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Molecular Characterization of Salmonella SP1 Component Proteins Involved in Pathogenicity and is Used for Potential Drug Targets.

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ABSTRACT

Secretary component proteins (SP1) is highly conserved in Salmonella Typhi outer membrane, it modulate host pathogen interaction that is highly conserved in bacterial outer membrane. The molecular mechanism of pathogenicity is complex and these proteins have a wide range of biological functions from host cell toxicity production and block different signaling pathways. Furthermore, our study is to identify molecular characteristic of SP1 component signaling molecules interplay pathogenicity, molecular interactions, sequence assembly and structural organization and drug binding interactions need to understand. Using Computational drug discovery methods to understand the disease targeted virulence factors in SP1 protein should provide new insight into the new evolution of bacterial pathogenesis which could lead to the development of novel therapeutic drug molecules. Here, we report SP-1 component SopE2, SipA, SopA and SopB proteins in disease pathogenesis and reported the antibacterial drugs that inhibit the disease progression and used as a potential drugs.

Keywords: SP1, Salmonella, Outer membrane proteins, Secretary Proteins, drug design, lead generations.

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INTRODUCTION

Salmonella Typhimurium is a gram negative enterobacterial pathogen possesses a specialized type-III secretary protein (SP-1) toxic effecter proteins inject into host cells, which trigger different signaling cascades such as rearrangement of cytoskeleton, lipid dephosphorylation, cell death in macrophages and other pro-inflammatory cytokines[1]. There are several toxin proteins such as SopE2, SptP, SipA, SopB, SipB, SipC are effective complex to host membrane that is required for translocation into host cell cytoplasm[2]. The SopE2 protein is direct activator of CDC42 protein by RhoGTPase exchange factor and acts as a potent cytoskeleton rearrangement and stimulates membrane to entry into host non-phagocytic cells[3, 4]. The RhoGTPase of host cell contains 10 different proteins that internally bound GDP and GTP activation and inhibition of downstream signalling cascades mediating cellular mobility, cellular adhesion, cytokinesis and gene expression[5, 6, 7]. The characterization of crystal structure has only 69-240 amino acids of which only 78-240 amino acids alone is complex with Cdc42 of two helix bundles, beta bundles and loops that mediates GEF-guanine nucleotide exchange factor through induced fit binding[8]. The SipA protein helps to bacterial internalization with host cells to translocate actin-binding protein that stimulates actin polymerization and triggers F-actin destabilizing proteins[9]. The crystal structure of proteins has chaperon binding domain complex with InvB, SipA shows 497-669 amino acids helps to actin-binding and polymerization[10]. The SopA protein is ubiquitination with host cell physiology to promote bacterial survive. The complex of SopA is internalize with E3 ubiquitination pathway and manipulated host pro-inflammatory response. The crystal structure contains two complex domains HECT-domain E3c complex and putative substrate binding domain is located near E2-ubiquitin binding site, this results SopA is selective effecter of host-bacterial interface[11]. SopB is an inositol phosphate phosphatase transition and GTPase binding activity protein. The inositol Cdc42 of RhoGTPase complex structurally and functionally mimics guanine nucleotide dissociation inhibition (GDI) by regulating GTPase nucleotide exchange and converts phosphatidylinositol 3, 4, 5-triphosphate (PtdIns 3,4,5-P3) protein. The persistence of PtdIns complex enters endocytic pathway results in vesicles enlarge and avoid immune system[12, 13]. In this study, we described secretary proteins SopE2, SipA, SopA and SopB proteins involved in pathogenesis, using computational drug discovery methods to predict reference lead compounds and their similar structures of potential drug candidates based on Pharmacophore, pharmcodynamics properties and molecular docking.

