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Research Article

Structural Analysis and *In-Silico* Inhibitor Interaction Studies of Leishmania donovani Heat-Shocked Proteins 83 (HSP83)

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Abstract: Leishmaniasis is a parasite disease prevalent in 88 nations worldwide, causing high morbidity and mortality in most developing countries. Since no vaccine or pharmaceutical treatment with the best therapeutic window is available, the World Health Organization has listed Leishmaniasis as a priority disease. The enzyme heat shock protein 83 (Hsp83), which is frequently found in cells, catalyzes cellular biological pathways to carry out tasks such as protein folding, intracellular protein trafficking, acquired thermotolerance, differentiation, adaptability, pathogenicity, persistence in the host cell and preventing proteins from being damaged by heat and other stresses. Therefore, HSP actively rewires cellular functions and signalling pathways, which is crucial for cell survival. Inhibition of HSP may interfere with pathogenesis and virulence by impairing several processes. Therefore, *L. donovani* heat shock protein 83 (LdHsp83) has been suggested as a potential leishmaniasis therapeutic target. Thus, in this study, we built the structure of HSP83 by homology modelling. We used *Leishmania primary* HSP90 crystal structure (PDB ID 3HJCA) as a template for constructing 3D models of LdHSP83 by comparative modelling approach using SWISS-MODEL, Phyre, GENO 3D program server and Prime 2.1 (Maestro 9.1, Schrodinger 2010) program tool. Based on overall stereochemical quality (PROCHECK, DOPE, Verify 3D), the best model was selected and further used for structural analysis. The energy-minimized, refined and characterized model was further investigated for antileishmanial activity with currently available antileishmanial drugs and enumerated virtual library of chemical compounds through a docking approach. A few combinations, including oxmetidine, had an excellent binding affinity with the Hsp83, as indicated by Glide Score (G Score) and Gold Fitness Score. These potential inhibitors were further studied for SAR and ADMET properties, respectively, by TSAR 3.3 and Qikprop 2.3, indicating the safety and efficacy of these compounds. Once preclinically and clinically examined, these compounds may further be implemented in leishmaniasis therapy.

Keywords: *Leishmania donovani,* Molecular Chaperone, Heat Shocked Proteins 83(HSPs 83), Inhibitor Search, Docking Study

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1. INTRODUCTION

Large tracts of the tropics, subtropics and the Mediterranean basin are habitats to the endemic disease leishmaniasis, which is spread by the bite of specific species of sand flies and is caused by obligate intramacrophage protozoan parasites of the genus *Leishmania.* [1]. It is caused by more than 23 different leishmanial species and spreads to people via 90 various species of sandfly including *Phlebotomus* and *Lutzomyia*. [2]. Of four main clinical types, Visceral Leishmaniasis (VL) is the most fetal. In most cases, VL develops gradually, starting with a low-grade fever and malaise, progressing to wasting and anaemia, protrusion of the abdomen from an enlarged liver and spleen, and ultimately, death in 2-3 years.[3]. The majority of instances, according to the World Health Organization (WHO), are found in India, East Africa, and Brazil. Each year, between 50 000 and 90 000 new cases of VL are thought to occur worldwide, although only 25 to 45 per cent of those cases are reported to WHO. It continues to rank among the most dangerous parasitic illnesses in terms of potential death. In 2020, ten countries—Brazil, China, Ethiopia, Eritrea, India, Kenya, Somalia, South Sudan, Sudan, and Yemen—accounted for more than 90% of all new cases reported to the WHO. [4]. The search for unique potential drug for treating visceral Leishmaniasis has been relatively constrained throughout the majority of the last 80 years. In the 1940s, meglumine antimoniate and sodium stibogluconate, the two pentavalent antimonials were first developed. After a few decades, amphotericin B was used, and then paromomycin, an inexpensive parenteral medication with a manageable toxicity profile. A significant development was the discovery of miltefosine, the only medication currently available for the oral treatment of visceral Leishmaniasis. [5] Eventually, various lipid amphotericin B formulations have been produced, including liposomal amphotericin B, which has similar efficacy to amphotericin B but less severe side effects. Since there are no effective human immunizations and efforts to control the vectors are challenging, chemotherapy is the sole therapeutic strategy. However, the drugs being utilized have several drawbacks. [6] They are expensive and toxic, and parasite resistance is also preventing them from working. This resistance is primarily to antimony, which, after nearly 70 years, still serves as the basis for antileishmanial and causes severe adverse reactions like nausea, vomiting, diarrhoea, and renal impairment when combined with miltefosine. To develop new medications that overcome the limitations of existing ones, researchers are looking at new biochemical targets because the current leishmaniasis treatment faces several issues. Therefore, there is an urge to discover novel potential inhibitors against *Leishmaniasis*. [7]. Heat Shock Proteins (HSPs) work as molecular chaperones and are crucial for protein folding, intracellular protein trafficking, and repairing proteins that have been damaged by heat and other stressors.[8]. HSPs are principally responsible for inducing the massive overexpression of the (HSPs), which is a crucial component of the heat shock response in both the stages of *Leishmania.*[9]. Certain enzymes of HSPs can be targeted to discover the potential antileishmanial drug. HSP83 may be targeted to discover an antileishmanial drug that will be significant for leishmaniasis patients by blocking the function required for survival and differentiation of the leishmania protozoan parasite. A computational approach to finding inhibitors is a less expensive and less time-consuming process, and it has produced a promising therapeutic candidate using structure-based virtual screening. In the present work, the 3D structure of *Leishmania donovani* HSP83 was built using homology modelling, which was further used for molecular docking studies to find an inhibitor that may be promising as an anti-leishmanial drug. The physicochemical and toxicological properties of potent molecules were tested using TSAR 3.3 and Qikprop 2.3.

