Cu- Catalyzed Synthesis of Alkylaminotroponyl Sulfones as *Pseudomonas aeruginosa* Quorum Sensing Inhibitors Targeting *lasI/R* QS Circuitry

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Abstract: The scarcity of novel bioactive molecules against multidrug-resistant (MDR) bacterial strains like *Pseudomonas aeruginosa* is alarming.[1] This bacterial virulence is regulated via Quorum sensing (QS), a cell-cell communication process. Disabling QS circuits (*las*, *pqs*, *rhl*) with small molecules has been proposed as a potential strategy to prevent bacterial pathogenicity. This modern strategy focuses on interruption of bacterial virulence, rather than killing them to tackle the drug resistance problem. Herein, we have performed the synthesis of rationally designed Alklyamionotroponyl Sulfone (ATS) derivatives by Cu-catalyzed C(sp^2)−H functionalization at tropone ring and the screening of their anti-QS activity against *P. aeruginosa*. Importantly, two sulfones (~20 μM) remarkably exhibit the down regulation of the *lasI/R* QS genes. These molecules also inhibit swarming motility, biofilm formation and pyocyanin production, which reduce *P. aeruginosa* virulence in cells. Hence, ATS derivatives could be considered as potential therapeutic candidates for the treatment of *P. aeruginosa* infections.[2]

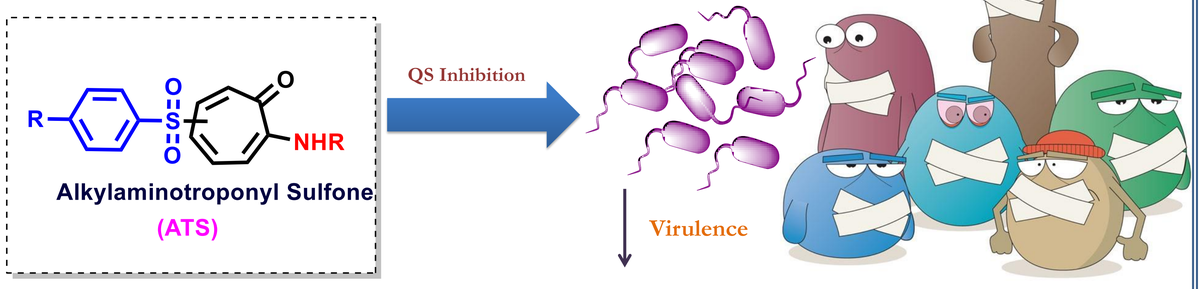
Objective- Rational design of ATS derivatives

Antimicrobial resistance (AMR) is a global threat !!!

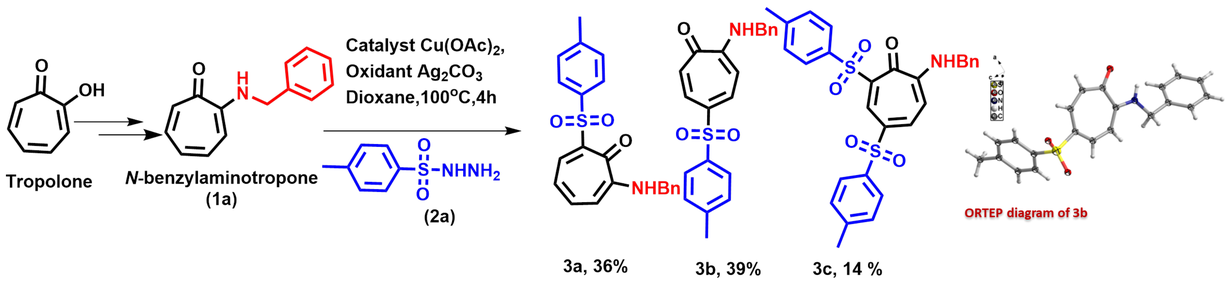
Virulence – Ability of an organism to infect the host and cause a disease

