Studies Towards the Synthesis of Novel Oxadiazole Derivatives for Antibiotic Screening Against *Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa.*

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Introduction

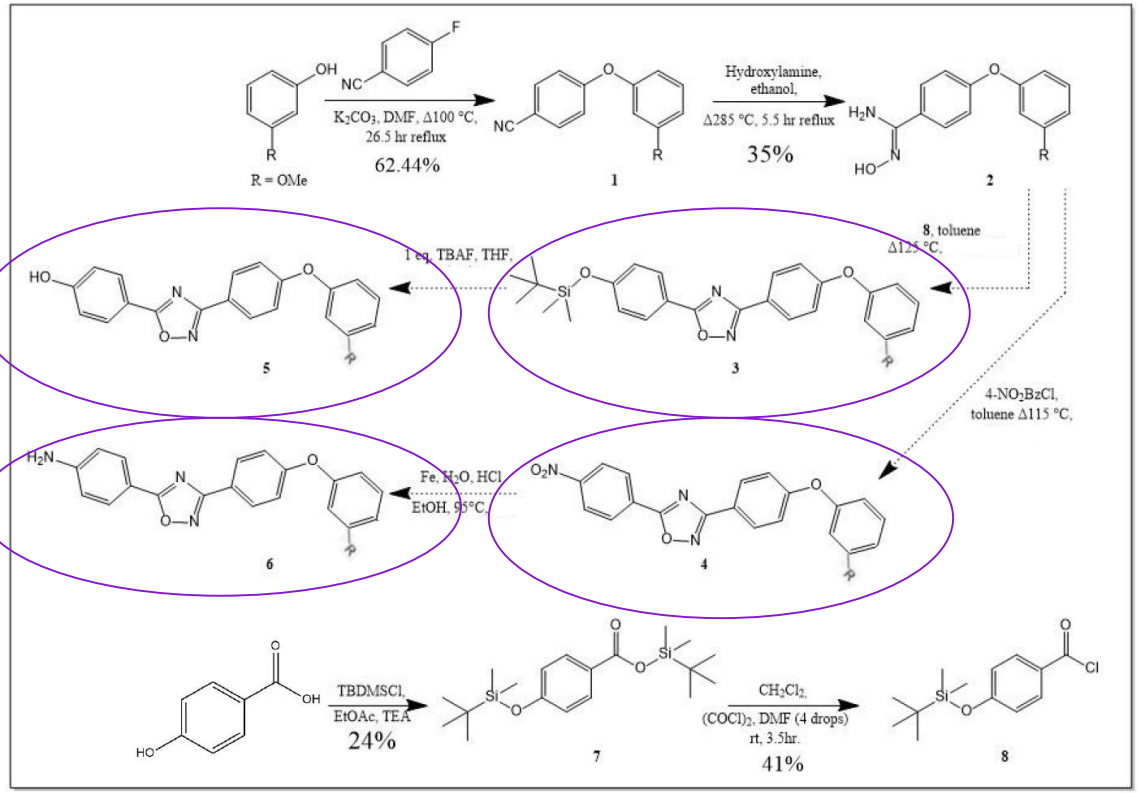
- Antibiotic resistance rendering current pharmaceutical drugs ineffective
  - 35,000 deaths yearly in the U.S. linked to antibiotic resistant bacteria.
- Current treatment techniques and limitations
- Methicillin-Resistant *Staphylococcus aureus* (MRSA)