MATERIALS AND METHOD

Identification of Target protein

A detailed literature study yielded that the cytosolic membrane proteins such as SopE2, SipA, SopA and SopB are potential drug targets against salmonella typhi in typhoid fever. Further analysis was focuses on identification on potential inhibitors targeted against cytosolic proteins using bioinformatics techniques. These inhibitors act as potential drug candidates towards the design of anti-bacterial drugs as therapeutics. The SopE2 (PDBID: 1R9K) is a translocate effecter activation protein for Cdc42 play guanine-nucleotide binding with Arp2/3 complex to the host membrane invasion[14]. The functional character is present in between 69-240 amino acids. The other protein SipA (PDBID: 2FM9) is a salmonella invasion protein A of crystal structure 2.2 Å, the structure contains complex of 2 macromolecules surface antigen SpaK and cell invasion protein SipA. The functional characteristic of protein is translocating into host cell by chaperon binding complex with InvB protein[15]. The structural motif structures with 23-262 amino acids which contain actins- binding and polymerization site is located to cause disease. SopB (PDBID: 4DID) crystal structure of resolution 2.3501 Å, the structure contains mutagenesis at C460S, K525A and K528A to decrease and loss of protein degradation and structural activity[16]. The overall protein structure shows inositol phosphate phosphatase group at 1-561 amino acid consensus sequence Cys-X(5)-Arg characteristic of Mg-independent phosphatase to cause host-pathogen interaction. The SopA (PDBID: 2QYU) is a eukaryotic ubiquitin ligase mimicking protein of crystal structure 2.1 Å, the function of the protein alter host cell physiology to survive in host tissue and involved in host E3 ubiquitination pathway [17].

Structural validation and Active site Prediction

The stereochemical quality of all crystal structures by analyzing residue-by-residue geometry using SAVS (Structural analysis and verification server) [18]. The overall quality of all amino acids is placed inside the allowed region to determine the compatibility of 3D structure alpha, beta, loop, polar and nonpolar amino acid arrangements. CASTp served used to predict structural pockets and cavities of active sites and ligand binding sites. Based on size and shape of 3D geometry of protein and ligand fit in active site to serve chemical modification and change conformational change in protein structure[19]. The more pockets of protein complex represent more active site and ligand binding amino acids is present in overall protein complex.

Ligand identification

Using literature search shows Catechin[20], Ciprofloxacin[21] and Oxadiazole[22] compounds is strongly inhibit salmonella typhi bacterial growth and is potentially used a lead compounds. Using Virtual screening methods to find the similar compounds with different molecular descriptor studies from Pubchem compound database shows, the Catechin has 102 similar compounds from literature, using drug likeliness property of rule of 5 shows only 22 compounds, using pharmacological actions against salmonella inhibitor shows only 3 compounds and these compounds is used as a potential lead compounds. Another compound such as Ciprofloxacin has 90 compounds of which only 15 compounds is used for drug likeliness property. Out of these compounds 4 compounds is potentially used as anti-bacterial agents. Oxadiazole is another anti-bacterial drug with similar compounds shows 26 compounds of which 8 compounds alone accepted for drug likeliness property. There are only 2 compounds alone shows antibacterial drug and is potentially used as antimicrobial drug candidates. The molecular optimization to study molecular descriptors using Hyperchem 7.5 professional. The pre-optimization of compounds using MM+ force field calculation to predict energy minimization based on single point and geometry optimization. The potential energy surface will calculate using HOMO (high occupied molecular orbital) and LUMO (low unoccupied molecular orbital) of semi-optimization technique. The QSAR properties of these compounds to calculate the molecular descriptors against different force fields. The QSAR property of force fields include Surface area (SAP), surface area in grid (SAG), molecular volume (MV), hydration energy (HE), polarizability (MP), refractivity (MR), LogP and molecular weight (MW).

Molecular Docking

All of the 9 drug likeliness and pharmacologically active similar compounds and 3 reference compounds such as Catechin, Ciprofloxacin and Oxadiazole against salmonella typhi cytosolic proteins. Using Molecular docking software Auto Dock 4.2 helps to dock protein with ligand molecule. In Auto Dock there are two different algorithms used such as Auto grid to calculate the active site amino acids present in flexible and rigid molecules. We fixed the grid around flexible molecule of X, Y and Z-axis at 80, 80, 80 to calculate the force field energy present in between active site pocket. Auto Dock helps to dock protein and ligand using genetic algorithm. The docking result represents orientation of protein-ligand interaction.

RESULTS AND DISCUSSION

Salmonella typhi disease target protein structures such as SopE2, SipA, SopA and SopB x-ray and NMR structures were downloaded from PDB database and the quality of all stereochemical property of amino acids were observed using SAVS. All the amino acids are arranges residue by residue of 98% quality score within Ramachandran plot and ProCheck results. The resultant protein structures are used for active site and ligand binding site prediction using CASTp server. The SopE2 structure show 19 pockets with 503.1 $Å^2$ of surface area and 610.9 Å of surface volume (Figure: 1 a). Another protein such as SipA has 35 pockets with 424.4 $Å^2$ surface areas and 1169.5 Å surface volumes (figure: 1 b). SopA has 88 pockets 3876.3 $Å^2$ surface area and 11639 Å surface volumes (Figure: 1 c) and SopB has 14 pockets with 124.6 $Å^2$ surface areas and 162.8 Å surface volumes (Figure: 1. d), the overall analysis of active site and ligand binding sites amino acids were presented in table 1.

