

THERAPEUTIC MATERIALS
AND BIOINTERFACIAL RESEARCH
REYNOLDS GROUP

Next Generation Antibiotics: Progress Toward the Synthesis of an Enzyme-Activated Nitric Oxide-Releasing Fluorescent Prodrug

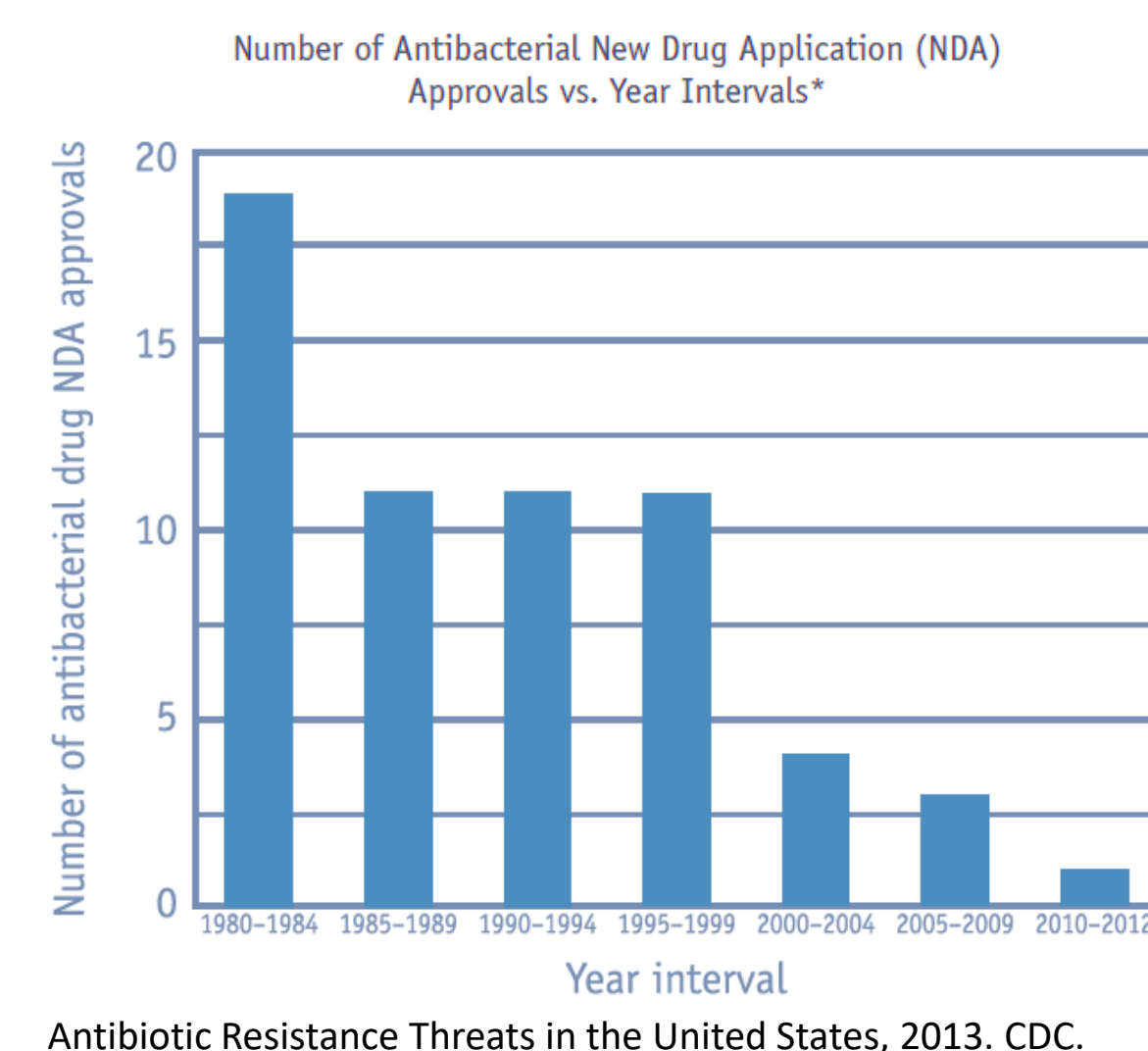
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Abstract

