# Development of antibacterial compounds targeting *Chlamydia trachomatis*

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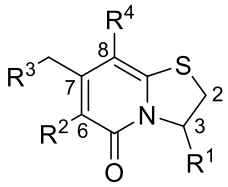
Every year vast amounts of broad-spectrum antibiotic are used to treat *Chlamydia trachomatis* infections. Chlamydia is the most common bacterial sexually transmitted disease with an estimated 131 million new cases yearly. The pathogen is also the leading infectious cause of blindness. WHO launched in 1996 an initiative to eliminate trachoma by 2020, now postponed to 2030 as trachoma remains a public health problem in 44 countries.

Our goal is to find a more specific treatment against *C. trachomatis* as it would avoid disrupting the normal microbiota and severely reduce the amount of broad-spectrum antibiotic used each year.




*C. trachomatis* inhibitors was identified in a screen of small compounds with a 2-pyridone backbone. Structure-Activity relationship (SAR) studies resulted in a second-generation compound effective at nM concentrations. Treatment with our most efficient compound disrupts the biphasic developmental cycle of *C. trachomatis* ocular disease causing serovar A, the genital disease causing serovar D and the more invasive lymphogranuloma venereum serovar L2. However, the same 2-pyridone concentrations do not inhibit the closely related mouse pathogen *C. muridarum* or the guinea pig pathogen *C. caviae.*

Investigating the mode of action, we found that *C. trachomatis* with mutations in the RNA helicase (CTL0077) and RNAse III (CTL059) genes exhibits resistance against the compound. These mutations do not confer a general antibiotic resistance but instead result in higher sensitivity to commonly used antibiotics. The 2-pyridone obstruct transcriptional activity as *C. trachomatis* progeny produced in its presence fail to initiate essential early gene transcription upon reinfection. To ascertain the molecular target of the compound further studies are needed.

To enhance the drug-like aspects, analogues were synthesized and analysed resulting in a compound with improved pharmacokinetic properties for oral uptake. Additional fine tuning is ongoing alongside vehicle and compound optimization for alternative treatment routes. As a step between cell culture and animal model we have set up an embryonated chicken egg model in which treatment with 2-pyridone compound extends median survival. This model allows for SAR studies in a complex system and the selection of a compound and vehicle that show no toxic effects or effects on embryo development.