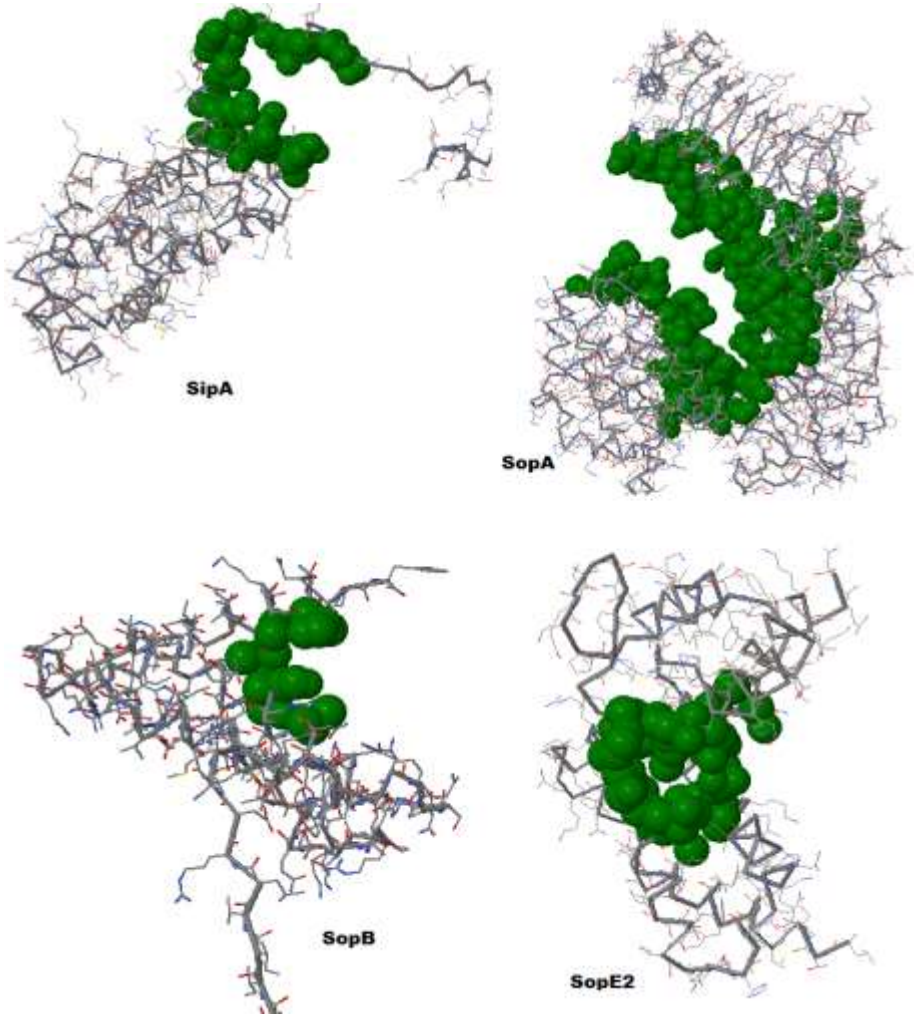

Figure 1 (a-d): The active site and binding pockets of salmonella typhi cytosolic proteins using CASTp server.

Table 1: The active site and ligand binding sites was predicted using CASTp server.

Name of the protein	No. of Pockets	Solvent accessible surface area	Molecular surface volume	Active Site amino acids
SipA	35	424.4	1169.5	GLN50, LEU51, GLU52, ASP53, PHE54, ALA56, LEU57, LYS59, GLN60, LEU63, PHE67, GLU74, ALA75, LYS77, GLU78, PHE80, THR81, MET93, SER108, LEU115, GLN126, LYS129, GLU156, THR198, LEU199, CYS217, LYS228, VAL257
SopA	88	3876.3	11639	THR206, PHE207, SER208, LYS209, LEU211, PRO213, PHE215, MET216, GLU217, ARG218, ASP219, GLY220, ASP221, ILE222, SER239, HIS240, LEU241, ASN260, TYR275, PRO394, ARG448, TRP781, ALA782.
SopB	14	124.6	162.8	LEU79, ASP82, LEU83, VAL86, GLN162, GLN165, LEU166, GLN169
SopE2	19	503.1	610.9	ALA113, ILE114, SER116, ALA117, VAL118, SER120, ASN121, PRO171, PHE172, Val173, LEU176, LYS198, GLU202, VAL205, MET206, GLN225, ILE228

Ligand preparation

The Pharmacological property of ligand compounds were selected from Pubchem compound database. We used molinspiration to predict Pharmacophore analysis to test molecular descriptors of drug likeliness property and the results were shows in table: 2. the combretastatin compound have same drug like properties but changes in conformational groups of OH at C12 position.

