Elucidating the binding interaction of pyrimido[4,5-*b*]indol-8-amine derivatives as potential GyrB inhibitors against *M. tuberculosis* using molecular docking calculations

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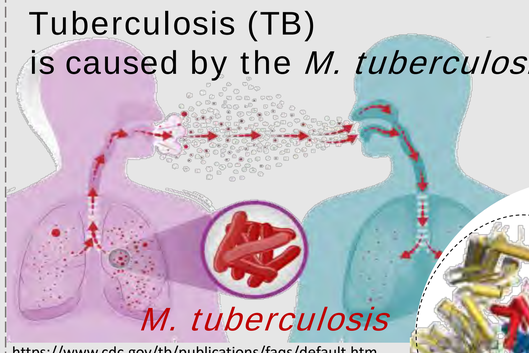
Introduction

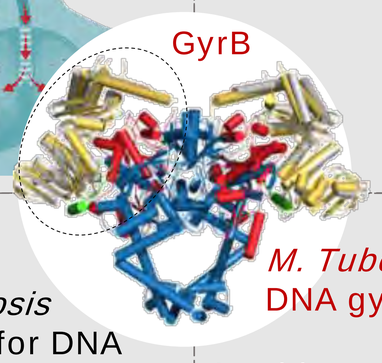
Tuberculosis (TB) is caused by the *M. tuberculosis*



WHO report in 2021

- 9.9 million people fell ill with TB
- 1.5 million people died from TB

"TB remains one of the world's top infectious killers"



DNA gyrase subunit B (GyrB) is a significant target for *M. tuberculosis* because it is required for DNA replication and transcription. Therefore, GyrB has been studied. The pyrimido [4,5-*b*] indol-8-amine derivatives have been reported as GyrB ATPase inhibitors against tuberculosis.

In this study, molecular docking calculations were carried out to understand insight into binding mode and binding interaction of compounds responsible for GyrB inhibition.

Material and method

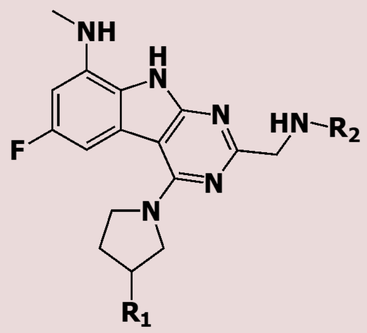
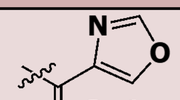
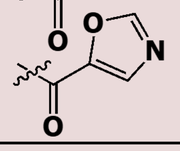


Figure 1. General structure

Table 1. structure and biological activities

Compound	R_1	R_2	*M. tuberculosis* gyrase ATPase inhibition (IC_{50}, **μ**M)
1	NH_2		0.025
2	NH_2		0.059

Compounds 1 and 2 were obtained from literature (Bioorganic Med. Chem. Lett. 2018;28:2998-3003) with *M. tuberculosis* gyrase ATPase inhibition as shown in Table 1. The general structure, pyrimido[4,5-*b*]indol-8-amine of the molecules are indicated in Figure 1.

The molecular docking calculations were performed using the Maestro 10.2 program. The GyrB ATPase domain of M. smegmatis complexed with co-crystal structure was downloaded from PDB (PDB code: 4BAE).The root-mean square deviation (RMSD) between co-crystal structure and receptor conformation **lower than 1 Å (0.86 Å) was used as** GyrB ATPase binding site for molecular docking calculation.

Results and discussion

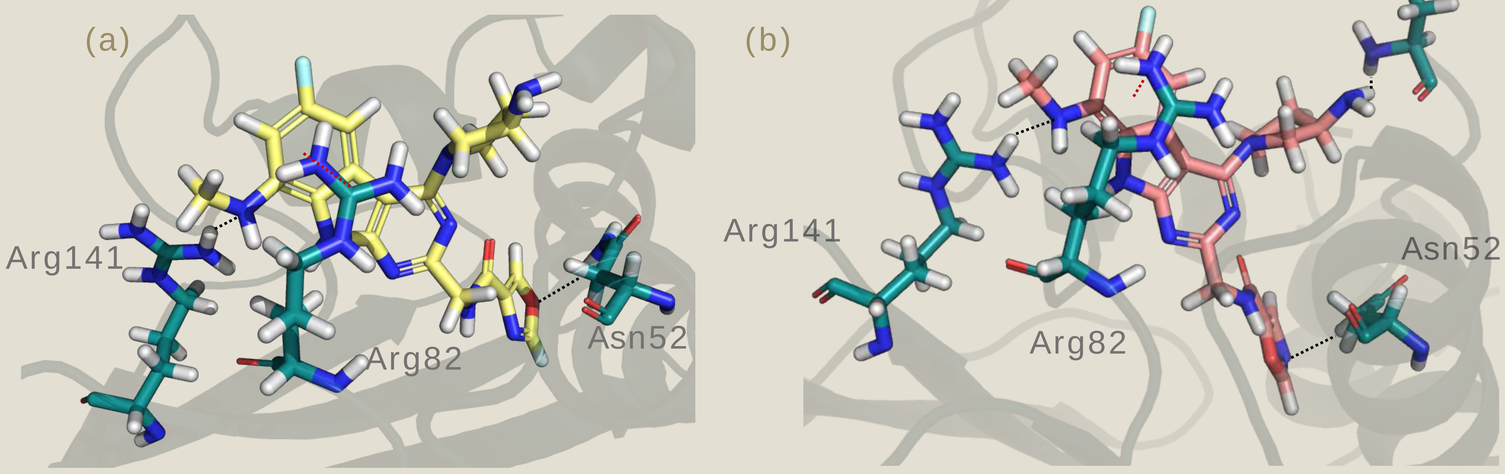


Figure 2. The binding mode and binding interactions of the compounds 1 (a) and 2 (b) obtained from molecular docking calculations. Black and red dashed lines indicate hydrogen bond and pi-cation interactions, respectively.

The binding mode of the compounds 1 and 2 were analyzed and are shown in Figure 2. Compounds 1 and 2 forms two hydrogen bond interactions with Asn52 and Arg141 residues. Cation-pi was obtained between benzene ring of the compounds 1 and 2 with the side chain of Arg82 residue. In addition, the binding affinity increase with H-bond interaction between O atom of compound 2 and Arg82 residue of GyrB pocket. Therefore, the molecular docking calculations were performed to confirm inhibition of compounds 1 and 2.

Conclusion

To understand the binging mode, binding interaction and binding energy of compounds, molecular docking calculations were carried out against GyrB. Based on the results, molecular docking calculations of the pyrimido[4,5-*b*]indol-8-amine derivatives showed crucial interactions between ligands and binding pocket. It may be said that the antitubercular property of the molecule could be via the inhibition of ATPase domain of GyrB enzyme. Therefore, the docking studies of pyrimido[4,5-*b*]indol-8-amine derivatives are important results for further rational design of novel GyrB inhibitor to combat drug resistant tuberculosis.

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