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Molecular Modeling of Ribosomal Protein L4 In HUNGARY 19A-6 Strain Of Streptococcus Pneumoniae And Analysis Of Lead Molecular Interaction

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ABSTRACT : Streptococcus pneumoniae is the major bacterial pathogen causing severe respiratory infections such as pneumonia, meningitis and septicaemia. HUNGARY19A-6 strain of Streptococcus pneumoniae is extremely virulent in pneumococcal pathogenesis which contains rpLD gene which synthesis Ribosomal protein L4. In this article we performed the insilico modeling studies of the virulent protein which is synthesized by the rpLD gene and validated the nature of the receptor based on their atomic interactions for future drug target for HUNGARY19A-6 strain of Streptococcus pneumoniae. We have also analyzed drug targets for the above mentioned protein by using the virtual structure based ligand screening approach. Protein-ligand complexes have been analyzed by docking studies using Discovery Studio and interactions have also been visualized along with the validation of pharmacokinetic descriptors.

Keywords: pneumonia, *Streptococcus pneumoniae,* Ribosomal Protein , HUNGARY19A-6, homology, molecular docking,

INTRODUCTION

Streptococcus pneumoniae resists under different environments during its life span. In most scenarios, the human nasopharynx is inhibited by the organism and it resides in human system in an asymptomatic way to cause severe infections. Bacterial diseases in human are mostly caused by *Streptococcus pneumoniae* (1-2). This disease is most common in humans and it exists as bacterial meningitis. The transition from commensal bacterium to an opportunistic pathogen is often occurred after another infection in respiratory tract, eg., pneumococcal pneumonia has been a leading secondary infection for causing death during the period of influenza based pandemics.It has been estimated that worldwide pneumococcal infections are responsible for the death of more than 1 million people (3-4). Common vaccinations Protocol in Germany recommend the usage of a heptavalent pneumococcal conjugate vaccine in 2006 for children < 2 years (5-6). In the United States and elsewhere, resistance to a range of antibiotics is increasing among clinical isolates of *S. Pneumoniae* (7-10).

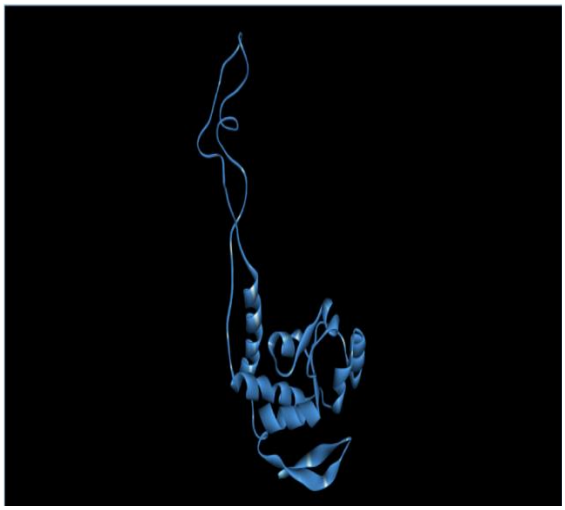
The genome of *S. pneumoniae* HUNGARY19A-6 virulent strain is of single chromosome with 2245615 base pairs having 39.6% of GC content. In this present study the Ribosomal protein (B1I8J9) is been studied.

MATERIAL AND METHODS

The sequence of the Ribosomal protein (B1I8J9) was obtained from UniProtKB. Since this protein do not have a structure, homology model building was performed using Modeler9v7. The template structure was obtained from protein data bank (PDB Id: 3BBO:B). The modeled structures were validated using SAVS, an online server. The CASTp server was used to analyze binding sites of the protein molecules Further, on the basis of high throughput method lead molecules having more affinity with the target proteins were obtained from DrugPort database. Then the structurally similar compounds were obtained using PubChem database. Finally a datset was created for potential ligands inhibiting the target proteins from the *Streptococcus pneumoniae* HUNGARY19A-6 strain using vegaZZ software. Accelrys Discovery Studio was used to analyze specific protein-ligand docked complexes and finally toxicity of the ligand molecules were analysed using ADMET descriptors.

RESULTS AND DISCUSSION

Homology modeling: Homology modeling was performed for Ribosomal protein (B1I8J9) and was modeled using the template structure (PDB Ids: 3BBO: B). The modeled protein was validated through SAVS and the validation results are shown in Table I. Based on the analysis of Ramachandran Plot, we found that found that 82.1% residues of target protein is present in the allowed region. The final modeled protein structures and their corresponding Ramachandran plots are shown in (Figure 1).