2. MATERIALS AND METHODS

2.1 Retrieval of protein sequences and Template crystal structures

The sequence of *L. donovani* HSP83 was retrieved from UniProtKB (http://www.uniprot.org/) database with Primary accession number P27890.[10] To obtain the closest match for the retrieved series, a BLAST search of a query sequence was performed against Protein Data Bank (http://www.pdb.org/pdb/). [11]. Several templates were found from the PDB database and ranked based on their identities, similarities and E-value. Finally, the selected template was used to build the model by pairwise sequence alignment using Clustal 2.1X standalone tool. [12].

2.2 *Primary sequence analysis*

The Prot Param tool was used to estimate various physical and chemical parameters of *L. donovani* HSP83. Atomic composition, theoretical pI, amino acid composition, molecular weight, extinction coefficient, predicted half-life, instability index, aliphatic index, and the overall hydropathicity are among the metrics that were calculated (GRAVY).[13]). The tool, BioEdit was used to determine the essential functions for protein and nucleic sequence editing, alignment, manipulation and analysis.[14].

2.3 *Secondary structure prediction of HSP83*

The self-Optimized Prediction Method (SOPM) was used to predict the secondary structure of proteins based on the alignment with proteins belonging to the same family. This improved SOPM method indicates amino acids for a three-state description of the secondary structure (alpha-helix, beta-sheet and coil) in a database containing 126 chains of non-homologous (less than 25% identity) proteins. In addition, joint prediction with SOPMA and a neural networks method (PHD) correctly predicts 82.2% of residues for 74% of co-predicted amino acids. [15].

2.4 *Prediction of Protein Family*

Prediction of protein function is of significance in studying biological processes. One approach for function prediction is to classify a protein into the functional family. Support Vector Machine (SVM) is a valuable method for such classification, which may involve proteins with various sequence distributions. The SVMProt classification system is trained from representative proteins of a number of functional families and seed proteins of Pfam-curated protein families. [16].

2.5 Homology modelling

Building the experimental three-dimensional structure of the target protein from the amino acid sequence of a comparable homologous protein 3D protein based on sequence alignment of target and template is referred to as homology modelling. As the 3D structure of HSP83 is absent, the protein homology model was built using different software such as Prime 2.1[17],

Swiss model [18], Phyre [19] and Geno 3D [20]. In addition, the model was further validated using other validation tools.

2.6 *Prediction of Binding Site of L. donovani HSP83*

The primary binding site on a receptor, such as a protein, is frequently revealed by the structure of a co-crystallized complex. However, the specific position of a binding site for interactions between proteins and their ligands or other proteins is occasionally unknown beforehand. Predictions about potential binding sites and the likelihood that a specific protein will bind ligands strongly can be made in this situation with the help of computer analysis. The binding site of *L. donovani* HSP83 was predicted using Site Map, which searches binding sites using a novel search grid of points called site points. To locate the sites after that, contour maps (site maps) are generated, producing hydrophobic and hydrophilic maps [21].

2.7 *In silico screening Procedure*

A virtual library was designed by retrieving all antibiotics including peptic ulcer inhibitors, novobiocin, geldanamycin, and coumermycin drugs, from the PubChem compound database on the National centre for biotechnology information (NCBI) server. A total of 295 compounds were selected and led to ligand preparation using ligprep 2.3 of *Maestro 9.1 suite of Schrodinger* [22]. As a result, a total of 5373 confirmation was obtained.

2.8 *Validation of docking and rescoring procedures*

Docking is a technique used in the science of molecular modelling that forecasts the preferred orientation of one molecule (ligand or macromolecule) to another molecule (macromolecule) when they are coupled together to create a stable complex. [23] The strength of the connection or binding affinity between two molecules can therefore be predicted using, for instance, scoring algorithms employing knowledge about preferred orientation. In this work, we used various scoring methods such as Grid-based Ligand Docking with Energetics (Glide) and Genetic Optimization for Ligand Docking (GOLD) to determine the binding affinity. To find potential ligand positions in the receptor's active-site area, Glide employs a hierarchical set of filters. Multiple groups of fields on a grid that offer increasingly more precise scoring of the ligand postures each represent the shape and characteristics of the receptor. [24-25] While, GOLD explores the entire range of ligand conformational flexibility using a genetic algorithm and permits protein target flexibility to a limited extent.[26]. Similar type of Docking interaction on Leishmania was performed by many publishers that showed promising results in in-vitro studies.[27,28]

2.9 *Prediction of ADMET analysis*

Based on Lipinski's rule of five, the physicochemical properties and absorption, distribution, metabolism, excretion and toxicity (ADMET) properties were calculated using QikProp [29] and TSAR 3.3 [30].

