

**Education:**

2004-2009 Ph.D., Chemistry; North Carolina State University

**Dissertation:** "The Development of Ageliferin Inspired Small Molecules as Antibiofilm and Antibacterial Agents Against Multidrug Resistant Bacterial Pathogens."

2000-2003 B.A. Biology; Minor Chemistry; University of North Carolina at Greensboro

**Appointments:**

**Independent Career Experience:**

2020-present Associate Professor (with Tenure), University of Florida, Department of Medicinal Chemistry

2019-present Graduate Coordinator, University of Florida, Department of Medicinal Chemistry

2014-2017 Affiliate Assistant Professor, University of Florida, Department of Chemistry

2013-2020 Assistant Professor, University of Florida, Department of Medicinal Chemistry

**Professional Experience:**

2009-2013 American Cancer Society Postdoctoral Fellow, University of Illinois at Urbana-Champaign, Chemistry Department (Advisor: Paul Hergenrother)

2004-2009 Graduate Assistant, North Carolina State University, Department of Chemistry (Advisor: Christian Melander)

2004-2007 Teaching Assistant, North Carolina State University, Department of Chemistry

2003-2004 Graduate/Teaching Assistant, University of South Florida, Department of Chemistry

**Honors and Awards:**

2024 American Cancer Society *ad hoc* Grant Reviewer

2023 American Cancer Society *ad hoc* Grant Reviewer

2023 NC State University Alumni Speaker (Chemistry Departmental Graduation Ceremony)

2022 Teaching Service Excellence Incentive Award (UF College of Pharmacy)

2022 Best Research Paper Award (UF Medicinal Chemistry Dept.)

2022 Year 2 Outstanding Teaching Team Award, UF COP (with Drs. Motychka, Peris, Grundmann)

2021 NIH Reviewer; Coccidioidomycosis Collaborative Research Centers

2020 Teaching Service Excellence Incentive Award (UF College of Pharmacy)

2020 NIH Reviewer; Combating Antibiotic-Resistant Bacteria Interdisciplinary Research Units (CARBIRU)

2019 Young Investigator Award, American Chemical Society (Division of Organic Chemistry)

2018 Teaching Service Excellence Incentive Award (UF College of Pharmacy)

2018-2023 Maximizing Investigators' Research Award; National Institute of General Medical Sciences

2018 Year 2 Outstanding Teaching Team Award, UF COP (with Drs. Motychka, Peris, Grundmann)

2018-2022 American Cancer Society Research Scholar

2017 Teaching Service Excellence Incentive Award (UF College of Pharmacy)

2017 Year 2 Outstanding Teaching Team Award, UF COP (with Drs. Motychka, Peris, Grundmann)

2017 NIH Reviewer; Partnerships for Countermeasures Against Select Pathogens: Therapeutics, Immunotherapeutics, and Vaccines Review Panel

2017	Teacher of the Year, College of Pharmacy, University of Florida (recognized at AACP Annual Meeting, <i>Pharmacy Education 2017</i> ; Nashville, TN)
2016	NIH Early Career Reviewer, Anti-Infective Drug Discovery and Mechanism of Resistance (DDR)
2015	Young Investigator Award, Center for Biofilm Engineering (Montana State University)
2015	Young Investigator Award, American Chemical Society (Division of Medicinal Chemistry)
2010-2013	American Cancer Society Postdoctoral Fellowship (UIUC)
2008-2009	Jimmy V Scholarship/Predoctoral Fellowship (NCSU)
2007	Sara & Chloe Novak Award for Excellence in Teaching of Organic Chemistry (NCSU)
2006-2007	Phi Lambda Upsilon Treasurer (NCSU)
2005	Phi Lambda Upsilon Membership (NCSU)
2004	Phi Beta Kappa Society Membership (UNC-Greensboro)
2003	Graduated <i>Summa Cum Laude</i> (UNC-Greensboro)
2003	Eberhart Award (Biology Department, UNC-Greensboro)
2003	Student Excellence Award (Honors College, UNC-Greensboro)
2003	American Chemical Society Organic Chemistry Award (Chemistry Dept., UNC-Greensboro)
2001-2002	Beta Beta Beta Society President (Biology Department, UNC-Greensboro)
2001	Beta Beta Beta Society Membership (Biology Department, UNC-Greensboro)

### **Research Interests:**

The overarching goal of the Huigens lab is to discover and develop novel small molecules that can be used in the treatment of human disease. Currently, our group is involved in: (1) developing innovative approaches to eradicate bacterial biofilms and resistant microbial pathogens, (2) ring distortion of complex indole alkaloids for drug discovery in areas of critical importance (opioid addiction, cancer, malaria) and (3) using synthetic medicinal chemistry to advance novel small molecules in targeted disease areas (i.e., cancer, myotonic dystrophy) in collaboration with disease experts. Graduate, undergraduate, pharmacy students and postdocs in our group receive training at the interface of chemistry and biology using a combination of synthetic organic chemistry, medicinal chemistry, chemical biology, and microbiology techniques/approaches.

### **Publications:**

#### ***From Independent Career at University of Florida (50 publications; \*Co-corresponding Author)***

64. Liu, K.; Xiao, T.; Yang, H.; Chen, M.; Gao, Q.; Brummel, B.R.; Ding, Y.; **Huigens III, R.W.** "Design, Synthesis and Evaluation of Halogenated Phenazine Antibacterial Prodrugs Targeting Nitroreductase Enzymes for Activation." *RSC Med. Chem.* **2023**, *14*, 1472-1481.  
- Front Cover Art Selection: <https://pubs.rsc.org/en/content/articlelanding/2023/md/d3md90030d>  
- Invited to be part of the "Antimicrobial Resistance" themed collection in *RSC Med Chem*.
63. Guijarro, M.V.; Kellish, P.C.; Dib, P.E.; Paciaroni, N.G.; Nawab, A.; Andring, J.; Kulemina, L.; Borrero, N.V.; Modenutti, C.; Feely, M.; Nasri, E.; Seifert, R.P.; Luo, X.; Bennett, R.L.; Shabashvili, D.; Licht, J.D.; McKenna, R.; Roitberg, A.; **Huigens III, R.W.**; Kaye, F.J.; Zajac-Kaye, M. "Discovery of a First-in-Class Multifunctional TYMS Non-Classical Antifolate Inhibitor with Potent *In Vivo* Activity that Prolongs Survival." *JCI Insight* **2023**, *8*, e158798.
62. Leas, D.A.; Schultz, D.C.; **Huigens III, R.W.** "Chemical Reactions of Indole Alkaloids That Enable Rapid Access to New Scaffolds for Discovery." *SynOpen* **2023**, *7*, 165-185.
61. Xiao, T.; Liu, K.; Gao, Q.; Chen, M.; Kim, Y.S.; Jin, S.; Ding, Y.; **Huigens III, R.W.** "Design, Synthesis and Evaluation of Carbonate-Linked Halogenated Phenazine-Quinone Prodrugs with Improved Water-Solubility and Potent Antibacterial Profiles." *ACS Infect. Dis.* **2023**, *9*, 899-915.
60. Liu, K.; Abouelhassan, Y.; Zhang, Y.; Jin, S.; **Huigens III, R.W.** "Transcript Profiling of Nitroxoline-Treated Biofilms Shows a Rapid Upregulation of Iron Acquisition Gene Clusters." *ACS Infect. Dis.* **2022**, *8*, 1594-1605.

59. Jenquin, J.R.; O'Brien, A.P.; Poukalov, K.; Lu, Y.; Frias, J.A.; Shorrock, H.K.; Richardson, J.I.; Mazdiyasni, H.; Yang, H.; **Huigens III, R.W.**; Boykin, D.; Ranum, L.P.W.; Cleary, J.D.; Wang, E.T.; Berglund, J.A. "Molecular Characterization of Myotonic Dystrophy Fibroblast Cell Lines for Use in Small Molecule Screening." *iScience* **2022**, 25, 104198.
58. **Huigens III, R.W.**; Brummel, B.R.; Tenneti, S.; Garrison, A.T.; Xiao, T. "Pyrazine and Phenazine Heterocycles: Platforms for Total Synthesis and Drug Discovery." *Molecules* **2022**, 27, 1112.  
- Invited to be part of a special issue "Heterocyclic and Organometallic Chemistry: Theme Issue in Honor of Prof. Dr. Daniel Comins's Great Contribution"; Selected as an "Editor's Choice" in Molecules
57. Liu, K.; Brivio, M.; Xiao, T.; Norwood IV, V. M.; Kim, Y. S.; Jin, S.; Papagni, A.\*; Vaghi, L.\*; **Huigens III, R. W.\*** "Modular Synthetic Routes to Fluorine-Containing Halogenated Phenazine and Acridine Agents that Induce Rapid Iron Starvation in MRSA Biofilms." *ACS Infect. Dis.* **2022**, 8, 280-295.
56. **Huigens III, R.W.**; Tenneti, S.; Xiao, T.; Garrison, A.T. "Pyrazines and Their Benzo Derivatives." Black, D.; Cossy, J.; Stevens, C. *Comprehensive Heterocyclic Chemistry IV.* **2022**, 8, 229-282. Oxford: Elsevier.  
- Invited by Professor Steven Weinreb
55. **Huigens III, R.W.**; Yang, H.; Liu, K.; Kim, Y.S.; Jin, S. "An Ether-Linked Halogenated Phenazine-Quinone Prodrug Model for Antibacterial Applications." *Org. Biomol. Chem.* **2021**, 19, 6603-6608.  
- Invited to be part of the OBC's themed collection: "Chemical Biology in OBC"; Selected as "Hot Article"
54. Norwood IV, V.M.; Murillo-Solano, C.; Goertzen II, M.G.; Brummel, B.R.; Perry, D.L.; Rocca, J.R.; Chakrabarti, D.\*; **Huigens III, R.W.\*** "Ring Distortion of Vincamine Leads to the Identification of Re-Engineered Antiplasmodial Agents." *ACS Omega* **2021**, 6, 20455-20470.
53. Yang, H.; Kundra, S.; Chojnacki, M.; Liu, K.; Fuse, M.A.; Abouelhassan, Y.; Kallifidas, D.; Zhang, P.; Huang, G.; Jin, S.; Ding, Y.; Luesch, H.; Rohde, K.H.; Dunman, P.M.; Lemos, J.A.; **Huigens III, R.W.** "A Modular Synthetic Route Involving *N*-Aryl-2-Nitrosoaniline Intermediates Leads to a New Series of 3-Substituted Halogenated Phenazine Antibacterial Agents." *J. Med. Chem.* **2021**, 64, 7275-7295.  
- Front Cover Art Selection: [Journal of Medicinal Chemistry | Vol 64, No 11 \(acs.org\)](#)  
- Featured Article  
- Viewpoint: Naclerio, G. A.; Sintim, H. O. "Starving Bacteria of Iron: A Potential Strategy to Disperse Bacterial Biofilms." *J. Med. Chem.* **2021**, 64, 7272-7274.
52. Fu, T.; Cai, Z.; Yue, Z.; Yang, H.; Fang, B.; Zhang, X.; Fan, Z.; Pan, X.; Yang, F.; Jin, Y.; Cheng, Z.; Wu, W.; Sun, B.L.; **Huigens III, R.W.**; Yang, L.; Bai, F. "Evolution of Resistance to Phenazine Antibiotics in *Staphylococcus aureus* and its Role During Co-infection with *Pseudomonas aeruginosa*." *ACS Infect. Dis.* **2021**, 7, 636-649.
51. Yang, H.; Liu, K.; Jin, S.; **Huigens III, R.W.** "Design, Synthesis and Biological Evaluation of a Halogenated Phenazine-Erythromycin Conjugate Prodrug for Antibacterial Applications." *Org. Biomol. Chem.* **2021**, 19, 1483-1487.  
- Invited to be part of the OBC's themed collection: "Chemical Biology in OBC"
50. **Huigens III, R.W.** "Targeting Bacterial Biofilms with Persister-Killing Agents." *Fut. Med. Chem.* **2021**, 13, 225-228.  
- Invited editorial
49. Xiao, T.; Liu, K.; **Huigens III, R.W.** "Progress Towards a Stable Cephalosporin-Halogenated Phenazine Conjugate for Antibacterial Prodrug Applications." *Bioorg. Med. Chem. Lett.* **2020**, 30, 127515.
48. Paciaroni, N.G.; Norwood IV, V.M.; Ratnayake, R.; Luesch, H.\*; **Huigens III, R.W.\*** "Yohimbine as a Starting Point to Access Diverse Natural Product-Like Agents with Re-programmed Activities against Cancer-Relevant GPCR Targets." *Bioorg. Med. Chem.* **2020**, 28, 115546.  
- Invited to be part of the "Chem/bio performance diversity" special issue in BMC