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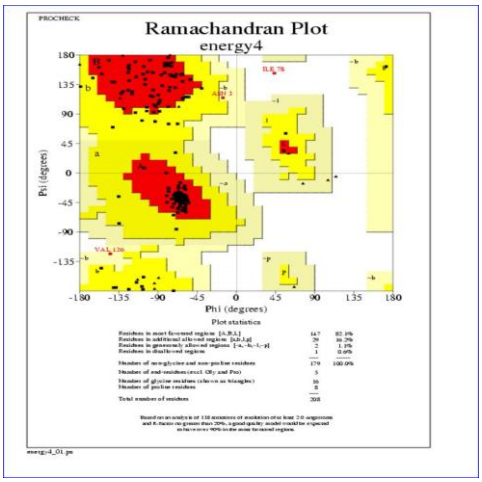

Figure 1. Structure of Ribosomal protein (B1I8J9) and its Ramachandran plot

Ligand Search: Ligands for proteins Ribosomal protein (B1I8J9) were retrieved from DrugPort sharing more identity with related protein sequence for which already a drug exists. The best analogs for each ligands were obtained from PubChem were chosen from the hit as shown in figure 2. The docking was performed with those analogs using Discovery Studio software. Dock score was calculated for all the analogs.

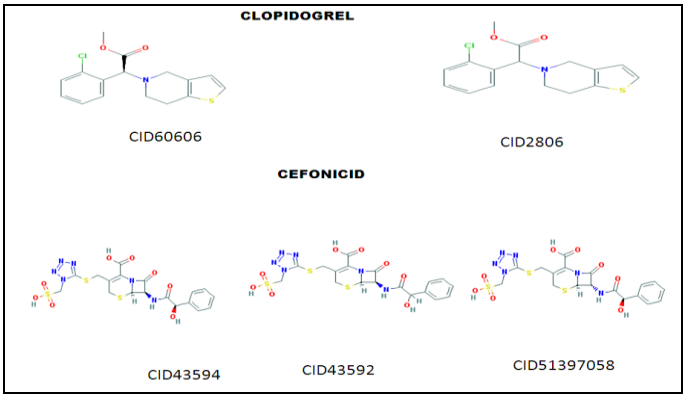

Figure 2. Analogs of ligands chosen from PubChem

Docking: The Clopidogrel ligand molecule had the best analog compounds methyl(2S)-2-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetate, methyl2-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetate with dock score of 29.95,24.824 respectively.

The Cefonicid ligand molecule had a best analog compounds ((6R,7R)-7-[[(2R)-2-hydroxy-2-phenylacetyl]amino]-8-oxo-3-[[1-(sulfomethyl)tetrazol-5-yl]sulfanylmethyl]-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid, (6R,7R)-7-[(2-hydroxy-2-phenylacetyl)amino]-8-oxo-3-[[1-(sulfomethyl)tetrazol-5-yl]sulfanylmethyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 6R,7S)-7-[[(2R)-2-hydroxy-2-phenylacetyl] amino]-8-oxo-3-[[1-(sulfomethyl)tetrazol-5-yl]sulfanylmethyl]-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid with dock score of 34.175,31.338,41.859 respectively.

The analog compounds with docking score more than 30.0 were considered to be the best for which ADMET studies were performed. The top scoring analogs, PLP (Piecewise Linear Potential), PMF (Potential of Mean Force) and Dock score are tabulated in Table II. The protein-ligand interactions at the binding site are shown in figure 3. Atomic interactions between receptor Ribosomal protein (B1I8J9) and its ligands are given in Table III.

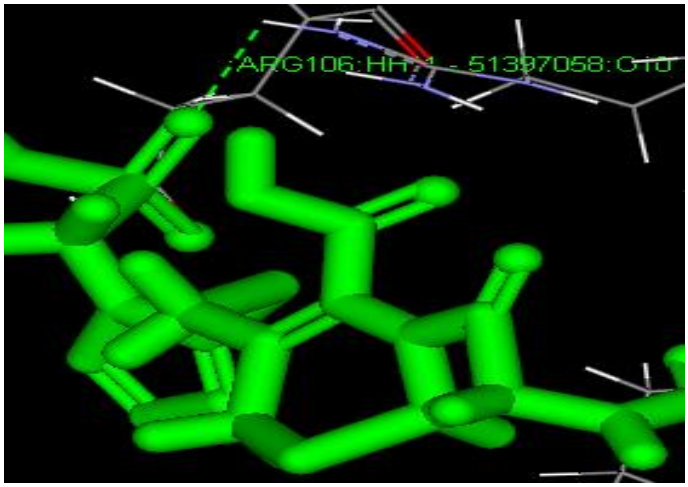

Figure 3. Docking of (6R,7S)-7-[[(2R)-2-hydroxy-2-phenylacetyl]amino]-8-oxo-3-[[1-(sulfomethyl)tetrazol-5-yl]sulfanylmethyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid with B1I8J9 of strain Hungary19-A