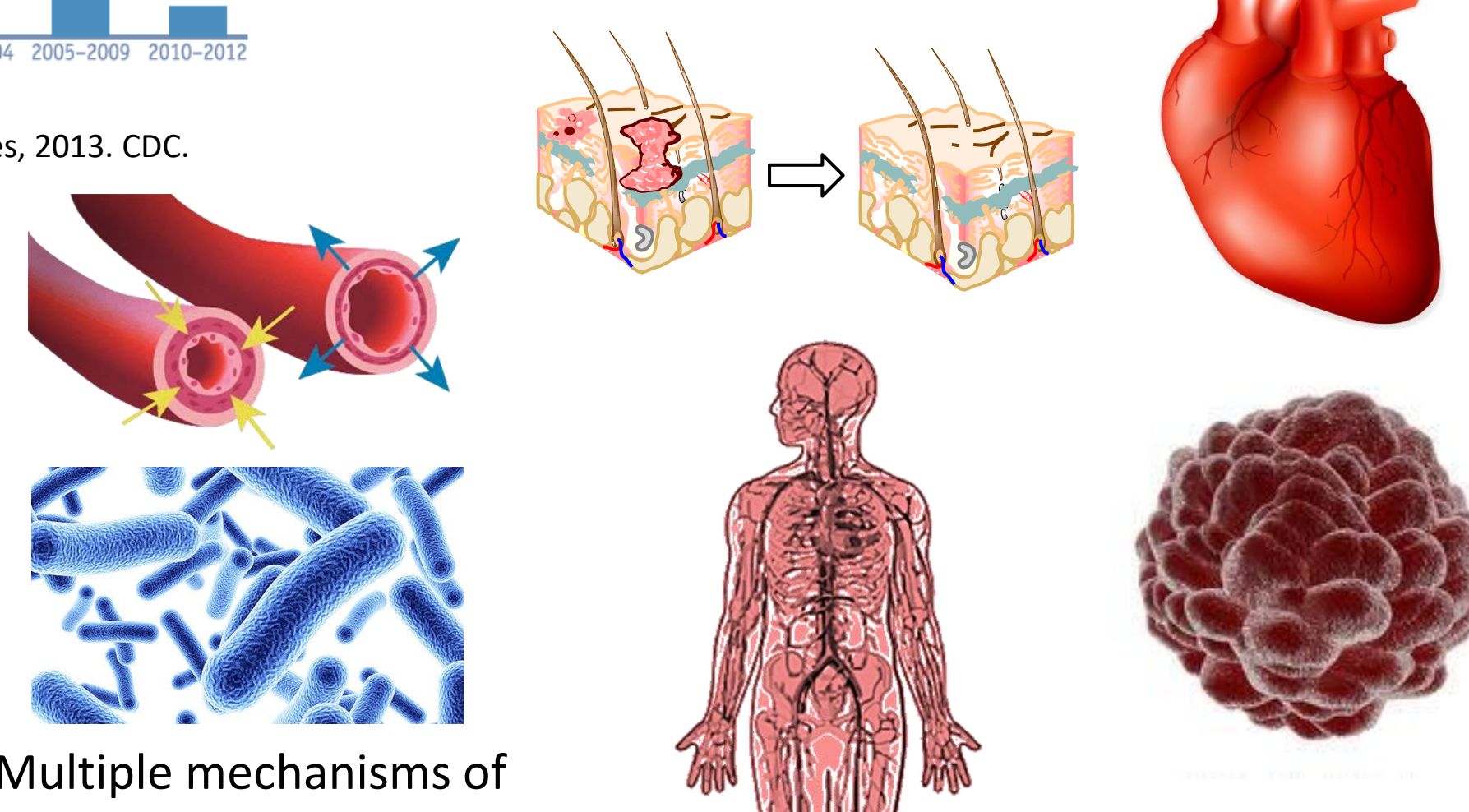
Bacterial resistance to antibiotics is spreading at an alarming rate, and without the development of new antibiotics, common infections will become deadly. The goal of this project is to synthesize an enzyme-activated antibiotic prodrug that detects and kills bacteria. The antibiotic will incorporate nitric oxide, a known antibacterial agent, and a fluorescent compound to visualize bacterial presence. A synthesis procedure was developed to synthesize a fluorescent compound attached to a small signaling compound. A nitric oxide donor will be added in the future. In the presence of bacteria, the antibiotic prodrug is designed to simultaneously fluoresce and release nitric oxide.