3. STATISTICAL ANALYSIS

The 3D model of the *L.donovani* HSP83 was built by Prime version 2.1, Swiss model, Phyre and Geno 3Dtools. The compounds were optimized using OPLS 2005 force field using ligprep, *version* 2.3, Maestro 9.1 suite of *Schrodinger*. The molecular nitration studies were performed by Glide *version* 5.5, Maestro 9.1 suite of *Schrodinger* and GOLD *version* 2.1. QikProp and TSAR 3.3 did the ADMET analysis.

4. RESULTS AND DISCUSSION

4.1 *Primary Sequence Analysis of HSP83*

The primary sequence of *L. donovani* HSP 83 UniProt ID; P27890 was retrieved in FASTA format having a sequence length: of 452 aa. The theoretical pI of protein was found to be 5.65. The total negatively charged residues (Asp + Glu) were found to be 82, and positively charged residues (Arg + Lys) were 74, as estimated by Protparam. The protein contains Glu and Lys residue, which indicate the protein's polar and hydrophilic nature, as shown in Figures 1a & 1b. The Grand average of hydropathicity (GRAVY) of protein is -0.669.

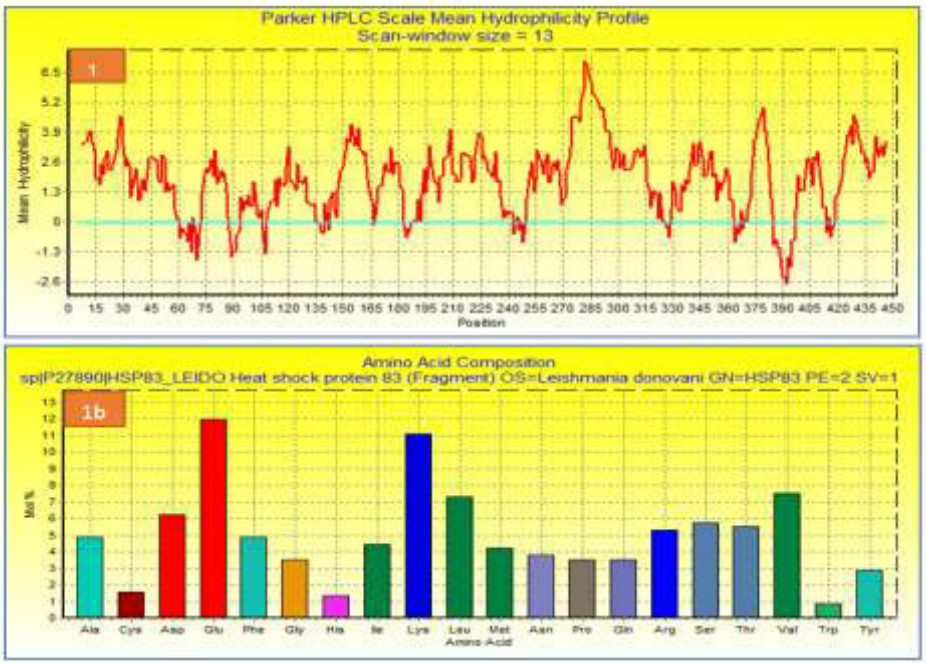

Fig 1a. Amino Acid Composition (1b) Hydrophilicity Profile Of *L. donovani* HSP83

4.2 *Secondary Structure Analysis of L. donovani HSP83*

The secondary structure of *L. donovani* HSP83 was estimated using SOPMA, which indicated the protein has 54.42% of alpha helix, 30.09% random coil, 11.95% of extended strands and 3.54% beta-turn. The systemic arrangement of the secondary structure sequence-wise is shown in Figure 2.

4.3 *Protein functional family of Leishmania HSP83*

The protein was predicted to belong to the Zinc-binding family with a P-value of 92.1%, All DNA-binding families with a P-value of 89.3% and DNA replication function with a P-value of 73.8% as predicted by SVMPROT.

