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Extended Abstract

Identification of Inhibitors of the Anti-Infective Target DXS Using Dynamic Combinatorial Chemistry †

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Antibiotic resistance is one of the biggest threats to humankind [1,2]. This global problem is aggravated by bacteria developing new resistance mechanisms and the emergence of extremely drug-resistant strains of the pathogens. In this alarming situation, novel targets for which inhibitors with an unprecedented mode of action can be developed are urgently required.

Our study aims at the development of selective and potent inhibitors of the important and underexplored anti-infective target DXS. This enzyme from the 2C-methyl-D-erythritol 4-phosphate pathway is entirely absent in humans but is essential for medically relevant pathogens (e.g., *Plasmodium falciparum, Mycobacterium tuberculosis, and Pseudomonas aeruginosa,*). Despite substantial efforts dedicated to the discovery of inhibitors for DXS, to date, very few active compounds have been reported, and none of them fulfill the requirements as an ideal candidate for further development. To address these issues and maximize the chances of success, we are using a combination of structure-based drug design and target-directed dynamic combinatorial chemistry (tdDCC) as hit-identification strategies for the first time for DXS. To expand structural diversity and obtain potent and selective inhibitors of DXS, we designed the dynamic combinatorial library for acyl hydrazone formation. Different heterocyclic hydrazides and aldehydes were chosen based on calculated estimated affinity using SeeSAR for all possible acyl hydrazone products. Biochemical evaluation of five hit compounds amplified in a first round of tdDCC experiment against *M. tuberculosis* DXS and *D. radioduran* DXS afforded inhibitors with IC_{50} in the range of 49–190 μM. Further improvement of the activity by a more tailor-made DCC-library and by SAR of hits obtained is underway.

References

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