Introduction

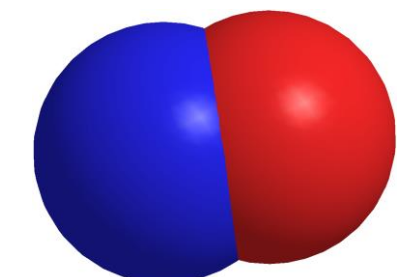


No new antibiotics

Deadly infections

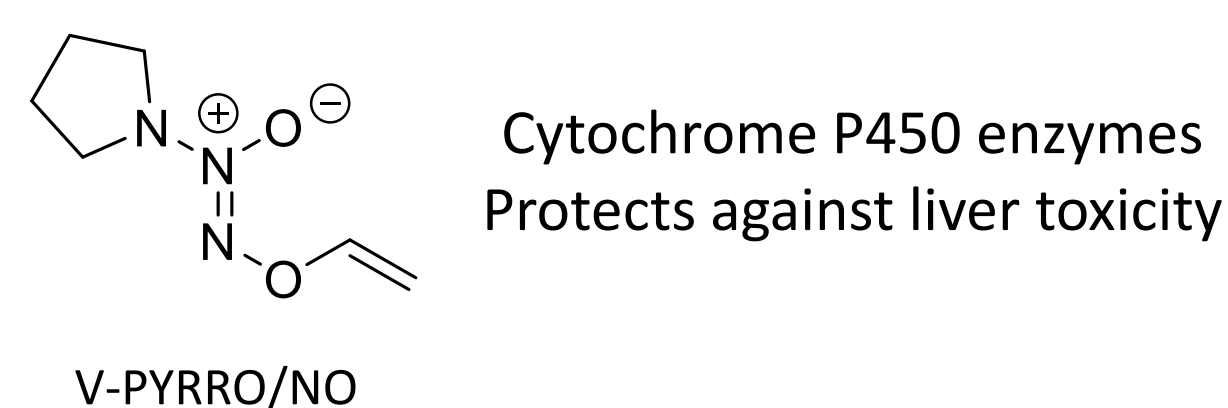
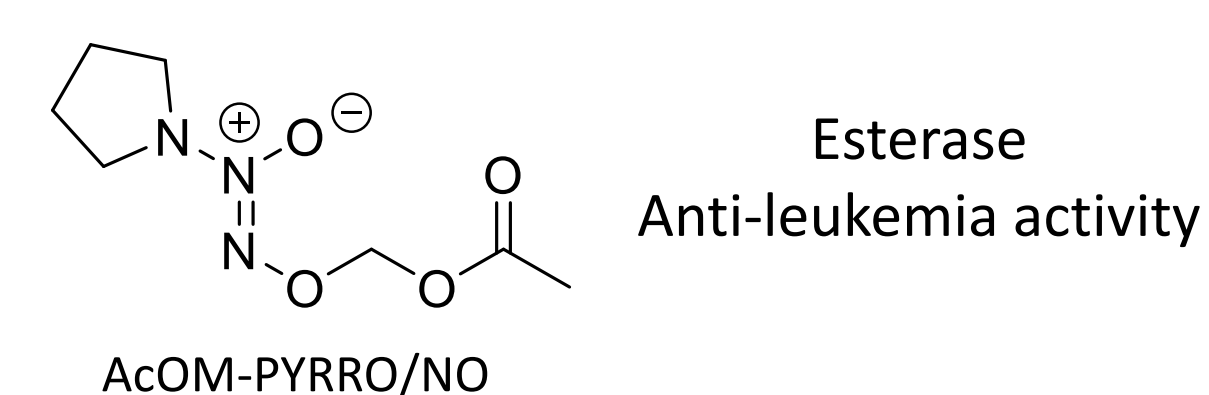
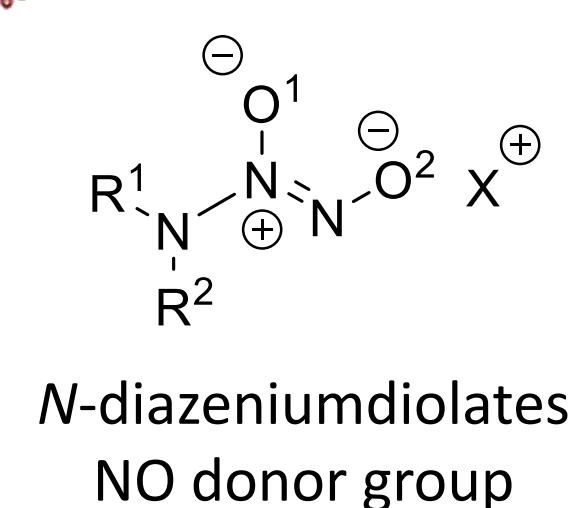