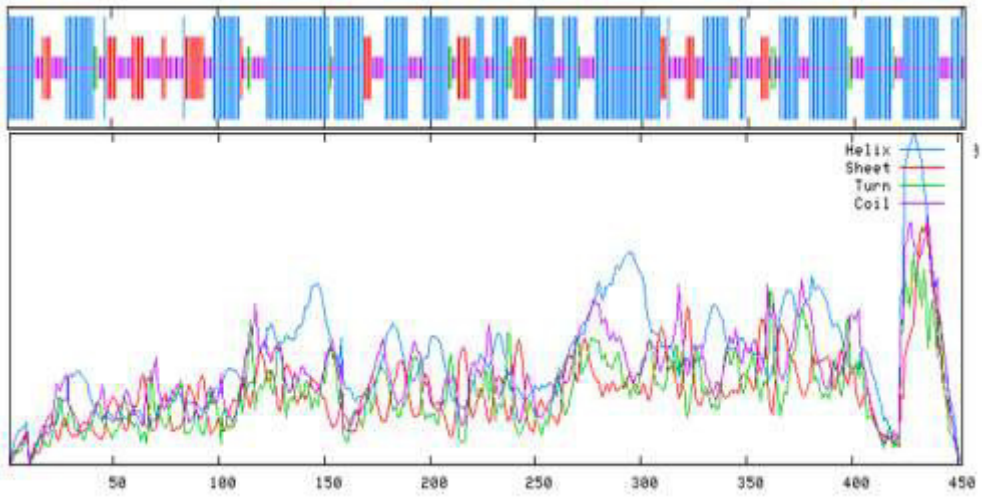

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Fig 2. Depicting The Secondary Structure Components Of HSP83

4.1 *Homology modelling*

4.1.1 Template selection and sequence alignment

A BLAST search was performed against the protein data bank (PDB) with the default parameter to find a suitable template for homology modelling. The sequence was aligned and the one that showed the maximum identity with a high score and lower e- value and 96% sequence identity was used as a reference structure to build a 3D model for ldHSP83 respectively. The ldHSP83 was modelled using a comparative modelling procedure using the PDB having ID 3HJC "Carboxy-Terminal Domain of Hsp80 as a template with a length 444 from *Leishmania* major, and the sequence alignment was carried out by Clustal 2.1X standalone tool as shown in Figure 3. The overall alignment of the query and template is suitable, along with query coverage, which indicates that the selected template is best suited for building the model.

Fig 3. Alignment For HSP83 Sequence Of *Leishmania donovani* With Template 3HJC_A

4.2 Model Building and Validation

The models are built from online servers and commercial tools such as Swiss, Phyre, Geno 3D and Prime2.1, and the Maestro 9.1 suite of Schrödinger. Discrete optimized potential energy (DOPE) indicates the stability of protein structure and the possibility of meeting the conformation of experimentally solved structure. Therefore, the predicted models were checked for the DOPE score. The model built using Prime was found to be more acceptable with the lowest DOPE score (-47469) among others and thus selected for further validation study (shown in Figure 4).

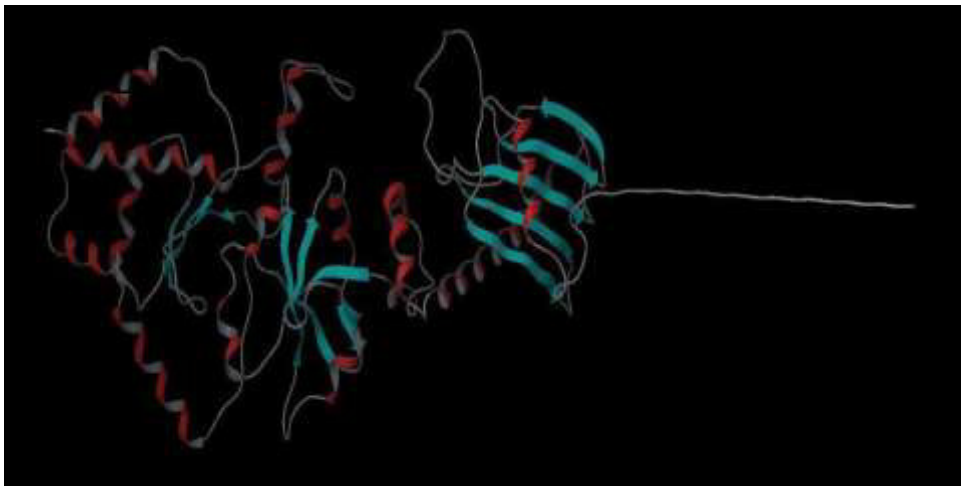

Fig 4. 3D View Of Prime Model Of *Ld*hsp83

Ramachandran plot qualities show the per cent of residues belonging to the plot's favourable, allowed and disallowed regions based on psi and phi torsion angles. PROCHECK assessed the overall stereochemical quality of the models. The model constructed by Prime2.1 showed 93.1% residues in favourable, 6.7% in additional allowed and 1% in the disallowed region (Leu 120), as shown in Figure 5. Overall, the active site residues fell into the qualified area, validating the model's good stereochemical quality.

