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International Journal of Medicine and Pharmaceutical Research

2013, Vol.1 (3): 262-267

ISSN 2321-2624

Research Article

Pharma Research Library

An Insilico design of Inhibitors of GspB, a virulence factor of *Streptococcus gordonii* in the causation of infective Endocarditis

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Abstract

Infective endocarditis is an infection of the endocardial surface of the heart. The disease may be fatal if untreated as the disease may lead to intractable congestive heart failure and myocardial abscesses. Among the members of the viridans group, *Streptococcus gordonii* is a leading cause of infective endocarditis. Platelet binding by *S. gordonii* is predominantly mediated by the cell surface glycoprotein GspB. The *S. gordonii* defective in the production of GspB is found to lose its ability to bind to the platelets. Thus the production of GspB inhibitors can be an effective drug in the prevention of infective endocarditis caused by *S. gordonii*. The three dimensional structure of GspB was retrieved from RCSB database. The possible binding sites of GspB were searched using binding site prediction online tool Q site finder. A total of 1000 ligands were generated with the help of software ACD chemsketch. Rapid virtual screenings of these compounds were performed in the docking tool iGEMDOCK v2.0. Based on the binding energy a total of six ligands were selected for the further study. The selected six ligands were then analyzed for drug-relevant properties based on "Lipinski's rule of five" and other drug like properties. The accurate docking of six ligands were performed using docking tool iGEMDOCK v2.0. From the present study, it has been found that (4-carbamoyl-5-hydroxy-6-iodo-1λ3-iodinin-2-yl) sodium, which is a novel compound can act has an inhibitor for the GspB.

Keywords: Streptococcus gordonii, infective endocarditis, GspB inhibitors, molecular docking

Introduction

Infective endocarditis is an infection of the endocardial surface of the heart. The disease may be fatal if untreated as the disease may lead to intractable congestive heart failure and myocardial abscesses [1]. In association with prior

injury or disease of the heart valves, the endothelial or exposed connective tissue surface becomes coated with platelets and fibrin, i.e., non-bacterial thrombotic vegetation [2]. The thrombotic vegetation contains platelets which facilitates the binding of bacteria. The platelets on the surfaces of damaged cardiac valves provide an attachment site for bacteria that is circulated in the blood [3]. This event is followed by the further accumulation of platelets at the site of infection [4]. At least 50% of all human cases of infective endocarditis result from viridans group of streptococci [5]. The propensity of these organisms to produce endovascular infection may be attributable in part to their ability to bind platelets [6]. Among the members of the viridans group, *Streptococcus gordonii* is a leading cause of infective endocarditis [7].

Platelet binding by *S. gordonii* is predominantly mediated by the cell surface glycoprotein GspB [8]. The 9.2-kb *gspB* gene encodes a protein of 3,072 amino acids, with a predicted molecular mass of 286 kDa [9]. GspB is a serine-rich repeat (SRR) adhesin of *S. gordonii* that mediates binding of this organism to human platelets via its interaction with sialyl-T antigen on the receptor glycoprotein Ib alpha. This interaction appears to be a major virulence determinant in the pathogenesis of infective endocarditis [10]. The *S. gordonii* defective in the production of GspB is found to lose its ability to bind to the platelets. Thus the production of GspB inhibitors can be an effective drug in the prevention of infective endocarditis caused by *S. gordonii*. In the present study an attempt has been made to design an effective inhibitor of GspB by structure based drug design followed by molecular docking studies.

Materials and Methods

Protein preparation

The three dimensional structure of GspB was retrieved from RCSB-PDB data base. Its PDB code is 3QC5.

Active site prediction

The possible binding sites of GspB were searched using binding site prediction an online tool Q site finder [11]. The binding sites which are more flexible were selected for this study.

Generation and optimization of Ligand

A total of 1000 ligands in 2D format were generated with the help of software ACD chemsketch [12]. The ligands were saved in mol 2 format. The OPEN BABEL software (www.vcclab.org/lab/babel/start.html) was used to convert mol format to pdb format. Rapid virtual screenings of these compounds were performed in the docking tool iGEMDOCK v2.0 [13]. A population size of 150 is set with 70 generation and one solution for quick docking. Based on the binding energy a total of six ligands were selected for the further study. The selected five ligands were then analyzed for drug- relevant properties based on “Lipinski’s rule of five”. Other drug like properties were analysed using OSIRIS Property Explorer (http://www.organicchemistry.org/prog/peo/) and Mol soft, the drug-likeness and molecular property explorer (http://www.molsoft.com/mprop/). On the basis of binding affinity and drug like properties, all these six ligands were taken for further molecular docking study.