47. Valentine-King, M.A.; Cisneros, K.; James, M.O.; **Huigens III, R.W.**; Brown, M.B. "Efficacy data of halogenated phenazine and quinoline agents and an NH125 analogue to veterinary mycoplasmas." *BMC Vet. Res.* **2020**, *16*, 107.
46. Norwood IV, V.M.; Brice-Tutt, A.; Eans, S.O.; Stacy, H.; Shi, G.; Ratnayake, R.; Rocca, J. R.; Abboud, K.A.; Li, C.; Luesch, H.; McLaughlin, J. P.; **Huigens III, R.W.** "Preventing Morphine-Seeking Behavior through the Re-engineering of Vincamine's Biological Activity." *J. Med. Chem.* **2020**, *63*, 5119-5138.  
 - Front Cover Art Selection: <https://pubs.acs.org/toc/jmcmar/63/10>  
 - Press Release: American Chemical Society News Service Weekly PressPac:  
<https://www.acs.org/content/acs/en/pressroom/presspacs/2020/acs-presspac-february-5-2020/re-engineered-plant-compound-treats-opioid-addiction-in-mice.html>  
 - Highlighted: Trauner, D.; Vepřek, N.A. "A Vincamine-Derived HCRT2 Agonist Prevents Morphine-Seeking Behavior in Mouse Models." *Synfacts* 2020, *16*, 724.  
 - Highlighted: David Newman. Hot Topics in Pharmacognosy: Recent "Ramblings" through the *Journal of Medicinal Chemistry*. "Reengineering of Vincamine into an Opioid Antagonist." American Society of Pharmacognosy. ASP Newsletter: Summer 2020, *56*, 2.
45. Paciaroni, N.G.; Perry, D.; Norwood IV, V.M.; Murillo-Solano, C.; Collins, J.; Tenneti, S.; Chakrabarti, D.\*; **Huigens III, R.W.\*** "Re-engineering of Yohimbine's Biological Activity through Ring Distortion: Identification and Structure-Activity Relationships of a New Class of Antiplasmodial Agents." *ACS Infect. Dis.* **2020**, *6*, 159-167.  
 - Selected as a "Featured Article" by ACS Infectious Diseases & Cover Art Selection
44. Liu, K.; **Huigens III, R.W.** "Instructive Advances in Chemical Microbiology Inspired by Nature's Diverse Inventory of Molecules." *ACS Infect. Dis.* **2020**, *6*, 541-562.  
 - Invited to be part of the "Chemical Microbiology" special issue in ACS Infectious Diseases
43. Jenquin, J.R.; Yang, H.; **Huigens III, R.W.**; Nakamori, M.; Berglund, J.A. "Combination Treatment of Erythromycin and Furamidine Provides Additive and Synergistic Rescue of Mis-splicing in Myotonic Dystrophy Type 1 Models." *ACS Pharmacol. Transl. Sci.* **2019**, *2*, 247-263.
42. Abouelhassan, Y.; Garrison, A.T.; Yang, H.; Chávez-Riveros, A.; Burch, G.; **Huigens III, R.W.** "Recent Progress in Natural-Product-Inspired Programs Aimed at Addressing Antibiotic Resistance and Tolerance." *J. Med. Chem.* **2019**, *62*, 7618-7642.  
 - C&EN Discovery Report. Reading List: Our picks of the patent and journal literature on antimicrobial resistance and antibiotics. 9-21-2020 issue.
41. Paciaroni, N.G.; Norwood IV, V.M.; Garcia, D.E.; **Huigens III, R.W.** "Microwave-Enhanced, Stereospecific Ring-Closure of Medium-Ring Cyanamide Ethers to Yohimbine." *Tetrahedron Letters* **2019**, *60*, 1182-1185.
40. **Huigens III, R.W.**; Abouelhassan, Y.; Yang, H. "Phenazine Antibiotic-Inspired Discovery of Bacterial Biofilm-Eradicating Agents." *ChemBioChem* **2019**, *20*, 2885-2902.
39. Abouelhassan, Y.; Zhang, P.; Ding, Y.; **Huigens III, R.W.** "Rapid Kill Assessment of an *N*-arylated NH125 Analogue against Drug-Resistant Microorganisms." *Med. Chem. Commun.* **2019**, *10*, 712-716.  
 - Invited article for themed collection, "Antimicrobial Resistance, 2019."
38. Norwood IV, V.M.; **Huigens III, R.W.** "Harnessing the Chemistry of the Indole Heterocycle to Drive Discoveries in Biology and Medicine." *ChemBioChem* **2019**, *20*, 2273-2297.  
 - Selected as a "Very Important Paper" by ChemBioChem
37. Valentine-King, M.A.; Cisneros, K.; James, M.O.; **Huigens III, R.W.**; Brown, M.B. "Turning the Tide against Antibiotic Resistance by Evaluating Novel, Halogenated Phenazine, Quinoline, and NH125 Compounds against *Ureaplasma* spp. Clinical Isolates and Mycoplasma Type Strains." *Antimicrob. Agents Chemother.* **2019**, *63*, e02265-18.
36. **Huigens III, R.W.** "The Path to New Halogenated Quinolines with Enhanced Activities against *Staphylococcus epidermidis*." *Microbiol. Insights* **2018**, *11*, 4. Invited Commentary



35. Abouelhassan, Y.; Zhang, Y.; Jin, S.; **Huigens III, R.W.** "Transcript Profiling of MRSA Biofilms Treated with a Halogenated Phenazine Eradicating Agent: A Platform for Defining Cellular Targets and Pathways Critical to Biofilm Survival." *Angew. Chem. Int. Ed.* **2018**, *57*, 15523-15528.
34. Basak, A.; Abouelhassan, Y.; Kim, Y.S.; Norwood IV, V.M.; Jin, S.; **Huigens III, R.W.** "Halogenated Quinolines Bearing Polar Functionality at the 2-Position: Identification of New Antimicrobial Agents with Enhanced Activity against *Staphylococcus epidermidis*." *Eur. J. Med. Chem.* **2018**, *155*, 705-713.
33. Garrison, A.T.; Abouelhassan, Y.; Kallifidas, D.; Tan, H.; Kim, Y.S.; Jin, S.; Luesch, H.; **Huigens III, R.W.** "An Efficient Buchwald-Hartwig/Reductive Cyclization for the Scaffold Diversification of Halogenated Phenazines: Potent Antibacterial Targeting, Biofilm Eradication and Prodrug Exploration." *J. Med. Chem.* **2018**, *61*, 3962-3983.
32. Yousaf, H.H.; Garrison, A.T.; Abouelhassan, Y.; Basak, A.; Jones, J.B.; **Huigens III, R.W.** "Identification of Nitroxoline and Halogenated Quinoline Analogues with Antibacterial Activities against Plant Pathogens." *ChemistrySelect* **2017**, *2*, 6235-6239.
31. Basak, A.; Abouelhassan, Y.; Zuo, R.; Yousaf, H.; Ding, Y.; **Huigens III, R.W.** "Antimicrobial Peptide-Inspired NH125 Analogues: Bacterial and Fungal Biofilm-Eradicating Agents and Rapid Killers of MRSA Persisters." *Org. Biomol. Chem.* **2017**, *15*, 5503-5512.  
- Cover Art Selection: <http://pubs.rsc.org/en/content/articlepdf/2017/ob/c7ob90114c>
30. Yang, H.; Abouelhassan, Y.; Burch, G.M.; Kallifidas, D.; Huang, G.; Yousaf, H.; Jin, S.; Luesch, H.; **Huigens III, R.W.** "A Highly Potent Class of Halogenated Phenazine Antibacterial and Biofilm-Eradicating Agents Accessed Through a Modular Wohl-Aue Synthesis." *Sci. Rep.* **2017**, *7*, 2003.
29. Abouelhassan, Y.; Basak, A.; Yousaf, H.; **Huigens III, R.W.** "Identification of *N*-Arylated NH125 Analogues as Rapid Eradicating Agents against MRSA Persister Cells and Potent Biofilm Killers of Gram-Positive Pathogens." *ChemBioChem* **2017**, *18*, 352-357.  
- Front Cover Art Selection: <http://onlinelibrary.wiley.com/doi/10.1002/cbic.v18.4/issuetoc>
28. Paciaroni, N.G.; Ratnayake, R.; Matthews, J.H.; Norwood IV, V.M.; Arnold, A.C.; Dang, L.H.; Luesch, H.; **Huigens III, R.W.** "A Tryptoline Ring Distortion Strategy Leads to Complex and Diverse Biologically Active Molecules from the Indole Alkaloid Yohimbine." *Chem. Eur. J.* **2017**, *23*, 4327-4335.  
- Cover Art Selection: <http://onlinelibrary.wiley.com/doi/10.1002/chem.201605731/full>
27. Abouelhassan, Y.; Yang, Q.; Nguyen, M.T.; Rolfe, M.; Yousaf, H. Schultz, G.S.; **Huigens III, R.W.** "Nitroxoline: A Broad-Spectrum Persister Cell- and Biofilm-Eradicating Agent Against Pathogenic Bacteria." *Int. J. Antimicrob. Agents* **2017**, *49*, 247-251.
26. Garrison, A.T.; **Huigens III, R.W.** "Eradication of Bacterial Biofilms with Natural Products and Their Inspired Analogues that Operate Through Unique Mechanisms." *Curr. Top. Med. Chem.*, **2017**, *17*, 1954-1964.  
- Invited Review for Thematic Issue: "Recent Advances in Anti-biofilm Strategies."
25. Garrison, A.T.; Abouelhassan, Y.; Yang, H.; Yousaf, H.H.; Nguyen, T.; **Huigens III, R.W.** "Microwave-Enhanced Friedländer Synthesis for the Rapid Assembly of Halogenated Quinolines with Antibacterial and Biofilm Eradication Activities against Drug Resistant and Tolerant Bacteria." *Med. Chem. Commun.* **2017**, *8*, 720-724.  
- Hot Article; Invited for Themed Issue: "New Talent: Americas"
24. Zuo, R.; Garrison, A.T.; Basak, A.; Zhang, P.; **Huigens III, R.W.\***; Ding, Y.\* "In vitro antifungal and antibiofilm activities of halogenated quinoline analogues against *Candida albicans* and *Cryptococcus neoformans*." *Int. J. Antimicrob. Agents* **2016**, *48*, 208-211.
23. Basak, A.; Abouelhassan, Y.; Norwood IV, V.M.; Bai, F.; Nguyen, M.; Jin, S.; **Huigens III, R.W.** "Synthetically Tuning the 2-Position of Halogenated Quinolines: Optimizing Antibacterial and Biofilm Eradication Activities via Alkylation and Reductive Amination Pathways." *Chem. Eur. J.* **2016**, *22*, 9181-9189.  
- Hot Article & Cover Art Selection: <http://onlinelibrary.wiley.com/doi/10.1002/chem.v22.27/issuetoc>