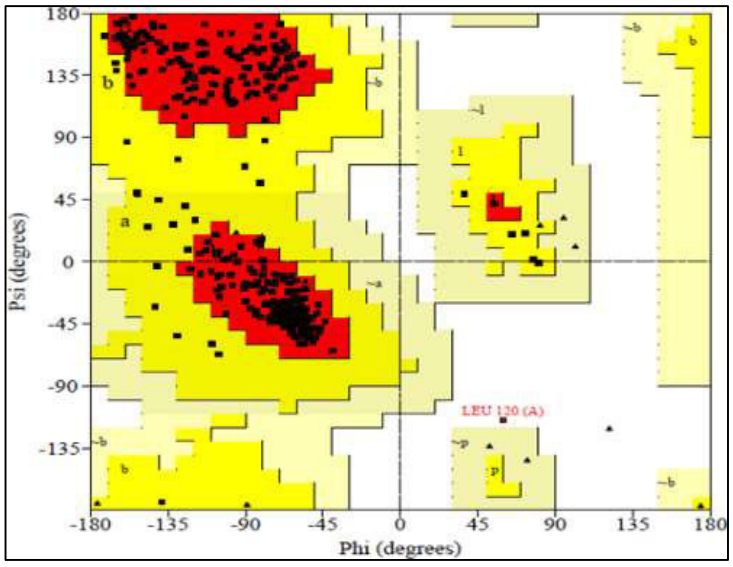

Fig 5. Ramachandran Plot Analysis Of Prime Model Of HSP83 Of *L. donovani*

The packing quality of each residue was assessed by the Verify 3D program, which uses a score function to analyze the compatibility of the residues with their environment in models. The vertical axis represents the average 3D-1D protein score for each residue in a 21-residue sliding window to help further validate the models. Residue with a score over 0.2 should be considered reliable. The score for all refined structures maximally lies above 0.2 which corresponds to an acceptable side-chain environment. To investigate how well the modelled system matches the X-ray data of the template, the prepared models and template were superimposed on the backbone atoms. The RMSD value of backbone atoms is reasonably good and quite similar to the template. The model built with Prime showed 100% superimposition and 0% RMSD as shown in Table 1. Entire evaluations suggest the suitability of the overall homology model for HSP83 of *L. donovani* built from Prime 2.1 (Maestro 9.1) and therefore selected to examine the protein-ligand interactions using docking studies.

Table 1. 3D-1D, RMSD evaluation scores for models		
Models	**Verify 3D-1D score**	**RMSD**
Template (3HJC_A)	0.84	-
Swiss model	0.71	0.052
Prime model	0.81	0.000
Phyre model	0.76	1.646
Geno-3D model	0.67	0.528

4.3 identification of active sites by using SiteMap

Out of five sites predicted by SiteMap 2.3, Site 1 was expected to be active, as shown in Figure 6. It consists of X (-71.24), Y (16.43) Z (1.97) coordinates of protein receptors. Site 1 binding site might be the active site as it has good volume, hydrophilic- hydrophobic surface map region as compared to other binding sites and was taken further for docking studies. In addition, the binding site covers domain residues critical to the chaperone activity of HSP83.

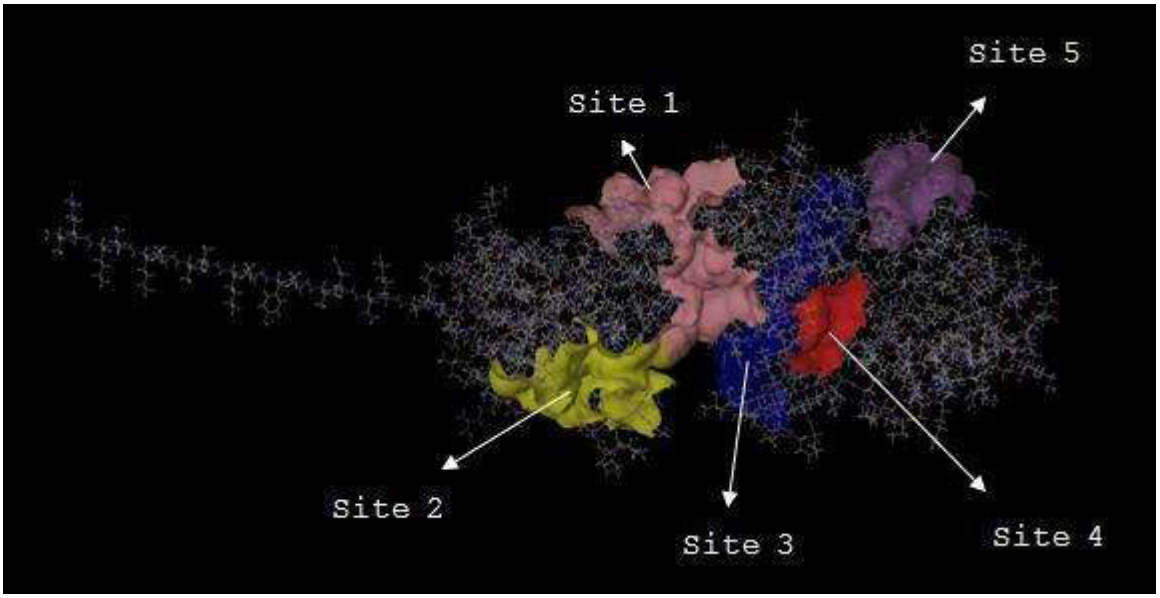

Fig 6. Active Site Characterization Of HSP83 Of *L. donovani.*

4.4 Protein-ligand interaction

All compounds in the virtual library were docked into Site 1 coordinates of the binding site of LdHSP83 by Glide and GOLD 2.1. These compounds were ranked based on their Glide Score and fitness score obtained using Glide 5.5 and GOLD 2.1, respectively. Sonali Das *et al.* have also performed docking studies on *L. donovani* HSP78 using GLIDE and GOLD tools and found potential lead compounds verified by experimental results.[31] The docking via random screening of different antibiotics, including peptic ulcer inhibitors, novobiocin, geldanamycin, coumermycin drugs etc., was performed against the target protein. The top potential inhibitors core has been selected according to their ranked GScore and Fitness Score as shown in (Table 2, Figure 7)