Protein-ligand docking

iGEMDOCK is an integrated virtual screening environment from preparations through post-screening analysis with pharmacological interactions . First, iGEMDOCK provides interactive interfaces to prepare both the binding site of the target protein and the screening compound library. Each compound in the library is then docked into the binding site by using the in-house docking tool GEMDOCK. Subsequently, iGEMDOCK generates protein-compound interaction profiles of electrostatic, hydrogen-bonding, and van der Waals interactions. Based on these profiles and compound structures, iGEMDOCK infers the pharmacological interactions and clusters the screening compounds for the post-screening analysis. Finally, iGEMDOCK ranks and visualizes the screening compounds by combining the pharmacological interactions and energy-based scoring function of GEMDOCK. The selected six ligands were subjected accurate docking (very slow docking) by setting population size of 800 is set with 80 generation and 10 solution. After the completion of the docking the post docking analysis was performed to find the docking pose and its energy values.

Results and Discussion

The 3D structure of GspB is shown Figure 1. It is made up of 3072 amino acids. Its 3D structure is viewed as PDB file with Rasmol structure colour scheme. Alpha helices are coloured magenta, beta sheets are coloured yellow, turns are coloured pale blue, and all other residues are coloured white.

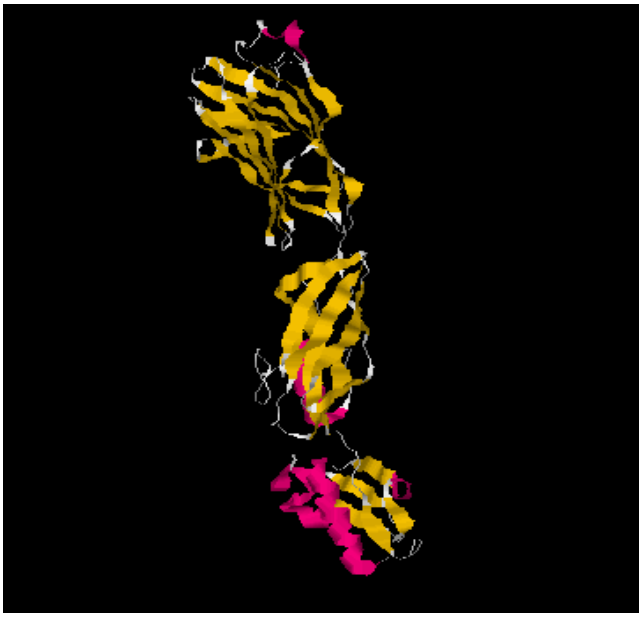

Figure 1: The 3D structure of GspB viewed with Rasmol structure colour scheme

A total of 1000 ligands were prepared based on the structure of the GspB protein using ACD chemsketch software. It was converted to pdb format using OPEN BABEL software. All the 1000 ligands were then subjected to virtual rapid screening with iGEMDOCK software and six compounds were found to have good fit with a low binding energy. The structure and the IUPAC name of the six ligands were shown in the Figure 2. The selected six ligands were then studied for its drug relevant properties.