- *Highlighted in Angew. Chemie Int. Ed.*: <http://onlinelibrary.wiley.com/doi/10.1002/anie.201682713/full>

22. Garrison, A.T.; Abouelhassan, Y.; Norwood IV, V.M.; Kallifidas, D.; Bai, F.; Nguyen, M.; Rolfe, M.; Burch, G.M.; Jin, S.; Luesch, H.; **Huigens III, R.W.** "Structure-Activity Relationships of a Diverse Class of Halogenated Phenazines that Targets Persistent, Antibiotic-Tolerant Bacterial Biofilms and *Mycobacterium tuberculosis*." *J. Med. Chem.* **2016**, 59, 3808-3825.
21. Paciaroni, N.G.; Borrero, N.V.; Rocca, J.R.; **Huigens III, R.W.** "Rapid Synthesis of Phenazine-1-Carboxylic Acid Derived Small Molecules from Diverse Anilines: Privileged Structures for Discovery." *Research & Reviews: Journal of Medicinal & Organic Chemistry* **2015**, 2, 67-76.
20. Garrison, A.T.; Abouelhassan, Y.; Kallifidas, D.; Bai, F.; Ukhanova, M.; Mai, V.; Jin, S.; Luesch, H.; **Huigens III, R.W.** "Halogenated Phenazines that Potently Eradicate Biofilms, MRSA Persister Cells in Non-Biofilm Cultures and *Mycobacterium tuberculosis*." *Angew. Chem. Int. Ed.* **2015**, 54, 14819-14823.
19. Basak, A.; Abouelhassan, Y.; **Huigens III, R.W.** "Halogenated Quinolines Discovered Through Reductive Amination with Potent Eradication Activities against MRSA, MRSE and VRE Biofilms." *Org. Biomol. Chem.* **2015**, 13, 10290-10294.  
- *2015 Hot Articles in Organic and Biomolecular Chemistry*
18. Abouelhassan, Y.; Garrison, A.T.; Bai, F.; Norwood IV, V.M.; Nguyen, M.; Jin, S.; **Huigens III, R.W.** "A Phytochemical-Halogenated Quinoline Combination Therapy Strategy for the Treatment of Pathogenic Bacteria." *ChemMedChem*, **2015**, 10, 1157-1162.
17. Garrison, A.T.; Bai, F.; Abouelhassan, Y.; Paciaroni, N.G.; Jin, S.; **Huigens III, R.W.** "Bromophenazine Derivatives with Potent Inhibition, Dispersion and Eradication Activities against *Staphylococcus aureus* Biofilms." *RSC Adv.* **2015**, 5, 1120-1124.
16. Abouelhassan, Y.; Garrison, A.T.; Burch, G.M.; Wong, W.; Norwood IV, V.M.; **Huigens III, R.W.** "Discovery of quinoline small molecules with potent dispersal activities against methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* biofilms using a scaffold hopping strategy." *Bioorg. Med. Chem. Lett.* **2014**, 24, 5076-5080.
15. Borrero, N.V.; Bai, F.; Perez, C.; Duong, B.Q.; Rocca, J.R.; Jin, S.; **Huigens III, R.W.** "Phenazine antibiotic inspired discovery of potent bromophenazine antibacterial agents against *Staphylococcus aureus* and *Staphylococcus epidermidis*." *Org. Biomol. Chem.* **2014**, 12, 881-886.

**Postdoctoral Studies at University of Illinois, Urbana-Champaign (with P. Hergenrother, 2 publications)**

14. Calvaresi, E.C.; Granchi, C.; Tuccinardi, T.; Di Bussolo, V.; **Huigens III, R.W.**; Lee, H.Y.; Palchaudhuri, R.; Macchia, M.; Martinelli, A.; Minutolo, F.; Hergenrother, P.J. "Dual targeting of the Warburg Effect with a glucose-conjugated lactate dehydrogenase inhibitor." *ChemBioChem* **2013**, 14, 2263-2267.
13. **Huigens III, R.W.**; Morrison, K.C.; Hicklin, R.W.; Flood Jr., T.A.; Richter, M.F.; Hergenrother, P.J. "A ring-distortion strategy to construct stereochemically complex and structurally diverse compounds from natural products." *Nature Chem.* **2013**, 5, 195-202.  
- *C&E News Highlight*: "Ringing In New Drug Candidates." **2013**, 91 (4), 9.  
- *Nature Chemistry Highlight*: Sharma, I.; Tan, D.S. "Drug Discovery: Diversifying Complexity." *Nature Chem.* **2013**, 5, 157-158.  
- *Faculty of 1000 Highlight*: <http://f1000.com/prime/717990389>.

**Graduate Studies at North Carolina State University (with C. Melander, 12 publications)**

12. Worthington, R.J.; Rogers, S.A.; **Huigens III, R.W.**; Melander, C.; Ritchie, D.F. "Foliar applied small molecule that suppresses biofilm formation and enhances control of copper-resistant *Xanthomonas euvesicatoria* on peppers." *Plant Disease* **2012**, 96, 1638-1644.
11. Reyes, S.; **Huigens III, R.W.**; Su, Z.; Simon, M.L.; Melander, C. "Synthesis and biological activity of 2-aminoimidazole triazoles accessed by Suzuki-Miyaura cross-coupling." *Org. Biomol. Chem.* **2011**, 9, 3041-3049.

10. Reed, C.S.; **Huigens III, R.W.**; Rogers, S.A.; Melander, C. "Modulating the development of *E. coli* biofilms with 2-aminoimidazoles." *Bioorg. & Med. Chem. Lett.* **2011**, *20*, 6310-6312.
9. Rogers, S.A.; **Huigens III, R.W.**; Cavanagh, J.; Melander, C. "Synergistic effects between conventional antibiotics and 2-aminoimidazole-derived antibiofilm agents." *Antimicrob. Agents Chemother.* **2010**, *54*, 2112-2118.  
- Science Magazine Highlight: "Sponging away antibiotic resistance." **2009**.
8. **Huigens III, R.W.**; Reyes, S.; Reed, C.S.; Bunders, C.; Rogers, S.A.; Steinhauer, A.T.; Melander, C. "The chemical synthesis and antibiotic activity of a diverse library of 2-aminobenzimidazole small molecules against MRSA and multidrug-resistant *A. baumannii*." *Bioorg. Med. Chem.* **2010**, *18*, 663-674.
7. Rogers, S.A.; **Huigens III, R.W.**; Melander, C. "A 2-aminobenzimidazole that inhibits and disperses gram-positive biofilms through a zinc-dependent mechanism." *J. Am. Chem. Soc.* **2009**, *131*, 9868-9869.  
- ChemBioChem Highlight: Musk Jr., D.J. "Zinc Fingered: New compounds that thwart gram-positive biofilm formation by sequestering zinc." *ChemBioChem* **2010**, *11*, 758-760.
6. **Huigens III, R.W.**; Rogers, S.A.; Steinhauer, A.T.; Melander, C. "Inhibition of *Acinetobacter baumannii*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* biofilms with a class of TAGE-triazole conjugates." *Org. Biomol. Chem.* **2009**, *7*, 794-802.
5. Melander, C.; Moeller, P.D.R.; Ballard, T.E.; Richards, J.J.; **Huigens III, R.W.**; Cavanagh, J. "Evaluation of dihydrooroidin as an antifouling additive in marine paint." *Int. Biodeterior Biodegradation* **2009**, *64*, 529-532.
4. Richards, J.J.; Ballard, T.E.; **Huigens III, R.W.**; Melander, C. "Synthesis and screening of an oroidin library for anti-biofilm activity." *ChemBioChem* **2008**, *9*, 1267-1279.
3. **Huigens III, R.W.**; Ma, L.; Gambino, C.; Moeller, P.D.R.; Basso, A.; Cavanagh, J.; Wozniack, D.J.; Melander, C. "Control of bacterial biofilms with marine alkaloid derivatives." *Mol. BioSyst.* **2008**, *4*, 614-621.
2. Richards, J.J.; **Huigens III, R.W.**; Ballard, T.E.; Basso, A.; Cavanagh, J.; Melander, C. "Inhibition and dispersion of proteobacterial biofilms." *Chem. Comm.* **2008**, *14*, 1698-1700.
1. **Huigens III, R.W.**; Richards J.J.; Parise, G.; Ballard, T.E.; Zeng, W.; Deora, R.; Melander, C. "Inhibition of *Pseudomonas aeruginosa* biofilm formation with bromoageliferin analogues." *J. Am. Chem. Soc.* **2007**, *129*, 6966-6967.  
- Faculty of 1000 Highlight.

#### **Patents (16 Total Issued and Provisional):**

##### ***From Independent Career at University of Florida (10 total; 6 patents issued, 4 provisional)***

16. Zajac-Kaye, M.; **Huigens, R.W.** "Thymidylate Synthase Inhibitors and Uses Thereof." PCT/US2022/048558. WO 2023/081141 A1. International Publication Date: 5/11/2023.
15. **Huigens III, R.W.**; Yang, H. "3-Substituted Phenazine Derivatives as Antimicrobial Agents." Application No. 17/692,536. US 2022 0289689 A1. Publication date: 9/15/2022.
14. **Huigens III, R.W.**; Garrison, A.; Abouelhassan, Y. "Preparation of phenazine derivatives as antimicrobial agents." PCT Int. Appl. **2017**, WO 2017011730 A2 20170119.
13. **Huigens III, R.W.**; Abouelhassan, Y.; Garrison, A. "Preparation of quinoline compounds and combination therapy for treating infectious diseases." PCT Int. Appl. **2016**, WO 2016154051 A1 20160929.
12. **Huigens III, R.W.**; Abouelhassan, Y.; Basak, A. "*N*-arylated analogues and uses thereof." Patent No. 11,419,335; Issued: 8/23/2022.
11. **Huigens III, R.W.**; Paciaroni, N.G.; Luesch, H. "Analogues of yohimbine and uses thereof." Patent No. 11,242,331; Issued: 2/8/2022.

10. **Huigens III, R.W.**; Norwood IV, V. M.; Luesch, H. "Analogues of vincamine and uses thereof." Patent No. 11,130,764; Issued: 9/28/2021.
9. **Huigens III, R.W.**; Garrison, A.; Abouelhassan, Y.; Yang, H.; Burch, G. "Phenazine derivatives as antimicrobial agents." Patent No. 11,053,205; Issued: 7/6/2021.
8. **Huigens III, R.W.**; Basak, A.; Abouelhassan, Y. "Halogenated quinoline derivatives as antimicrobial agents." Patent No. 11,008,290; Issued: 5/18/2021.
7. **Huigens III, R.W.**; Jin, S. "Substituted phenazines as antimicrobial agents." Patent No. 9,856,225; Issued: 1/2/2018.

