Insilico Analysis Of Docking Studies CGSP Strain Of Streptococcus Pneumoniae

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ABSTRACT: Various current examinations are done on the effectiveness of characteristic parts to battle the intrusion by Streptococcus pneumoniae strain CGSP14. The primary goal is to propose the most good simple exacerbate that could be viable to focus on the protein. This consideration has been picked up as before cases as a rule established in medication improvement. These cases and contextual investigations give interfaces between target proteins and the analogs. Numerous other comparative works have been found to discover most ideal ligand intensify that could be successful to focus on the target protein.

Keywords: Streptococcus pneumonia, CGSP14, Target, Protein, Ligand.

INTRODUCTION

STRAIN ANALYSIS OF STREPTOCOCCUS PNEUMONIA

In recent years, the whole genome sequencing of various Streptococcus pneumoniae strains have increased manifold and there is an urgent need to provide organism specific annotations to the specific scientific community (1). Strain selected in this work is CGSP14 which is virulent strain, through which the unstructured proteins are selected with the appropriate function, are modeled and are next preceded with docking and analysis work.(2)

INTRODUCTION

In 1881, the organism, known later in 1886 as the pneumococcus for its role as a cause of pneumonia, was first isolated simultaneously and independently by the U.S. Army physician George Sternbergand the French chemist Louis Pasteur. The organism was termed diplococcus pneumoniae from 1920 because of its characteristic appearance in Gram-stained sputum.(3) It was renamed Streptococcus pneumoniae in 1974 because it was very similar to streptococci. S.pneumoniae played a central role in demonstrating that genetic material consists of DNA.(4) In 1928 Frederick Griffith demonstrated transformation of life turning harmless pneumococcus into a lethal form by co-inoculating the live pneumococci into a mouse along with heat-killed virulent pneumococci.(5) In 1944 Oswald Avery, Colin MacLeod, and Maclyn McCarty demonstrated the transforming factor in Griffith's experiment was not protein, as was widely believed at the time, but DNA. Avery's work marked the birth of the molecular era of genetics. (6)

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METHODS

STRAIN CGSP14

The arrangement of intrigue has been sought through the DNA matter seek against every single pneumococcal strain and the outcomes are appeared in Strain CGSP14 is serotype 14, which is a standout amongst the most well-known pneumococcal serotypes that causes obtrusive pneumococcal infections around the world.(7,8) Strain CGSP14 is a clinical strain disengaged from a youngster in Taiwan who had a necrotizing pneumonia with muddling hemolytic uremic disorder. Serotype 14 strains regularly express protection from an assortment of antimicrobial specialists.(12,13) Strain CGSP14 contains 80 inclusion arrangement components, just 12 of which still give off an impression of being flawless. It encodes 18 antimicrobial obstruction determinants, almost 50% of which were related with versatile hereditary components and were probably procured by flat quality exchange. Different qualities that may add to pathogenicity of strain CGSP14 are likewise encoded in these versatile components(9,10,11). The main objective of this work is to obtain the best dock score as the result so that it will be responsible for suppressing pneumonia infection which act as a drug target and it helps to analyze the structured proteins and to dock them with the analogues taken from ligands to inhibit the Infection. The identification of strains and their respective proteins related to their study functions and pathways were done.(15,16) The modelling of the proteins with the help of the target sequence and a template was performed and validated the models so that it can be used for docking. Ligands were identified based on their functions and screening of the ligands was done based on ADMET properties. Active binding sites of the proteins are identified and the analogues were docked. The interactions between docked molecules are studied based on various factors like dock score, energy function etc. The appropriate analogues for protein of the strain are identified. (7,8)

SELECTION OF PROTEINS BASED ON FUNCTION

The proteins that are coded by these genes have various functions including regulation of neurotransmitters whose level variations are responsible for change in behavior leading to aggression. But most of these proteins are involved in other major pathways like immune system. So proteins like these cannot be inhibited, as it could block crucial functions of proteins. Therefore only proteins that have regulation of neurotransmitters responsible for mood swings as their main

function are regarded in this project. Antagonists or agonists of these proteins are then identified and taken as ligands based on their expression.(140

STRAIN CSP14

Homoserine kinase
Homoserinekinase is a protein includes in aminoacidbiosynthesis.Its family is made out of surprising homoserine kinases, from a subset of microscopic organisms, which have a protein kinase overlap. These proteins don't bear any likeness to the GHMP family homoserine kinases present in most microorganisms and eukaryotes.

