Young Career Focus: Dr. Joshua Pierce (North Carolina State University, USA)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Joshua Pierce (North Carolina State University, USA).

Biographical Sketch

Dr. Joshua Pierce

Joshua Pierce was born and raised in northwestern Pennsylvania (USA) and obtained a B.S. with Honors in chemistry from the University of Pittsburgh (USA). Upon graduation he continued with graduate studies at the same university under the direction of Professor Peter Wipf. His research was focused on organometallic methods development, natural product total synthesis and medicinal chemistry.

After defending his thesis in the fall of 2008, Joshua moved across the country to begin postdoctoral studies with Professor Dale L. Boger at The Scripps Research Institute (USA). Research interests centered around complex natural product analogue synthesis, semi-synthesis, and antimicrobial compound development centered on the natural product vancomycin.

Together, these research experiences provided an appreciation of the important role complex molecule synthesis can play in organic chemistry, medicinal chemistry and chemical biology. Since joining NC State's Department of Chemistry (USA) in 2012, the Pierce group has focused on addressing problems in natural products synthesis and organic methods development with a constant goal of high-impact contributions at the chemistry/biology interface. In addition to developing his research program, he also became involved in the Comparative Medicine Institute at NC State where he is an Associate Director of the Emerging and Infectious Diseases Program, was named a NC State University Faculty Scholar in 2017, and in 2018 was promoted to the rank of Associate Professor with tenure.

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Dr. J. Pierce Research in the Pierce group is focused on harnessing the diverse architectures of marine natural products to inspire advances in chemical reaction development, chemical biology and therapeutic lead identification. We have built a program centered on the synthesis of natural products (with a focus on marine natural products) and their use as chemical probes to study biological processes. To accomplish the synthesis of such targets, novel reactions and/or adaptations of existing reactions are required – as well as constant evaluation of innovative synthetic strategies to construct complex organic structures in an efficient and scalable manner. As shown in Figure 1, our program is based on molecule-driven discovery: a constant feedback loop of novel chemistry, chemical biology and biology to generate new projects and exciting discoveries at the chemistry/biology interface.

SYNFORM *When did you get interested in synthesis?*

Dr. J. Pierce I became interested in organic synthesis as a sophomore undergraduate at the University of Pittsburgh. I was a pre-med student and planned to be a biological sciences major until two key things happened: 1) I fell in love with chemistry thanks to amazing professors of both honors general chemistry and organic chemistry and 2) I realized for the first time in my academic training that organic chemistry could directly contribute to the development of treatments for human disease. I was instantly fascinated by the art of organic synthesis and the beauty of complex organic structures – and immediately motivated to begin research in this area. Once in the lab, the rest was history and I have remained fascinated with this area to this day.

