. A plot is generated using the value of the error function versus position of a 9-residue sliding window which is calculated by comparing the statistics from highly refined structures [29].

E. Structure Scanning

The structure was further scanned for presence of pockets on its surface using the RaptorX server [30]. RaptorX is a protein structure prediction server developed by Xu group, excelling at predicting 3D structures for protein sequences without close homologs in the Protein Data Bank (PDB). Given an input sequence, RaptorX predicts its secondary and tertiary structures, contacts, solvent accessibility, disordered regions and binding sites. The PDB file of homology structure of *L. donovani* UGM was put on server and program was run to analyze topologically. The resulting files were downloaded from the site and analyzed on Chimera.

F. Docking Studies

To observe whether the proposed homology model of *L. donovani* UGM interacts with ligand other than substrate and activator, two antifungal compounds (table 1), was selected for docking study. Docking was done using Autodock4. For preparing dock files, polar hydrogen atoms and kollman charges were added to the homology model of *L. donovani* UGM and saved as .pdbqt. Further, gasteiger charges was added to the ligand and saved as .pdbqt. Program was run by giving command to cygwin command line. As the docking completed, a .dlg file is generated showing docking poses of ligands and binding energy of ligand. The docked ligand were visualized and analyzed on Chimera.

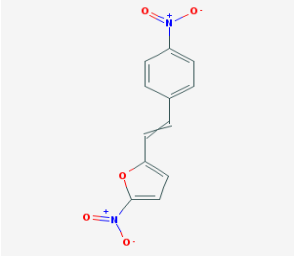
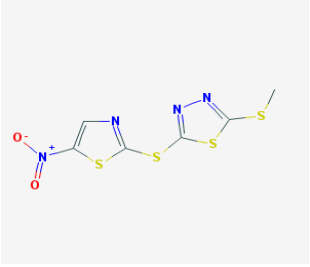
SNo	Name	Structure	Ref
1	2-nitro-5-(4-nitroStyryl)furan (MW=260.20)		31
2	2-(methylthio)-5-[(5-nitro-1,3-thiazol-2-yl)thio]-1,3,4-thiadiazole) (MW=292.39)		31

TABLE 1. DETAILS OF ANTIFUNGAL COMPOUNDS SELECTED FOR STUDY

III. RESULTS

A. Alignment and Homology Modeling Of UGM

The details of sequence alignment of *Leishmania* species and *T cruzi* are given in the figure 1. On comparing the *Leishmania* UGM sequence with that of other Leishmania spp and *T cruzi* UGM, most of the amino acid residues are highly conserved among Leishmania spp. However, variation in amino acids residues between *T. cruzi* and *L. donovani* UGM sequence is visible.