Anthranilate phosphoribosyl transferase

Anthranilatephosphoribosyl transferase is a protein includes in aminoacid biosynthesis. It catalyzes a standout amongst the most essential biochemical responses: the exchange of a ribose bunch between a sweet-smelling base and phosphate groups.More explicitly, AnPRT encourages the development of a carbon-nitrogen bond between 5-phospho-alpha-D-ribose 1-diphosphate (PRPP) and anthranilate.

Dihydroxy- acid dehydratase
Dihydroxy- acid dehydratase is a protein includes in aminoacid biosynthesis. Two dehydratases, dihydroxy- acid dehydratase and 6-phosphogluconate dehydratase have been appeared to be developmental related. This family speaks to dihydroxy-acid dehydratase (DAD). It contains a chemically fundamental group and catalyzes the fourth step in valine and isoleucine biosynthesis.

LIGAND IDENTIFICATION

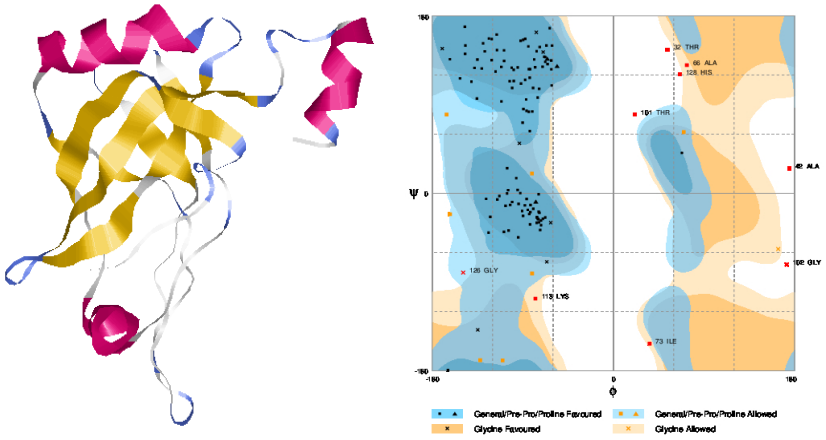
Table 1. *ANALOGUE SELECTION*

ANALOGUE NAME	MOL WT	MOL FORMULA/DRUG NAME
Sodium 6[3-(2-Cholorophenyl)-5-Methyl-1	334.39 g/mol	$C_{16}H_{18}N_2O_4S$/Penicillin G
Sodium(2S,5R,6R)-6-[3-(@-Cholorophenyl)-5	372.48 g/mol	$C_{16}H_{17}KN_2O_4S$ /Penicillin G
(2R,4S)-2[(1R)-2-amino-2-oxo-1	331.347 g/mol	$C_{17}H_{18}FN_3O_3$/Ciprofloxacin
Calcium 3,3-dimethyl-7-oxo-6-[(2-phenyl)]	385.82 g/mol	$C_{17}H_{21}ClFN_3O_4$/Ciprofloxacin
1-Cyclopropyl-6fluro-4-oxo-7,3-carboxylic acid hydrochloride	495.344 g/mol	$C_{14}H_{36}Cl_2N_2O_{12}$/Spectinomycin
3-(R) – N,N- dibenzyloxycarbonyl -3- aminomethyl-dihydrospectinomycin	495.344g/mol	$C_{14}H_{26}Cl_2N_2O_7$ /Spectinomycin
Calcium 3,2 dimethyl-7- oxo-6-[(2-phenyl)]	516.719 g/mol	$C_{31}H_{48}O_6$/Fusidic Acid
16- dcacetoxy- 7-beta-hydroxy	519.719 g/mol	$C_{31}H_{47}NaO_6$/ Fusidic Acid