Table 2. Glide score and Fitness score of top potential inhibitors			
PubChem CID/ Name	**PubChem/ IUPAC name**	**Glide Score**	**Fitness Score**
51710/ oxmetidine	5-(1,3-benzodioxol-5-ylmethyl)-2-[2-[(5-methyl- 1H-imidazole-4-yl)methylsulfanyl]ethylamino]-1H-pyrimidine-6-one	-9.8	73.98
18320861/ Polaprezinc	zinc 2-(3-aminopropanoylamino)-3-(1H-imidazol-5- yl) propanoic acid	-9.58	59.98
2680/ Cetraxate	3-[4-[4-(aminomethyl)cyclohexanecarbonyl] oxyphenyl] propanoic acid	-8.76	46.04
932/ Naringenin	5,7-dihydroxy-2-(4-hydroxyphenyl)-2,3- dihydrochromen-4-one	-8.17	59.75
47610/3-o-methylcatechi n	2-(3,4-dihydroxy phenyl)-3-methoxy-3,4-dihydro- 2H-chromene-5,7-diol	-7.59	58.83
78168/5-	5-(hydroxymethyl)-1H-pyrimidine-2,4-dione	-7.57	34.36

hydroxymethyl uracil			
107684/ Promac	zinc 2-[(3-azanidyl-1-oxidopropylidene) amino]-3- (1H-imidazol-5-yl) propanoate	-7.54	51.15
4594/ omeprazole	6-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2- yl)methylsulfinyl]-1H-benzimidazole	-7.26	61.10
15008962/ Pantoprazole sodium	sodium 5-(difluoromethoxy)-2- [(3,4- dimethoxypyridin-2-yl) methylsulfinyl] benzimidazol-1-ide	-7.12	62.12

Out of all, the docking scores of oxmetidine showed the best result using both docking tools. Oxmetidine is a peptic ulcer inhibitor and H2 receptor antagonist. Oxmetidine formed Hydrogen bonding interaction with the following residues of the target receptor active site, such as GLU 163 (O atom formed two bonds), MET 198 (H atom formed one bond) & GLU 247 (O atom formed one bond). In contrast, residues such as TYR 190, LYS 170, and THR 246 are involved in van der walls interactions, as shown in Figure 8, Figure 9 and 10. Docking with both tools depicts that the Oxmetidine is binding with the identical active site residues and in the same pocket with good binding affinity. A similar type of molecular modelling and docking studies to find potential inhibitors for Hsp90 in *Leishmania spp.* was performed by Fernanda A. H. Batista et al. and Luana Carneiro Palma *et al.* [32 -33] that has shown successful candidates in in-vitro studies too. Further, oxmetidine and chemical substituents of oxmetidine may be preclinically tried for pharmaceutical R & D to develop an antileishmanial drug.