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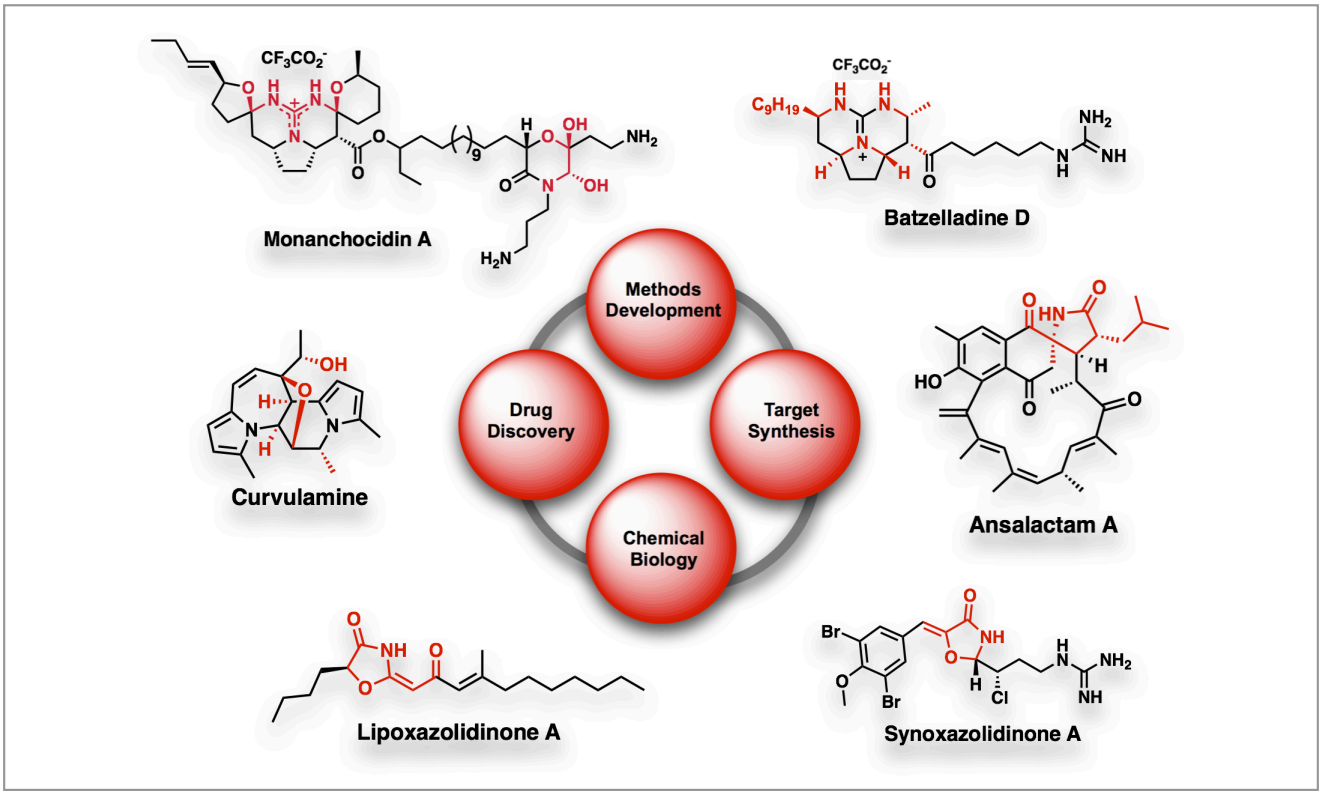


Figure 1 Representative natural products that provide inspiration for a feedback loop of discovery in organic methods, synthetic strategy, chemical biology and drug discovery in the Pierce group

SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Dr. J. Pierce Organic synthesis is thought of as a 'mature' field relative to many of the emerging areas of scientific research, yet every time I teach organic chemistry or embark on a new target molecule it reminds me how much is left to discover. The notion that we can make any molecule if provided enough resources may indeed be accurate – but as a community we are far from the efficiency and practicality that is required to address critical issues related to health, energy and the environment. Innovation in organic chemistry is thriving, and these efforts are in concert with, not in competition with, cutting-edge biosynthetic approaches to both simple and complex molecules. These two areas should work together to find innovative solutions for accessing biologically relevant compounds, as both approaches have inherent strengths and weaknesses – at least for the foreseeable future. It is these novel bioactive compounds, only available through synthesis, that provide value from the innovations in synthetic methods and strategy and thereby provide critical chemical probes for biology, with an ultimate goal of developing novel therapeutics. Synthetic organic chemistry remains the only general approach to install pinpoint modifications on complex molecules and to rapidly access diverse, non-natural molecular architectures. A variety of computational and robotic technologies may influence the approaches taken to design and execute some synthetic efforts in the future; however, organic synthesis will remain vibrant in the coming decades as the practitioners of the field continue to innovate and evolve with the changing times of science and society.

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Dr. J. Pierce As mentioned previously, our group leverages natural products to inspire innovation in organic synthesis, chemical biology and drug discovery. Of particular interest is the development of novel small molecules for the study and treatment of infectious disease. Natural products have served as a key platform for the development of antimicrobials and the development of new antibiotics is of great importance.