Nitric Oxide (NO)



Multiple mechanisms of action against bacteria

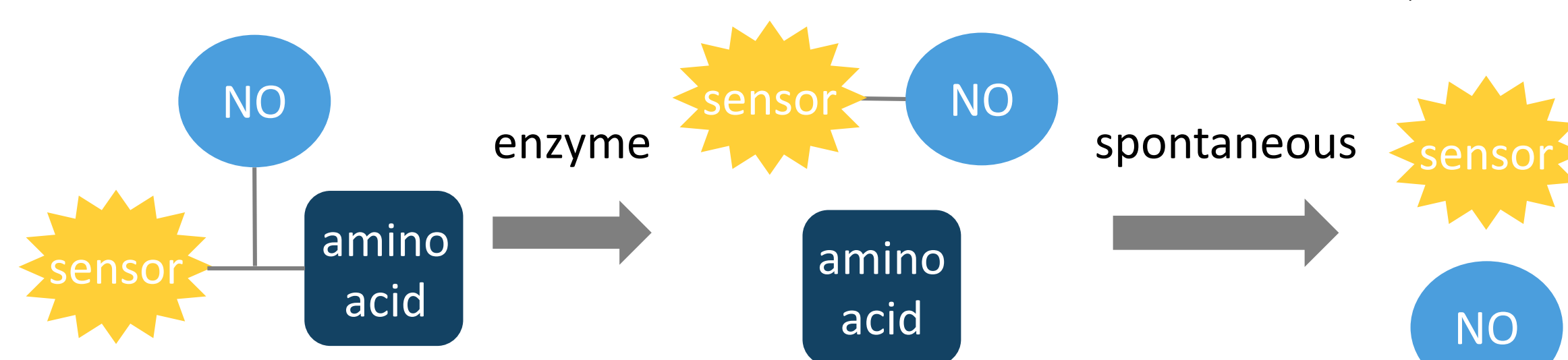
Prodrugs



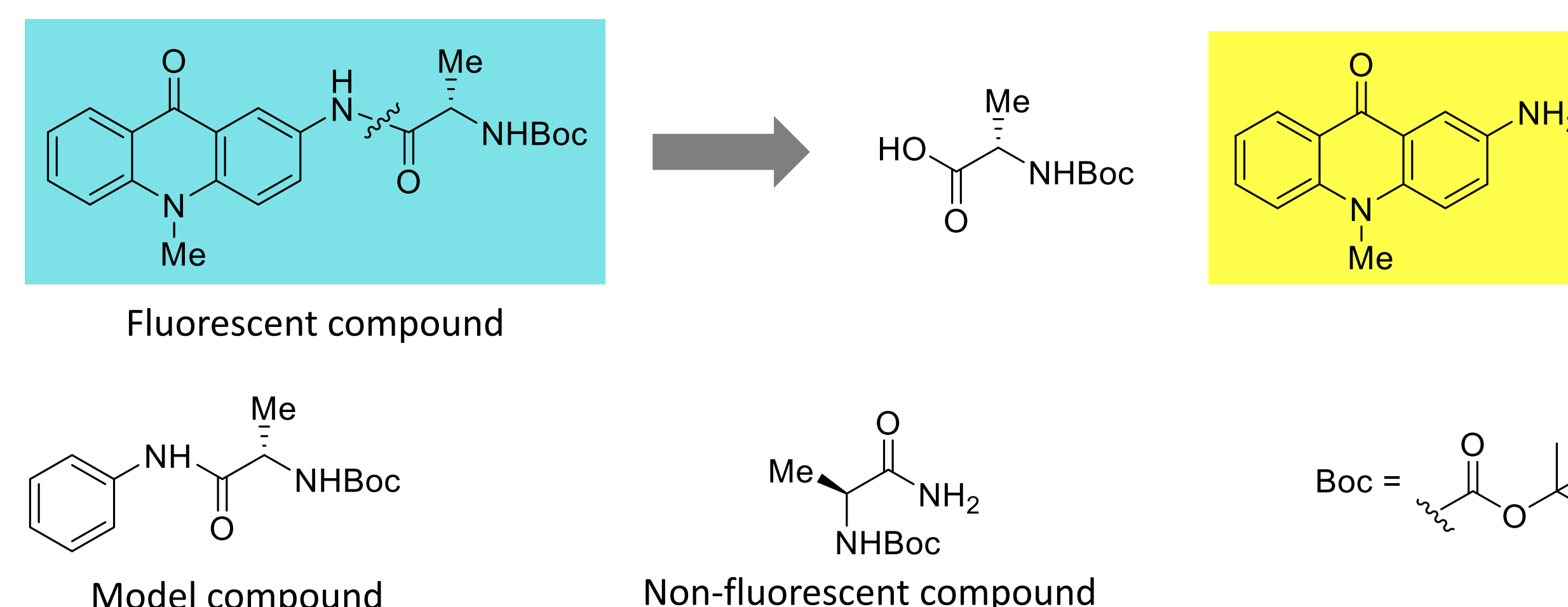
Project Idea