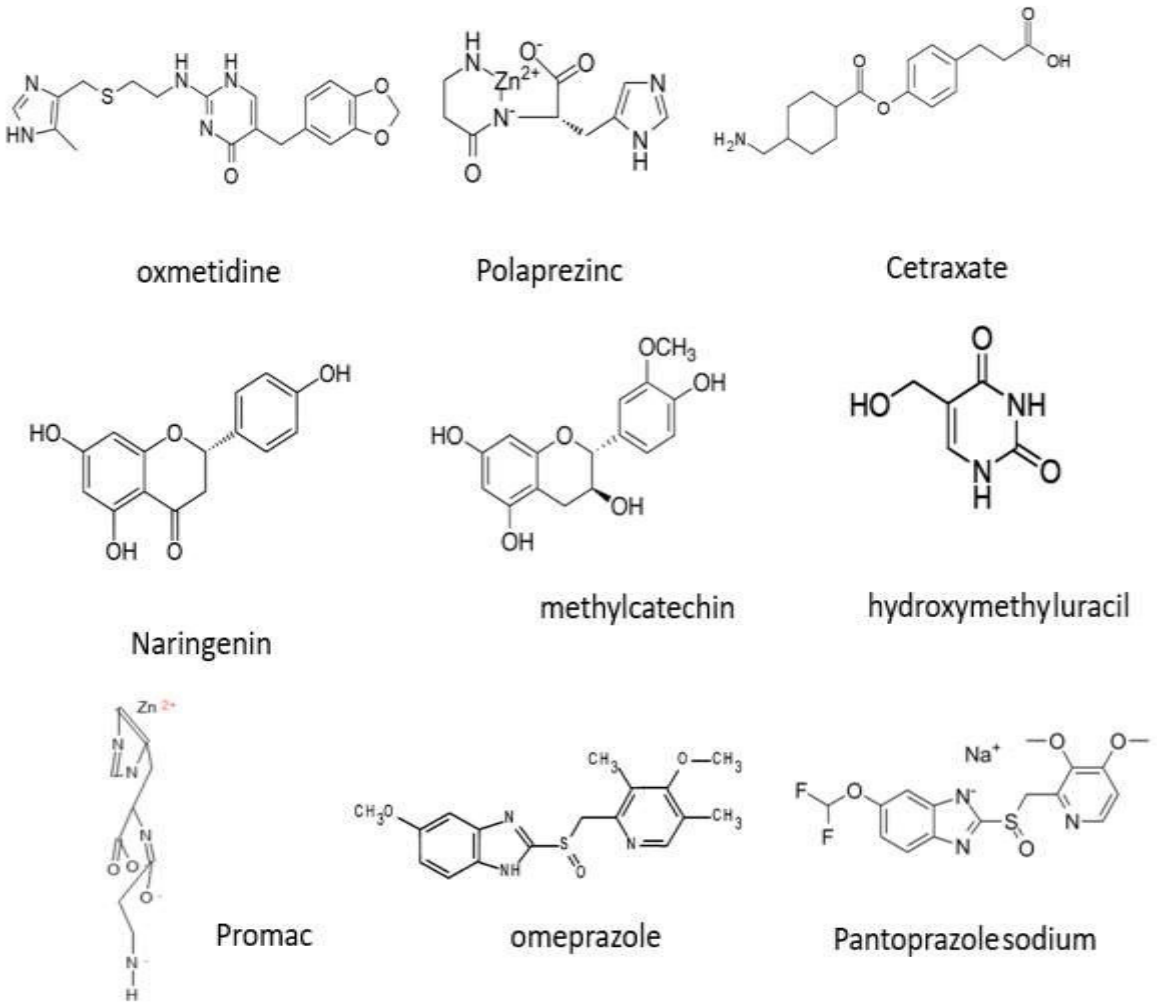

Fig 7. Chemical Structures of Top Potential Inhibitors

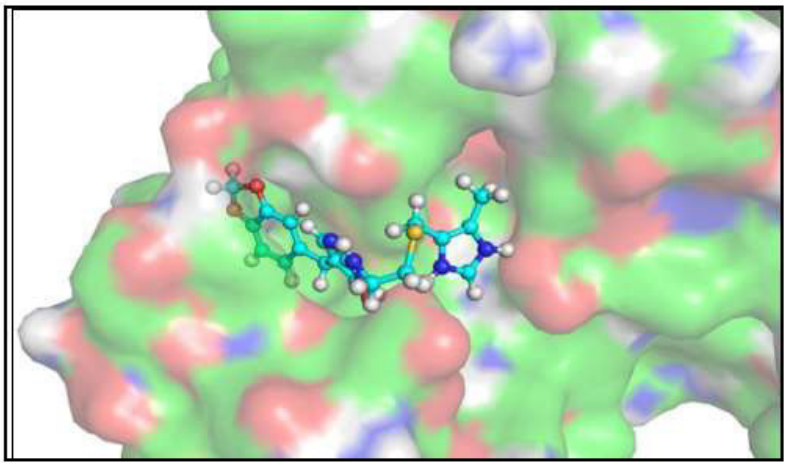

Fig 8. Potential Surface View Oxmetidine Fit In Active Site Cavity of Protein

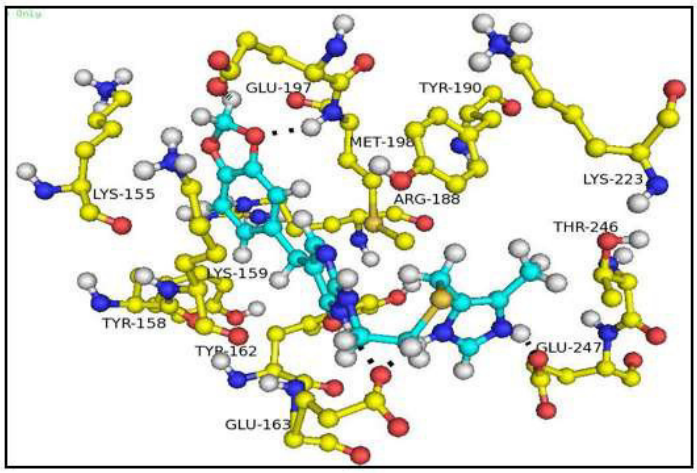

Fig 9. Hydrogen Bond Interactions Shown By Oxmetidine (In Cyan Color) with the Active Site Residues (In Yellow Color). Black Dotted Lines Indicate Hydrogen Bonding Between Ligand and Active Site Residues