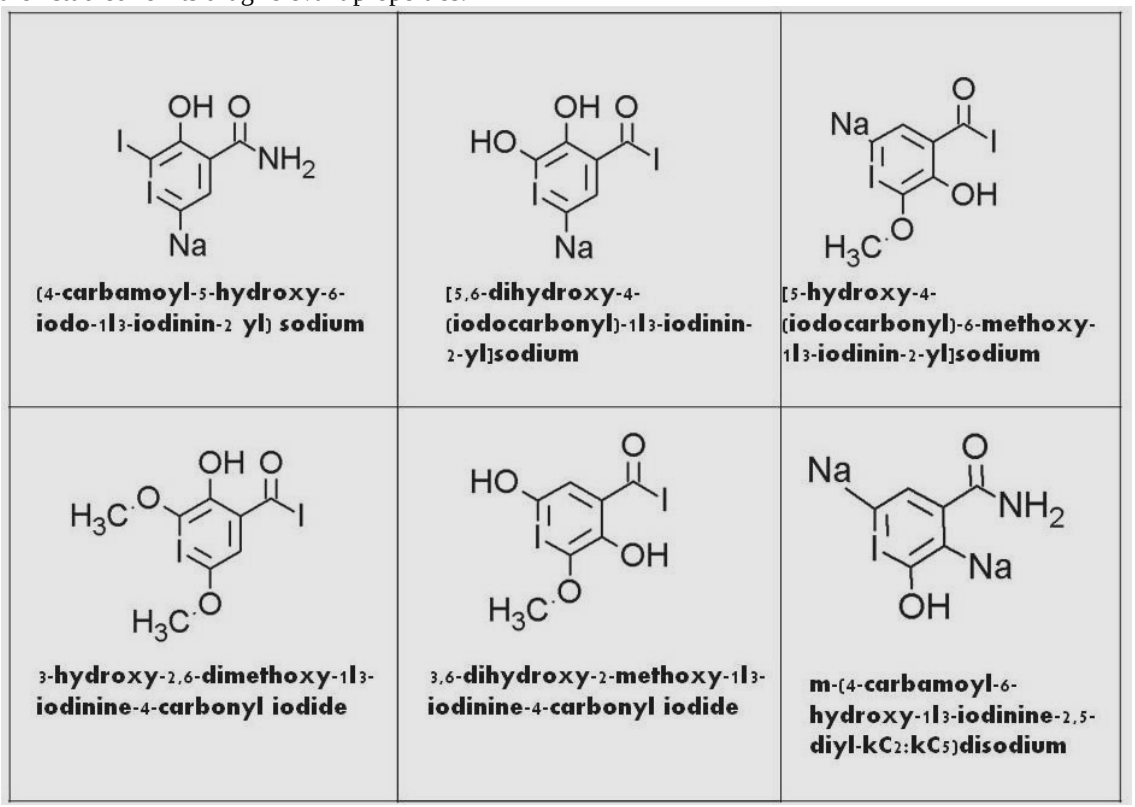

Figure 2: The structure and IUPAC name of the six ligands

The Table 1 depicts the values related to the Lipinski's rule of Five. From the table it is evident that all the five selected ligands obey the rule. The Table 2 shows the drug relevant properties of the five ligands. They all possess good drug score and drug likeness.

Table 1: The Lipinski's properties of the selected six ligands

S. No.	Ligand	Molecular weight	Xlog p	H bond donor	H bond acceptor
1.	(4-carbamoyl-5-hydroxy-6-iodo-1λ3-iodinin-2-yl)sodium	399.0	0.68	5	6
2.	[5,6-dihydroxy-4-(iodocarbonyl)-1λ3-iodinin-2-yl]sodium	400.0	-0.32	4	5
3.	[5-hydroxy-4-(iodocarbonyl)-6-methoxy-1λ3-iodinin-2-yl]sodium	414.0	0.13	3	4
4.	3-hydroxy-2,6-dimethoxy-1λ3-iodinine-4-carbonyl iodide	422.0	-0.57	4	5
5.	3,6-dihydroxy-2-methoxy-1λ3-iodinine-4-carbonyl iodide	408.0	-1.02	2	3
6.	m-(4-carbamoyl-6-hydroxy-1λ3-iodinine-2,5-diyl-kC2:kC5)disodium	423.0	0.23	4	6

Table 2: The drug relevant properties of selected six ligands

S.No.	Ligand	Drug likeness	Drug score	Mutagenic	Tumorigenic	Irritant
1.	(4-carbamoyl-5-hydroxy-6-iodo-1λ3-iodinin-2-yl)sodium	2.01	0.92	No	No	No
2.	[5,6-dihydroxy-4-(iodocarbonyl)-1λ3-iodinin-2-yl]sodium	0.55	0.71	No	No	No
3.	[5-hydroxy-4-(iodocarbonyl)-6-methoxy-1λ3-iodinin-2-yl]sodium	0.72	0.72	No	No	No
4.	3-hydroxy-2,6-dimethoxy-1λ3-iodinine-4-carbonyl iodide	O.79	0.80	No	No	No
5.	3,6-dihydroxy-2-methoxy-1λ3-iodinine-4-carbonyl iodide	0.72	O.69	No	No	No
6.	m-(4-carbamoyl-6-hydroxy-1λ3-iodinine-2,5-diyl-kC2:kC5)disodium	0.65	0.21	No	No	No

After the confirmation of ADME properties, the six ligands were then subjected to further molecular docking with iGEMDOCK subjecting to accurate docking (very slow docking) by setting population size of 800 is set with 80 generation and 10 solution. The results were projected in the Table 3. From the table it is clear the first ligand (4-carbamoyl-5-hydroxy-6-iodo-1λ3-iodinin-2-yl) sodium is found to have excellent fitting compared to other ligands based on the docking energy values. The results clearly indicate that the ligand should have a good inhibitory property for GspB protein. Its docking pose was shown in the Figure 3. Further this compound has drug likeliness score of 2.01 and a drug score of 0.92 and hence can be a potential drug candidate in the prevention of infective endocarditis caused by *S. gordonii*.

