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Identification of inhibitors of the anti-infective target DXS using ligand-based virtual screening

The enzymes of the methylerythritol phosphate (MEP) pathway are important drug targets given that pathogens such as *Mycobacterium tuberculosis* and Plasmodium falciparum use this pathway for the biosynthesis of the essential isoprenoid precursors isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), while humans exclusively utilize an alternative pathway. The thiamine-diphosphate-dependent enzyme 1-deoxy-D-xylulose-5-phosphate synthase (DXS) catalyzes the first and rate-limiting step of the MEP pathway. To expand the structural diversity and obtain potent and selective inhibitors of DXS, we performed a ligand-based virtual screening (LBVS) campaign based on shape similarity to screen the ZINC database, starting from previously discovered DXS inhibitors as references. Biochemical evaluation of the top-scoring compounds against *Mycobacterium tuberculosis* DXS and further rounds of LBVS using the best hits as references afforded inhibitors in the single-digit micromolar range. In addition to the promising biochemical activity, the hits are active in cell-based assays against *Plasmodium falciparum* and even drug-resistant strains of Mycobacterium tuberculosis. Further, assays demonstrated their selectivity over mammalian thiamine-diphosphate-dependent enzymes, their lack of cytotoxicity and validated DXS as the intracellular target.

Biography

Anna K H Hirsch has completed Natural Sciences at the University of Cambridge, spent one year at the Massachusetts Institute of Technology and did her Master's project. She has received her PhD from the ETH Zurich under the supervision of Professor F Diederich. She has further joined the group of Professor Jean-Marie Lehn in Strasbourg as Postdoctorate and then took the position as an Assistant Professor at the University of Groningen. Later, she was promoted to Associate Professor. In 2017, she became Head of the Department for Drug Design and Optimization at the Helmholtz Institute for Pharmaceutical Research Saarland, Germany.

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