Kaylen Lathrum Creighton University

# Betty A. and Donald J. Baumann Family Scholarship Fund Application Form

1. **Name and NetID**

Kaylen Lathrum, kdl36295

2. **Chemistry faculty research director**

Dr. James Fletcher

3. **Proposal title**

Regioselective annulation reactions of 1,5-diaryl-1,2,3-triazoles with quinoline and isoquinoline subunits

4. **Proposal description. Please limit the proposal to about 500 words and include figures as appropriate. Your proposal should briefly outline the overall project and its goal(s). If you have previous results related to your proposed project, concisely summarize those results and describe what you expect to accomplish during the time frame of the scholarship.**

In the Fletcher lab, we synthesize trisubstituted- 1,2,3- triazolium salts (Figure 1), a recently developed class of quaternary ammonium compounds (QAC) antiseptics.[1] The proposed antimicrobial mechanism of these compounds is derived from the N-benzylation reaction to form the salt.[2] The addition of charge and a large hydrophobic group provide a detergent-like mechanism that disrupts the cell membranes of microorganisms.[3] Using a click chemistry approach, series of trisubstituted-1,2,3- triazolium salts can be synthesized by varying subunit identities and determining potency trends across groups. Our recent study successfully prepared a family of quinoline/isoquinoline substituted triazoles. Bridged compounds were prepared via click chemistry (2A and 3A in Figure 2), and "fused-ring" analogs were made through an additional Pd-catalyzed annulation reaction[4] (2B and 3B in Figure 3). The intent of this series was to investigate a secondary mode of activation through DNA intercalation derived from the flat structure of the fused molecule. Minimum inhibitory concentration (MIC) assays were performed to determine potency of fused-ring analogs compared to unfused analogs.[5]

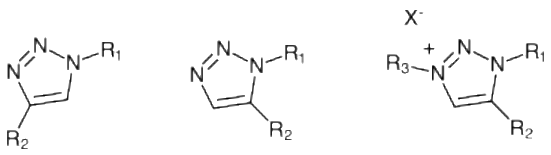

***Figure 1.*** *Examples of 1,4-disubstituted-1,2,3-triazole (left), 1,5-disubstituted-1,2,3-triazole (middle), 1,2,4-trisubstitted-1,2,3-triazolium salt (right) where $R_3$ is a tert-butylbenzyl group.*

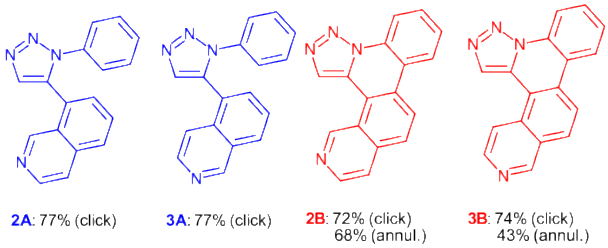


***Figure 2.*** *Examples of previously synthesized 1,5-disubstituted-triazoles. Both bridged (blue) and fused-ring (red) analogs shown.*

A significant result from the study was the unexpected potency of neutral fused-ring compounds (2B and 3B in Figure 2). Active through an unknown mechanism, these compounds do not require the final synthesis step: N-benzylation reaction of the 1,5-diaryl-1,2,3- triazole. These compounds inspired further investigation of additional regioisomers within this heterocycle family. Where previously reported 4-, 5- and 8-connected quinoline/isoquinoline rings ensured formation of only a single annulation regioisomer, the current study focuses on analogs where two annulation regioisomers are possible due to connectivity (Figure 3).

