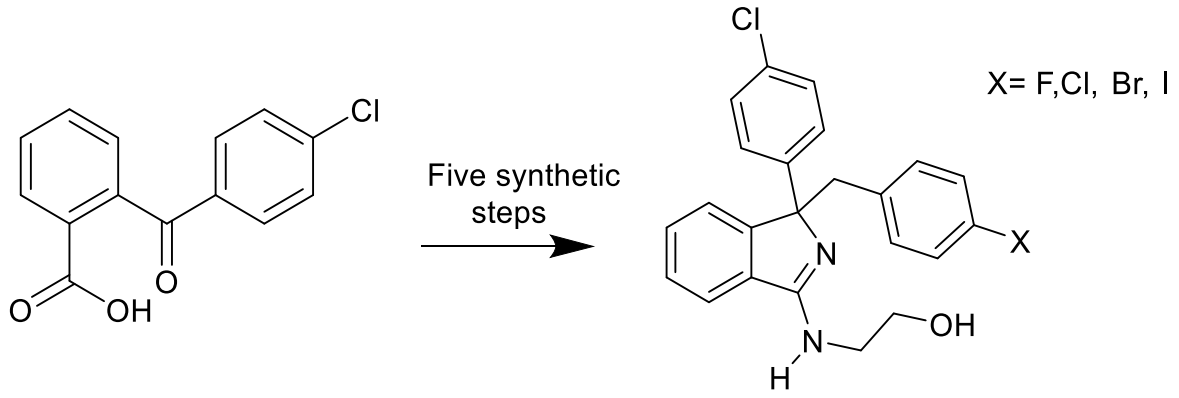
Junhui Huang

Drew University, Class of 2020
Major: **ACS-Biochemistry**
Minor: **Mathematics; Physics**

Faculty Advisor: **Vincent Gullo, Ph.D.,** Director and Research Fellow
Research Institute for Scientists Emeriti (RISE)

Synthesis of Novel Antibacterial Compounds

Due to the increase of multidrug resistant microorganisms, many researchers are working on the discovery and synthesis of new antibacterials. Drew University students discovered and synthesized analogs of a class of compounds called isoindoles in order to increase their antibacterial activity. The initial result of this work showed that a para-chlorobenzyl substituent provided the best antibacterial activity. It was observed that specifically the para-methylbenzyl and the meta-chlorobenzyl analogs were less potent. Based on these observations, it was hypothesized that a stronger electron withdrawing group such as fluorine on the para position could lead to a more potent antibacterial. A novel antibacterial compound (2-((1-(4-chlorophenyl)-1-(4-fluorobenzyl)-1H-isoindol-3-yl)amino)ethan-1-ol) was synthesized. Liquid chromatography/mass spectroscopy (LC/MS) was utilized to monitor the reaction sequence. ^{1}H and ^{13}C NMR were employed to confirm all structures. The antibacterial activity of this new analog was compared to the para-chlorobenzyl analog. The result showed that the para-fluorobenzyl substituent was less active than para-chlorobenzyl. Based on this result, analogs with the halogens bromine and iodine were synthesized. Evaluation of the antibacterial activity showed that the para-bromobenzyl analog was the most potent compound. The final objective is to synthesize a novel compound comparable or superior to marketed antibacterials.



Synthesis of Novel Antibacterial Compounds

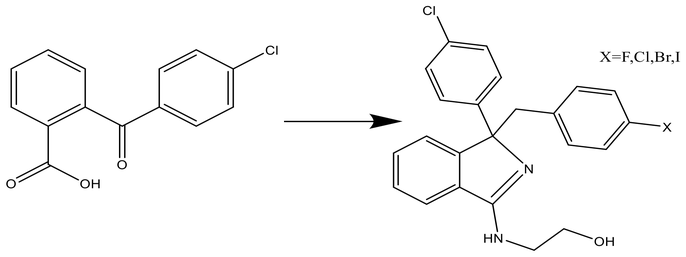
Junhui Huang*, Dr. Vincent Gullo

Research Institute for Scientist Emeriti, Drew University, Madison, NJ

Abstract:

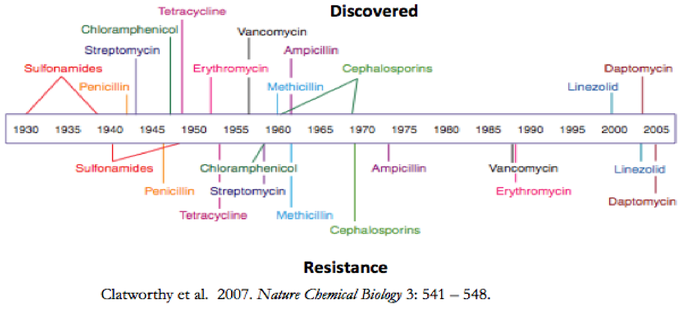
Due to the increase of multidrug resistant microorganisms, many researchers are working on the discovery and synthesis of new antibacterials. Drew University students discovered and synthesized analogs of a class of compounds called isoindoles in order to increase their antibacterial activity. The initial results showed that a para-chlorobenzyl substituent provided the best antibacterial activity. Based on other student's previous results, it was hypothesized that a stronger electron withdrawing group such as a fluorine on the para position could lead to a more potent antibacterial. A novel antibacterial compound (JH-5) was synthesized. Unexpectedly, the result showed that the para-fluorobenzyl substituent was less active than para-chlorobenzyl compound. Based on this result, analogs with the halogens bromine and iodine were synthesized. Evaluation of the antibacterial activity showed that the para-bromobenzyl analog was the most potent compound. The final objective is to synthesize a novel compound comparable or superior to marketed antibacterials.

The goal of my research:



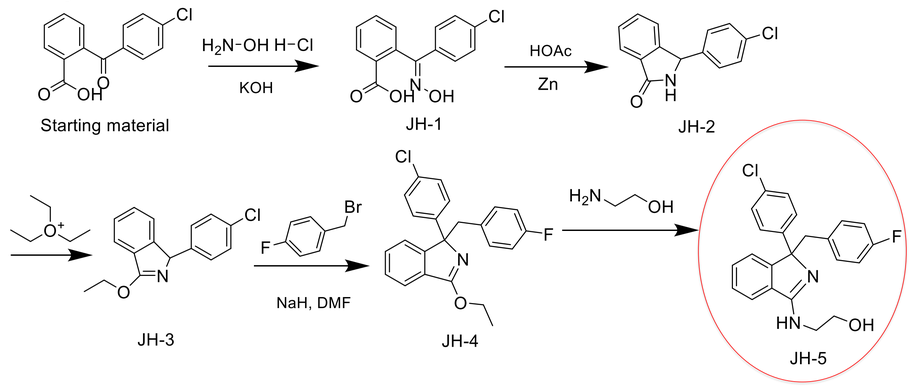
Introduction:

According to CDC, at least 2.8 million people get antibiotic-resistant infections, and more than 35,000 people die every year in the U.S. With the increase of antibacterial resistance all over the world, there is an urgent need for novel antibacterial compounds. My research focused on optimizing an isoindole compound discovered at Drew University by changing substituents on this molecule to study the structure activity relationship (SAR).