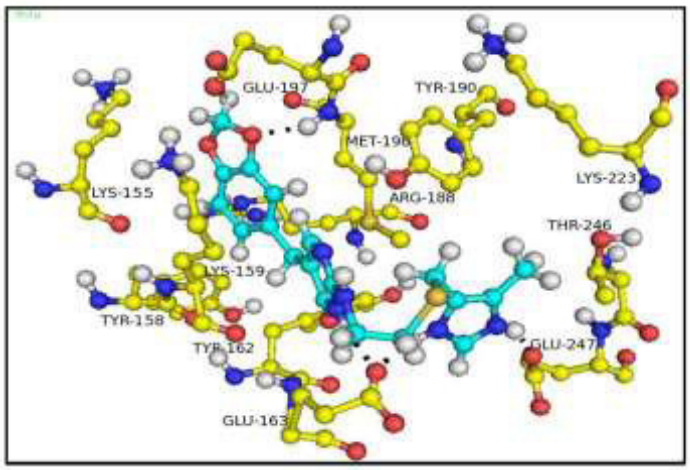

Fig 10. Hydrogen Bonding Interaction Between Oxmetidine and Protein Residues in Silver Viewer of GOLD Results (The Distance Shown in Å)

4.4 *TSAR study*

TSAR is a powerful QSAR, property prediction and statistical analysis tool. It accelerates the design and selection of single compounds and libraries for screening. The top compounds with the best glide score were selected for statistical analysis for a 3D descriptor to measure the number and statistical value of descriptor properties of those chosen compounds. The presence and absence of different descriptors of all compounds selected, calculated and measured with the help of TSAR 3.3 and QikProp are in Table 3(a) and 3(b).

Table 3a. TSAR study of top potential inhibitors

PubChem ID	Molecular surface Area	Molecular volume	Ellipsoidal volume	Total dipole moment	Rotatable bonds	No. of H-bond Donor	No. of H-bond Acceptor	Polarizability (Å3) (13-70)	log P (octanol/water) (-2-6)	logS (water/solid)
CID_18320861	228.629	171.782	263.736	43.7355	5	2	5	18.663	-2.559	0.494
CID_51710	**371.25**	**303.064**	**1992.13**	**20.9748**	**1**	**3**	**7**	**37.01**	**2.867**	**-4.055**
CID_15008962	331.117	256.875	1638.14	6.13877	6	4	6	34.186	2.441	-2.337
CID_4594	335.934	254.23	1741.46	19.4622	6	1	4	35.113	2.23	-2.317
CID_107684	245.634	173.087	439.256	27.7055	1	3	6	20.043	-1.638	-0.854
CID_78168	143.497	100.45	145.515	5.31946	6	1	3	11.842	-0.508	-1.167
CID_47610	282.812	217.179	1179.87	3.57168	5	2	6	29.876	1.247	-3.252
CID_932	244.301	192.342	489.458	3.44844	2	4	5	27.813	1.642	-3.416
CID_2680	316.29	239.887	1075.66	72.6416	6	1	4	32.125	0.114	-3.322

4.5 ADME analysis

Table 3b. ADME analysis of top potential inhibitors by QikProp 2.3

PubChem Id	Polarizability (Å3) (13-70)	log P (octanol/gas) (8-35)	log P (octanol/water) (-2-6)	log S (water/solid)	log IC50 for HERG blockage (<5)	log BB (brain/blood) (-3-1.2)	log Caco-2 P (<25 poor, >500 great)
CID_18320861	18.663	14.245	-2.559	0.494	- 4.043	-1.217	2.399
CID_51710	37.01	21.116	2.867	-4.055	- 5.109	-0.82	989.516
CID_15008962	34.186	18.005	2.441	-2.337	- 5.212	-0.449	53.647
CID_4594	35.113	17.793	2.23	-2.317	- 5.045	-0.645	46.601
CID_107684	20.043	18.141	-1.638	-0.854	- 1.115	-1.581	0.889
CID_78168	11.842	10.159	-0.508	-1.167	- 2.808	-1.274	73.766
CID_47610	29.876	18.86	1.247	-3.252	- 5.004	-1.614	119.981
CID_932	27.813	14.665	1.642	-3.416	-5	-1.387	135.184
CID_2680	32.125	17.99	0.114	-3.322	- 3.798	-1.336	8.876

5. CONCLUSION

The robust homology model of *L. donovani* HSP83 was built in conjunction with docking with well-known HSP inhibitors and peptic ulcer inhibitors to produce valuable structural insights for ligand binding. HSP actively rewires cellular functions and signalling pathways essential for cell survival. We carefully examined the role of the crucial residues in the active site, including GLU 163, MET 198, GLU 247, TYR 190, LYS 170, and THR 246, which are essential for interaction. Nine compounds out of 295 HSP and peptic ulcer compounds displayed more significant interaction. Glide Score (G Score) and Gold Fitness Score suggested that oxmetidine has a better affinity for binding to Hsp83. The SAR and ADMET features of these putative inhibitors were further investigated using TSAR 3.3 and Qikprop 2.3, demonstrating the safety and efficacy of these compounds. These substances may be used additionally for potential application in leishmaniasis therapy after being evaluated for effectiveness in preclinical and clinical settings.

6. AUTHOR CONTRIBUTION STATEMENT

Rani Mansuri and Pankaj Kumar Mundotiya have conceptualized and designed the study, and Anupama Diwan has reviewed and improved the manuscript. In addition, Jagbir Singh provided scientific assistance with tools.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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