***From Postdoctoral Studies at University of Illinois at Urbana-Champaign (1)***

6. Hergenrother, P.J.; **Huigens III, R.W.**; Morrison, K.C.; Hicklin, R.W.; Flood, T.A. "Complex and structurally diverse compounds." Patent No. 10,081,592; Issued: 9/25/2018.

***From Graduate Studies at North Carolina State University (5)***

5. Melander, C.; Rogers, S.A.; **Huigens III, R.W.** "Inhibition and dispersion of bacterial biofilms with benzimidazole derivatives." PCT Int. App. 2010, WO/2010/144686.
4. Melander, C.; Cavanagh, J.; Ritchie, D.; Rogers, S.A.; **Huigens III, R.W.** "Inhibition of biofilms in plants with triazole derivatives." PCT Int. Appl. 2010, WO/2010/077603.
3. Melander, C.; Cavanagh, J.; Ritchie, D.; **Huigens III, R.W.**; Ballard, T.E.; Richards, J.J.; Lindsey, J.S. "Inhibition of biofilms in plants with imidazole derivatives." Patent No. 8,278,340; Issued: 10/2/2012.
2. Melander, C.; Rogers, S.A.; **Huigens III, R.W.**; Reed, C.S. "Inhibition and dispersion of bacterial biofilms with imidazole-triazole derivatives." Patent No. 7,897,631; Issued: 3/1/2011.
1. Melander, C.; Cavanagh, J.; **Huigens, R.W.**; Ballard T.E.; Richards, J.J. "Inhibition of bacterial biofilms with imidazole derivatives." Patent No. 7,906,544; Issued: 3/15/2011.

**Invited Talks & Seminars (Independent Career; 64 Combined Seminars & Professional Talks):**

**Research Seminars/Lectures at Other Universities (26):**

26. *"Phenazines & Indole Alkaloids as Platforms for Discovery."* University of Georgia, Department of Pharmaceutical & Biomedical Sciences. 1-24-2024. (Host: David Crich)
25. *"Indole Alkaloids & Phenazine Antibiotics as Platforms for Discovery."* University of Alabama, Department of Chemistry and Biochemistry. 3-3-2022 (Host: Matthew Thompson)
24. *"Halogenated Phenazines: Potent Antibacterial Agents that Eradicate Biofilms."* University of Southern Mississippi; School of Biological, Environmental, and Earth Sciences. (zoom seminar). 11-19-2021 (Host: Dmitir Mavrodi)
23. *"Indole Alkaloids and Phenazine Antibiotics as Platforms for Discovery."* Louisiana State University, Department of Chemistry (Chemical Biology Seminar; zoom). 4-16-2021 (Host: Mario Rivera)
22. *"Indole Alkaloids: New Starting Points for Drug Discovery."* University of Rochester, School of Medicine & Dentistry (MBI 403 - Drug Discovery; graduate & senior undergraduate course; zoom lecture). 2-12-2021 (Host: Paul Dunman)
21. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* University of Rochester, Department of Chemistry (Organic Seminar). 11-8-2019 (Host: Rudi Fasan)
20. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* Penn State University, Department of Chemistry (Organic Seminar). 9-26-2019 (Host: Steven Weinreb)
19. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* The Scripps Research Institute (Scripps Florida), Department of Chemistry. 5-13-2019 (Host: Tom Kodadek)
18. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* University of Nebraska Medical Center, Department of Pharmaceutical Sciences. 4-5-2019 (Hosts: Martin Conda-Sheridan, Corey Hopkins)



17. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* University of Illinois at Urbana-Champaign, Department of Chemistry (Organic Seminar). 2-28-2019 (Host: Paul Hergenrother)
16. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* Purdue University, Department of Chemistry (Organic Seminar). 1-15-2019 (Host: Herman Sintim)
15. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* University of Central Florida, Burnett School of Biomedical Sciences; College of Medicine. 12-7-2018. (Hosts: Tara Strutt, Kyle Rohde)
14. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* University of Georgia, Department of Chemistry (Organic Seminar). 11-8-2018. (Host: Eric Ferreira)
13. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* Emory University, Department of Chemistry. 11-7-2018. (Host: Bill Wuest)
12. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* Georgia Institute of Technology, Department of Chemistry & Biochemistry. 11-6-2018. (Host: M.G. Finn)
11. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* University of Minnesota, Department of Medicinal Chemistry. 10-30-2018. (Host: Daniel Harki)
10. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* Virginia Commonwealth University, Department of Chemistry. 10-2-2018. (Host: Ashton Cropp)
9. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* University of Virginia, Department of Chemistry. 9-21-2018. (Host: Michael Hilinski)
8. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* University of North Carolina at Chapel Hill, Joint Seminar in Chemical Biology & Medicinal Chemistry and Chemistry. 8-29-2018. (Host: Jeff Aubé & Kevin Frankowski)
7. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* North Carolina State University, Department of Chemistry (Organic Division Seminar). 8-27-2018. (Host: Joshua Pierce)
6. *"Phenazine Antibiotics and Indole Alkaloids: New Platforms for Discovery."* University of Illinois at Chicago, Department of Medicinal Chemistry & Pharmacognosy. 4-27-2018. (Host: Terry Moore)
5. *"Phenazine Antibiotics and Indole Alkaloids: New Platforms for Discovery."* University of Texas at Arlington, Department of Chemistry & Biochemistry. 4-13-2018. (Host: Alejandro "Alex" Bugarin)
4. *"Phenazine Antibiotics and Indole Alkaloids: New Platforms for Discovery."* Clemson University, Department of Chemistry. 2-1-2018. (Host: Daniel Whitehead)
3. *"Phenazine Antibiotics and Indole Alkaloids: New Platforms for Drug Discovery."* Florida State University, Department of Chemistry & Biochemistry (Organic Division). 11-16-2017. (Host: Justin Kennemur)
2. *"Phenazine Antibiotics and Indole Alkaloids: New Platforms for Drug Discovery."* University of North Carolina at Greensboro, Department of Chemistry & Biochemistry. 11-3-2017. (Host: Terry Nile)
1. *"Pseudomonas Inspired Discovery of Novel Antibacterial Agents."* University of South Florida, Department of Chemistry. 4-3-2014. (Host: Bill Baker)

#### **Conference/Symposium Research Seminars (17):**

17. *"Rapid Generation of Ring Fusion Scaffolds from Indoles & Indole Alkaloids as a Platform for Discovery."* University of Florida's 5<sup>th</sup> Drug Discovery Symposium; Jupiter, FL. 4-20-2023.
16. *"Indole Alkaloids: A Platform to Expand Chemical Diversity for Drug Discovery."* FloHet Conference, University of Florida (Chemistry Department). 3-7-2022.
15. *"Indole Alkaloids and Phenazine Antibiotics as Synthetic Platforms for Discovery."* New Trends in Organic Synthesis. XXXV Symposium. University of Milan, Italy. (zoom presentation) 11-30-2021.
14. *"Ring Distortion of Indole Alkaloids as a Synthesis Platform for Drug Discovery."* American Chemical Society Southeastern Regional Meeting (SERMACS), Session: Frontiers in Organic Synthesis and Catalysis. Birmingham, AL. 11-12-2021.
13. *"Eradicating Resistant and Tolerant Bacteria with Phenazine Antibiotic Inspired Small Molecules."* American Chemical Society Southeastern Regional Meeting (SERMACS), Session: Small Molecules for the Disruption of Bacterial Processes. Birmingham, AL. 11-11-2021.

12. *"Indole Alkaloids: New Starting Points for Drug Discovery."* FloHet Conference, University of Florida (Chemistry Department). 3-2-2020.
11. *"Harnessing the Indole Heterocycle to Rapidly Access Complex and Diverse Compounds from Indole Alkaloids."* Young Investigator Symposium, Division of Organic Chemistry, American Chemical Society Meeting, San Diego, CA. 8-27-2019.
10. *"Ring Distortion of Indole Alkaloids: A New Platform for Drug Discovery."* 17<sup>th</sup> Annual Congress of International Drug Discovery Science & Technology. Kyoto International Conference Center (ICC), Japan. 7-25-2019.
9. *"Phenazine Antibiotic Inspired Discovery of Biofilm-Eradicating Agents."* University of Florida's 3<sup>rd</sup> Drug Discovery Symposium. 4-26-2019.
8. *"Ring Distortion of Complex Indole Alkaloids: Reengineering Biological Activity to Address New Disease Areas."* 94<sup>th</sup> Florida Annual Meeting and Exposition (FAME Conference), Division of Organic Chemistry, American Chemical Society, Palm Harbor, FL. 5-5-2018.
7. *"Ring Distortion of Indole Alkaloids: A New Platform for Drug Discovery."* FloHet Conference, University of Florida (Chemistry Department). 3-6-2018.
6. *"Ring Distortion of Indole Alkaloids: A New Platform for Drug Discovery and the Identification of Antiplasmodial Agents."* American Microbiology Society 103<sup>rd</sup> Southeastern Branch Meeting: 11-11-2017.
5. *"Natural Product Inspired Synthetic Medicinal Chemistry: Functional and Complexity Driven Discoveries."* 93<sup>rd</sup> Florida Annual Meeting and Exposition (FAME Conference), Division of Organic Chemistry, American Chemical Society, Palm Harbor, FL. 5-5-2017.
4. *"Tryptoline-Based Ring Distortion Strategies to Explore New Chemical Space."* University of Florida Drug Discovery Symposium. 4-29-2016.
3. *"Phenazine Antibiotic Inspired Discovery of Biofilm-Eradicating Small Molecules."* Montana Biofilm S&T Meeting, Young Investigator: Center for Biofilm Engineering, Montana State University. 7-15-2015.
2. *"Discovery of Phenazine and Quinoline Biofilm Eradicators."* 91<sup>st</sup> Florida Annual Meeting and Exposition (FAME Conference), Organic Chemistry Div., American Chemical Society, Palm Harbor, FL. 5-8-2015.
1. *"Discovery of Halogenated Phenazine and Halogenated Quinoline Small Molecules with Antibacterial and Antibiofilm Activities against Staphylococcal Biofilms."* Young Investigator Symposium, Division of Medicinal Chemistry, 249<sup>th</sup> American Chemical Society Meeting, Denver, CO. 3-22-2015.

#### **Miscellaneous Research Seminars and Talks (15):**

15. *"Eradicating Bacterial Biofilms with Halogenated Phenazine Small Molecules."* University of Florida, College of Pharmacy, PharmTalk Presentation. 3-21-2023. (Host: Jatinder Lamba)
14. *"Becoming a Champion of Research, One Synthesized Compound at a Time."* University of Florida; Department of Medicinal Chemistry. Seminar. 5-3-2022. (Host: Lina Cui)
13. *"Natural Product-Inspired Discoveries at the Chemistry-Biology Interface."* University of Florida; Department of Chemistry, Chemical Biology Seminar. 4-1-2022. (Host: Matthew Eddy)
12. *"Halogenated Phenazines: Potent Antibacterial Agents that Eradicate Biofilms."* Curie Co. (zoom seminar). 2-14-2022. (Host: Christian Kasey).
11. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* University of Florida; Department of Chemistry, Organic Chemistry Seminar. 10-31-2019. (Host: Alex Grenning)
10. *"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Discovery."* University of Florida; CNPD3 Seminar Series, Department of Medicinal Chemistry. 10-16-2019. (Host: Chenglong Li)
9. *"Phenazine Antibiotic Inspired Discovery of New Biofilm-Eradicating Agents."* University of Florida; Oral Biology Department, College of Dentistry. 4-15-2019. (Host: Jose Lemos)
8. *"Better Living Through Chemistry: Ring Distortion to Re-engineer New Treatments for Opioid Addiction."* University of Florida, College of Pharmacy, PharmTalk Presentation with Jay McLaughlin (co-presenter of collaborative project within UF COP). 11-27-2018.

