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Design and Synthesis of Methyltransferase Inhibitors to Treat Pseudomonas aeruginosa Infections

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Design and Synthesis of Methyltransferase Inhibitors to Treat *Pseudomonas aeruginosa* Infections

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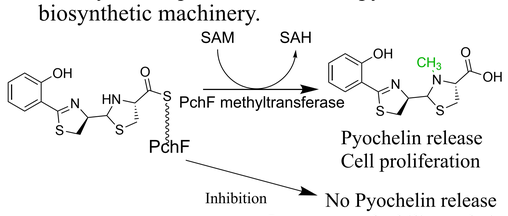
INTRODUCTION

- *Pseudomonas aeruginosa* is a leading cause of hospital-acquired infections, with a mortality rate of 39%.
- Antibiotic-resistant *P. aeruginosa* is rapidly emerging, rendering conventional antibacterial agents obsolete. This drives the need to develop novel treatments.
- Pyochelin is an important metabolite and virulence factor produced by *P. aeruginosa*, and pyochelin-deficient mutants demonstrate decreased virulence and impaired growth.
- PchF is a key protein that methylates *nor*-pyochelin via an embedded methyltransferase, and methylation activity is required to release pyochelin from the biosynthetic machinery.



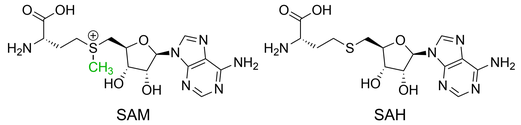


Figure 1. Inhibition of PchF methyltransferase activity can prevent release of Pyochelin, diminishing the growth ability and virulence of the bacteria.

OBJECTIVE

- Given the importance of pyochelin in pathogenesis, small-molecule inhibitors of the PchF methyltransferase could be a viable novel approach to treating antibiotic-resistant *P. aeruginosa*.
- Synthesize an inhibitor for the *P. aeruginosa* PchF methyltransferase to selectively target and treat infections.

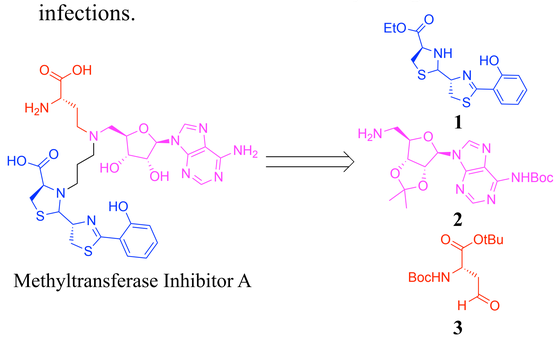
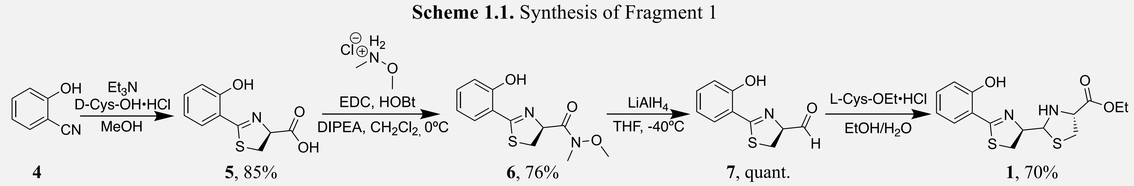


