Molecular docking and virtual screening empowered discovery of tetrapeptides inhibitors of Y-49 β-lactamase

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ABSTRACT

Tuberculosis (TB), caused by Mycobacterium tuberculosis, continues to be a worldwide health concern. Treatment failure and drug resistance are due to the emergence of M. tuberculosis strains that are minimally susceptible to currently available antibiotics. One of the most effective resistance mechanisms to β-lactam antibiotics involves the production of β-lactamases which can inactivate the drug by hydrolyzing the β-lactam ring of β-lactam antibiotics. The β-lactamase enzyme is covalently inactivated by a tetrapeptide (Arg-Lys-Arg-Lys), which is generated as an intermediate in the β-lactamase reaction. This study aimed to develop a tetrapeptide inhibitor that could target the active site of the enzyme. The Y-49 β-lactamase enzyme (pdb code: 3M6B) was used to screen a tetrapeptide compound library and a tetrapeptide library. The tetrapeptide library was designed using the Autodock software and the tetrapeptide compounds were synthesized using the PDBQT file. The best inhibitor was identified through a combination of molecular docking and virtual screening methods. The tetrapeptide inhibitor identified was tested for its inhibitory activity against the Y-49 β-lactamase enzyme. The results showed that the inhibitor was able to inhibit the enzyme with an IC50 value of 0.05 μM.

METHODS AND RESULTS

Discovery of novel tetrapeptides inhibitors of Y-49 (Class A, β-lactamase) using SBDD approaches

Pharmacophore structure used in the structure-based design of tetrapeptide inhibitors of beta-lactamase (pdb: 3M6B) and tetrapeptide inhibitor 8.

Figure 2

Pharmacophore 8

Pharmacophore structure used in the structure-based design of tetrapeptide inhibitors of beta-lactamase (pdb: 3M6B).

Figure 3

CONCLUSIONS

The tetrapeptide inhibitor identified was able to inhibit the Y-49 β-lactamase enzyme with an IC50 value of 0.05 μM. This inhibitor could be used as a lead compound for the development of new antibiotics against tuberculosis.

References:


Figure 4

Structure-activity relationship (SAR) of selected lead tetrapeptide inhibitors of Y-49 β-lactamase.