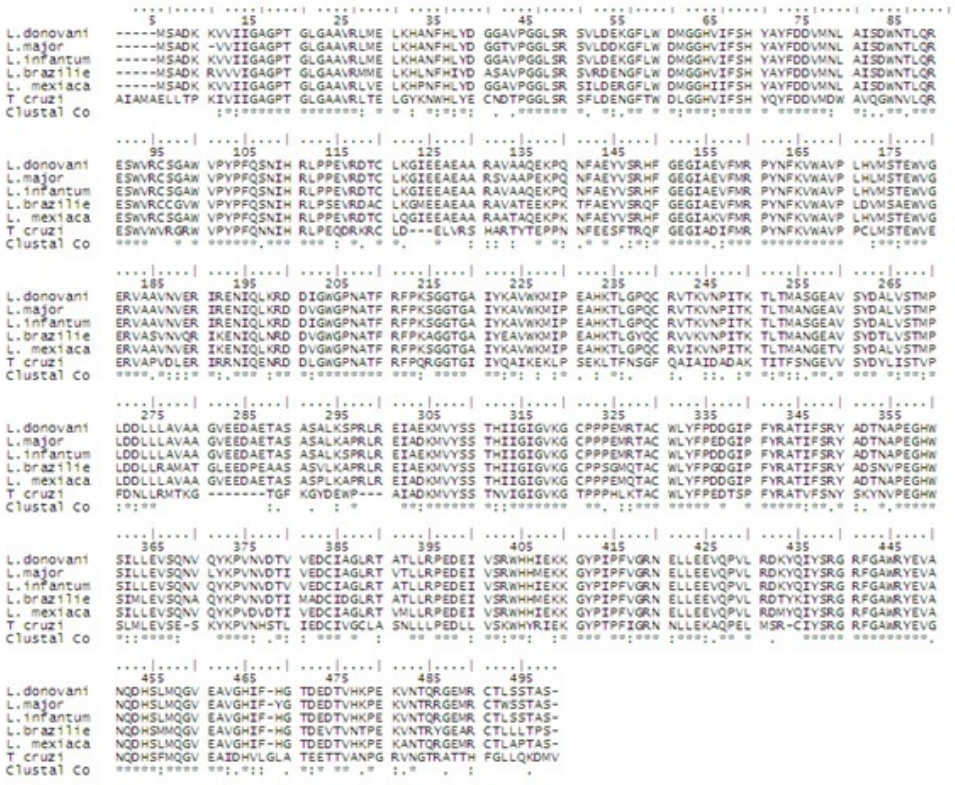


FIGURE 1. ALIGNMENT OF AMINO ACID SEQUENCES OF (UGM) OF *LEISHMANIA SPECIES*AND *T CRUZI.* * INDICATES THE CONSERVED SITES; - REPRESENTS A GAP INTRODUCED FOR ALIGNMENT OPTIMIZATION.

B. Template Alignment and Modeling

The target sequence was searched with BLAST against the primary amino acid sequence contained in the SMTL. A total of 41 templates were found. Further, an initial HHblits profile has been built using the procedure outlined in [25] followed by 1 iteration of HHblits against NR20. The obtained profile has then been searched against all profiles of the SMTL. A total of 1868 templates were found. Overall 2846 templates were found and the best template 4DSH (*T cruzi* UDP galactopyranose mutase) was selected for model making (table 2)

SNo	species	Template (PDB ID)	Sequence identity	Sequence similarity	Search by	Sequence coverage
1	*T cruzi*	4dsh.1.A	59.87	0.48	HHblits	0.95

TABLE 2. DETAILS OF *T.CRUZI* TEMPLATE CHAIN AS SELECTED FOR HOMOLOGY MODELING.

C. Structure Analysis

The homology model of *L. donovani* UGM was viewed on PyMOL. (Figure 2). As shown in the figure 2 the UGM model is composed of α-helix and β sheets. The overall structure is a monomer and single chain. In addition, the homology model shows a negative Qmean score (-2.5).Further structure analysis was done for the presence of pockets on the protein surface which has been mentioned further.

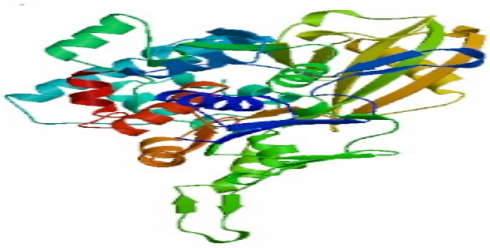


FIGURE 2. THE THREE DIMENSIONAL VIEW OF MODELED STRUCTURE OF *Leishmania* UGM (PDB FILE DOWNLOADED FROM SWISS MODEL SERVER)

D. Structure Validation

The PROCHECK analysis shows that the 87.7% residues are in most favored region including 11.9% in additionally allowed region. Moreover 0.5% residues are found in generously allowed region. No residue is found at disallowed region (figure 3 and table 3).