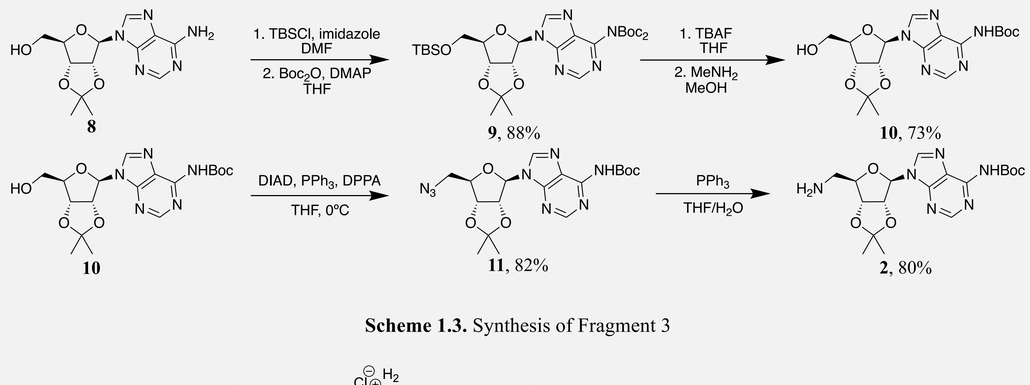
Figure 2. Methyltransferase Inhibitor A can be synthesized by combining three fragments. Fragment 1, salicylic acid derivative; Fragment 2, adenosine derivative; Fragment 3, L-Aspartate derivative.

RESULTS

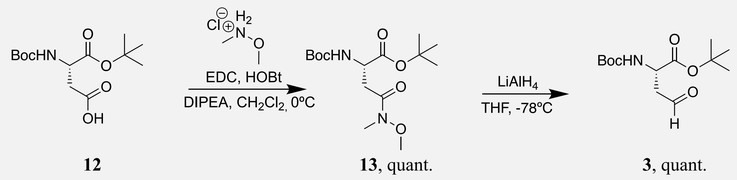
Scheme 1.1. Synthesis of Fragment 1



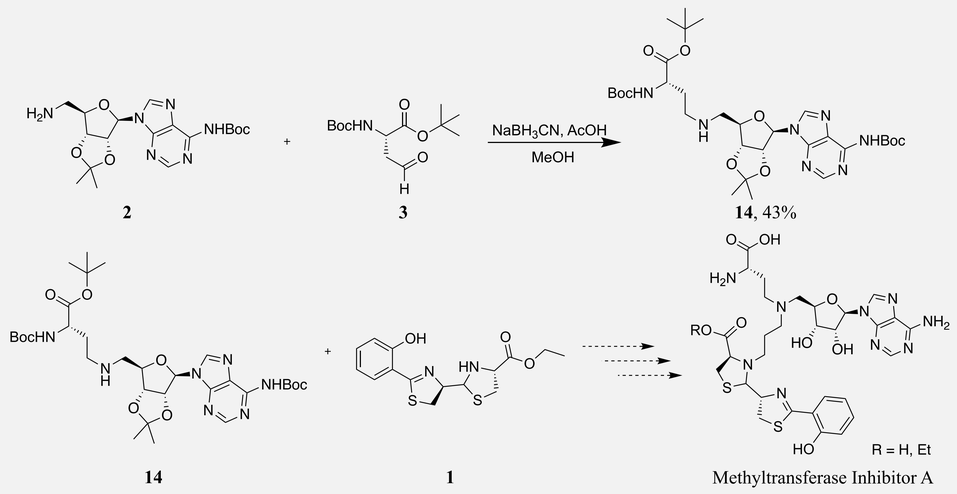
Scheme 1.2. Synthesis of Fragment 2



Scheme 1.3. Synthesis of Fragment 3



Scheme 1.4. Combination of fragments 1, 2, and 3 yields Methyltransferase Inhibitor A



CONCLUSIONS AND FUTURE WORK

- Optimized synthesis of fragment 1 (4 steps, 45% yield), fragment 2 (6 steps, 42%), and fragment 3 (2 steps, quant. yield).
- Coupled fragments 2 and 3 en route to completed inhibitor.
- Work is currently underway to link fragment 1
- Inhibition assays will be performed to determine inhibitory activity against PchF.
- This approach can be adapted as a general method to prepare methyltransferase inhibitors against other pathogens that utilize these enzymes to produce key metabolites/virulence factors.

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- The summer research experience will strengthen my upcoming graduate school applications.
- Results from this project will constitute a significant portion of my Honors Thesis in Biochemistry.