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Abstract

Development of New Anti-Virulence Agents to Tackle Multi-Resistant *Pseudomonas aeruginosa* †

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Abstract: The multi-resistant opportunistic bacterium *Pseudomonas aeruginosa* has been identified by the WHO as one of the most threatening pathogens of our time and a priority for the development of new treatments. The biofilms produced by this micro-organism act as protective barriers. They increase its pathogenicity *via* a persistence towards the immune system and its resistance to antibiotics. Biofilm formation is coordinated by Quorum Sensing (QS), which is a bacterial communication network responsible for virulence pathways expression according to the population density. In *P. aeruginosa*-specific QS system *pqs*, the transcription factor PqsR regulates the activation of virulence-related genes via the recognition of its auto-inducer PQS (Pseudomonas Quinolone Signal). This circuit stimulates the secretion of virulence factors, such as pyocyanin, and the establishment of biofilms. Therefore, the development of non-bactericidal agents that disrupt QS connections appears to be a promising alternative to conventional medicines without creating selection pressure issues. These new anti-virulence agents (AVAs) could restore the efficacy of antibiotics when used in combination therapy. In particular, the design of AVAs that inhibit PqsR appears to be a sustainable approach to specifically combat *P. aeruginosa*. Bi-aromatic PqsR inhibitors possessing a 4-aminoquinoline moiety have been described in the literature. Moreover, our team recently discovered a series of 2-heteroaryl-4-quinolones that display interesting anti-biofilm and anti-pyocyanin activities. We now aim to develop a family of 2-heteroaryl-4-aminoquinolines as new AVAs that can potentially inhibit PqsR. The synthesis and the physicochemical and biological evaluation of those novel molecules will be described in the poster.

Keywords: multi-resistant bacteria; pseudomonas aeruginosa; biofilm; quorum sensing; anti-virulence agents

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