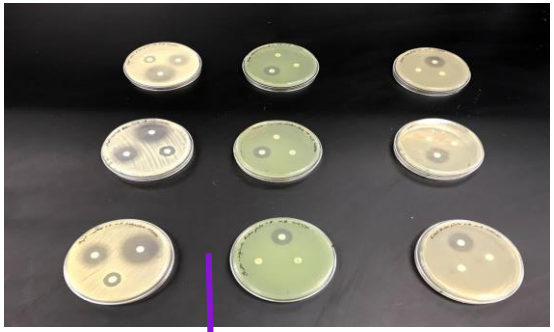
Background

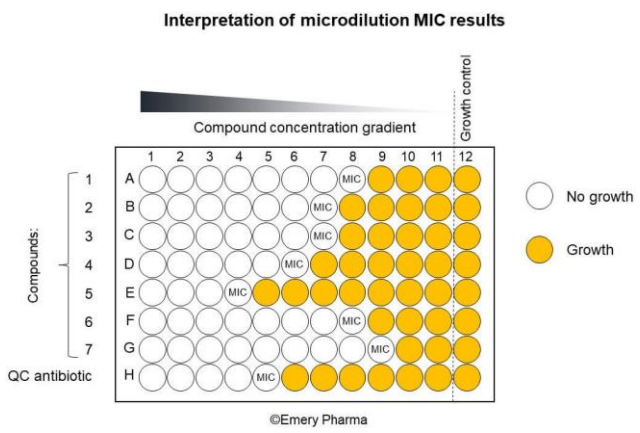
- MRSA clinical resistance and target sites for inhibition of cell wall biosynthesis
  - mecA gene ➔ PBP2a
- Computer-generated structural relationship analysis
  - New oxadiazole class of non-β-lactam antibiotics (O'Daniel, et. al)
- Undergraduate oxadiazole synthesis & microbiological assay standardization

Our Hypothesis

We hypothesize that treatment of derivatized oxadiazole class and selected control antibiotics to pathogenic species will exhibit a significant drop in bacterial growth.

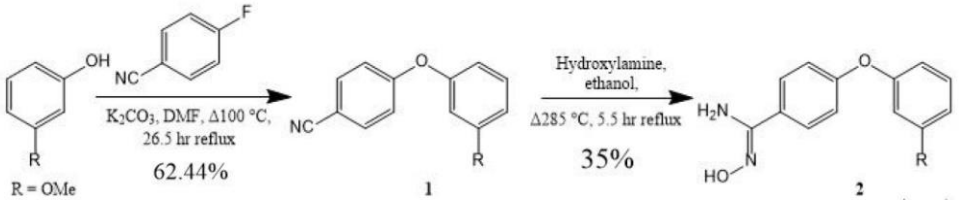




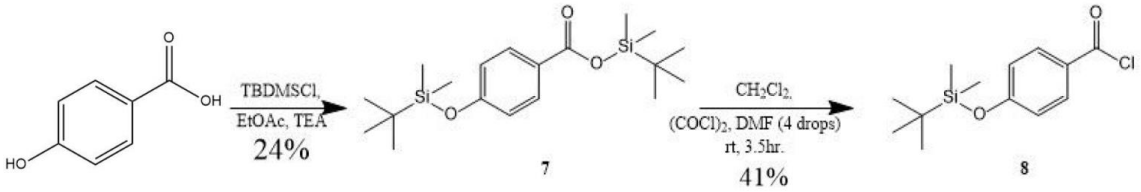


https://emerypharma.com/biology/minimum-inhibitory-concentration/

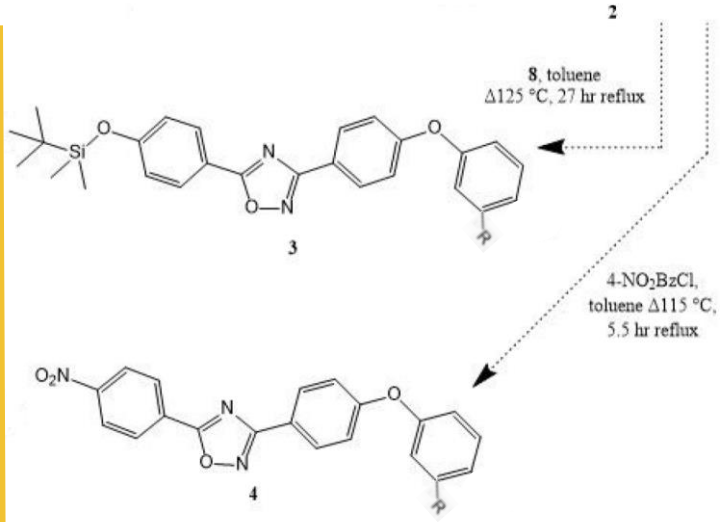
Antibiotic Synthesis



Benzamidine (**2**)