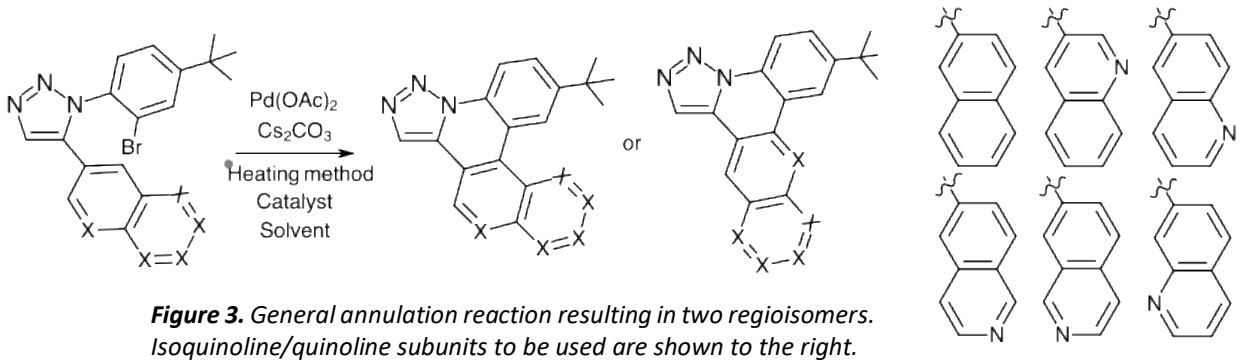


***Figure 3.*** *General annulation reaction resulting in two regioisomers. Isoquinoline/quinoline subunits to be used are shown to the right.*

This study will aim to synthesize the series of 3-, 6-, and 7- connected, fused-ring 1,5- diaryl-1,2,3- triazoles and evaluate how quinoline/isoquinoline identity and connectivity direct regioisomer distributions. Additionally, both N- and C- connected isoquinoline/quinoline analogs will be synthesized (Figure 4). Reaction conditions will be altered to determine whether annulations regioselectivity can be increased and, further, whether regioisomers can be separated. Ultimately, this study will investigate whether these previously unreported compounds can be synthesized, and in what regioisomer distribution. If successfully isolated, this generation of neutral triazoles can be subjected to MIC assays to evaluate the presence of additional potent, neutral compounds. Or, continued to the typical trisubstituted- 1,2,3- triazolium salts, compared against prior generations to determine potency trends.

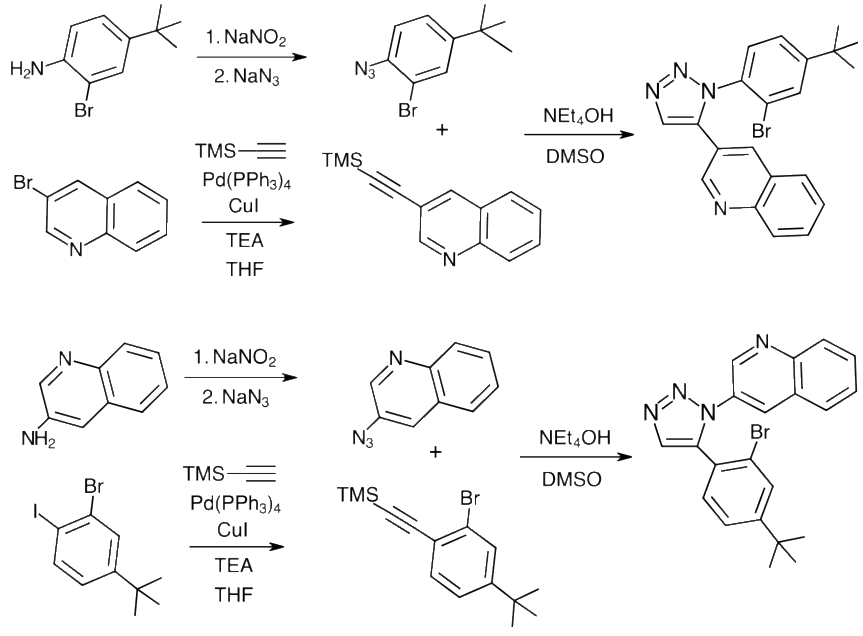


***Figure 4.*** *Reaction Scheme to synthesize brominated 1,5-diaryl-1,2,3-triazoles (precursors to annulation reaction). Both C-connected (top) and N-connected isoquinoline/quinoline analogs will be prepared.*