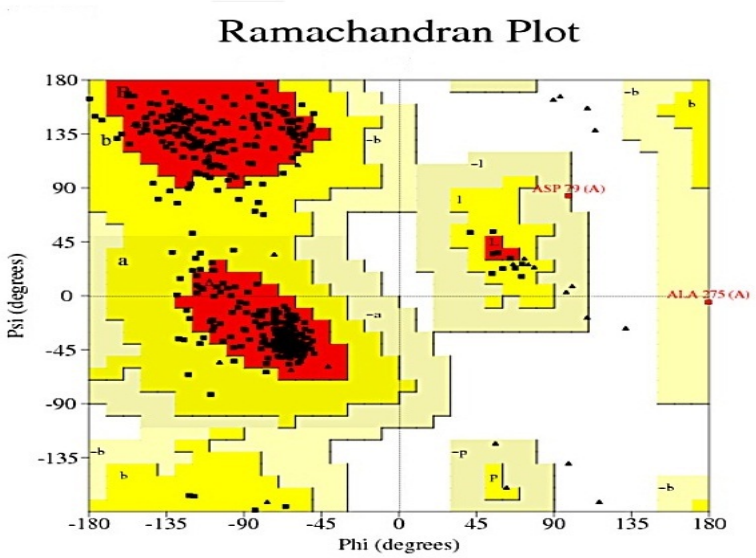


FIGURE 3. RAMACHANDRAN PLOT OF *LEISHMANIA* UGM STRUCTURE SHOWING THE POSITIONS OF AMINO ACIDS

Plot Statistics		
Residues in most favored regions	362	87%
Residues in additional allowed regions	49	11.9%
Residues in generously allowed regions	2	0.5%
Residues in disallowed regions	0	0.0%

TABLE 3. DETAILS OF PROCHECK ANALYSIS OF MODELED STRUCTURE OF *Leishmania* UGM

ERRAT statistics shows that the overall quality factor for the modeled structure was found to be 91.966%. The ERRAT plot is shown in figure 4.

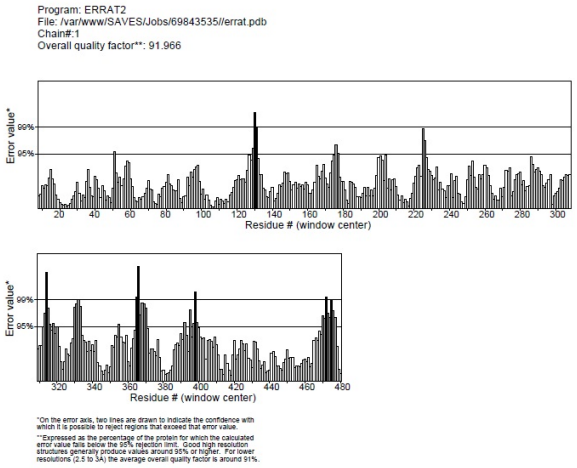


FIGURE 4. ERRAT PLOT SHOWING THE ERROR VALUE PER RESIDUE

E. Pockets on Surface

Further, the constructed model UGM was scanned topologically and the result obtained from the server shows the presence of three domains on its surface which bind UDP, FAD and SO4 as ligands (Table 4) As shown in the table 4

Pocket	ligand	Binding residues
1	FAD	Ile10 Pro14 The15 Asp35 Leu43 Ser44 Met57 His60 Val61 Cys235 Arg236 Val237 Thr263 Met264 Thr306 Tyr407 Arg436 Ala445 Asn446 Gln447 Ser450
2	GDU	Tyr98 Pro99 Phe100 Gln101 Phe153 Met154 Tyr157 Asn158 Trp162 Arg177 Val178 Asn202 Tyr328 Arg338 Tyr407 Tyr442
3	SO4	Pro318 Pro319 Arg390 Glu320
4	UDP	Phe137, Met 154 Asn158, Val178 Trp 173 Trp 162, Tyr 442, Tyr402 Arg177 Ala 179, Tyr 157, Val 161, Tyr 98, Tyr328, Arg 338, Trp 326, Gln 101 Phe 153, Phe100, Pro99