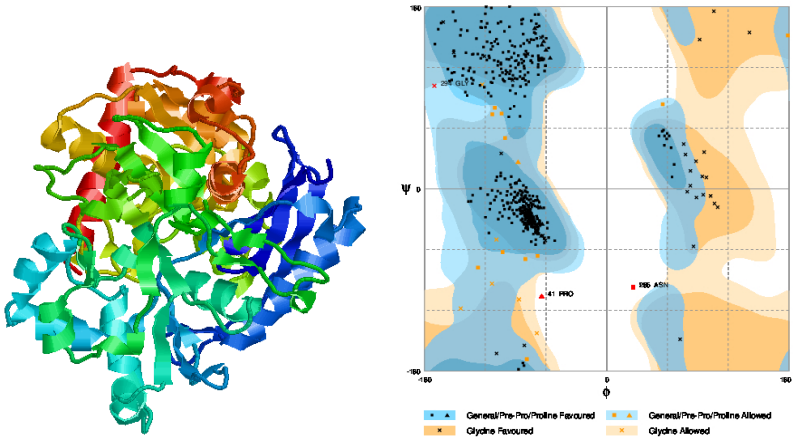
PROTEIN MODELING

Now the proteins that did not have 3D structures did not have inhibitors as well but still they play a major role in aggression by their over expression. So these proteins are modeled by using the tool Modeller v 9.10. This tool uses a template that is obtained by running blastp against PDB and the sequence of the target protein. Basically there are three types of modeling- homology modeling, ab-initio modeling and threading. Homology modeling is the preferred one as it is the construction of atomic resolution model of the target protein from its amino acid sequence and experimental 3D structure of a related homologous protein called as template. This modeling method relies on the identification of 1 or more protein structures likely to resemble the structure of the query sequence, and on the production of an alignment that maps residues in the query sequence to the residues in the template sequence. The sequence identity of the template should be at least above 70% to the query sequence. Then the resulting model is validated using SAVS parameters and verified if energy minimization has to be done.

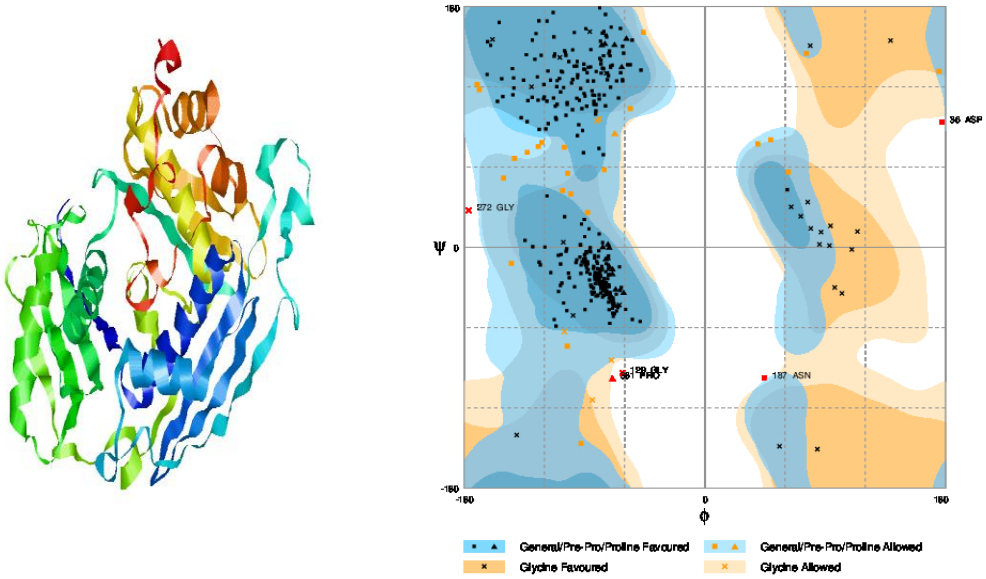
STRUCTURED PROTEINS – Strain CGSP14



(A)