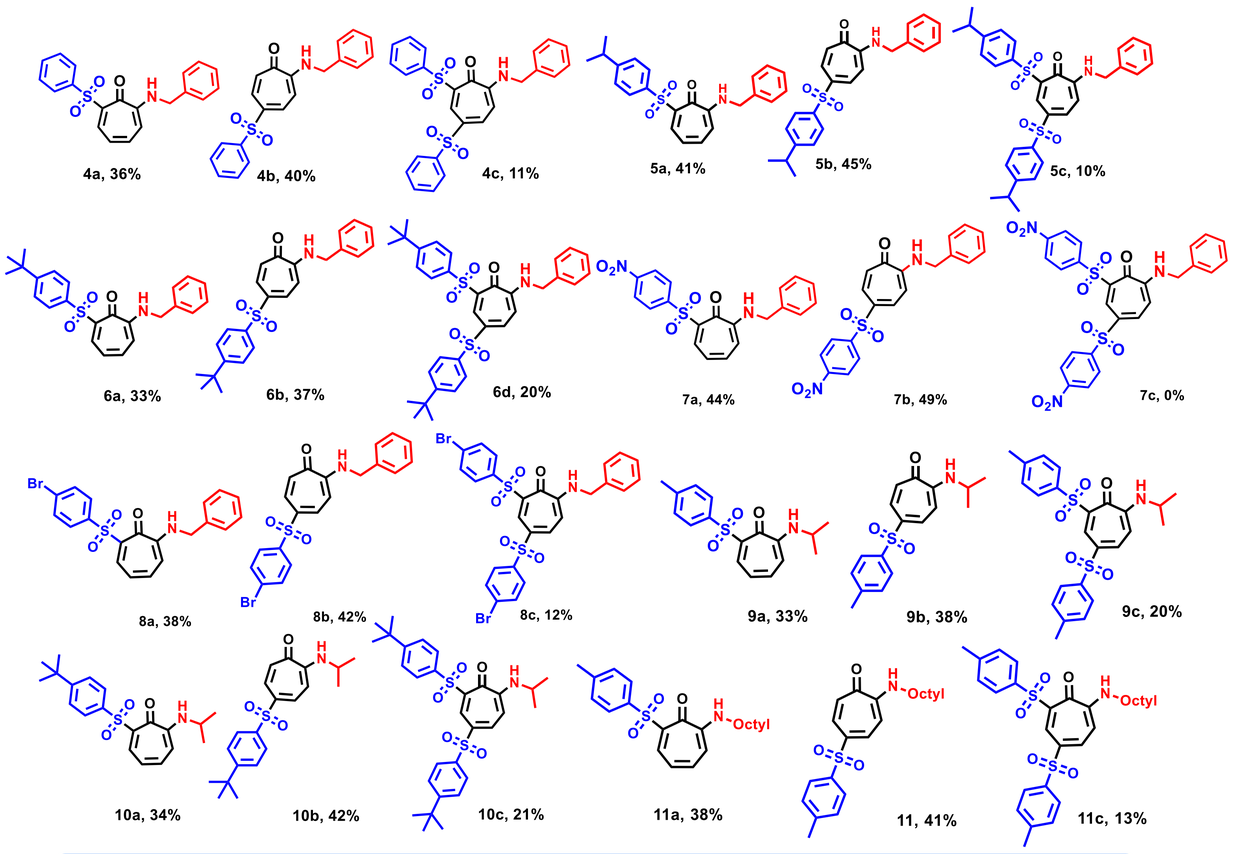
Quorum sensing- a cell-cell communication process– chemical signalling system

Regulation of gene expression, Cell population density, Controlling virulence factors

