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Synthesis and target profiling of PQS and HHQ probes by chemical proteomics

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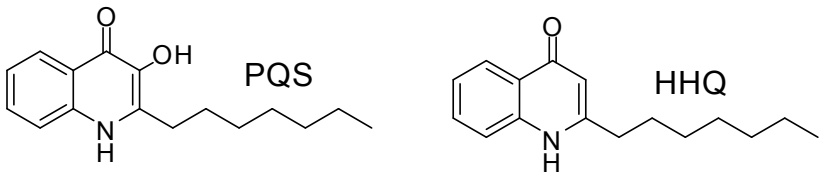
Pseudomonas aeruginosa is the most common gram-negative bacterium found in nosocomial infections. It primarily infects immunocompromised individuals and cystic fibrosis patients. Among the key compounds involved in the regulation of virulence factor production of these bacteria are quinolones, such as 2-heptyl-3-hydroxy-4(1H)-quinolone (Pseudomonas Quinolone Signal, PQS) and its direct precursor 2-heptyl-4(1H)-quinolone (HHQ). We have developed an efficient synthesis that allows access to PQS and HHQ photoaffinity probes from readily available starting materials. The probes contain a photoreactive group, a diazirine moiety, and a handle which will allow us to perform biorthogonal chemistry in order to pull down potential proteins that bind the bioactive quinolones. These studies will further enhance our understanding of PQS-mediated quorum sensing systems, and they will enable the development of methods that can modulate these signalling networks effectively, with possible therapeutic applications for the treatment of human bacterial infections.



The structure of PQS together with its biosynthetic precursor 2-heptyl-4-quinolone (HHQ); both have been shown to be involved in the quorum sensing of *P. aeruginosa.*

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Notes: