Exploring hit-identification strategies for energy-coupling factor transporters, a novel target for the development of antibiotics

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There is an urgent requirement for the development of antibiotics with a novel mode of action. We applied various hit-identification strategies – structure-based design, dynamic combinatorial chemistry, protein-templated click chemistry and virtual screening – in the search for new ligands for the energy-coupling factor (ECF) transporters. ECF transporters are a class of ATP-binding cassette (ABC) transporters that mediate the uptake of vitamins in prokaryotes. They consist of an energizing module and a substrate-binding protein (S-component). Different S-components can interact with the same energizing module. [1] ThiT is the thiamine-specific Scomponent.[2] Based on the co-crystal structure of ThiT-thiamine, we designed and synthesized thiamine analogues to identify which residues are key for substrate binding and to elucidate the mechanism of transport. Ligand-binding assays show that the new compounds bind with high affinity to ThiT (K_d = 4–660 nM). Co-crystallization studies of some of the compounds with ThiT confirmed the predicted binding mode and provide insight into the molecular recognition of thiamine by ThiT.[3].

A structure-based virtual screening campaign provided us with the first allosteric inhibitors of the transporter for folate.[3] Our hits constitute a starting point for the development of novel antibiotics against pathogenic bacteria that depend on this class of transporters.

Literature:

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