Table 2: Lipinski rule of 5 to understand Pharmacophore properties of lead compounds using molinspiration.

Ligand	miLogp	TPSA	natoms	MW	nON	nOHNH	nrotb	volume
Combretastatin	1.9	77.392	24.0	334.368	6	2	7	307.3
Combrestatin_A2	1.9	77.392	24.0	334.368	6	2	7	307.3
Combrestatin_A3	1.9	77.392	24.0	334.368	6	2	7	307.3
Ciproxin HC	1.617	94.826	26.0	362.466	5	3	2	343.063
Ciloxan	-0.701	74.569	24.0	331.347	6	2	3	285.46
Ciprofloxacin hydrochloride	-0.701	74.569	24.0	331.347	6	2	3	285.46
Ciprofloxacin	1.617	94.826	26.0	362.466	5	3	2	343.063
CCRIS 5440	0.942	123.911	16.0	222.16	8	2	3	172.315
Oxolamine	3.007	42.162	18.0	245.326	4	0	6	241.82
pleconaril	4.771	74.19	27.0	381.354	6	0	7	317.898

Pharmacophore analysis of structure selected lead molecules were screened using QSAR properties. The best confirmations of compound are based on aromatic rings (R), hydrogen donors (D) and one positive ionisable group (P). There are seven physico chemical properties of lead compounds such as highest surface area (SAP) and high surface grid (SAG) increases the refractivity, it the refractivity increases the hydration energy also increases. The increases bioavailability of lead compounds has increased aqueous solubility that helps to good dissolution in aqueous media. Using Energy minimization of compounds using Semi-empirical calculation shows the electrostatic interaction of HOMO and LUMO properties were represented in table: 3.

Table 3: Semi-empirical calculation to predict electrostatic energy surface and QSAR analysis of lead compounds to understand molecular descriptors.

Ligands	HOMO	LUMO	SAP (A^2)	SAG(A^2)	MV (A^3)	HE (Kcal/ mol)	cLogP	MR A^3	MP A^3	MW amu
Combretastatin	+15.689	-8.370	683.62	646.59	1071.52	-19.69	-2.91	97.29	34.93	334.37
Combrestatin_A2	+4.846	-8.771	677.96	639.21	1063.57	-19.41	-2.91	97.29	34.93	334.37
Combrestatin_A3	+4.144	-8.762	683.62	646.59	1071.52	-19.69	-2.91	97.29	34.93	334.37
Ciloxan	+6.356	-3.518	328.36	512.87	858.39	-6.85	-1.85	90.21	32.88	331.35
Ciprofloxacin	+9.219	-12.081	298.67	518.22	872.01	-5.27	-1.85	90.21	32.88	331.35
Ciprofloxacin hydrochloride	+9.593	-2.628	328.36	512.87	858.39	-5.22	-1.85	90.21	32.88	331.35
Ciproxin HC	+9.219	-12.081	298.67	518.22	872.01	-6.85	-1.85	90.21	32.88	331.35
CCRIS 5440	+3.711	-2.506	365.50	423.30	637.88	-25.17	-0.72	53.96	19.66	222.16
Oxolamine	+6.625	-4.851	556.49	539.25	866.75	-7.27	2.49	76.53	28.20	245.32
pleconaril	+6.554	-4.190	647.43	649.41	1066.50	-	3.02	96.33	35.15	381.35

Molecular Docking

The docking of competitive bioactive reference compounds combretastatin, Ciprofloxacin and Oxolamine along with their similar chemical structures were used for molecular docking against SipA, SopA, SopB and SopE2 protein structures.

SipA protein docking with training compounds

The SipA protein is strong interaction with combretastatin compound by forming 6 hydrogen bonds of docking energy -2.56 kcal/mol within active site amino acids such as Lys129, gln126, leu199, thr198. Other reference compound such as Ciprofloxacin is formed 3 hydrogen bonds within active site amino acid such as lys228 and leu115, the predicted training ciprofloxacin

similar compound such as Ciproxin HC is bound with SipA active site amino acid by forming 2 hydrogen bonds within active site amino acid Ser108, Glu156 table: 4a, figure: 2a.