7. *"From Organic Chemistry to Drug Discovery."* University of Florida Student Science Training Program (for high school students). 7-3-2018.
6. *"From Organic Chemistry to Biofilm Eradication."* University of Florida Student Science Training Program (for high school students). 6-19-2017.
5. *"Synthetic Medicinal Chemistry Driven Discoveries."* University of Florida; Department of Biochemistry and Molecular Biology, College of Medicine. 3-29-2017. (Host: Linda Bloom)
4. *"From Organic Chemistry to Biofilm Eradication."* University of Florida Student Science Training Program (for high school students). 6-20-2016.
3. *"From Organic Chemistry to Biofilm Eradication."* University of Florida Student Science Training Program (for high school students). 7-13-2015.
2. *"Targeting Staphylococcal Biofilms: Discovery of Bromophenazine and Quinoline Anti-Biofilm Agents."* University of Florida; Oral Biology Department, College of Dentistry. 12-8-2014. (Host: Jeannine Brady)
1. *"Pseudomonas Inspired Discovery of Novel Antibacterial Agents."* University of Florida; Department of Chemistry, Biochemistry Division Seminar. 4-11-2014. (Host: Steven Bruner)

#### **Other Professional Development or Invited Talks (6):**

6. *"Becoming a Lifelong Learner at the Chemistry-Biology Interface."* University of Florida. NIH/NIGMS Chemistry-Biology Interface Predoctoral Training Program. 10-2-2023.
5. NC State University Alumni Speaker. Chemistry Departmental Graduation Ceremony. Raleigh, NC. 5-5-2023. (Hosts: Reza Ghiladi & Joshua Pierce)
4. *"Checking In With Our PhD Students."* University of Florida, College of Pharmacy, Gainesville, FL. 10-25-2022.
3. *"Studying: The Upfront Investment."* University of Florida, College of Pharmacy, Mid Semester Orientation for 1PD Students, Gainesville, FL; 9-27-2022. (Host: Teresa Cavanaugh)
2. *"Conflict Resolution: Definitions, Strategies and Results."* University of Florida, College of Pharmacy, Student Organizational Annual Retreat (SOAR), Jacksonville, FL; 1-12-2019. (Host: Susan Garcia)
1. *"Career Path & Research Experiences."* University of Florida, College of Pharmacy, General Body Meeting, Jacksonville, FL; 3-24-2021. (Host: Lauren Hoggarth; zoom presentation)

#### **Invited Poster Presentations (Independent Career, 1):**

1. *"Efforts to Expand Our Antibiotic Arsenal to Eradicate Persistent Bacterial Biofilms."* 253<sup>rd</sup> American Chemical Society Meeting, San Francisco, CA; 4-5-2017. Division of Medicinal Chemistry.

#### **Huigens Lab Personnel:**

- 1.) Prof. Robert W. Huigens III (associate professor of medicinal chemistry)
- 2.) Dr. Qiwen Gao (postdoctoral fellow, 2022-present)
- 3.) Eli Levit (graduate student, 2020-present)
- 4.) David Blanco (graduate student, 2021-present)
- 5.) Alexis Bragg (graduate student, 2022-present)
- 6.) Erin Solomon (graduate student, 2022-present)
- 7.) Logan Spillman (undergraduate student, 2024-present)

#### **Former Huigens Lab Personnel/Trainees:**

##### Graduate Students Mentored (10 total graduates)

##### PhD Graduates (7)

- 1.) Dr. Aaron Garrison (2013-2017; PD: Craig Lindsley, Vanderbilt; current: Senior Scientist, AstraZeneca)
- 2.) Dr. Akash Basak (2014-2017; PD with Christian Melander, Notre Dame; current: Aurigene)
- 3.) Dr. Nicholas Paciaroni (2013-2018; PD: Tom Kodadek, Scripps Florida; current: Deluge Biotechnologies)

- 4.) Dr. Yasmeeen Abouelhassan (2014-2018; current: Fellow, Center of Anti-infection Research and Development, Hartford HealthCare)
- 5.) Dr. Verrill Norwood (2014-2019; PD: Jeff Aubé, UNC-Chapel Hill; current: Senior Scientist II, Cambrex)
- 6.) Dr. Hongfen Yang (2015-2020; PDs: Rob Huigens, UF; Stephen F. Martin, UT-Austin; current: Lecturer, School of Public Health, University of South China)
- 7.) Dr. Ke Liu (2018-2023; PD: Peijun Ma, St. Jude Children's Research Hospital)

"PD" = indicates postdoc positions obtained following graduation

#### Master's Graduates (3)

- 1.) Sahar Alghamdi (Med Chem, 2014-2016)
- 2.) Gena Burch, PharmD (Med Chem, 2014-2017)
- 3.) Michael Goertzen (Med Chem, 2019-2022)

#### Postdoctoral Fellows Mentored (8)

- 1.) Dr. Nicholas Borrero (2013; current: Senior Process Scientist, AMPAC Fine Chemicals)
- 2.) Dr. Alejandra Chavez-Riveros (2018-2019; current: teaching/research, Technological University of Mexico)
- 3.) Dr. Srinivasarao Tenneti (2019-2020; current: Senior Scientist, TCG GreenChem Inc.)
- 4.) Dr. Tao Xiao (2019-2021; current: Associate Director II, WuXi AppTec at Chengdu, China)
- 5.) Dr. Hongfen Yang (2020-2021; current: Lecturer, School of Public Health, University of South China)
- 6.) Dr. Daniel Schultz (2022; current: Postdoc with Craig Lindsley, Vanderbilt)
- 7.) Dr. Beau Brummel (2021-2023; current: Paraza Pharma Inc.; Montreal, Canada)
- 8.) Dr. Derek Leas (2020-2023; current: Postdoc with Guangrong Zheng, University of Florida)

#### Visiting & Rotating Graduate Students Mentored (2)

- 1.) Faika Bashoglu (visiting graduate student; 2016-2017)
- 2.) Hens Laurent (rotation/graduate student, 2021)

#### Pharmacy Student Researchers Mentored (7)

- 1.) Benjamin Duong (2013)
- 2.) Wilson Wong (2014)
- 3.) Thandiwe Jolly (2015)
- 4.) Melanie Rolfe (2015)
- 5.) Tho Nguyen (2015)
- 6.) Zach Johnson (2018)
- 7.) Natalie Ourhann (2019)

#### Undergraduate Student Researchers Mentored (9)

- 1.) Cristian Perez (Chemistry major, 2013-2014)
- 2.) Alexander Valdes (Biochemistry major, 2014)
- 3.) Grace Hester (Chemistry major, 2015-2016)
- 4.) Minh Nguyen (Biochemistry major, 2014-2016; UF Research Scholar Awardee)
- 5.) Hussain Yousaf (Biology major & post-baccalaureate researcher; 2014-2017)
- 6.) Austin Arnold (Chemistry major; 2015-2017)
- 7.) Daniel Garcia (undergraduate summer student, 2018 SURF program trainee)
- 8.) Cayle Gao (Biochemistry major, Mathematics minor; 2018-2019)
- 9.) Sadie Milhous (Microbiology and Cell Science major; 2021-2022)

#### High School Student Researchers Mentored (3)

- 1.) Sam Goldstein (SSTP trainee; 2015)
- 2.) Charles Mock (home schooler in Gainesville; 2015)
- 3.) William Wang (SSTP trainee, 2016)

### **Mentored Undergraduate, Pharmacy, Graduate Student & Postdoctoral Awards/Honors:**



- 1.) Gena Burch: Best Poster Award, 2015 UF COP Research Showcase (Professional Student Division)
- 2.) Minh Thu Nguyen: UF, 2015 University Scholars Program (Undergraduate Award, \$1,750)
- 3.) Yasmeen Abouelhassan: 2015-2016 International Graduate Student of the Year, Medicinal Chemistry
- 4.) Yasmeen Abouelhassan: Best Poster Award, 2016 UF Drug Discovery Symposium (Graduate Division)
- 5.) Gena Burch: 2016 Merck Award for Outstanding Research (Pharm.D. Student Research)
- 6.) Yasmeen Abouelhassan: 2015/2016 Best Graduate Student Seminar (Junior Division, \$100)
- 7.) Gena Burch: 2016-2017 Rho Chi Award (AFPE Pre-Doctoral Fellowship, \$7,500)
- 8.) Gena Burch: 2016/2017 Best Graduate Student Seminar (Junior Division, \$100)
- 9.) Yasmeen Abouelhassan: 2017 Marilyn Little Scholarship (Graduate Award, \$1,000)
- 10.) Wilson Wong: 2017 Merck Award for Outstanding Research (Pharm.D. Student Research)
- 11.) Nicholas Paciaroni: 2<sup>nd</sup> UF Drug Discovery Symposium, Oral Competition Winner; 2017
- 12.) Verrill "Chip" Norwood IV: 2<sup>nd</sup> UF Drug Discovery Symposium, Poster Award Winner; 2017
- 13.) Yasmeen Abouelhassan: 2<sup>nd</sup> UF Drug Discovery Symposium, Poster Award Winner; 2017
- 14.) Yasmeen Abouelhassan: 31<sup>st</sup> Annual Research Showcase, UF COP, Oral Competition Winner, Senior Division; 2018
- 15.) Yasmeen Abouelhassan: Emerging STEM Scholar Award, Association for Academic Women (AAW); 2018. (\$1,000 from Dr. Aysegul Gunduz's NSF CAREER to promote young women in STEM)
- 16.) Dr. Alejandra Chávez-Riveros: National Council of Science and Technology (CONACYT) Postdoctoral Fellowship from Mexico; Award Project Title: "Synthesis of Yohimbine Derivatives." (CVU No. 346860)
- 17.) Verrill "Chip" Norwood IV: 3<sup>rd</sup> UF Drug Discovery Symposium, Oral Competition Winner; 2019
- 18.) Dr. Alejandra Chávez-Riveros: 3<sup>rd</sup> UF Drug Discovery Symposium, Poster Award Winner; 2019
- 19.) Yasmeen Abouelhassan: Best Research Paper Award (first author: *Angew. Chem. Int. Ed.* **2018**, 57, 15523-15528.), Department of Medicinal Chemistry; 2019
- 20.) Michael Goertzen: Student Trainee Appointed, T-32 Chemistry-Biology Interface Predoctoral Training Program (NIGMS, NIH); 2020-2021
- 21.) Dr. Beau Brummel: Postdoctoral Trainee Appointed, T-90 Oral Biology Training Program (NIH); 2021-2023
- 22.) Dr. Verrill "Chip" Norwood IV: Best Research Paper Award (first author: *J. Med. Chem.* **2020**, 63, 5119-5138.), Department of Medicinal Chemistry; 2021
- 23.) Dr. Derek Leas: Postdoctoral Trainee Appointed, T-32 CA25793, Team-Based Interdisciplinary Cancer Research Training Program (NIH), UF Health Cancer Center; 2021-2023
- 24.) David Blanco: Student Trainee Appointed, T-32 Chemistry-Biology Interface Predoctoral Training Program (NIGMS, NIH); 2022-2024
- 25.) Ke Liu: T-32 Chemistry-Biology Interface Training Program, Poster Award Winner; 2022
- 26.) Ke Liu: International Student Award (COP & UF International Center Award); 2022
- 27.) Ke Liu: Best Research Student Award, Department of Medicinal Chemistry, UF; 2023