Table 3: The results of iGEMDOCK showing binding energies of six selected ligands

S.No.	Ligand	Total binding Energy (kcal/mol)	Vanderwaals force	H Bond	Electrostatic bond
1.	(4-carbamoyl-5-hydroxy-6-iodo-1λ3-iodinin-2-yl)sodium	-94.5832	-74.6102	-19.9729	0
2.	[5,6-dihydroxy-4-(iodocarbonyl)-1λ3-iodinin-2-yl]sodium	-64.2151	-34.878	-29.3371	0
3.	[5-hydroxy-4-(iodocarbonyl)-6-methoxy-1λ3-iodinin-2-yl]sodium	-64.4711	-43.4975	-20.9736	0
4.	3-hydroxy-2,6-dimethoxy-1λ3-iodinine-4-carbonyl iodide	-72.7098	-58.6674	-14.0424	0
5.	3,6-dihydroxy-2-methoxy-1λ3-iodinine-4-carbonyl iodide	-65.2493	-49.6153	-15.634	0
6.	m-(4-carbamoyl-6-hydroxy-1λ3-iodinine-2,5-diyl-kC2:kC5)disodium	-62.3832	-34.2286	-28.1546	0

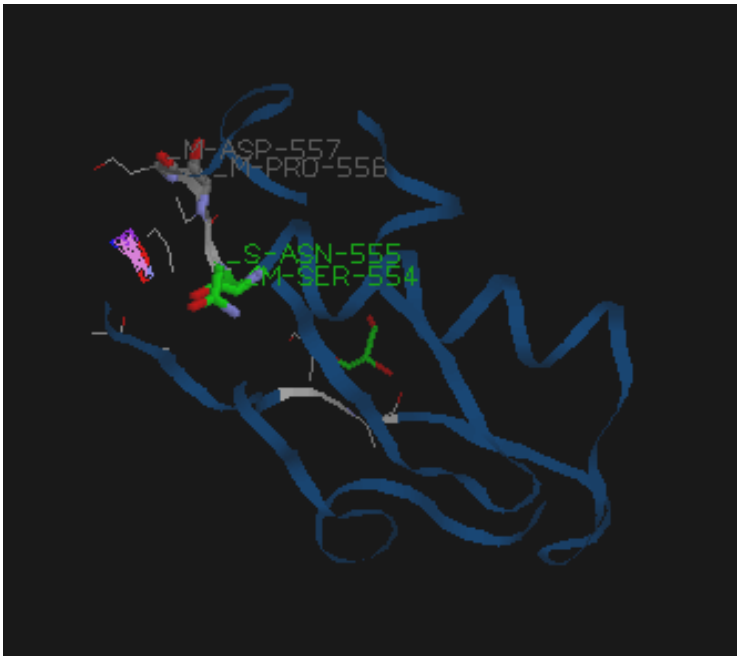

Figure 4: Docking pose of GspB with (4-carbamoyl-5-hydroxy-6-iodo-1λ3-iodinin-2-yl) sodium

Conclusion

The GspB protein of *S. gordonii* is found to be the major virulence factor involved in the causation of infective endocarditis. Hence the inhibitors of the GspB protein can be an effective drug in the prevention of infective endocarditis caused by *S. gordonii*. In the present study the ligands were generated and were studied for its ability to inhbit the GspB protein by molecular docking method. Six ligands with good inhibitory properties were generated among which (4-carbamoyl-5-hydroxy-6-iodo-1λ3-iodinin-2-yl) sodium, a novel compound is found to be very excellent drug candidate based on the molecular docking studies and its ADME properties.

Acknowledgements

We thank Prof. J. Mala, Chairperson, and Tagore group of Colleges, for providing necessary facilities for the present study. We are thankful to Dr. T. N. Swaminathan, Advisor and Dr. Chitraa R. Chandran, Principal, Tagore Dental College and Hospital for their kind support and encouragement.

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