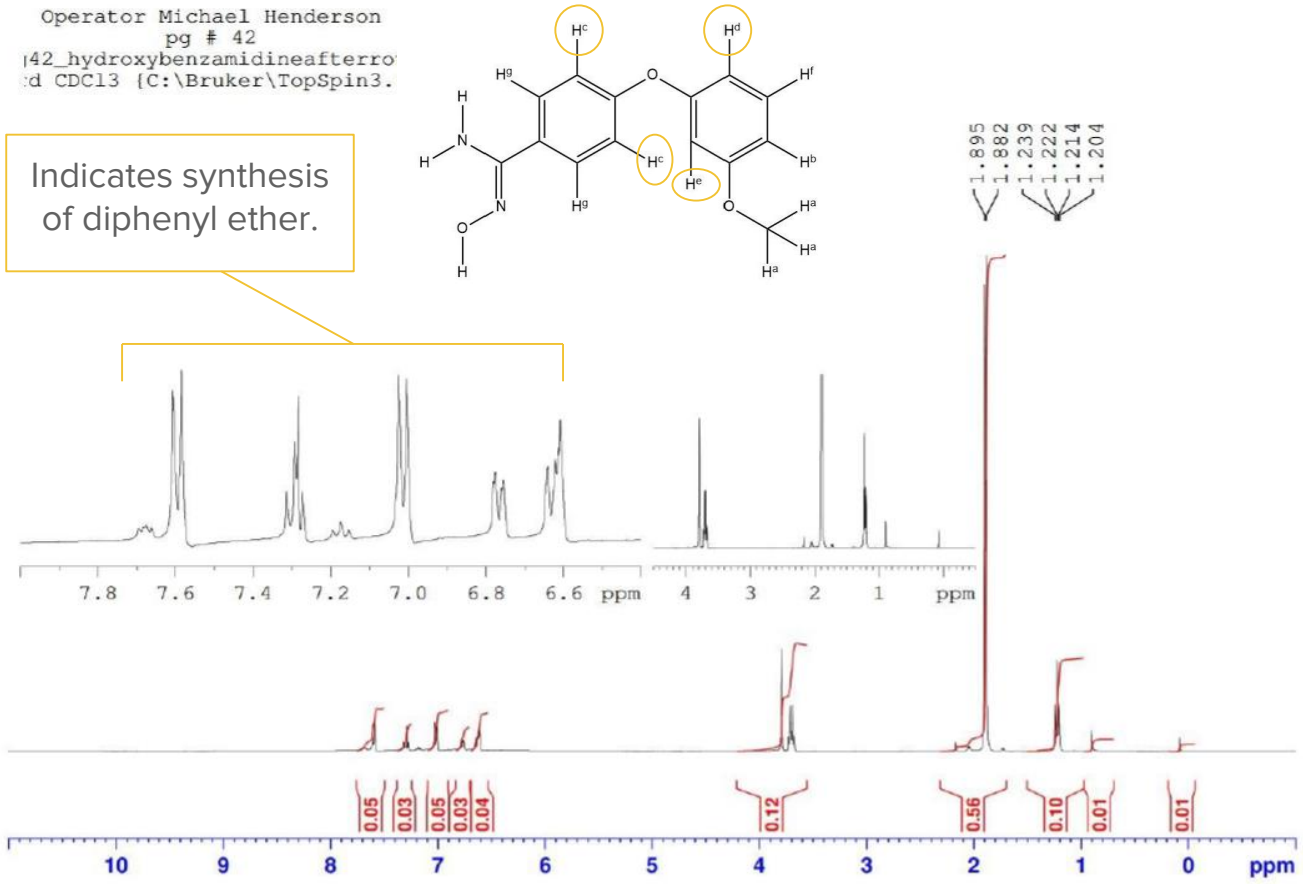


Benzoyl chloride (**8**)

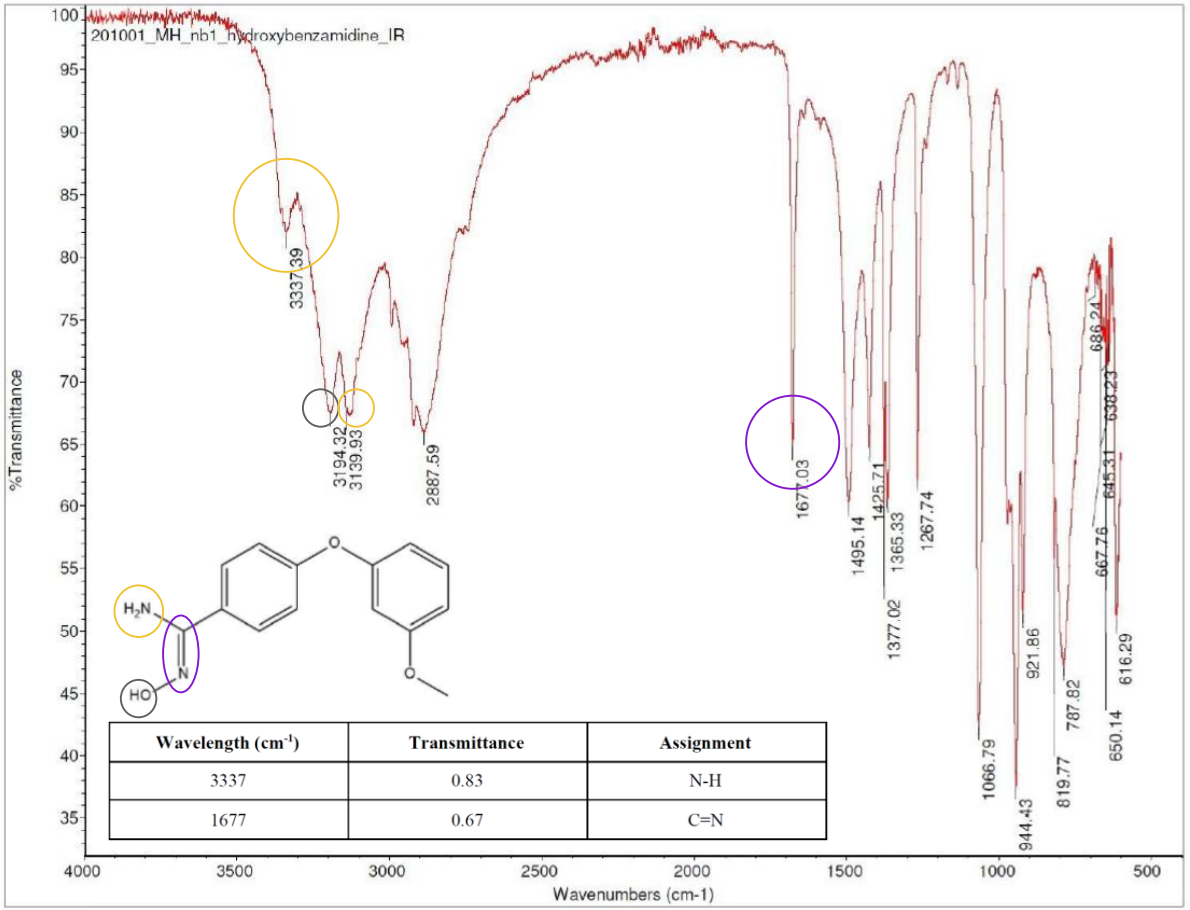


Silyloxy- and Nitrophenyl-Oxadiazole (**3**) & (**4**)

Benzamidine (**2**)



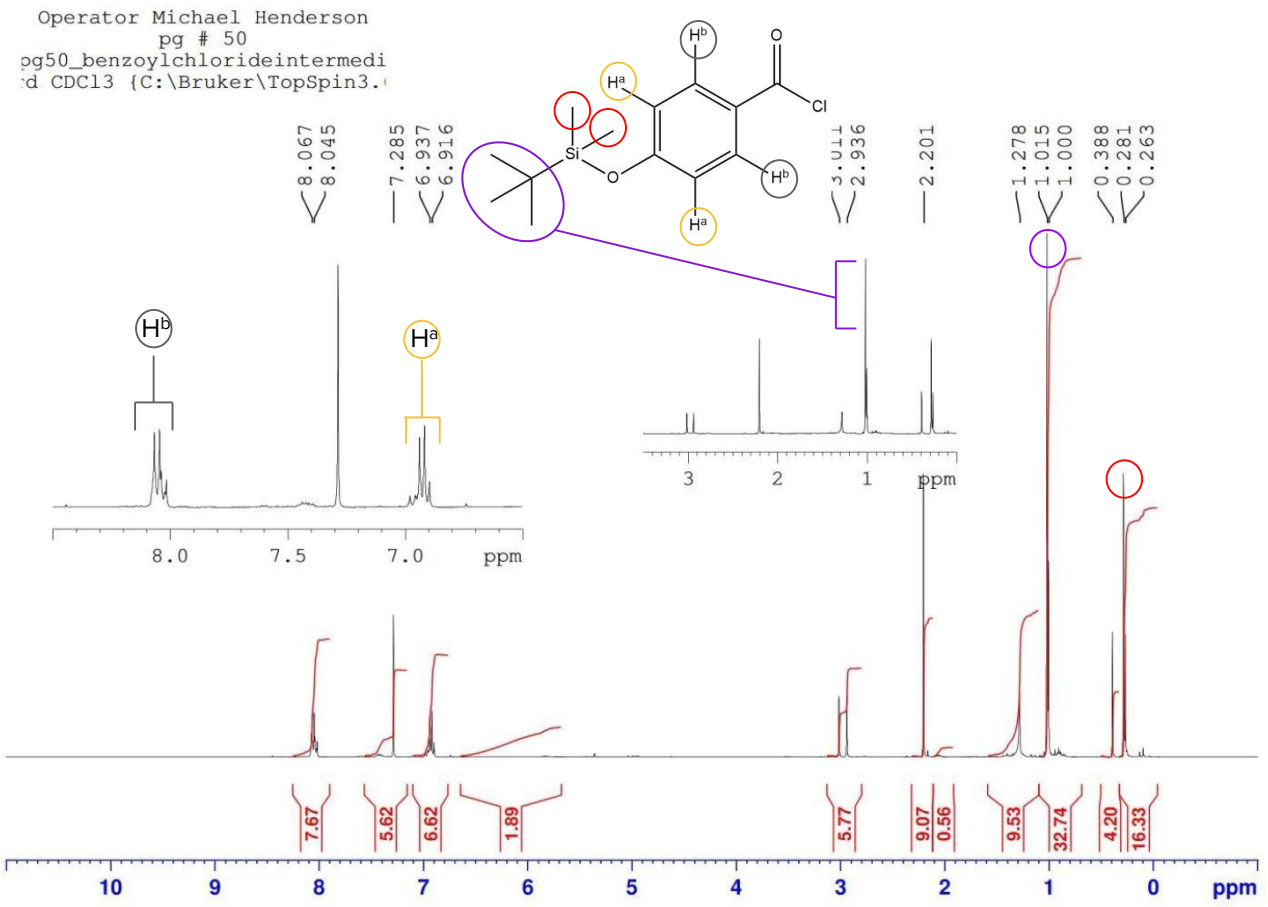
Key intermediate for synthesis of purposed novel oxadiazoles.



Wavelength (cm^{-1})	Transmittance	Assignment
3337	0.83	N-H
1677	0.67	C=N

Benzamidine (**2**)

- Yield: 35%
- Upon rotary evaporation, clear crystals aggregated.
- IR signals consistent with expected IR wavelength ranges.

