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Exploring the chemistry and biology of benzofuran based natural products: Identification of novel antibacterial agents

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Antibiotics are viewed as one the most important factors contributing to human health and prosperity. However, the indiscriminate use of antibiotics has led to the emergence of multi-resistant "superbugs" e.g. the gram-negative pathogen *Pseudomonas aeruginosa* that resist many antibiotic treatments including combination therapies. Our ability to prevent and treat infectious diseases is today severely threatened and the need for new antibacterial therapies is evident. Many clinically relevant gram-negative pathogens e.g. *Salmonella* spp., *Chlamydia* spp., *Shigella* spp., *Pseudomonas* spp. and *Yersinia* spp. use a conserved syringe-like machinery called the type III secretion (T3S) system to inject toxins into the cytosol of host cells. The toxins block host cell functions and thereby create a niche that allows bacterial growth. The T3S system is essential for pathogens to evade the host immune defense and agents that inhibit the system will attenuate virulence without directly affecting growth of the pathogen. This chemical attenuation could enable the host to clear the infection and we hypothesize that the selective pressure for resistance will be significantly lower than for conventional antibiotics.

Recently, we have employed phenotypic screening to discover (-)-hopeaphenol, a resveratrol tetramer, as an irreversible and selective inhibitor of T3S in *Y. pseudotuberculosis* and *P. aeruginosa* [1, 2]. The chemistry of resveratrol oligomers is however challenging and their syntheses generally require multistep procedures [3]. To further explore the chemistry and biology of resveratrol based natural products we have ongoing projects covering total synthesis or resveratrol dimers and development of synthetic methodology [4-7], diversity-oriented synthesis [8,9] leading to potent anti-chlamydial compounds [9] as well as design, synthesis and applications of fluorescent probes and affinity reagents for target identification.

[1] *PLoS ONE* 8, **2013**, e81969; [2] *J. Nat. Prod.* 77, **2014**, 2633; [3] *Chem. Rev*. 115, **2015**, 8976; [4] *Eur. J. Org. Chem.* **2016**, 426; [5] *Adv. Synth. Cat.* 358, **2016**, 4085; [6] *ChemistrySelect,* 2, **2017**, 6245; [7] *Org. Lett.* 20, **2018**, 6650; [8] *ACS Comb. Sci.* 19, **2017**, 370; [9] *Eur. J. of Med. Chem.* 143, **2018**, 1077.