Create a small molecule that detects and kills bacteria

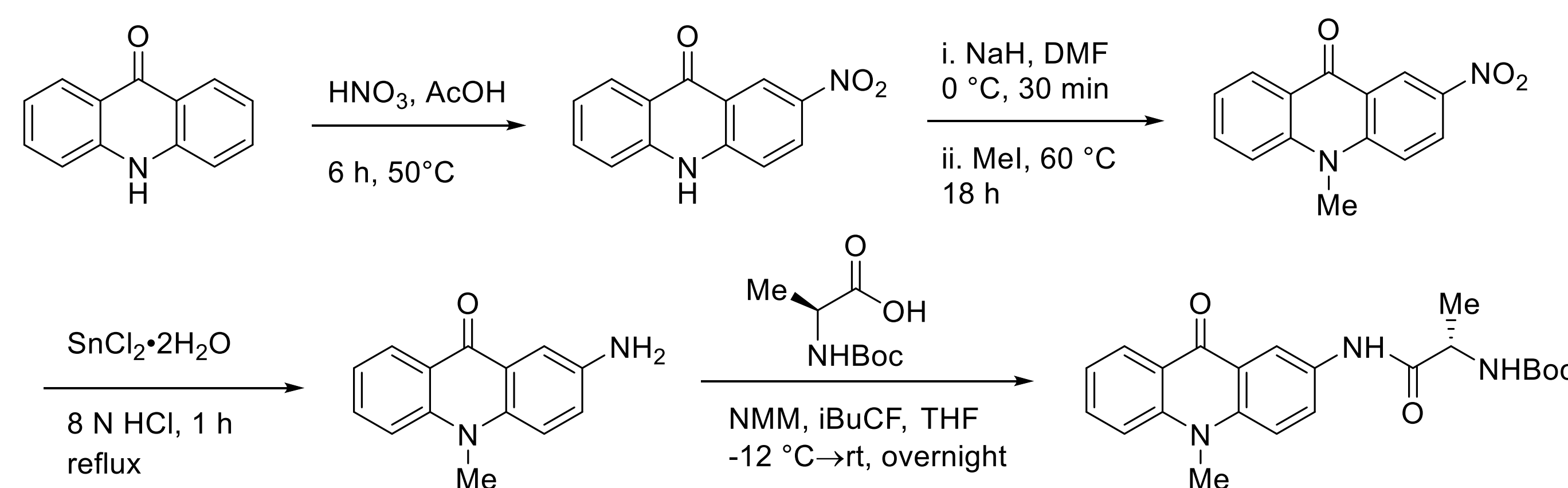
- Enzymatically-activated NO prodrug senses bacteria, releases NO to kill bacteria