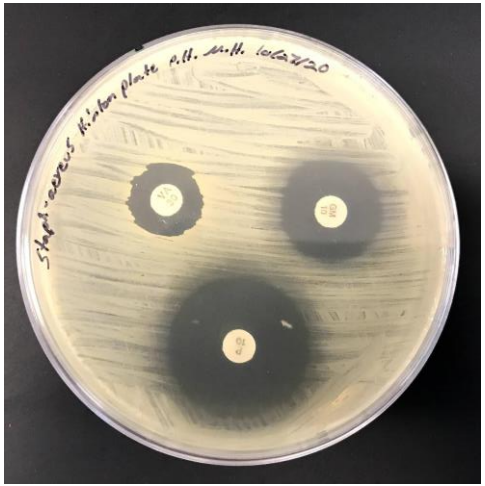


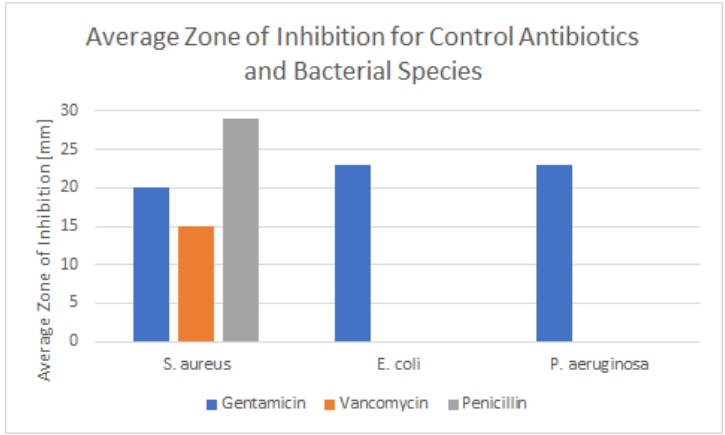
Benzoyl chloride (**8**)

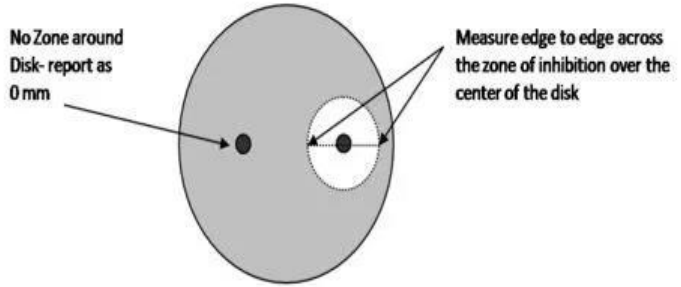
- Intermediate for (**3**).
- Yield: 41%
- ^{1}H NMR data consistent with reported NMR.
- Product appeared as a yellow-brown oil and used immediately.

Kirby Bauer

- Microbial Species
  - *E. coli*
  - *S. aureus*
  - *P. aeruginosa*
- Antibiotics
  - Gentamicin
  - Penicillin
  - Vancomycin

