ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Comparative Modelling of Shikimate Kinase (M Tb) and Molecular Docking Studies of its Known Inhibitors

Sweta Sinha, Rajasulochana P, Ramesh Babu PB, and Krishnamoorthy P

School of Bioengineering, Department of Bioinformatics, Bharath University, Chennai, Tamil Nadu, India.

ABSTRACT

Tuberculosis (TB) made resurgence in the mid-1980s and now kills approximately 3 million people a year. The re-emergence of tuberculosis as a public health threat, the high susceptibility of HIV-infected persons and the proliferation of multi-drug-resistant strains have created a need to develop new drugs. Shikimate kinase (SK) and other enzymes in the shikimate pathway are attractive drug targets for development of non-toxic antimicrobial agents, herbicides and anti-parasitic drugs, because the pathway is essential in these species whereas it is absent from mammals. The object of our study is shikimate kinase (SK), the fifth enzyme of this pathway. The 3D model of Shikimate kinase protein was generated via different modelling servers and the one with least RMSD with its already reported crystal structure was chosen for further computational analysis. Docking of the model with reported inhibitors was done and docking scores were generated. Our work was focused to study and analyze the role of this protein for finding the best possible inhibitor that could become a possible drug target.

Keywords: Shikimate Kinase; Mycobacterium Tuberculosis; Comparative Modelling servers; Superimposition server; Chemsketch software; Docking software (Schrodinger Software).

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Tuberculosis (TB) is the most important cause of human death from a curable infectious disease. It is estimated that, worldwide, one hundred million people are infected annually and about ten million develop the disease, with five million of those progressing to an infectious stage, culminating with approximately three million deaths. According to the World Health Organization, the overall incidence of TB increases approximately 0.3% per year. Besides, the high susceptibility of HIV/AIDS infected patients to TB is also a health problem. Therefore, there is an urgent need for the discovery and development of new and better drugs for the TB treatment [1].

Enzymes of the shikimate pathway (SP) are promising targets for the development of antimicrobial agents [2] and herbicides [3], because they are essential to the survival of algae, higher plants, bacteria, fungi, apicomplexan parasites and absent in mammals [4]. It is a seven-step biosynthetic route that converts erythrose 4-phosphate to chorismate, a precursor of aromatic amino acids and many other essential compounds [5].

Shikimate Kinase (SK) is a member of the nucleoside mono phosphate kinases (NMP kinases) family, which suffer large conformational changes during catalysis [6]. The enzymes of this family are composed of three domains: the CORE, which contains a highly conserved phosphate binding loop (P-loop), the LID domain, which undergoes substantial structural changes upon substrate binding, and the NMP-binding domain which is responsible for the recognition and binding of a specific substrate [7].

Molecular docking is a simulation method that predicts the conformation of a receptor-ligand complex, in which the receptor can be either a protein or a nucleic acid, and the ligand is a small molecule. This computer simulation can generate many possible positions for the ligand in the receptor-binding pocket. Therefore, a criterion is necessary that will allow comparisons of all possible positions of the ligand, and then a selection can be made for the best position.

Our goal here is to compare the 3D models of shikimate kinase protein taken from five different server and select the best model depends on root-mean-square deviation (RMSD) and Z-Score, we used this model as Mycobacterium tuberculosis Shikimate Kinase (MtSK) structure [8] as a target for the molecular docking simulations. Docking is frequently used to predict the binding orientation of small drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. We describe the results obtained in terms of the DOCKING scores and modes of interaction in the ligand binding process.