Already, using a multistep synthesis scheme analogous to the previous study, I have successfully prepared compounds up until annulation. Azides and alkynes were prepared via Sandmeyer[6] and Sonogashira couplings[7], respectively, from commercially available amine and bromo groups located at the 3,-6, or 7- positions of quinolines and isoquinolines. Quinoline/isoquinoline groups were each prepared to an alkyne and an azide then base-catalyzed click reactions[8] were performed between 2-bromo-4-*tert*-butylazidobenzene or 2-bromo-4-*tert*butylphenylacetylene, respectively (Figure 4). This produced a total of twelve C- and N-connected quinoline/isoquinoline 1,5-diaryl-1,2,3-triazoles. These compounds were successfully prepared in sufficient yields and characterized via $^{1}$H NMR.

Remaining work includes variation of the annulation reaction conditions: heating method (thermal vs. microwave), Pd catalyst, and solvent (Figure 3). These changes will be performed on one representative analog. Optimized conditions then applied to the entire series. Regioisomer distributions will be monitored via $^{1}$H NMR. Regioisomer separation will be attempted using automated flash columns. Analogs that can be isolated cleanly will be subjected to antiseptic studies using minimum inhibitory concentration assays and compared to compounds of our prior study.

**References**

1. Fletcher, J.T. *Bioorg. Med. Chem. Lett.* **2018**, *28* (20), 3320–3323.
2. Fletcher J.T. *Synthesis (Stuttg)* **2010**, *2010* (19), 3339–3345.
3. Minbiole, K.P.C. *Tetrahedron Lett.* **2016**, *72*, 3559–3566.
4. Wang, J. *Synlett* **2019**, *30*, 1452-1456.
5. CLSI *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*; 2015; Vol. 35.6.
6. Lejcher, C.A. *Med. Chem. Res.* **2022**, *31* (3), 474–484.
7. Lei Y, *Tetrahedron Lett.* **2016**, *57*, 1100-1103.
8. Kwok, S.W. *Org. Lett.* **2010**, *12* (19), 4217–4219.

## 5. Presentation of research results (past and future conferences, publications, seminars, etc.)

Lathrum, K.D., Hanneken, E.M., Grzelak, K.R., & Fletcher, J.T. “Pentacyclic aromatic heterocycles from Pd-catalyzed annulation of 1,5-diaryl-1,2,3-triazoles” *Accepted to Beilstein Journal of Organic Chemistry*

Lathrum, K.D. & Fletcher, J.T. “Regioisomer distributions in annulation reactions of 1,5-diaryl-1,2,3-triazoles with quinoline and isoquinoline subunits,” American Chemical Society Midwest Regional Meeting, Colombia MO (2025, poster)

Lathrum, K.D., Hanneken, E.M., & Fletcher, J.T. “Antiseptic salts from isoquinoline-substituted 1,2,3-triazoles.” Presented at multiple conferences, including:

- Gulf Coast Undergraduate Research Symposium, Houston, TX (2025, Oral by invitation through Barry Goldwater Scholarship)
    - Received: Outstanding Presentation in Biological & Synthetic Chemistry Award for recognition excellence of research and presentation during GCURS
- Nebraska Academy of Sciences, Lincoln, NE (2025, Oral)
- American Chemical Society National Meeting, San Diego, CA (2025, Poster)
- Creighton University Research Week, Omaha, NE (2025, Poster)
- American Chemical Society Midwest Regional Meeting, Omaha, NE (2024, Poster)

Lathrum, K.D. & Rivera, G., “The effect of load on femur symmetry: A test comparing bipedal and quadrupedal rodents,” Creighton University Research Week, Omaha, NE (2024, Poster)

6. **Post-graduate plans (job market, graduate school, medical school, etc.)**

I plan to attend graduate school and earn my PhD in chemistry. Ultimately, I wish to pursue a career in academia that involves both teaching and research.

7. **Number of semesters involved in research, including current semester (summers count as two semesters)**

10

8. **Anticipated graduation date**

May 2026