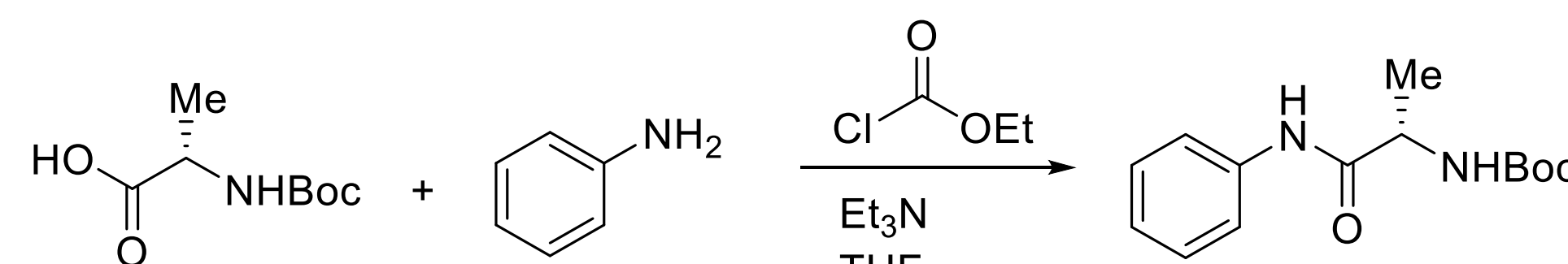
Protease Sensor Synthesis



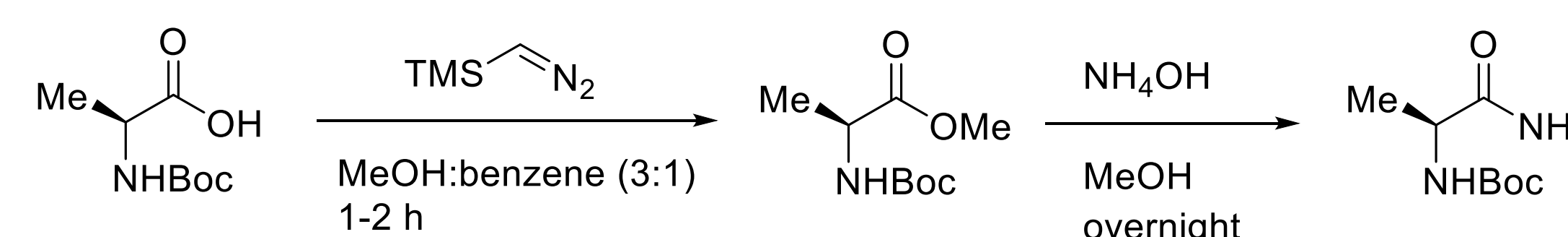
Fluorescent Sensor Synthesis



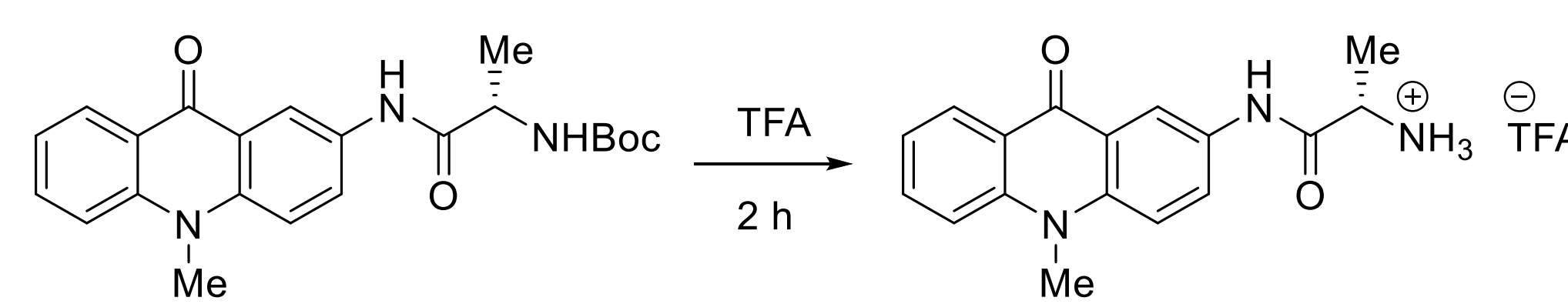
Model Compound Synthesis



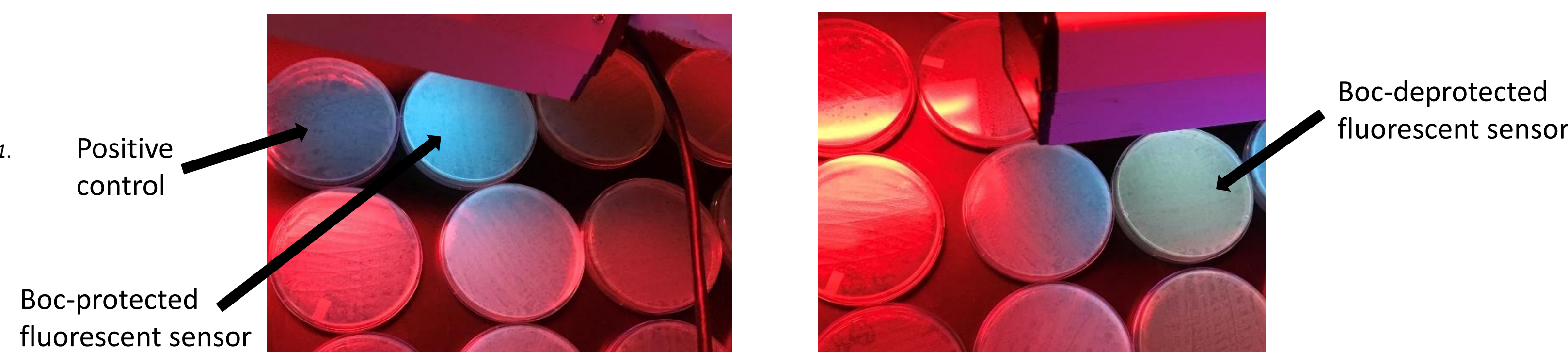
Non-Fluorescent Compound Synthesis



Bacterial Studies

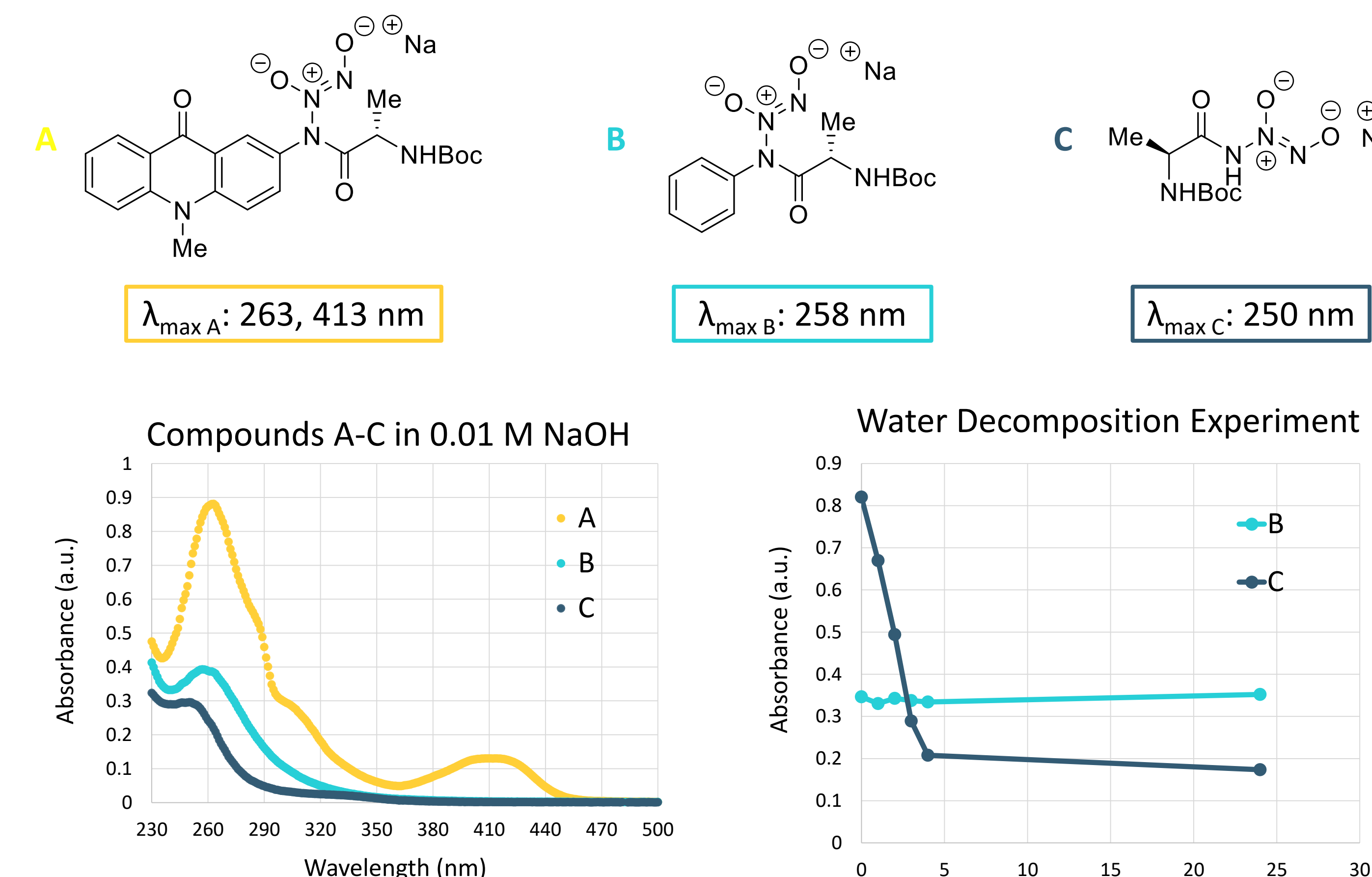


Fluorescent color of synthesized compounds changes as expected in the presence of *Pseudomonas aeruginosa*