TABLE 4 THE DETAILS OF BINDING RESIDUES ON EACH POCKET ON THE SURFACE OF *L. DONOVANI* UGM WITH RESPECTIVE LIGAND

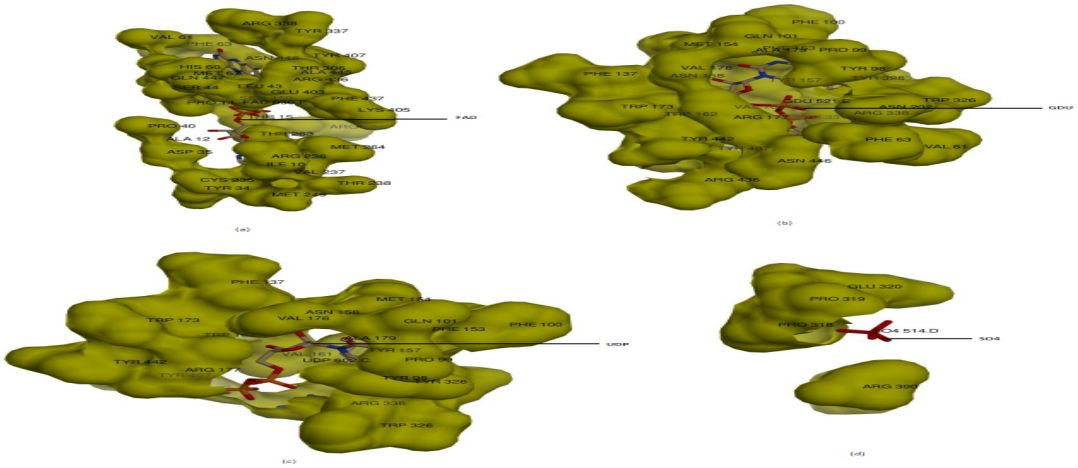


FIGURE 5. REPRESENTATION OF POCKETS ON THE SURFACE OF L. DONOVANI UGM WITH THE LIGANDS (A) FAD (B) GDU (C) UDP AND (D) SO_4

F. Docking With Antifungal Compounds

To understand the interaction between the *L.donovani* UGM and antifungal synthetic compounds, docking studies were perfrmed using Autodock4 program. The antifungal compounds were selected randomly from the previous studies and binding models were predicted. Figure 6 represent the docking poses of the 2-(methylthio)-5-[(5-nitro-1,3-thiazol-2-yl)thio]-1,3,4-thiadiazole (compound 1) and 2-nitro-5-(4-nitroStyryl)furan (compound 2). The predicted model of compound 1 shows the H- bonding interaction with residues at binding site i.e Arg177, Tyr442, Try407, Asn446, Phe63, Asp448, Gln447, Arg436 (figure. 6). On the other hand Arg436, Leu43, Gln447, Ser44, Ser450, Pro14, Thr15 residues interacts nicely with compound 2 at the protein binding site (figure 6) (table 5). Moreover both the compounds binds at the same regions as activator/ substarte binds i.e FAD, **GDU** and UDP respectively. Residues Tyr442, Tyr407 and Arg177 are binding residues for UDP, also involved during the interaction of compound 1 with UGM. Additionally, Gln447, ser44,Arg436,ser450, Pro14 and Thr15 are present at binding pocket when FAD interacts with UGM. Same residues are involved when compound 2 bind UGM.

SNo	Compounds	Binding Energy	Binding residues
1.	2-(methylthio)-5-[(5-nitro-1,3-thiazol-2-yl)thio]-1,3,4-thiadiazole) [compound 1]	-8.20 kcal/mol	Arg177, Tyr442, Tyr1407, Asn446, Phe63, Asp448, Gln447, Arg436
2.	2-nitro-5-(4-nitroStyryl) furan [compound 2]	-7.70 kcal/mol	Arg436, Leu43, Gln447, Ser44, Ser450, Pro14, Thr15

TABLE 5.THE ANTIFUNGAL COMPOUNDS SHOWING THE BINDING ENERGY AND BINDING RESIDUES. COMMON BINDING RESIDUES BETWEEN FAD/UDP AND COMPOUNDS ARE UNDERLINED

