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Ring fused 2-pyridones inactivate the virulence regulator PrfA of *Listeria monocytogenes*

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The rapid emergence of bacterial resistance to antibiotics is a serious global problem and new therapeutic options to treat severe bacterial infections are therefore urgently required. The bacterium Listeria Monocytogenes is a Gram positive saprophyte, responsible for the severe disease listeriosis in humans upon ingestion. It is one of the most problematic food borne pathogens due to its ability to grow at low temperatures, low oxygen conditions and in high salt concentrations. From a small in-house library, we have identified several ring fused 2-pyridone molecules that attenuate *L. monocytogenes* infectivity by reducing the expression of virulence genes, without compromising bacterial growth. The inhibitors bind to and prevent activation of PrfA, the central transcriptional virulence regulator in *L. monocytogenes*. The ring fused 2-pyridone C10 binds to PrfA with an IC50 ≈1 μM according to ITC measurements. The structural basis for inhibition was elucidated by the structurally resolved complex between C10 and PrfA. This represents the first structurally resolved complex between an inhibitor and a Crp family transcriptional regulator. Here, we will present a new generation of improved ring fused 2-pyridone molecules, which have been designed and developed based on the PrfA•C10 crystal structure. These demonstrate increased solubility and improved activity in our biological screen. Co-crystallization of the new structures with PrfA has also provided a more detailed illustration of the inhibitor mode of action.

Biography

Martina Kulen is a PhD student in Prof. Fredrik Almqvist group at the Department of Chemistry, Umeå University, Sweden.

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