#### **Teaching (including invited lectures) at University of Florida:**

- 1.) **PHA 6472:** Organic Synthesis of Drug Molecules (S 2016, S 2018, S 2020, S 2022, S 2024; 3 credit hours; graduate-level course on advanced organic synthesis, including drug synthesis; Course Coordinator)
- 2.) **PHA 6447:** Drug Design I (S 2014, F 2015, F 2017-2021; 2014-2015: 6-hour lecture series, "Discovery of New Antibacterial Agents"; 2017-2023: 7-hour lecture series on intermediate & advanced organic chemistry, including reaction mechanisms of various cancer therapy warheads; graduate-level course)
- 3.) **PHA 6935:** Drug Design II (S 2018-2020: 5-hour lecture series on "Heterocyclic Chemistry"; 2-hour lecture series on the "Chemical Synthesis of Antibiotics")
- 4.) **PHA 5433:** Fundamentals of Medicinal Chemistry (F 2014; 5 lectures on: "Physiochemical Principles of Drug Molecules"; pharmacy student course)

- 5.) **PHA 5438:** Medicinal Chemistry II (S 2015; 4 lectures on: "Antibiotic Resistance, Tetracyclines and Fluoroquinolone Antibiotics"; pharmacy student course)
- 6.) **PHA 5439:** Principles of Medicinal Chemistry & Pharmacology I (F 2015-2023; 6-10 hour lecture module with active learning: "Relationships of functional groups to pharmacological activity"; pharmacy course)
- 7.) **PHA 5782C:** Patient Care 2 (F 2016-2023; Medicinal Chemistry Topics and lecture hours Include: Antibiotics, 3 hours, 2016-2023; Antiemetics, 0.75 hours, 2016-2017. Second-year pharmacy course.)
- 8.) **PHA 5878C:** Patient Care 3 (F 2016-2017; Medicinal Chemistry Topics and lecture hours include: Antihyperlipidemics, 1 hour)
- 9.) **PHA 5784C:** Patient Care 4 (S 2017-2020, 2022-2023; Medicinal Chemistry Topics and lecture hours Include: Vitamins, 0.75 hours; Weight Loss Drugs, 0.25 hours)
- 10.) **PHA 5930:** Seminar in Pharmacy Research (F 2019, S2020, F 2020; Co-Leader of Course, F 2019, F 2020; Course Leader: Dr. Larisa Cavallari; faculty from each department present their research, 2 hour elective, two weeks of daily seminars and team-based learning sessions, 9 & 17 students enrolled in this new course during semesters Co-coordinated)
- 11.) **GMS 6009:** Principles of Drug Action (S 2015 lecture: "Complexity-to-Diversity in Drug Synthesis"; S 2016-2020 lectures: "Antibiotics"; graduate-level course in the College of Medicine, UF)
- 12.) **PHA 6935:** Selected Topics in Pharmacy (S 2015, F 2020, F 2021, S 2023; advanced chemical synthesis topics, including: total synthesis of biologically active natural products, reaction mechanisms, complex transition states, project design, chemical synthesis from the literature, chalk talk presentations led by students; 1-2 credit hour graduate-level course)
- 13.) **PHA 6936:** Special Topics: Grant Writing (Summer 2019-2020; lecture titled, "Significance, What to Include"; involved in workshops to assist students with drafts of proposal documents and provide feedback).
- 14.) **PHA 6934:** Seminar in Medicinal Chemistry (2015-2016 academic year). Coordinator of seminar series in Medicinal Chemistry, which typically involves graduate student seminars on literature topics.
- 15.) **PHA 6894:** Introduction to Graduate Studies (Summer 2021-2023, lecture on "Putting your best self forward" to discuss CVs, biosketches & personal statements; 2023-2024, Course Coordinator, lecture on "First Year Essentials & Program Milestones"; College-wide course for all first year PhD students).
- 16.) **BCH 4905:** Science for Life Research Seminar (F 2015, 2017, 2018; invited lecture to discuss a career in science and our lab's research interests)

#### **University of Florida Affiliations:**

- 1.) Emerging Pathogens Institute
- 2.) Center for Natural Products, Drug Discovery and Development (CNPD3)
- 3.) UF Health Cancer Center
- 4.) Chemistry Department (2014-2017 to mentor Akash Basak as a PhD student)

#### **Service:**

##### **To the University of Florida, College of Pharmacy:**

2021-present	Faculty Governance Council (Faculty Senator, COP)
2021-present	Mass Spec User Advisory Committee (UF Chemistry)
2020-present	Tenure & Promotion Committee (College of Pharmacy)
2020-2023	Steering Committee, T-32 Chemistry-Biology Interface Research Training Program
2019-present	Graduate Coordinator, Department of Medicinal Chemistry
2016-present	Academic and Professional Standards Committee, UF COP
2016-2018	Admissions Committee, UF COP (half line with Prof. Yousong Ding)
2015-2019	Faculty & Staff Hiring Committees for Medicinal Chemistry (multiple hiring committees)
2014-2016	Financial Aid and Student Awards Committee, UF COP

### **Grant Application Reviews:**

- 2024 American Cancer Society (eight grant applications reviewed)
- 2023 American Cancer Society (five grant applications reviewed)
- 2022 American Chemical Society Petroleum Research Fund (one grant application reviewed)
- 2021 American Chemical Society Petroleum Research Fund (one grant application reviewed)
- 2021 NIH Reviewer; Coccidioidomycosis Collaborative Research Centers (three U-19 applications reviewed)
- 2020 NIH Reviewer; Combating Antibiotic-Resistant Bacteria Interdisciplinary Research Units (CARBIRU; three U-19 applications reviewed)
- 2019 Space Research Initiative (SRI) Call for UF-Led Proposals (five grant application reviewed)
- 2018 INBRE (IDeA Network of Biomedical Research Excellence; Puerto Rico, one grant application reviewed)
- 2017 NIH Reviewer; Partnerships for Countermeasures Against Select Pathogens: Therapeutics, Immunotherapeutics, and Vaccines Review Panel (academic & industry collaborative grant applications; six grant applications reviewed)
- 2017 American Chemical Society Petroleum Research Fund (one grant application reviewed)
- 2016 NIH Reviewer; Anti-Infective Drug Discovery and Mechanism of Resistance (DDR; four grant applications reviewed)
- 2015 PROSPER Award Reviewer (UF College of Pharmacy; four grant applications reviewed)

### **Reviewer for the following Journals (reviewed at least one manuscript for the following journals):**

*Chemical Reviews, Nature Chemistry, Journal of the American Chemical Society, Angewandte Chemie, PNAS, Accounts of Chemical Research, ChemComm, Organic Letters, Journal of Medicinal Chemistry (≥16), Organic Chemistry Frontiers, Scientific Reports, ACS Chemical Biology, European Journal of Medicinal Chemistry, Journal of Organic Chemistry, Analytical Chemistry, Gels, Antimicrobial Agents and Chemotherapy, International Journal for Antimicrobial Agents, Molecular Microbiology, Organic & Biomolecular Chemistry, ACS Infectious Diseases (≥10), Journal of Natural Products, Biochemistry, ACS Medicinal Chemistry Letters, Bioorganic Chemistry, ACS Sensors, ACS Omega, RSC Advances, ChemBioChem, SYNLETT, ChemMedChem, Tetrahedron, Tetrahedron Letters, PLOS ONE, MedChemComm, RSC Medicinal Chemistry, Bioorganic & Medicinal Chemistry, Chemical Biology & Drug Design, Synthesis, New Journal of Chemistry, Journal of Medical Microbiology, Antibiotics, Marine Drugs, Bioorganic & Medicinal Chemistry Letters, Molecules, Future Microbiology, ARKIVOC, International Journal of Environmental Research and Public Health, Reviews in Biotechnology and Biochemistry*

### **Service at Scientific Conferences:**

- 9.) Discussion Leader, Symposium Series, 21<sup>st</sup> Florida Heterocyclic and Synthetic Chemistry (FloHet) Conference, University of Florida, 3-13-2024.
- 8.) Poster Judge, Chemistry-Biology Interface Predoctoral Training Program 2<sup>nd</sup> Annual Mini-Symposium, University of Florida. 10-14-2023.
- 7.) Poster Judge, Chemistry-Biology Interface Predoctoral Training Program 1<sup>st</sup> Annual Mini-Symposium, University of Florida. 9-24-2022.
- 6.) Organizer, Chemistry-Biology Interface Predoctoral Training Program 1<sup>st</sup> Annual Mini-Symposium, University of Florida. 9-24-2022.
- 5.) Discussion Leader, Symposium Series, 18<sup>th</sup> Florida Heterocyclic and Synthetic Chemistry (FloHet) Conference, University of Florida, 3-5-2018.
- 4.) Chair & Organizer, "Synthesis-Driven Drug Discovery" Session, 2017 UF Drug Discovery Symposium, 9-22-2017.
- 3.) Poster Judge, 93<sup>rd</sup> Florida Annual Meeting and Exposition (FAME Conference), Division of Organic Chemistry, American Chemical Society, Palm Harbor, FL. 5-6-2017.
- 2.) Chair, Session on Organic Chemistry related to Medical Chemistry & Chemical Biology (American Chemical Society, Organic Division), 92<sup>nd</sup> Florida Annual Meeting and Exposition (FAME), 5-6-2016.

1.) Oral Competition Judge, College of Pharmacy Research Showcase, University of Florida. 2-26-2014.

**Other Service to the Profession:**

1.) Provided External Letter for Dr. Alejandro Bugarin's Promotion to Associate Professor (with Tenure) at Florida Gulf Coast University. Submitted 1-2021.

**Funding Awarded:**

1R35GM153272 (NIGMS, NIH)

*"Indole Alkaloids and Halogenated Phenazines: Platforms for Discovery"*

4/1/2024 to 1/31/2029; \$1,243,350 (direct; \$1,804,799 total)

Role: PI

1R01DE032555-01A1 (NIDCR, NIH)

*"Mechanisms of Metal Ion Homeostasis of Oral Streptococci"*

9/1/2023 to 5/31/2028; \$151,970 (direct costs to Huigens lab)

PI: Lemos; Role: Co-I

Maureen Keller-Wood PROSPER Excellence Award (UF, COP)

*"Advancing Halogenated Phenazines as Broad-Spectrum Bacterial Biofilm-Eradicating Agents."*

7/1/2023 to 6/30/2023; \$40,000.

Role: PI

1R35GM128621 (NIGMS, NIH)

*"Indole Alkaloids and Phenazine Antibiotics: New Platforms for Drug Discovery"*

8/1/2018 to 3/31/2024; \$1,175,000 (direct; \$1,738,730 total)

Role: PI

1R21AI159191 (NIAID, NIH)

*"Optimization and Mechanistic Studies of Halogenated Phenazines and Quinolines as Anti-Tuberculosis Therapeutics."*

3/25/2021 to 2/28/2024; \$ 303,875 (direct; \$431,275 total award; Huigens Lab: \$55,000 direct; \$83,875 total)

Role: MPI (with K. Rohde, primary contact)

American Cancer Society Research Scholar Grant

131947-RSG-18-013-01-CDD: *"Alkaloid Ring Distortion: A Platform for New Cancer Therapies"*

7/1/2018 to 12/31/2022; \$660,000 (direct; \$792,000 total)

Role: PI; Collaborators: H. Luesch, R. Ratnayake

NHMFL User Award

*"Development of Halogenated Phenazine Prodrugs and Antibiotic Conjugates as Antibacterial Therapeutics"*

AMRIS NMR Facility, University of Florida; 8/23/2017 to 12/31/2018; \$5,000.

