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Abstract

New 2-heteroaryl-4-aminoquinolines as *Pseudomonas aeruginosa* virulence quenchers †

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Abstract: In the struggle against multi-drug resistant bacterial infections, the opportunistic pathogen *Pseudomonas aeruginosa* has been identified by the WHO as a priority for the development of new treatments. This gram-negative bacterium produces a characteristic cytotoxic pigment called pyocyanin and is able to form biofilms that act as protective barriers against the immune system and antibiotics. Its pathogenicity is coordinated by the quorum sensing that is a bacterial communication network responsible for pathogenicity expression according to the population density. In the *P. aeruginosa* specific system pqs, the transcription factor PqsR regulates the activation of virulence-related genes via recognition of its auto-inducer PQS (*Pseudomonas* Quinolone Signal). This circuit stimulates the secretion of pyocyanin as well as the establishment of biofilms. Therefore, the development of quorum quenchers that disrupt connections without affecting bacterial growth appears as a promising strategy to circumvent selection pressure issues mediated by conventional antibiotherapy. These new anti-virulence agents (AVA) could restore the efficacy of antibiotics when used in bitherapy. In particular, the design of PqsR inhibitors as AVA seems like a sustainable approach to combat *P. aeruginosa* specifically. Bi-aromatic molecules targeting PqsR have been reported in the literature. Meanwhile, our team discovered a hit 2-heteroaryl-4-quinolone compound that displays interesting anti-biofilm and anti-pyocyanin activities. By structural analogy, we have recently developed a new family of 2-heteroaryl-4-aminoquinolines with promising anti-virulence properties. The synthesis of those new AVA as well as their physicochemical and biological evaluation is described in the poster.

Keywords: Multi-drug resistant bacteria; Pseudomonas aeruginosa; Biofilm; Quorum Sensing; Anti-virulence agents.

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