MATERIALS AND METHODOLOGY

DATABASE USED:

NCBI - National Center for Biotechnological Information.
PDB – Protein Data Bank

ISSN: 0975-8585

TOOLS USED:

Some of the automated servers used are as follows:

- $(PS)^2$server.
- 3D –JIGSAW.
- ESyPred3D Web Server 1.0.
- Multiple Mapping Method Server
- Swiss-Model.
- Dali pairwise comparision
- Schrodinger Software

METHODS:

MTsk sequence was obtained from NCBI and template from BLAST-P. For comparative modelling servers used were $(PS)^2$ server, 3D –JIGSAW, ESyPred3D Web Server 1.0., Multiple Mapping Method Server and Swiss-Model. To get the best structure from the all five predicted structures, model was superimposed with the crystal structure of MTsk reported in PDB database using Dali Pairwise Comparison. To draw the structure of ligands, we used the "ChemSketch" software. Using SCHRODINGER SOFTWARE, the protein was docked with the ligands and the docking scores were obtained. At the end of docking, the ligand residue was highlighted and neighbouring amino acid and/or heme residues within 4 angstroms were selected. The programme was commanded to hide the unselected the residues so as to determine amino acids lining the binding cavity. Also, hydrogen bonds bumps were monitored.

RESULTS AND DISCUSSION

The superimposition of all the five predicted models with the crystal structure of Shikimate kinase protein of Mycobacterium tuberculosis from Dali Pairwise Comparison, PDB ID: 2IYT, was done to get the best predicted model of Shikimate kinase protein according to their RMSD value, Z-Score, %id, etc.

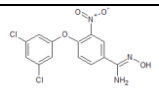
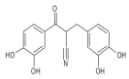
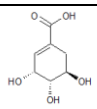
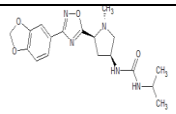
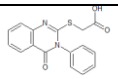
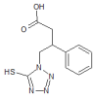
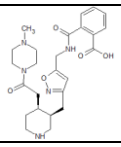
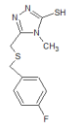
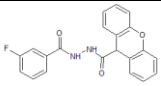
Further docking studies were carried out on the predicted model from **ESyPred3D** server using Schrodinger Software.

Table No.1: The Tabular form of Obtained Results

S. No.	Server Names	Z-Score	RMSD	lali	Nres	%id
1.	$(PS)^2$	19.0	3.8	159	175	92
2.	3D-JIGSAW	18.8	2.3	149	161	96
3.	ESyPred3D	20.4	2.0	152	166	97
4.	MMM Server	20.9	2.1	152	165	100
5.	SWISS-MODEL	20.8	2.4	155	166	100

Table No.2: 10 Best Ligand Structures Along With Their Docking Scores

ISSN: 0975-8585

S.No.	Compound Name	Compound Structure	Docking Score
1.	SPB01099		-6.174338
2.	AG538		-6.151543
3.	Control shikimate		-6.138796
4.	Control 6-S-fluoroshikimate		-6.089551
5.	ZINC20464408		-5.777331
6.	asxb1		-5.75549
7.	diver1		-5.538557
8.	ZINC20462780		-5.484212
9.	MW 1		-5.354823
10.	RH00016		-5.231464