Role: PI

Muscular Dystrophy Association, Inc.

*"IMPEDE: Inhibition of Microsatellite Promoted Expression of Deleterious Expansions in Myotonic Dystrophy"*

8/1/2017 to 7/31/2020; \$300,000 total award (\$72,000 to Huigens Lab); PI: J. Andrew Berglund, Role: Co-I

2016-2017 College of Pharmacy Teacher of the Year (University of Florida)

Paul Doering endowment, awarded: \$2,625



NHMFL User Award

*“Structure Elucidation of Complex and Diverse Small Molecules from Vincamine Using High-Field NMR”*

AMRIS NMR Facility, University of Florida; 1/1/2017 to 12/31/2018; \$5,000.

Role: Co-PI with Mr. Verrill M. Norwood IV (graduate student)

University of Florida Research Opportunity Seed Fund Award

*“Nitroxoline Small Molecules as Cures for Persistent Bacterial Infections”*

Division of Sponsored Research; University of Florida; 6/1/2016 to 5/31/2018; \$89,000

Role: PI; Co-Investigators: G. Schultz, G. Drusano, A. Louie

1R01CA188132-01A1 (NCI, NIH)

*“Studies on Thymidylate Synthase as a Tumor-Promoting Oncogene for Development of New Allosteric Inhibitors for Cancer Treatment”* Active: 1/1/2016 to 12/31/2020; \$78,000 (direct costs to Huigens lab)

The goal of this study is to develop thymidylate synthase small molecule inhibitors as anticancer agents.

PI: Zajac-Kaye; Role: Co-Investigator

Emerging Pathogens Institute Seed Grant (University of Florida)

*“Halogenated Quinoline Small Molecules as Bacterial Biofilm Eradicating Agents”*

Emerging Pathogens Institute; University of Florida; 1/1/2015 to 12/31/2015; \$81,091

Role: PI; Co-Investigator: S. Jin

University of Florida Research Opportunity Seed Fund Award

*“Development of Potent 2,4-Dibromophenazine Antibacterial Antibiofilm Agents”*

Division of Sponsored Research; University of Florida; 6/1/2014 to 5/31/2016; \$84,000

Role: PI; Co-Investigators: S. Jin, V. Mai

American Cancer Society Postdoctoral Fellowship

119265-PF-10-117-01-CDD: *“Englerin A: Chemical Inspiration for Novel Renal Cancer Treatments”*

Highlighted: [https://www.eurekalert.org/pub\\_releases/2010-05/acs-ac051710.php](https://www.eurekalert.org/pub_releases/2010-05/acs-ac051710.php)

7/1/2010 to 3/31/2013; \$150,000 (3 years).

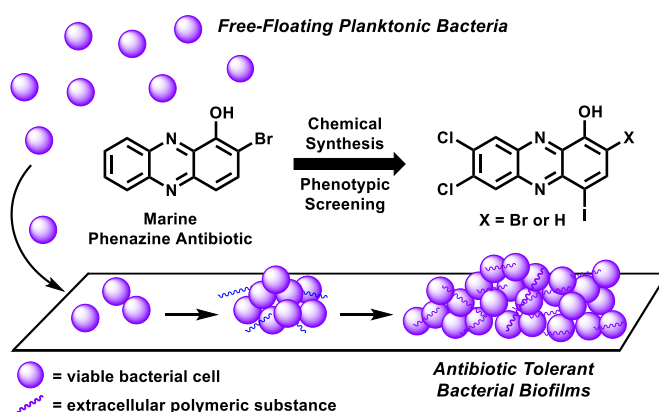
Role: PI; Mentor: P. Hergenrother

## Short Description of Research Program Highlights.

The overarching goal of our research program is to develop innovative discovery strategies to identify new molecules that can begin to address critical diseases in human health. To do this, our lab integrates synthetic organic chemistry, medicinal chemistry, chemical biology, microbiology, and molecular biology approaches to solve a number of important problems. Our lab has established two distinct natural product-inspired platforms aimed to: (1) identify new small molecules that eradicate persistent (antibiotic-tolerant), surface-attached bacterial biofilm communities, and (2) utilize indole alkaloids to rapidly synthesize diverse and complex compound libraries for biological screening relevant to malaria, opioid addiction, and cancer.

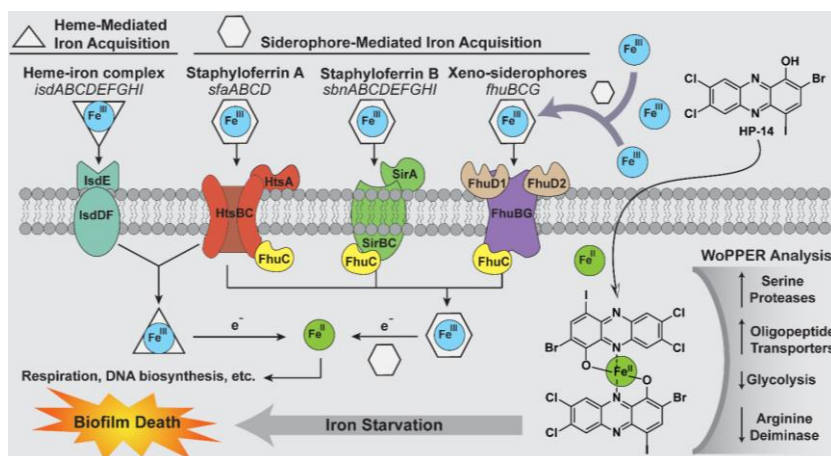
### Discovery of Halogenated Phenazines that Eradicate Bacterial Biofilms.

**A.)** We discovered a highly potent series of biofilm-eradicating agents inspired by the marine phenazine natural product 2-bromo-1-hydroxyphenazine. Impressively, our synthetic halogenated phenazine (HP) analogues were found to be >100-fold more potent than the natural phenazine compound in antibacterial assays and effectively eradicated MRSA, MRSE, and VRE biofilms through a unique mechanism. In addition, we showed that vancomycin and other front-running antibiotics used to treat MRSA infections were completely inactive in our biofilm eradication assays (using Calgary Biofilm Devices), demonstrating a unique activity profile for our HP analogues.

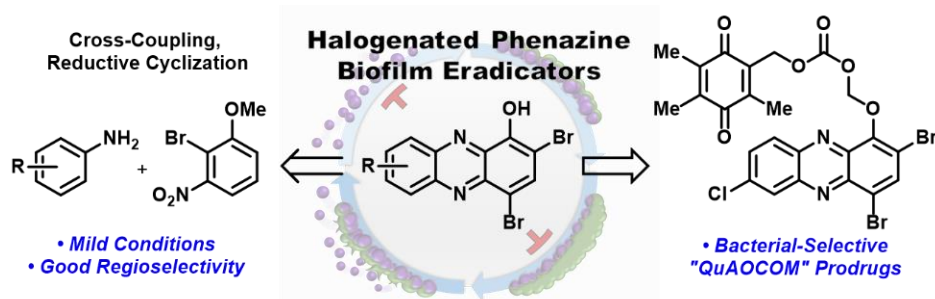


**Figure 1.** Discovery of potent halogenated phenazine biofilm eradicating agents. *Angew. Chem. Int. Ed.* **2015**, 54, 14819-14823.

**B.)** In 2018, our lab published an exciting paper where we subjected surface-attached MRSA biofilms to a potent biofilm-eradicating agent our lab previously discovered (halogenated phenazine analogue HP-14) and utilized RNA-seq technology in combination with WoPPER gene cluster analysis to determine that this small molecule was rapidly inducing iron starvation in MRSA biofilms. This platform not only allowed us to determine the mode of action for our halogenated phenazines, but also provided insights to the critical importance that iron homeostasis has on antibiotic tolerant bacterial biofilm communities. Information gained from these investigations could lead to new strategies for treating chronic and recurring biofilm-associated bacterial infections.



**Figure 2.** RNA-seq coupled with a WoPPER gene cluster analysis demonstrates that HP-14 induces rapid iron starvation in MRSA biofilms leading to eradication of these surface-attached bacterial communities. *Angew. Chem. Int. Ed.* **2018**, 57, 15523-15528.

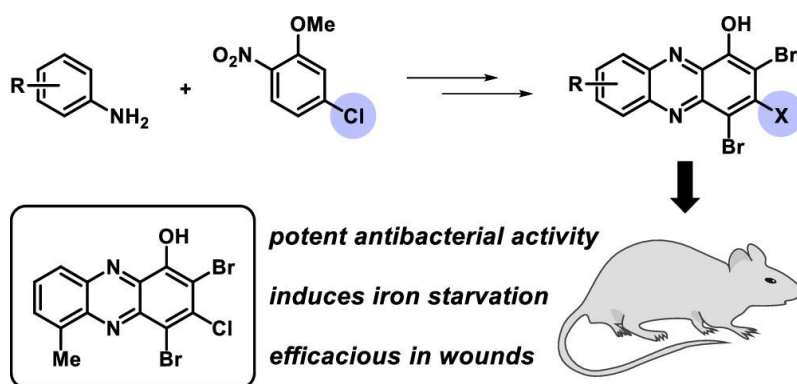


**C.)** Our lab recently developed an efficient modular synthesis to new and diverse halogenated phenazine biofilm eradicating agents using a Buchwald-Hartwig reaction, followed by a sodium borohydride reductive cyclization. This route allowed for the rapid synthesis of 1-methoxyphenazines, which were elaborated into halogenated phenazines that demonstrated

**Figure 3.** Development of a modular synthetic route to diverse halogenated phenazine compounds and diverse prodrug versions of active compounds. *J. Med. Chem.* **2018**, 61, 3962-3983.

potent biofilm-killing activities against several major human pathogens (e.g., MRSA, MRSE, VRE biofilms). In addition, we developed several prodrug motifs as we work towards translating these provocative discoveries into human therapeutic agents.

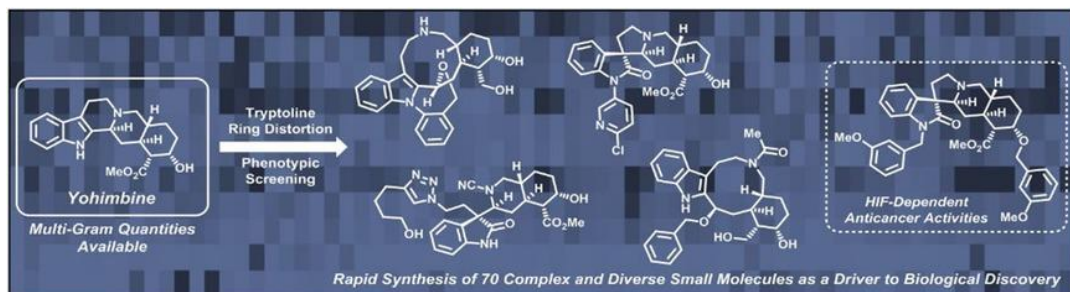
**D.)** More recently, our group reported the chemical synthesis and antibacterial assessment of a new series of analogues that incorporated functionality at the 3-position of the HP scaffold. We identified analogue HP-29 (shown in Figure 4) that demonstrates potent antibacterial activities against multiple Gram-positive human pathogens and *M. tuberculosis*. Similar to other HP's, many of the new analogues reported in this paper demonstrated incredibly potent biofilm eradication activities against a panel of pathogens. In addition, HP-29 demonstrated *in vivo* efficacy against *Staphylococcus aureus* and *Enterococcus faecalis* dorsal wound infection models in mice.



