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Identification of novel chemical agents with antibacterial activity against *Mycobacterium* by *in silico* structure-based drug screening

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The increasing prevalence of drug-resistant tuberculosis (TB) (i.e. multidrug-resistant TB: MDR-TB, extensively drug-resistant TB: XDR-TB), which is resistant to several effective antibiotics, presents a major global health threat [1]. The enoyl-acyl carrier protein reductase of *Mycobacterium tuberculosis* (InhA) is a key enzyme of the mycobacterial type Ⅱ fatty acid biosynthesis pathway (FAS-Ⅱ). In this pathway, the InhA plays major role in the production of mycolic acid and is known as a target protein for first-line drug isoniazid (INH), an effective antibiotics for TB chemotherapy [2].

In this study, we attempted to identify novel chemical compounds specifically targeting the InhA. We performed a hierarchical *in silico* SBDS [3,4] using InhA crystal structure data (PDB ID: 2H7I) and the virtual chemical library (ChemBridge, CA) including 154,118 chemicals. We then evaluated the antibiotic effects of the candidate chemicals, and we found two hits (KE3 and KE4), which were able to inhibit the growth of model mycobacteria strains (*M. vanbaalenii* and *M. smegmatis*). We also performed similarity analysis to identify five additional chemicals (KES1-KES5) with similar structures to the active chemicals from ChemBridge compound library, containing 461,383 compounds. The most potent inhibitors (KE4 and KES4) do not have any toxic effects in model intestinal bacteria (*E. coli* BL21 and JM109 strains) and mammalian cells (MDCK and SH-SY5Y cells). Moreover, we also confirmed that these chemicals directly inhibit the enzymatic activity of InhA.

In conclusion, the structural and experimental information regarding these novel chemical compounds is likely to be useful for the hit-to-lead optimization of new antibiotics for the treatment of TB. Furthermore, our screening methodology presented in this study could contribute to the further identification of novel hit compounds for other candidate medicinal drugs.

References

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