(B)



(C)

Figure 1. *Structures and corresponding Ramachandran plots of Strain CGSP14*

Figure 1 shows the 3D structures that have been modeled using Phyre 2. The sequence of the target protein and the template that has the most similar sequence are used to build the target protein structure. The above figures show the models of proteins as viewed in discovery studio visualize. The Ramachandran plot shows the phi-psi torsion angles for all residues in the structure (except those at the chain termini). Glycine residues are separately identifies by triangles as these are not restricted to the regions of the plot appropriate to the other side chain types. The colouring/shading on the plot represents different regions described in Morris et. al(1992): the darkest areas shown in red corresponds to the core regions representing the most favourable combinations of phi-psi values. Considerably 90% of the residues should be in core region. The percentage of the residues in the core regions is one of the better guides to the stereochemical quality.

Table 2. *Favored regions and allowed regions of the protein models as predicted by Ramachandran plot*

Target Protein	Length	Template	Length	Similarity	RAMACHANDRAN PLOT		
					Favoured	Allowed	Outliers
Homoserine kinase	371	1JZQ_A	342	99%	92.0%	5.1%	2.9%
Anthranliate phosphoribosyl transferase	481	1GAX_A	420	98%	95.9%	3.1%	0.9%
Dihydroxy-acid dehydratase	330	2vQC_A	298	82%	96.1%	2.9%	1.0%

The above table 2 shows the sequence length of the target proteins, the template ID that is selected based on the blastp search. It also provides the sequence length of the template and the results of Ramachandran plot. By analyzing the Ramachandran plot for each protein model the amount of favored regions, allowed regions and disallowed regions are identified, hence validating the modeled structures.

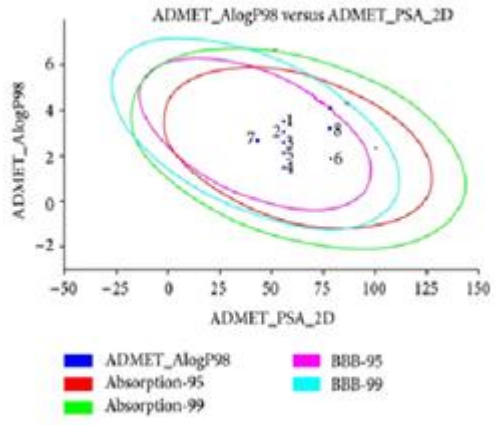


Figure 2. *SELECTION OF LIGANDS BY ADMET ANALYSIS*

Ligands to be used as inhibitors of these proteins are screened using ADMET analysis

INTERACTION OF HOMOSERINE KINASE WITH ANALOGUES

Table 3. *Docking results Homoserine kinase with analogues*

Name	Electrostatic Energy	Potential Energy	Vander Waals Energy	Dock Score
Calcium 3,2 dimethyl-7- oxo-6-[(2-phenyl)]	-6.14	12.529	-1.75	26.94
16- dcacetoxy- 7-beta-hydroxy	-56.906	74.75	-8.307	22.23

The table 3 provides information on the molecules of ligands that bind with the binding site of the protein. It also shows the number of H bonds and the distance between the binding molecules. Internal energies of the molecules are also mentioned in the table above.