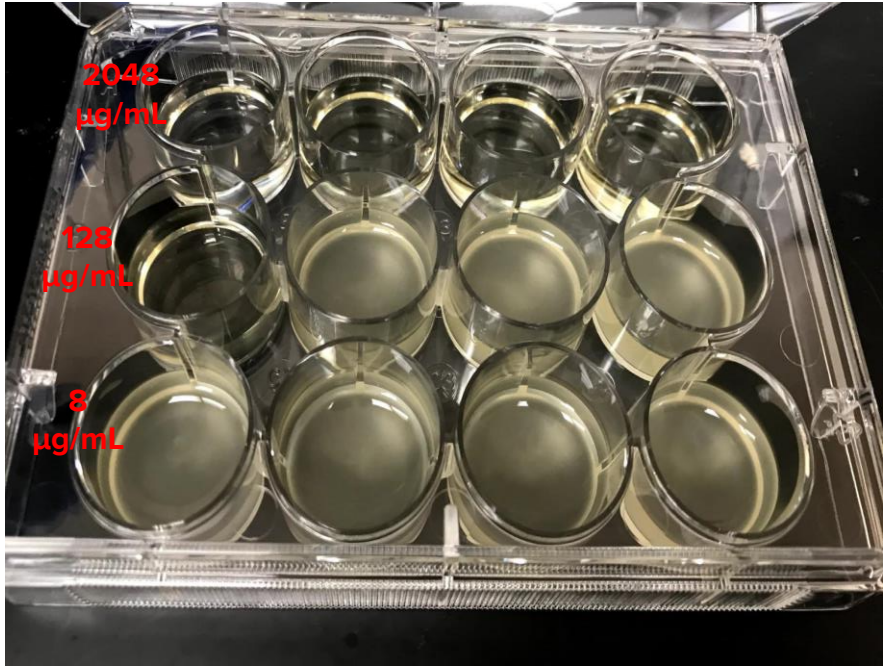




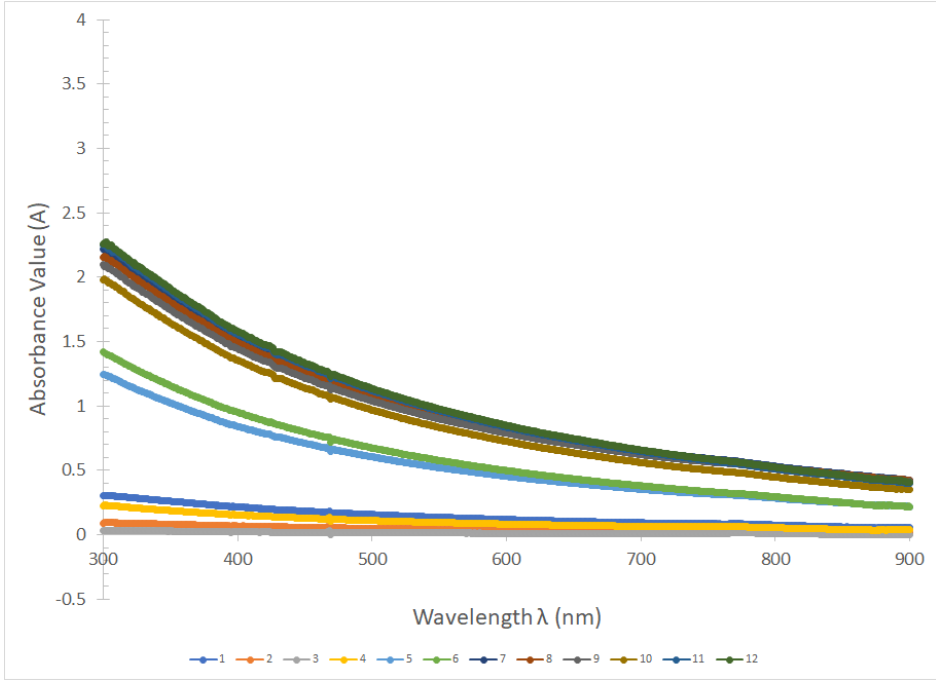


https://microbeonline.com/antimicrobial-susceptibility-testing-procedure-modified-kirby-bauer-method/

MIC Assay



E.Coli 12 well treated with Gentamicin after 24hrs incubation at 37℃. Top left corner is well 1, bottom right corner is well 12



Absorbance vs Wavelength for the MIC assay of *E-coli* treated with Vancomycin

Kirby Bauer & MIC Assay Results

- *E. coli*
  - Resistant to vancomycin and penicillin
  - Sensitive to gentamicin
- *P. aeruginosa*
  - Resistant to vancomycin and penicillin
  - Sensitive to gentamicin
- *S. aureus*
  - *Intermediate resistance to vancomycin*
  - *Sensitivity to penicillin and gentamicin*

Minimum Inhibitory Concentration (µg/mL)			
	S. aureus	E. coli	P. aeruginosa
Gentamicin	8	16	16
Vancomycin	4	256	256
Penicillin	4	256	1024

Summary

- Pathogenic species - MRSA have developed resistance to current antibiotics
- Meta-phenyl substituent on a diphenyl ether oxadiazole was not realized; although it may possess higher antibiotic activity than para-substituent.
- Gold standard microbiological assays proved possible at Carroll College.

Conclusion

Ongoing Novel Oxadiazole Synthesis in Course-Based Undergraduate Research Experience (CURE) Laboratories

Our results showcase an effective screening method for future novel meta-phenyl and para-phenyl substituent oxadiazoles.

Acknowledgements

We thank Dr. David M. Hitt for his initiative and continued guidance in synthetic approaches to derivatize novel antibiotics.

We thank Dr. Theresa McHugh for providing her expertise on techniques and tools necessary to optimize the microbiological assays.

We thank Carroll College for the use of their facilities for making this possible.