Small-molecule modulators of thiamine transport in pathogenic bacteria

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Energy Coupling Factor (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. ThiT is the thiamine-specific S-component. Based on the cocrystal structure of ThiT-thiamine, we have designed and synthesized thiamine analogues to identify which residues are the key for substrate binding and to elucidate the mechanism of transport.

Figure 1: (a) Schematic of target ECF-type ABC transporter. Multiple S-components (yellow) interact with the same energizing module (red and blue). (b) Structure of thiamine (1) and designed and synthesized modulators (2–6). Ligand-binding assays have been performed by following quenching of the intrinsic fluorescence, and they showed that the new compounds bind with high affinity to ThiT (Kd = 4–660 nM). Co-crystallization studies of compounds 3a and 5 with ThiT confirmed the predicted binding model. The newly synthesized molecules may be potent inhibitors of the transporter and would validate it as a novel target for the development of antibiotics with a novel mode of action.

Biography

Anna K H Hirsch studied Natural Sciences at the University of Cambridge and spent her third year at the Massachusetts Institute of Technology. Her Master’s project focused on the double conjugate addition of dithiols to propargylic carbonyls under the supervision of Professor S V Ley. She received her PhD in 2008 from the ETH Zurich working on the design and synthesis of the first inhibitors for the kinase IspE under the supervision of Professor F Diederich. Subsequently, she joined the group of Professor Jean-Marie Lehn at ISIS (Strasbourg). Her research interests focus on rational approaches to drug design.