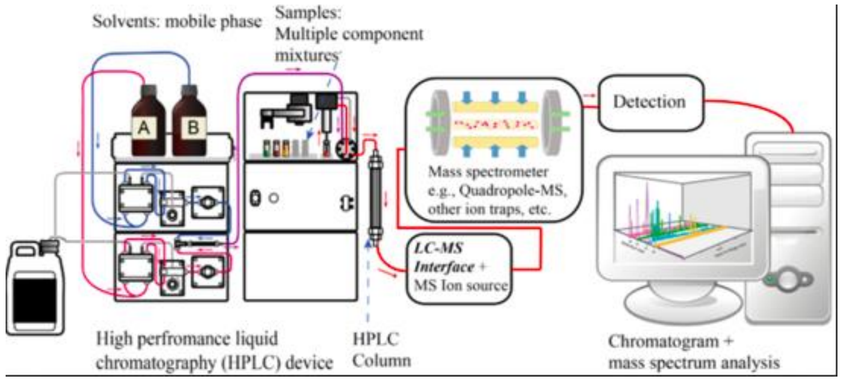
Clatworthy et al. 2007. *Nature Chemical Biology* 3: 541 – 548.

Synthetic Route:

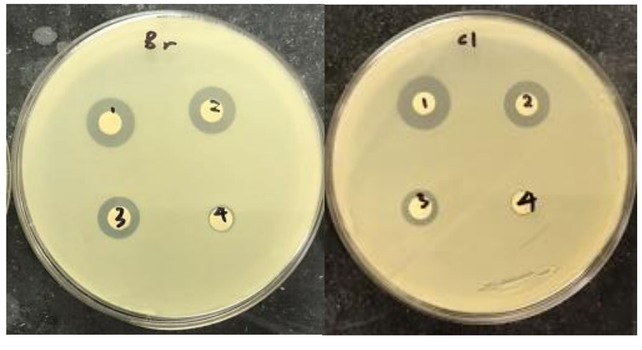


Overall methodology:

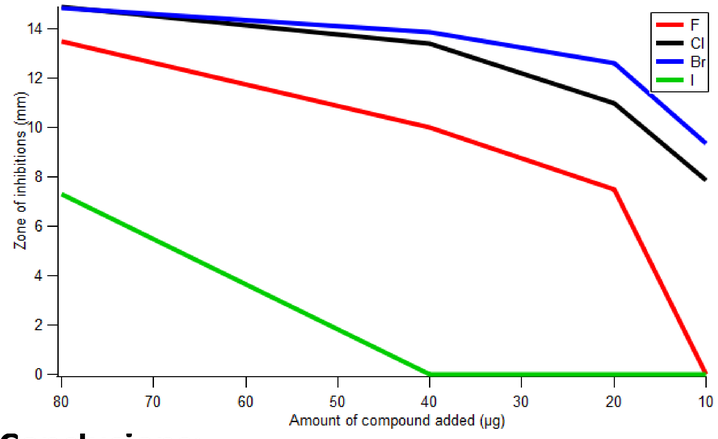
1. Run a reaction
2. Monitor the reaction by LC/MS
3. Purification
4. Analysis : LC/MS and 1H and 13C NMR
5. Biological Assay (Agar plates against S.*aureus*)
6. Structure-activity Relationship (SAR)
7. Repeat with different reagents.



Agar diffusion assay of Br and Cl compounds



Antibacterial activity results:



Conclusions:

1. The para-bromo and para-chlorobenzyl analogs have the most potent antibacterial activity in the agar diffusion assay as compared to para-iodo and para-fluoro analogs
2. Electronegativity of the halogens doesn't correlate with antibacterial activity.
3. The para-bromo analog appears to be a slightly more potent antibacterial than the para-chloro analog

Discussion and future plans:

The ultimate goal of this research project is to develop a potent antibacterial that can be used to treat bacterial infections. Based on my results, the halogen substituents at the para position on the benzyl ring have a significant impact on antibacterial activity. Based on the synthetic route, future students can readily add different heterocyclic rings or even non-heterocyclic substituents at the benzyl position. Future students can also change the ethanolamine side chain to explore the antibacterial effects.

Key References:

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Houlihan, W. J., Kelly, L., Pankuch, J., Koletar, J., Brand, L., Janowsky, A., & Kopajtic, T. A. Mazindol Analogues as Potential Inhibitors of the Cocaine Binding Site at the Dopamine Transporter. *J. Med. Chem*, **2002,** *45*(19), 4097–4109.

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