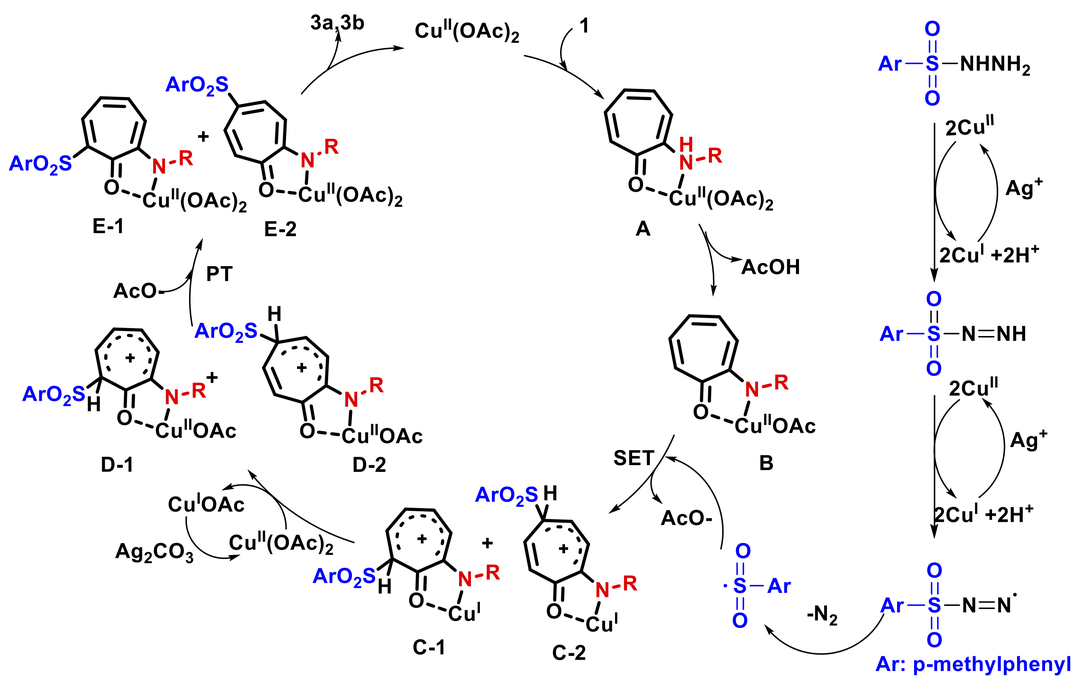


Synthesis and substrate scope of ATS derivatives





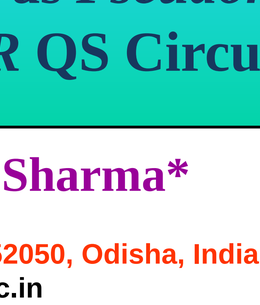
Plausible reaction mechanism of ATS formation



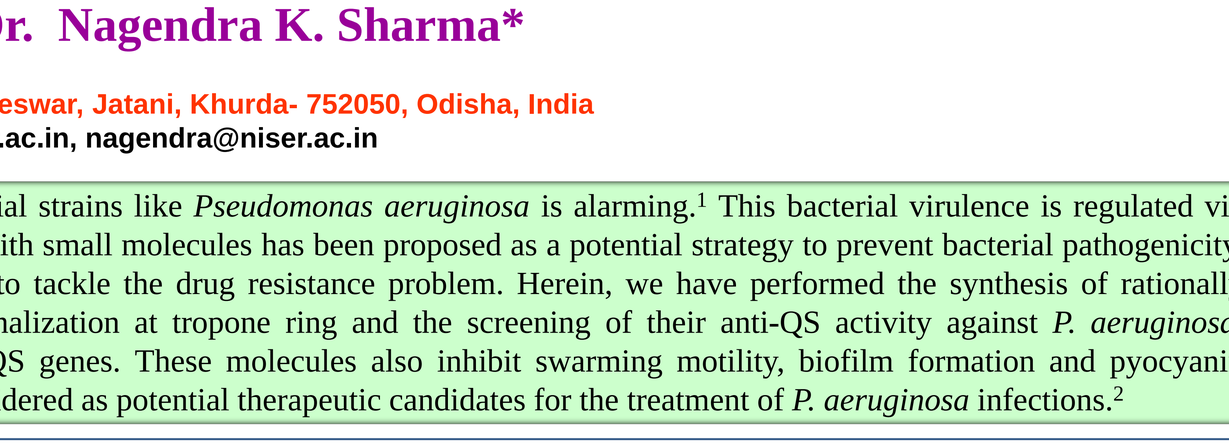
Follows radical pathway (Support- reaction with TEMPO)

Anti-biofilm, anti-swarming & anti-pyocyanin activities

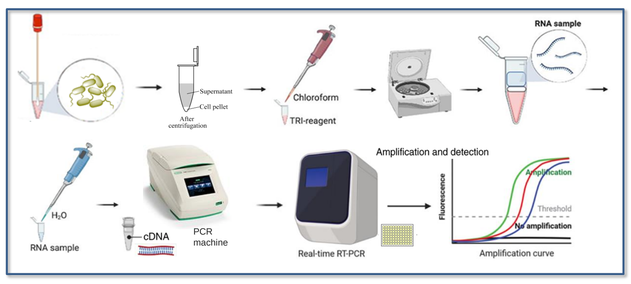
- Biofilm Assay
- Swarming Assay
- Pyocyanin Assay