**Figure 4.** Identification of HP-29, which demonstrates potent antibacterial activities, bacterial biofilm eradication while showing good *in vivo* efficacy in wound infection models in mice. *J. Med. Chem.* **2021**, 64, 7275-7295. *Featured Article, Front Cover*

### Indole Alkaloid Ring Distortion: A Chemical Synthesis Platform for Discovery

**E.)** We have shown that yohimbine, a complex indole alkaloid available on multigram scale, is an ideal starting point for the rapid generation of complex and diverse molecules to explore new areas of chemical space. We synthesized a unique

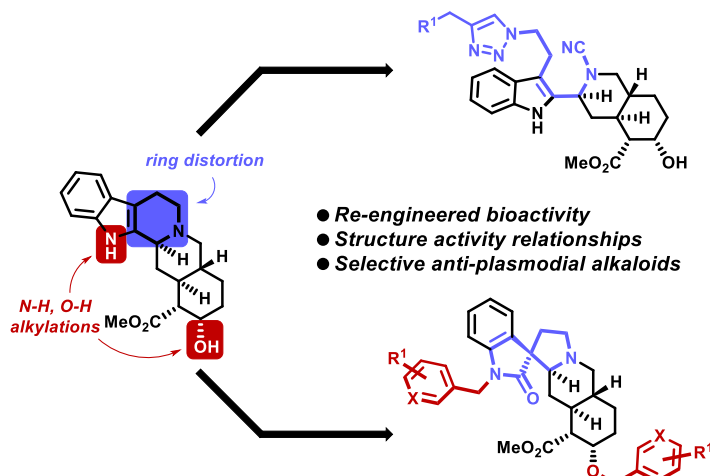


**Figure 5.** Yohimbine as a starting point for the synthesis of complex & diverse compounds to explore chemical space. *Chem. Eur. J.* **2017**, 23, 4327-4335. *Cover Art*

compound library of 70 small molecules within a diversity of complex molecular scaffold-types. Initial biological screening of this library led to the discovery of small molecule modulators (activators and inhibitors) of the Nrf2-antioxidant response element (ARE), and a HIF-dependent anticancer agent.

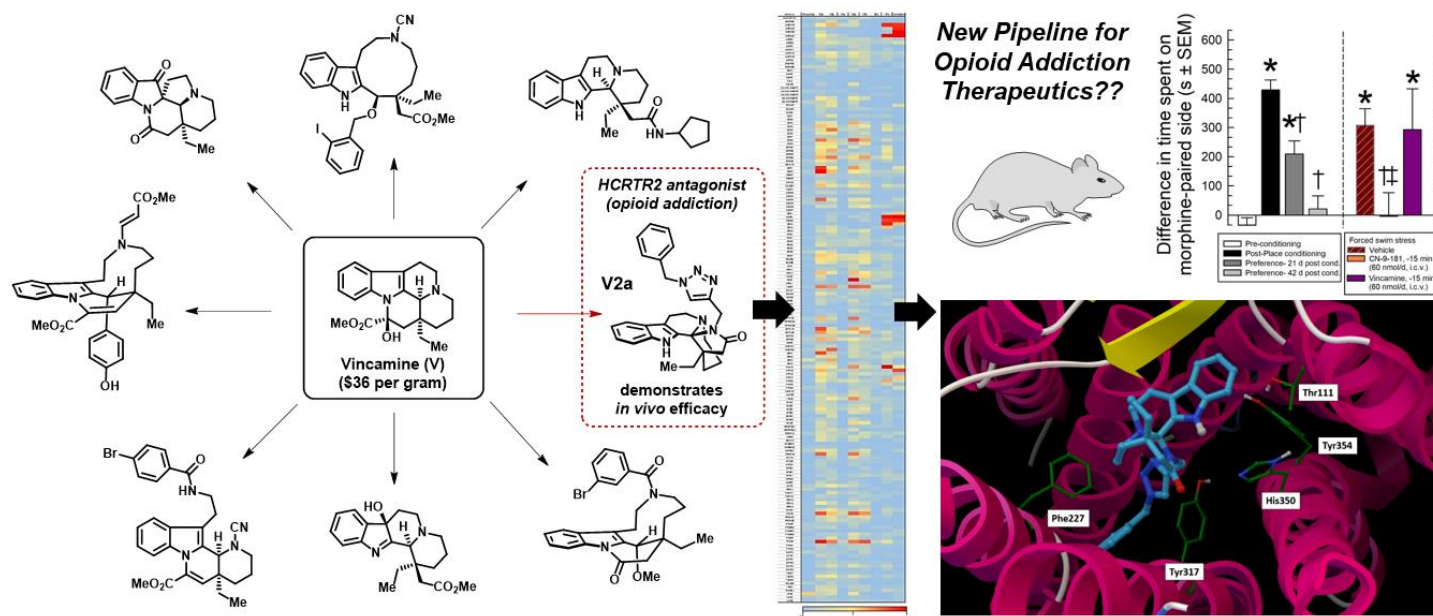


**F.)** We recently published an exciting paper in *ACS Infectious Diseases* titled “Re-engineering of Yohimbine’s Biological Activity through Ring Distortion: Identification and Structure-Activity Relationships of a New Class of Antiplasmodial Agents” (Figure 6). This work highlights our ring distortion platform, where we utilize yohimbine as starting points to rapidly synthesize complex and diverse collections of compounds for biological screening. This featured article highlights the discovery of novel antimalarial agents in collaboration with Professor Debopam Chakrabarti (UCF), which may serve as future therapeutic agents or probes to explore the biology of plasmodial parasites.



**Figure 6.** Re-engineered yohimbine analogues that demonstrate antiplasmodial activities. *ACS Infect. Dis.* **2020**, 6, 159-167. *Featured Article, Front Cover*

**G.)** The most exciting biological discovery from our indole alkaloid ring distortion platform is compound V2a, which is derived from our vincamine efforts to rapidly synthesize complex and diverse small molecules for discovery. V2a demonstrates selective antagonistic activities against hypocretin receptor 2 (HCRT2), which is a GPCR target relevant in opioid reward (Figure 7). V2a was investigated in mouse models and was shown to prevent both acute morphine conditioned place preference (CPP) and stress-induced reinstatement of extinguished morphine CPP in mice. These findings demonstrate the potential that ring distortion chemistry has towards re-engineering the biological activity of an indole alkaloid for important applications to human health. Our immediate plans are to capitalize on the encouraging findings we have had with V2a and utilize iterative rounds of computer-aided design, chemical synthesis, and biological evaluation to optimize new clinical agents to address the opioid crisis in the United States.



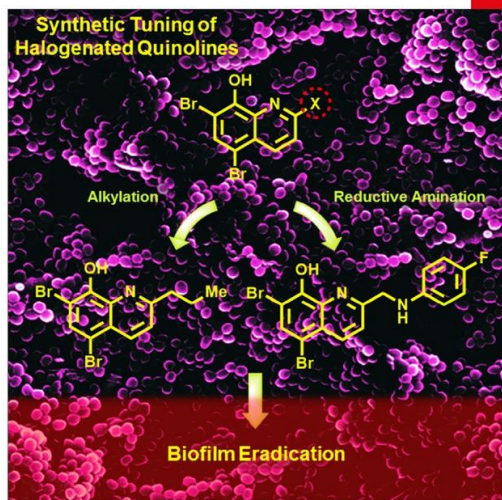
**Figure 7.** Ring distortion of vincamine and subsequent biological screening lead to the discovery of a novel compound with re-engineered activities that prevent morphine-seeking behaviors in mice. Future work is aimed to rationally design optimized analogues through the use of computational tools. *J. Med. Chem.* **2020**, 63, 5119-5138. *Front Cover*



# CHEMISTRY

A European Journal

www.chemeurj.org



2016-22/27

**Cover Picture:**  
R. W. Huigens III et al.  
Synthetically Tuning the 2-Position of Halogenated Quinolines:  
Optimizing Antibacterial and Biofilm Eradication Activities via Alkylation  
and Reductive Amination Pathways



WILEY-VCH

A EUROPEAN JOURNAL OF CHEMICAL BIOLOGY

# CHEMBIOCHEM

SYNTHETIC BIOLOGY & BIO-NANOTECHNOLOGY

Potent Biofilm Eradication

Chemistry & Life Sciences

4/2017

**Front Cover:**  
R. W. Huigens III et al.  
Identification of N-Arylated NH125 Analogues as Rapid Eradicating  
Agents against MRSA Persister Cells and Potent Biofilm Killers  
of Gram-Positive Pathogens

www.chembiochem.org

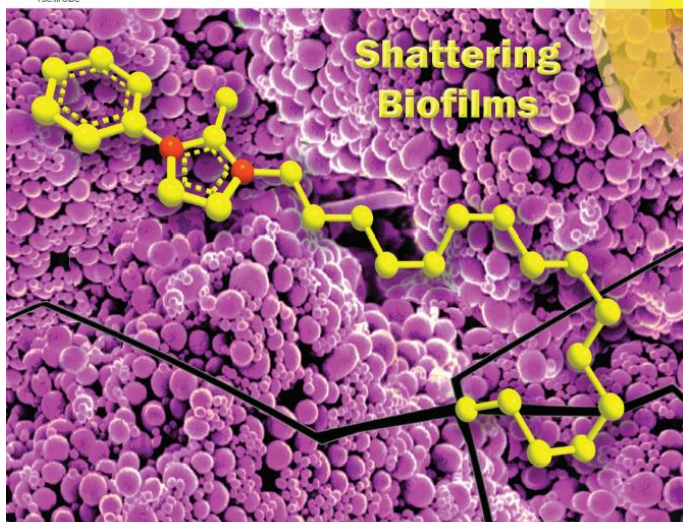
A Journal of  
ChemPubSec  
Europe

WILEY-VCH

# Organic & Biomolecular Chemistry

Volume 15 | Number 26 | 14 July 2017 | Pages 5431–5644

rsc.li/obc



ISSN 1477-0520



**PAPER**  
Robert W. Huigens et al.  
Antimicrobial peptide-inspired NH125 analogues: bacterial and fungal  
biofilm-eradicating agents and rapid killers of MRSA persisters

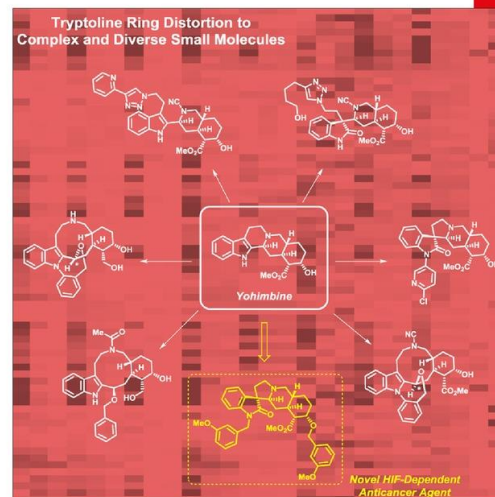
# CHEMISTRY

A European Journal

www.chemeurj.org



2017-23/18



**Cover Picture:**  
R. W. Huigens III et al.  
A Tryptoline Ring-Distortion Strategy Leads to Complex and Diverse  
Biologically Active Molecules from the Indole Alkaloid Yohimbine



WILEY-VCH