Table III. Atomic interactions between receptors and ligands

Drug	Ligand	Receptor		Ligand	Distance
		Amino acid	Atom	Atom	
Clopidogrel	CID60606	GLN 40	HE 22	O4	2.28284
	CID2806	ARG 106	HH 11	O4	2.24977
Cefonicid	CID43594	GLU 158	OE 1	H40	2.44465
	CID43592	LYS 174	HZ 2	O11	1.96306
	CID51397058	ARG 106	HH 11	O10	2.29249

ADMET properties for the analogs of ligands having better dock score and maximum interaction with the active site residues

were analyzed and shown in figure 4. Based on our analysis, it has been found that the analogs which had maximum dock score have proper lopP, Absorption and Blood Brain Barrier values.

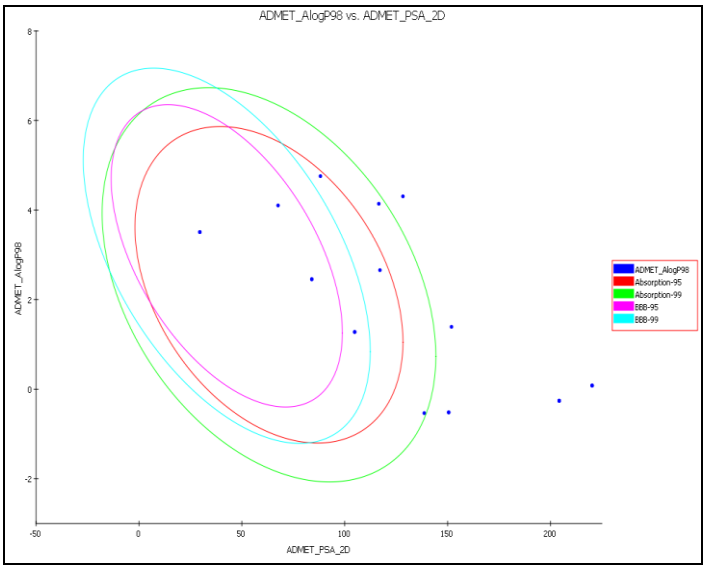

Figure 4. ADMET Plot for analogs of HUNGARY19A-6.

CONCLUSSION

The results conclude based on docking studies that (6R,7S)-7-[[(2R)-2-hydroxy-2-phenylacetyl]amino]-8-oxo-3-[[1-(sulfomethyl)tetrazol-5-yl]sulfanylmethyl]-5-thia-1-azabi cyclo[4.2.0]oct-2-ene-2-carboxylic acid is the best ligand for Ribosomal protein (B1I8J9) with the Dock score of 41.85 with 1 Hydrogen bond. ADMET descriptors were also analyzed for the drug candidates. Hence, this protein can be considered as the drug targets and the above mentioned ligand having highest dock score may be considered as the drug candidate.

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Table 1 The percentage of residues of modeled structure present in the allowed region of Ramachandran plot as predicted by SAVS with its similarity and template description.

Target Protein	Sequence length	Template	Description of template	Length	Similarity(%)	Ramachandran Plot (%)
Ribosomal protein (B1I8J9)	207	3BBO:B	Spinacia Oleracea	211	35.1	82.1

Table II The dock score for ligands obtained from drug port for Ribosomal protein (B1I8J9)

Ligands	Analogues	Site	H-bonds	Amino acid	Dock score
Clopidogrel	methyl(2S)-2-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetate	2	1	GLN40	29.95
	methyl2-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetate	2	1	ARG106	24.824
Cefonicid	(6R,7R)-7-[[(2R)-2-hydroxy-2-phenylacetyl]amino]-8-oxo-3-[[1-(sulfomethyl)tetrazol-5-yl]sulfanylmethyl]-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid.	3	1	GLU158	34.175
	(6R,7R)-7-[(2-hydroxy-2-phenylacetyl)amino]-8-oxo-3-[[1-(sulfomethyl)tetrazol-5-yl]sulfanylmethyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid	3	1	LYS174	31.338
	(6R,7S)-7-[[(2R)-2-hydroxy-2-phenylacetyl]amino]-8-oxo-3-[[1-(sulfomethyl)tetrazol-5-yl]sulfanylmethyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.	3	1	ARG106	41.859