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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.

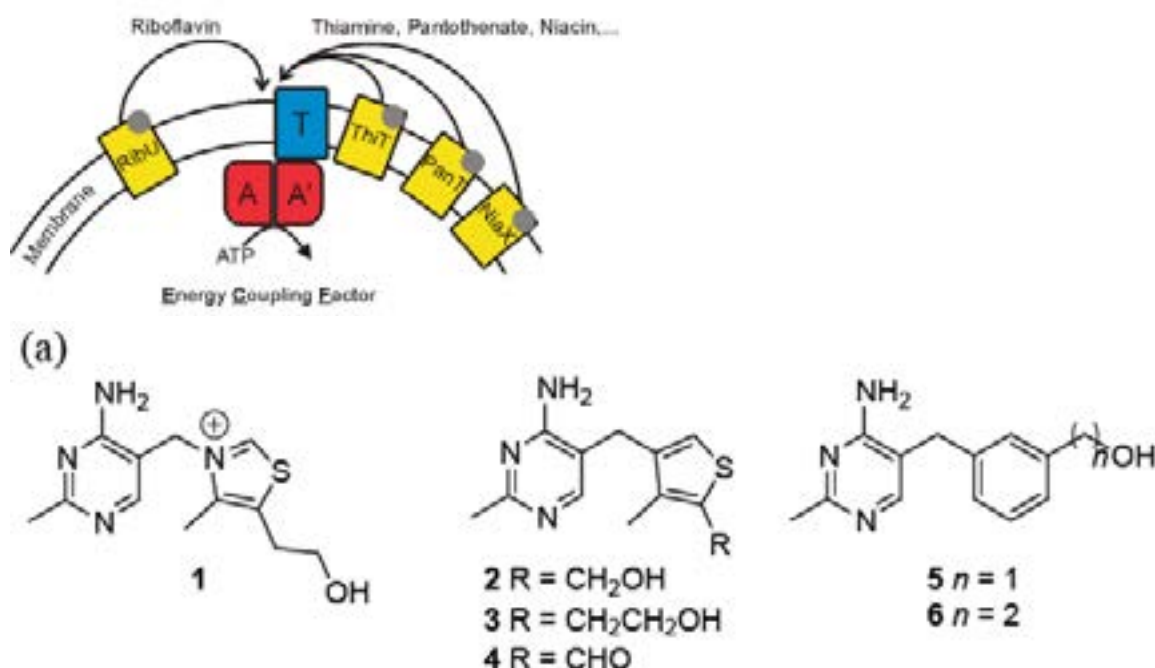


Figure 1: (a) Schematic of target ECF-type ABC transporter. Multiple S-components (yellow) interact with the same energizing module (red and blue). (b) Structure of thiamine (1) and designed and synthesized modulators (2-6). Ligand-binding assays have been performed by following quenching of the intrinsic fluorescence, and they showed that the new compounds bind with high affinity to ThiT ($K_d = 4-660$ nM). Co-crystallization studies of compounds 3a and 5 with ThiT confirmed the predicted binding model.⁴ 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.

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