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Design, synthesis and X-ray crystallographic study of NAmPRTase inhibitors as anti-cancer agents

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NAmPRTase (PBEF/Visfatin) plays a pivotal role in the salvage pathway of NAD biosynthesis. NAmPRTase has an attractive target for anti-cancer agents that induce apoptosis of tumor cells via a declining plasma NAD level. In this report, a series of structural analogs of FK866 (1), a known NAmPRTase inhibitor, was synthesized and tested for inhibitory activities against the proliferation of cancer cells and human NAmPRTase. Among them, compound 7 showed similar anti-cancer and enzyme inhibitory activities to compound 1. Further investigation of compound 7 with X-ray analysis revealed a co-crystal structure in complex with human NAmPRTase, suggesting that Asp219 in the active site of the enzyme could contribute to an additional interaction with the pyrrole nitrogen of compound 7. This work was supported by the "GIST Systems Biology infrastructure Establishment Grant (2011)".

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Structural studies of DnaK in complex with proline rich antimicrobial peptides

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Bacterial infections are a major cause of death worldwide. Due to increasing resistance against the commercially available antibiotics over the past few decades, novel antimicrobial drug classes with new mode of actions are required for future treatments. Small proline rich antimicrobial peptides (PR-AMPs) from mammals and insects were identified to target the E.coli Hsp70 chaperone DnaK after cell penetration. Binding of the peptides to DnaK compromises the activity of the chaperone and thus the viability of the bacterial cells, in particular under conditions of stress. The non-lytic cell penetration of PR-AMPs to Gram-negative bacteria makes them a promising drug candidate against human infections. Therefore, structural informations about the interactions between peptide inhibitors and DnaK are necessary for a better understanding of the mode of action.

After recombinant expression of the substrate binding domain in E.coli and subsequent purification, we crystallized the domain with several PR-AMPs. Elucidation of the binding mode of the peptides and characterization of the substrate specificity of DnaK will allow a structure-guided development of peptide inhibitors as antimicrobial agents targeting DnaK.

Keywords: antibiotic, resistance, phosphotransferase