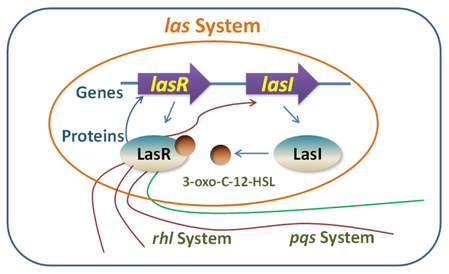


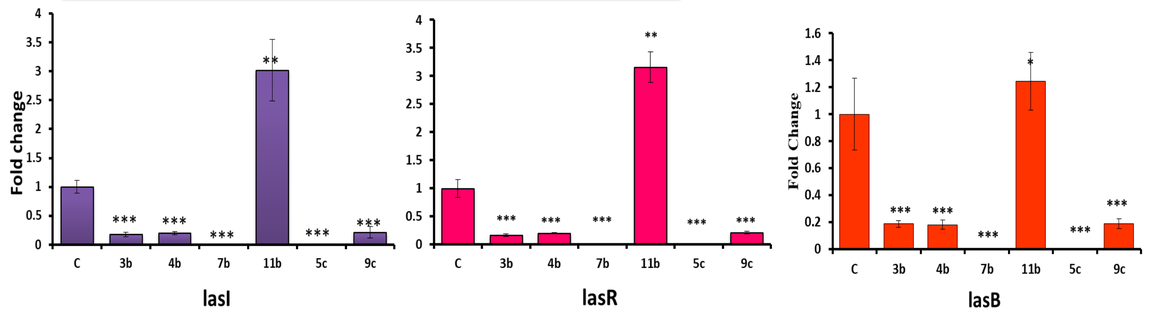
Concentration dependent studies



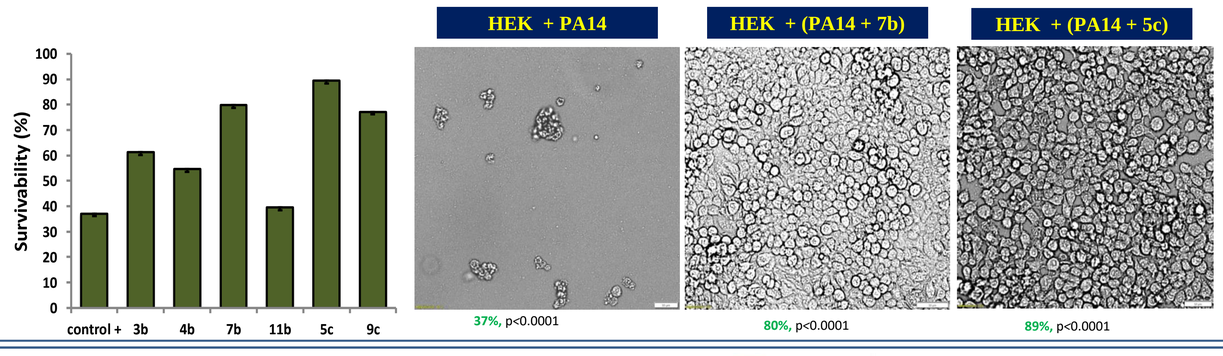
Targeting the PA14 *las* system





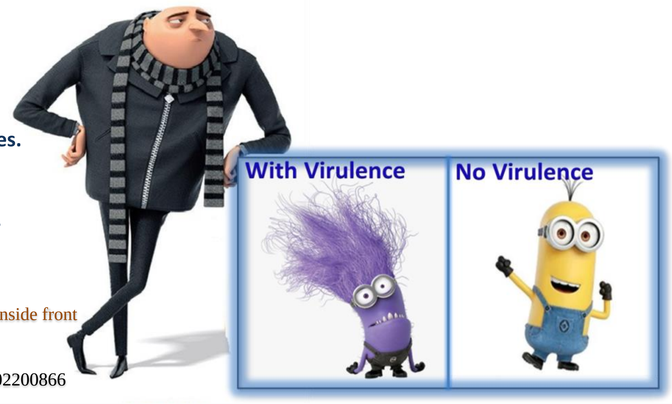


ATS-mediated attenuation of PA cytotoxicity



Conclusions

- Design & Synthesis of novel ATS derivatives by C-H activation method.
- Antagonism against Pseudomonas aeruginosa (PA14).
- Shows antiswarming, antipyocyanin and antibiofilm properties.
- Down-regulation of *lasI/R /B* genes in PA14 up to ~99.9% .
- Non-cytotoxic & improved cell viability up to ~89%.
- Potential therapeutic drugs for the treatment of PA infection.



References

- S. Meher, N. K. Sharma*, *New J. Chem.* **2023**, *47*, 5593-5597 (Highlighted- inside front cover page, March 2023 issue)
- S. Meher, S. Kumari, M. Dixit*, N. K. Sharma*, *Chem Asian J.* **2022**, *17*, e202200866

Acknowledgement: SM thanks NISER,HBNI and DAE India for infrastructure and fellowship. SM also thanks Dr. Manjusha and Dr. Supriya for their kind help.