ISSN: 0975-8585

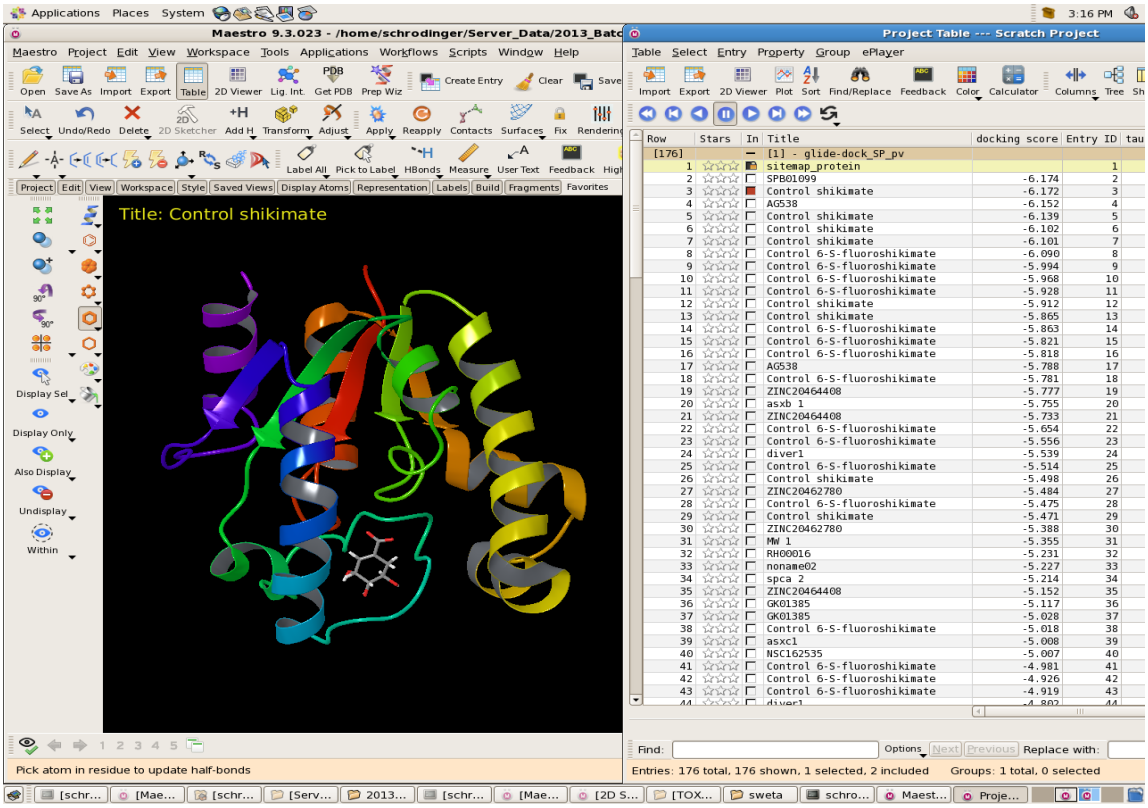


Figure No.1: Docking Scores

CONCLUSION

Predicted model using **ESyPred3D** server was showing least rmsd value with the already reported crystal structure which showed that this server is predicting M Tb SK with good accuracy. Further docking studies were carried out on the predicted model from **ESyPred3D** server using Schrodinger Software, in which interaction of 33 known inhibitors were seen with the rigid protein structure of Shikimate Kinase (M Tb) and the docking score were analysed. The inhibitor found with best docking score was having Pubchem ID-SPB01099 with a docking Score of -6.17434 value.

REFERENCE

[1] Basso LA, Pereira Da Silva LH, Fett-Neto AG, De Azevedo Jr WF, Moreira IS, Palma MS, Calixto JB, Astolfi Filho S, dos Santos RR, Soares MBP, Santos DS. Mem Inst Oswaldo Cruz 2005;100:475–506.

[2] Davies GM, Barrett-Bee KJ, Jude DA, Lehan M, Nichols WW, Pinder PE, Thain JL, Watkins WJ, Wilson RG. Antimicrob Agents Chemother 1994;38:403–406.

[3] Coggins JR. The shikimate pathway as a target for herbicides. In: Dodge AD (ed) Herbicides and Plant metabolism. Cambridge University Press, Cambridge, UK, 1989: pp 97–112.

[4] Bentley R. Crit Rev Biochem Mol Biol 1990;25:307–384.

ISSN: 0975-8585

[5] Ratledge C. Nutrition, growth and metabolism. In: Ratledge C, Stanford JL (eds) The Biology of the Mycobacteria 1982;1:185–271.
[6] Vonrhein C, Schlauderer GJ, Schulz GE. Structure 1995; 3:483–490.
[7] Gu Y, Reshetnikova L, Li Y, Wu Y, Yan H, Singh S, Ji X. J Mol Biol 2002; 319:779–789.
[8] Dias MV, Vasconcelos IB, Prado AM, Fadel V, Basso LA, De Azevedo Jr WF, Santos DS Acta Crystallogr F Struct Biol Cryst Commun 2007;63:1–6.
[9] Holm L, Park J. Bioinformatics 2000;16(6):566-7.
[10] Lambert C, Leonard N, De Bolle X, Depiereux E. Bioinformatics 2002; 18(9): 1250-1256.