UMEÅ UNIVERSITET

New Alternatives to Combat *Listeria monocytogenes* and *Chlamydia trachomatis*

Design, Synthesis, and Evaluation of Substituted Ring-Fused 2-Pyridones as Anti-Virulent Agents

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Akademisk avhandling

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Abstract
Antibiotic resistance has become a global health burden with the number of resistant bacteria continuously increasing. Antibiotic drugs act by being either bactericidal (killing bacteria) or bacteriostatic (inhibiting growth of bacteria). However, these modes of action increase the selective pressure on the bacteria. An alternative treatment strategy to antibiotics is anti-virulence therapies that inhibits virulence of the pathogenic bacteria. The term "virulence" summarises a number of factors that the bacteria need to colonise a new niche and as a consequence its ability to infect and cause diseases. By inhibiting virulence, instead of killing, the selective pressure on the bacteria can be reduced and consequently decreases the rapid development of resistance. This thesis describes two projects focusing on development of anti-virulence agents, with the ring-fused 2-pyridone scaffold as the central character, targeting the bacteria *Listeria monocytogenes* and *Chlamydia trachomatis*.

The first project is targeting *L. monocytogenes*, which is the cause for listeriosis in humans. This can develop into life-threatening encephalitis and meningitis as well as cause severe complications for developing fetus. The target in *L. monocytogenes* is the transcriptional regulator PrfA that control almost all virulence factors in this bacterium. We have designed and synthesised potent substituted ring-fused 2-pyridones, which at low micromolar concentrations block activation of the virulence regulator PrfA and thus attenuate the bacterial infection. Co-crystallisation of the active ring-fused 2-pyridones with PrfA resulted in determination of the exact substance interaction site in the protein. This facilitated further structure-based design that resulted in improved compounds capable of attenuating *L. monocytogenes* in an *in vivo* model.

The second project targets *C. trachomatis*, which is the causative agent behind the most common sexually transmitted infection as well as the eye infection trachoma. By structure-activity relationship analysis of previously tested ring-fused 2-pyridones, we have designed and synthesised non-hydrolysable ring-fused 2-pyridone amide isosteres. The most potent analogues inhibit *C. trachomatis* infectivity at low nanomolar concentrations, without showing host cell toxicity or affecting the viability of commensal microbiota. Introduction of heteroatom substituents at specific sites of the ring-fused 2-pyridone scaffold, resulted in improved pharmacokinetic properties of the analogues and further evaluation *in vivo* was performed.

Keywords
Antibiotic resistance, anti-virulence, *Listeria monocytogenes*, *Chlamydia trachomatis*, ring-fused 2-pyridone, organic synthesis, structure-based design, PrfA, drug design, structure-activity relationship.

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