Bacterial studies performed by Bella Neufeld of the Reynolds group

UV-Vis Product Analysis



NO addition reactions run by Lei Yang of the Schoenfish group at UNC Chapel Hill

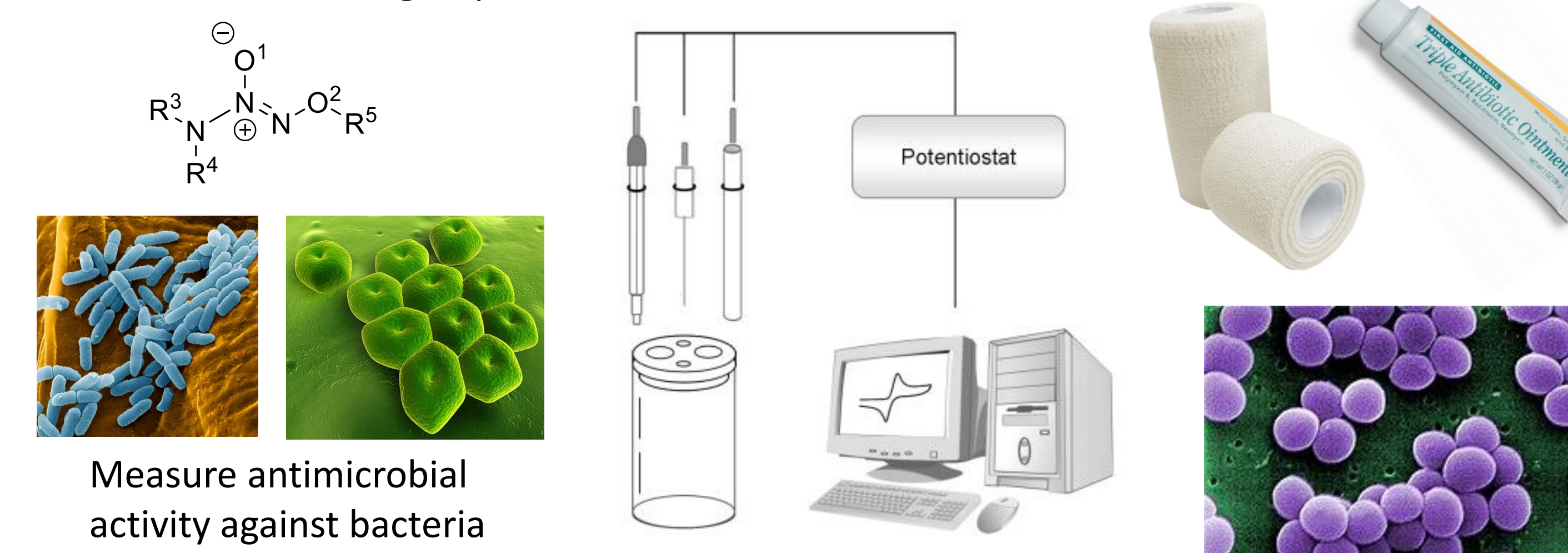
Conclusions

- Synthesized fluorescent sensor, attached amino acid, fluoresces in presence of *P. aeruginosa*
- Attached amino acid to model compound
- Attached amino acid to non-fluorescent compound
- Analyzed samples reacted with NO, diazoniumdiolate group on non-fluorescent compound

Future Directions

Add diazoniumdiolate group

Measure NO release



References and Acknowledgements

- Special thanks to Dr. Melissa Reynolds for her help and guidance. Thanks to Bella Neufeld of the Reynolds group for performing the bacterial studies, and Lei Yang of the Schoenfish group for performing the NO addition reactions.
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