Table: 4a: Molecular Docking of sipA protein with selected lead molecules using Auto Dock 4.2.

Ligand	No. H Bonds	Docking Score	Amino acid
Combrestatin	6	-8.72719	GLN126, CYS197, Lys129
Ciprofloxacin	3	-11.6202	LYS228,LEU115
Ciproxin HC	2	-5.95672	SER101, GLU156
CCRIS 5440	3	-2.5	LYS217,VAL257

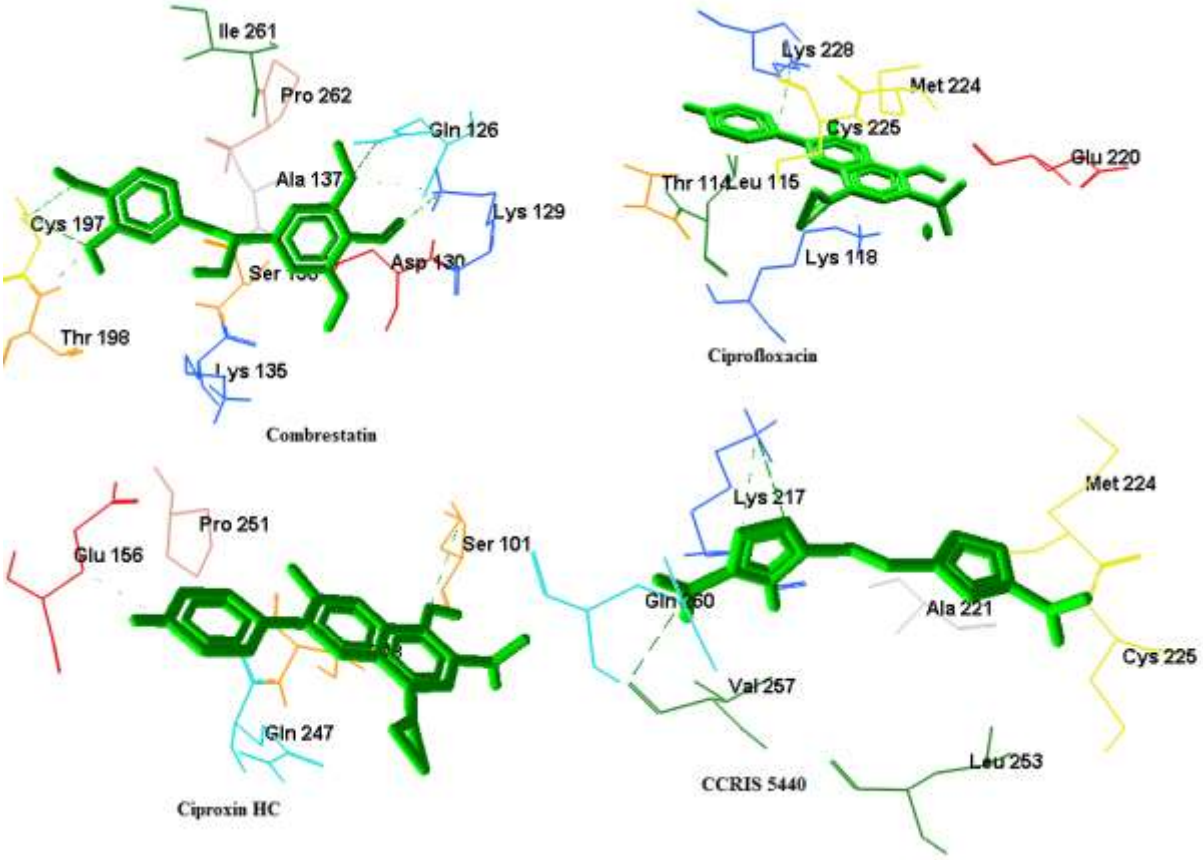

Figure 2a: Molecular docking poses of SipA protein with selected lead molecules.

SopA protein docking with training compounds

SopA protein is docked with reference compounds and their similar structures. The combrestatin and their similar compounds show only 2 hydrogen bonds within active site amino acids Arg218, Asp219, Gly220 and Asn260 with interaction energy of -16.894 kcal/mol. The another reference compound such as ciprofloxacin also has 2 hydrogen bonds within active site amino acids Gly384, Gly385 and Arg386 with bond energy of -15.3858 kcal/mol. Oxolamine has no interaction with protein structure but their similar compounds such as CCRIS 5440 and pleconaril is strong interaction with active site amino acids Gln274, Asn322, Met333, Leu335,

Leu336 and Ser381, of target protein by forming 4 hydrogen bonds with interaction energy of -13.0588 kcal/mol, table: 4b, figure: 2b

Table 4b: Molecular Docking of sopA protein with selected lead molecules using Auto Dock 4.2.