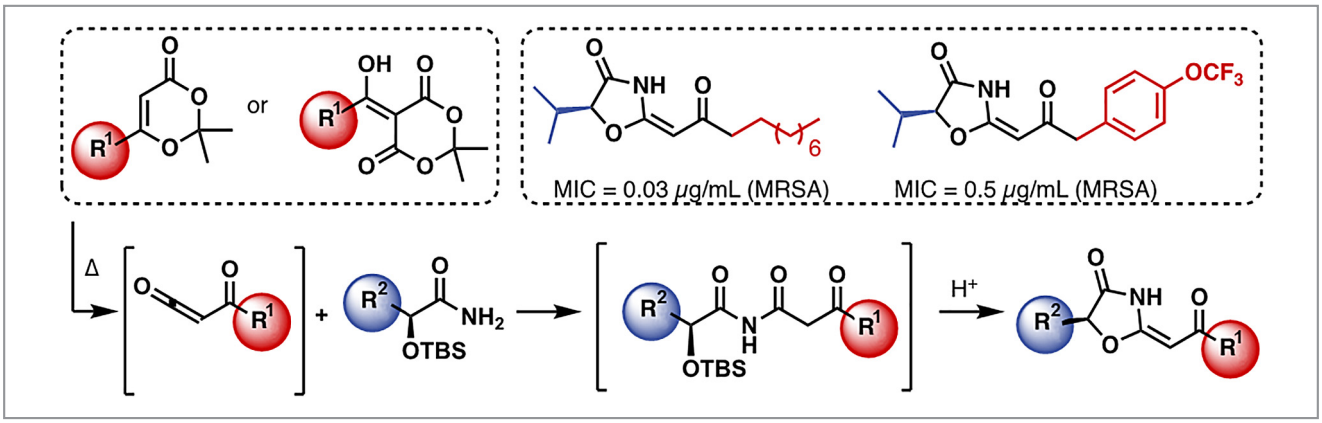
As an example of our efforts in this area, we have developed novel approaches to oxazolidinone heterocycles in our efforts toward the synoxazolidinone and lipoxazolidinone natural products. In our initial disclosure of the synoxazolidinones,[1] we presented an imine acylation protocol that can be used to prepare either 4-oxazolidinones or pyrrolidinones depending on the conditions employed, we completed a five-step total synthesis, and we revealed simplified analogues with anti-biofilm properties via a non-toxic mechanism.[2] These efforts have now been extended to an asymmetric process, the products have been derivatized via rearrangements and oxidative cleavage to prepare valuable building blocks for other classes of natural products, and we now have analogues that are significantly more potent than the natural products themselves.[3–5] Figure 1 shows some of the representative natural products that our group works toward, constantly evolving as new methods arise from our synthetic work and new biological targets are revealed through chemical biology efforts.

SYNFORM *What is your most important scientific achievement to date and why?*

Dr. J. Pierce Two key achievements stand out and both are related to infectious disease. The first is my contribution as a postdoc to the Boger lab's efforts to develop a novel analogue of vancomycin that overcomes resistance through a single atom change. I was fortunate to be the first to test our key amidine analogue and demonstrate that a long-standing hypothesis in the group was indeed accurate. These efforts have since led to many follow-up studies and may pave the way for a next-generation vancomycin in the years to come. The second is my own group's efforts to develop the lipoxazolidinone family of natural products (Scheme 1).[6] We have developed a rapid approach for their synthesis, optimized novel analogues with improved activity and have demonstrated that these 4-oxazolidinone heterocycles inhibit both protein synthesis and cell-wall biosynthesis in Gram positive bacteria. These efforts, in addition to an array of additional studies, provide the groundwork for a comprehensive effort to advance the 4-oxazolidinones as potential antibiotics. We are extremely excited at the prospect of uncovering the precise mechanisms by which these molecules function and to optimize their properties as drug leads going forward.

REFERENCES

(1) N. V. Shymanska, I. H. An, J. G. Pierce *Angew. Chem. Int. Ed.* **2014**, *53*, 5401–5404.
(2) G. A. Edwards, N. V. Shymanska, J. G. Pierce *Chem. Commun.* **2017**, *53*, 7353–7356.
(3) N. V. Shymanska, J. G. Pierce *Org. Lett.* **2017**, *19*, 2961–2964.
(4) A. Q. Cusumano, M. W. Boudreau, J. G. Pierce *J. Org. Chem.* **2017**, *82*, 13714–13721.
(5) A. Q. Cusumano, J. G. Pierce *Bioorg. Med. Chem. Lett.* **2018**, in press.
(6) J. J. Mills, K. Robinson, T. E. Zehnder, J. G. Pierce *Angew. Chem. Int. Ed.* **2018**, *57*, 8682–8686.



Scheme 1 Synthesis and development of novel antimicrobial agents based on the lipoxazolidinone natural products