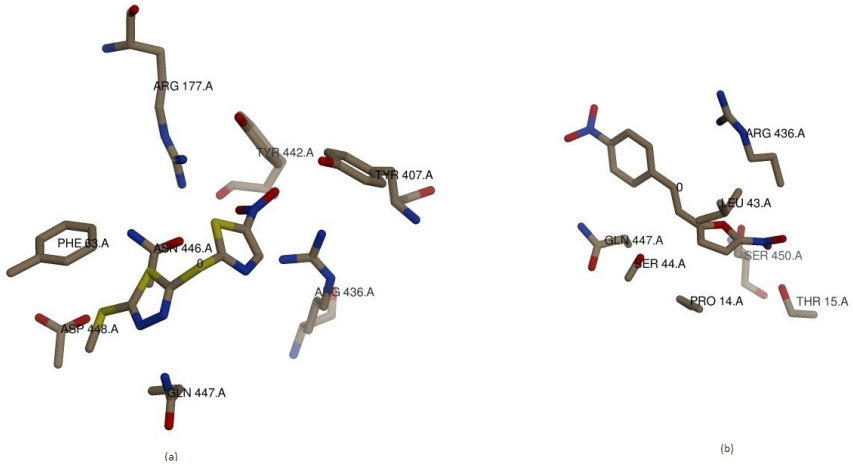


FIGURE 6. DOCKING POSES OF (A) 2-(METHYLTHIO)-5-[(5-NITRO-1,3-THIAZOL-2-YL)THIO]-1,3,4-THIADIAZOLE) (B) 2-NITRO-5-(4-NITROSTYRYL) FURAN. 0 INDICATES THE POSITION OF HETEROATOM i.e LIGAND (ANTIFUNGAL COMPOUND) SURROUNDED BY ALL INTERACTING AMINO ACID RESIDUES SHOWING THEIR POSITIONS IN THE PROTEIN CHAIN.

G. Model Availability

The PDB file of homology model of *L. donovani* UGM was submitted to Protein Model Data Base (http://www.caspur.it/PMDB) and an ID has been assign to this structure. This model is now available at PMDB website with ID PM0080084.

IV. CONCLUSION

Leishmaniasis is a major public health problem and there are no effective vaccine is available till date. The disease control strategy is not very reliable as well as costly to make its reach to every needy person. However, the present repertoire of drugs is very restricted and increasing drug resistance has posed a major concern. The first step in drug discovery is to identify a suitable drug target. As we have known a lot from the genome sequences of *Leishmania* which gives opportunity to identify novel drug targets

that are unique to these parasites. To the best of our knowledge no structure (homology model and crystal structure) is available for *L. donovani* UGM. We constructed a homology model of *L. donovani* by automated method using the crystal structure of *T. cruzi* as template. The server produced a good quality three dimensional model as depicted by Qmean Z-score - 2.5 where negative value indicates reliability of the structure. Further, PROCHECK analysis of our modeled structure of *Leishmania* UGM proves that the stereochemically structure is fine. Moreover ERRAT plot also shows satisfactory values for the structure. Moreover the topological analysis of this homology model has the FAD, UDP, GDU and SO4 binding pocket on its surface, as predicted by the online server. Further to predict the binding models of homology structure of *L. donovani* UGM, a molecular docking was performed with two antifungal compounds. The predicted binding model of both compound 1 and 2 interacts with the same amino acid residues at the binding region of UGM as those binds with FAD, UDP, activator and substrate (table 6). These evidences suggest that the both compounds interfere at the functional site of the UGM. Since previous studies revealed that Gal_f is an important constituent of LPG (Lipophosphoglycan) and GIPL (Glycoinositolphospholipids), which are known to be essential molecules for parasite survival as well as infectivity to mammalian host. [32-36]. It has been observed that for host parasite interactions, cell surface plays a crucial role in the recognition of host and evading the immune system. The importance of LPG and GIPL are well studied and observed that these molecules facilitates host specific cell recognition, growth of parasite and subsequent pathogenesis. Inhibition of UGM results in lack of Gal_f molecules subsequently unable to produce LPG and GIPL in *Leishmania* promastigotes, thus parasite survival is reduced in mammalian host lead to disease elimination. Concluding that this is the first homology model for *L. donovani* UGM interacts with antifungal compounds at the same site where FAD and UDP interact. Thus our proposed homology model and predicted binding modes of compound 1 and 2 would be useful for future drug designing against *L. donovani* and could offer a probable remedy for the disease.