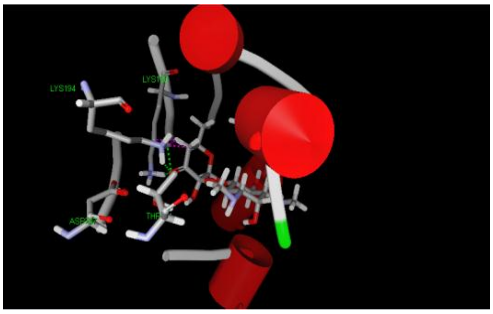


Figure 3. *Interaction of homoserine kinase with analogues*

INTERACTION OF ANTHRANILATE PHOSPHORIBOSYL TRANSFERASE WITH ANALOGUES

Table 4. *Docking results anthranilate phosphoribosyl transferase with analogues*

Name	Electrostatic Energy	Potential Energy	Vander Waals Energy	Dock Score
1-Cyclopropyl-6fluro-4-oxo-7,3-carboxylic acid hydrochloride	-43.725	-23.958	-6.617	33.93
3-(R) – N,N-dibenzyloxycarbonyl -3- aminomethyl-dihydrospectinomycin	-36.768	-24.356	-2.120	39.76

The table 4 provides information on the molecules of ligands that bind with the binding site of the protein. It also shows the number of H bonds and the distance between the binding molecules. Internal energies of the molecules are also mentioned in the table above.

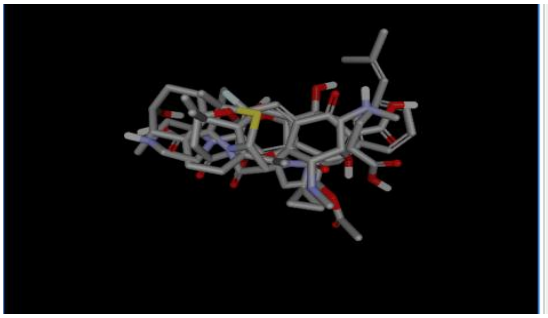


Figure 4. *Interaction of Anthranilate phosphoribosyl transferase with analogues*

INTERACTION OF DIHYDROXY-ACID DEHYDRATASEWITH ANALOGUES

Table 5. *Docking results of Dihydroxy-acid dehydratasewith analogues*

Name	Electrostatic Energy	Potential Energy	Vander Waals Energy	Dock Score
Sodium 6[3-(2-Cholorophenyl)-5-Methyl-1	-6.14	12.529	-1.75	20.53
Sodium(2S,5R,6R)-6-[3-(@-Cholorophenyl)-5	-43.725	-23.958	-6.617	32.43

The table 5 provides information on the molecules of ligands that bind with the binding site of the protein. It also shows the number of H bonds and the distance between the binding molecules. Internal energies of the molecules are also mentioned in the table above.

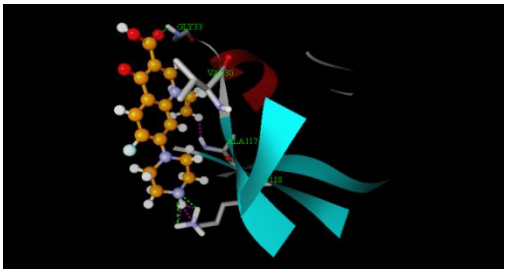


Figure 5. *Interaction of dihydroxy-acid dehydratasewith analogues*

SUMMARY AND CONCLUSION

The scope of this study is to find the strains and their respective proteins that are solely responsible for to act as drug target that suppress the pneumococcal infection. Homology modeling was performed for proteins and was modeled using the template structure. The outcome of docking studies conclude that the protein Anthranilate phosphoribosyl transferase is finest analogue with the Dock score of 39.76 of strain CGSP14 and ADMET descriptors were also analyzed for the drug candidates. Hence, this protein can be considered as the drug target and the above analyzed analogue having highest dock score may be considered as the drug candidate. These proteins are modeled and then the ligands to inhibit these proteins are identified from literary papers and drug databases. The ligands are screened for certain properties. Then the proteins are docked with the ligands to find the suitable inhibitors. Interaction between these molecules are studied. Thus the suitable inhibitors of the proteins of the strains are found.

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