Ligand	No. H Bonds	Docking Score	Amino acid
Combrestatin	2	-16.894	ASN260,GLY220
Combrestatin_A2	2	-19.8752	ASN260,ASP219
Combrestatin_A3	3	-10.1551	ASN260,ASP219,ARG218
Ciprofloxacin	2	-15.3858	GLY385,GLY384
Ciproxin HC	2	-11.6731	ARG386,Gly384
CCRIS 5440	4	-11.5459	SER381,ASN322,MET333
pleconaril	4	-13.0588	LEU335,LEU336,GLN274

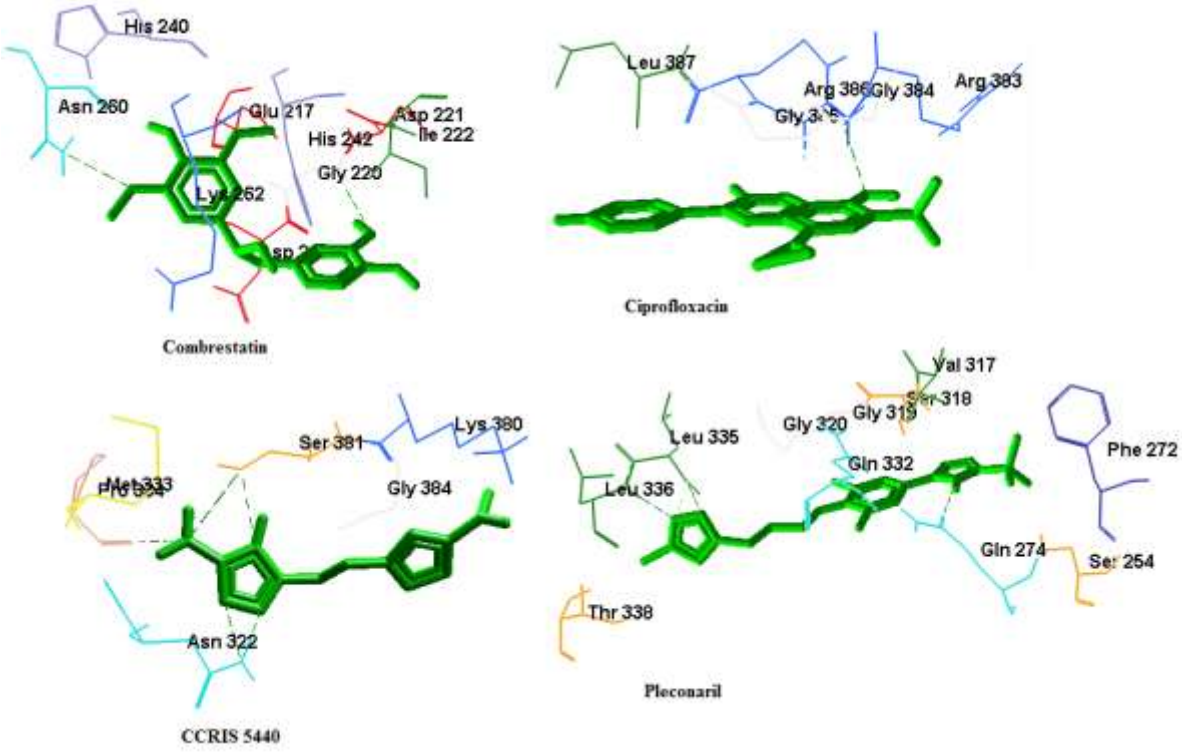

Figure: 2b. Molecular docking poses of SopA protein with selected lead molecules.

SopB protein docking with training compounds

The protein SopB is interacted with reference molecule such as combrestatin with 3 hydrogen bonds within active site amino acids of Thr139, Asp143, Val90 and Ile135 with interaction energy of -10.6103 kcal/mol. Ciprofloxacin has 4 hydrogen bonds with target protein structure of active site amino acids Ser69, Ser72, Glu121 and Lys125 of energy -13.5522 kcal/mol and CCRIS-5440 has 5 hydrogen bonds with amino acids Gln165, Leu79, Ala124, and Leu83 of energy -8.4172 kcal/mol shows strong interaction against target protein table: 4c, figure: 2c.