V. ACKNOWLEDGMENT

Financial assistance received from SERB, Department of Science and Technology (SB/YS/LS-203/2013), New Delhi, India is greatly acknowledged. AS is highly thankful to SERB, New Delhi for Young Scientist fellowship.

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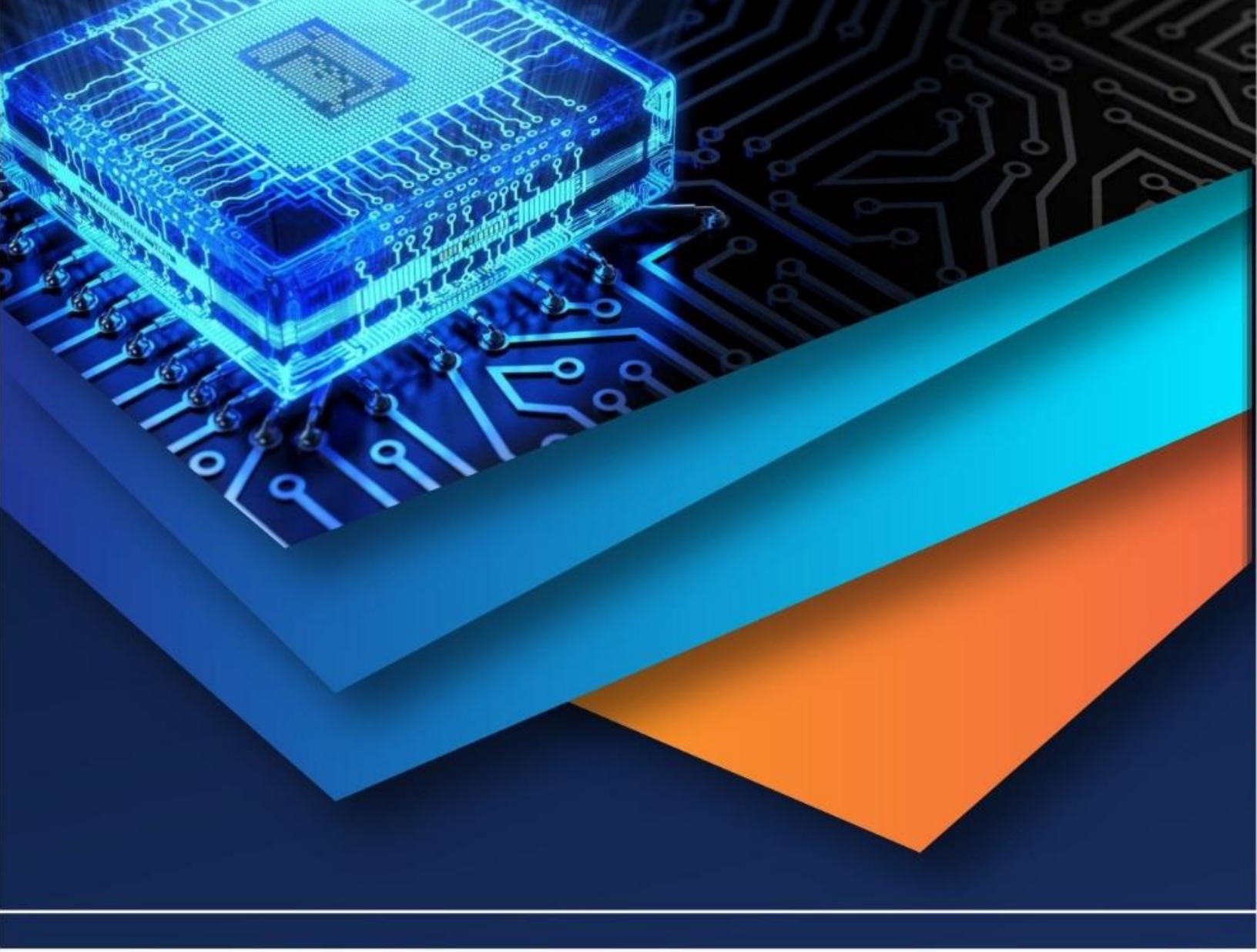

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