Discovery of the lead molecules targeting the first step of the histidine biosynthesis pathway of Acinetobacter baumannii

Anamika Singh, Nabeel Ahmad, T. P. Singh, Sujata Sharma and Pradeep Sharma

Department of Biophysics, AIIMS, New Delhi-110029 (India)
singhanamika378@gmail.com

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Acinetobacter baumannii is a multidrug-resistant, opportunistic, nosocomial pathogen [1] for which a new line of treatments is desperately needed. We have targeted the enzyme of the first step of the histidine biosynthesis pathway, viz., ATP-phosphoribosyltransferase (ATP-PRT) [2]. The three-dimensional structure of ATP-PRT was predicted on the template of the known three-dimensional structure of ATP-PRT from Psychrobacter arcticus (PaATPPRT) [3] using a homology modeling approach. High-throughput virtual screening (HTVS) of the antibacterial library of Life Chemicals Inc., Ontario, Canada was carried out followed by molecular dynamics simulations of the top hit compounds. In silico results were then biochemically validated using surface plasmon resonance spectroscopy. We found that two compounds, namely, F0843-0019 and F0608-0626, were binding with micromolar affinities to the ATP-phosphoribosyltransferase from Acinetobacter baumannii (AbATPPRT). Both of these compounds were binding in the same way as AMP in PaATPPRT, and the important residues of the active site, viz., Val4, Ser72, Thr76, Tyr77, Glu95, Lys134, Val136, and Tyr156, were also interacting via hydrogen bonds. The calculated binding energies of these compounds were $-10.5$ kcal/mol and $-11.1$ kcal/mol, respectively. These two compounds can be used as the potential lead molecules for designing antibacterial compounds in the future, and this information will help in drug discovery programs against Acinetobacter worldwide.

Figure 1. A. F0843-0019 (best hit ligand 1), B. F0608-0626 (best hit ligand 2). The figures show the spatial (left) as well as the two-dimensional view (right) of binding site interactions of best-hit ligand complex_F0843-0019 and complex_ F0608-0626, respectively.

References:

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