Table 4c: Molecular Docking of sopB protein with selected lead molecules using Auto Dock 4.2.

Ligand	No. H Bonds	Docking Score	Amino acid
Combrestatin	3	-10.6103	Thr139, Val90, Ile135
Combrestatin_A2	1	-4.76794	Asp143
Combrestatin_A3	1	-4.76794	Asp143
Ciprofloxacin	4	-13.5522	Ser69, Ser72, Glu121, Lys125
Ciproxin HC	3	-13.5773	Thr58, Trp59
CCRIS 5440-2	5	-8.4172	Gln165, Leu79, Ala124, Leu83

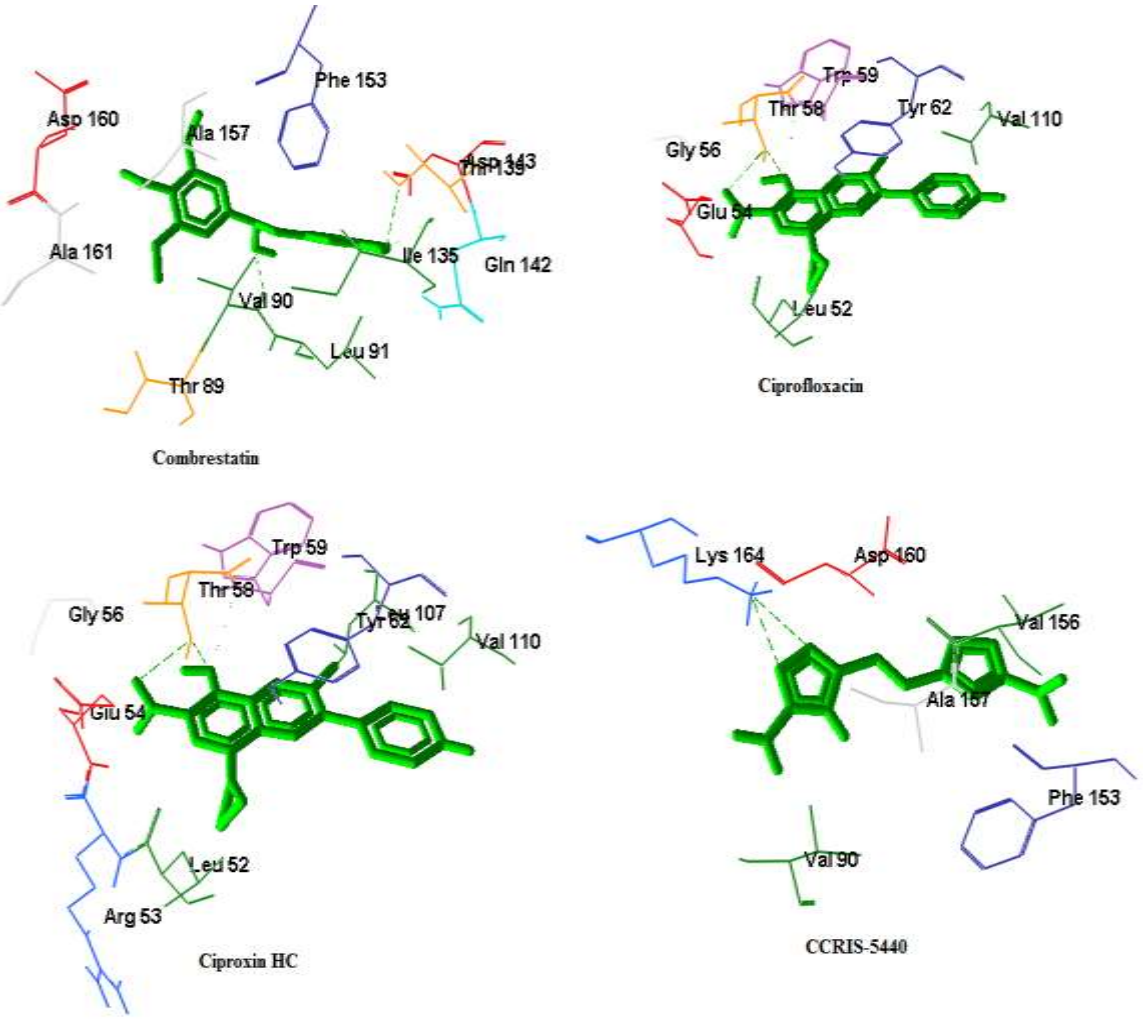

Figure 2c: Molecular docking poses of SopB protein with selected lead molecules.

SopE2 protein docking with training compounds

The SopE2 protein structure has strong interaction with combrestatin having 4 hydrogen bonds within active site amino acids Glu112, Thr110, Gln109, and Phe172 of interaction energy -8.9442 kcal/mol. The other compounds show week interaction with target protein table: 4d, figure: 2d.

Table 4d: Molecular Docking of sopE2 protein with selected lead molecules using Auto Dock 4.2.

Ligand	No. H Bonds	Docking Score	Amino acid
Combrestatin	4	-8.96442	GLU112,THR110,GLN109,PHE172
Combrestatin_A2	1	-3.75957	LYS90
Combrestatin_A3	2	-0.77014	GLN109,SER116
Ciprofloxacin	2	-0.496874	TRY106,ASN99
Ciprofloxacin hydrochloride	2	-8.94173	ASN99,TYR106
Ciproxin HC	2	-1.20863	TRY106,ASN99
Oxolamine	1	-1.49941	TYR106
CCRIS 5440	2	-2.46966	ASN230,GLN223

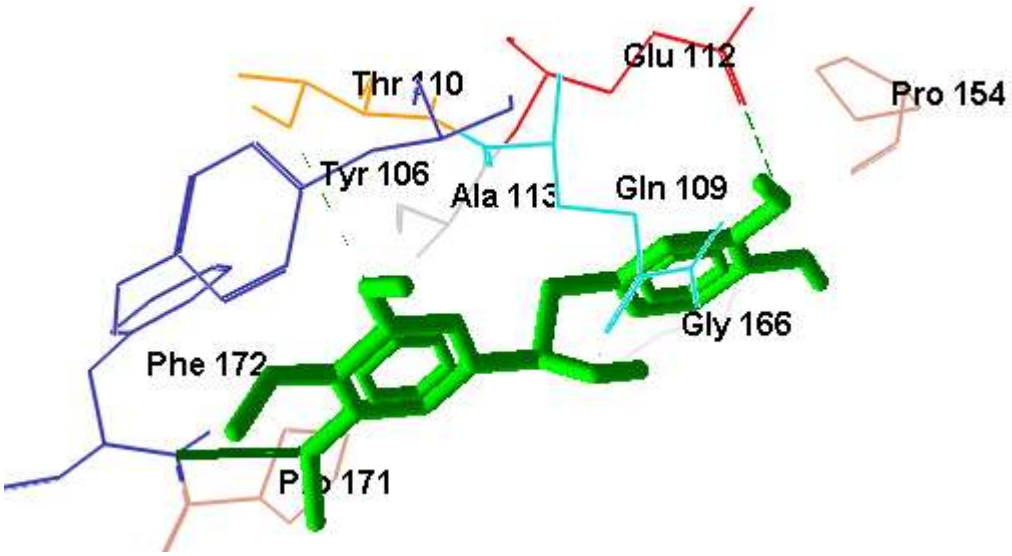

Figure 2d: Molecular docking poses of SopE2 protein with selected lead molecules.

CONCLUSION

In this study, we identified the properties of chemical structures along with disease target proteins using molecular modeling, Pharmacophore, pharmcodynamic and molecular docking study. The reference compounds such as Combrestatin, Ciprofloxacin and Oxolamine is more effective drug molecules against salmonella typhi infection. But using molecular docking study against SopA, SopB, SipA and SopE2 protein structures with reference compounds, Combrestatin and Ciprofloxacin is more effective drug with the selected target protein with strong interaction within active site amino acids by forming 2-4 hydrogen bonds. Only with SipA protein alone is forming 6 hydrogen bonds within target amino acids. The other similar compounds such as CCRIS 5440 of Oxolamine determinant is more effective against all membrane proteins and is more predictive target drug against target proteins, the results of this

drug interaction within active site amino acids by forming 2-5 hydrogen bonds with all the protein structures with strongest interaction energy. The Ciproxin HC compounds also good interaction with target protein by forming 2-4 hydrogen bonds. The Pharmacophore analysis of these compounds shows positive potential energy of HOMO and negative potential energy surface in LUMO along with QSAR properties shows combrestatin, ciprofloxacin, CCRIS5440 and Ciproxin HC compounds is good salmonella typhi membrane protein inhibitors against typhoid fever. Furthermore these lead compounds are potentially used for clinical applications.

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Conflict of interest

All authors are accepted for publishing this article. No authors will conflict this article.

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