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

1. **Name and NetID**

   Connor Price
   CAP86582

2. **Chemistry faculty research director**

   Dr. James Fletcher

3. **Proposal title**

   Chemosensing Properties of Tridentate Aminopyridine Click Chelators

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.**

   Proposal is attached.

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

   1. Connor Price and James T. Fletcher. "Determination of 1,4-disubstituted-1,2,3-triazole Fluorophore Chemosensors" poster presentation at the 2023 Creighton University Research Week/St. Albert Day poster event, Creighton University, March 28, 2023.
      Top Physical/Natural Sciences Poster

   2. Connor Price and James T. Fletcher. "Determination of 1,4-disubstituted-1,2,3-triazole Fluorophore Chemosensors" poster presentation at the Omaha American Chemical Society Poster Presentation event, Creighton University, July 6, 2023.

   3. Connor Price and James T. Fletcher. "Chelating Aminopyridyltriazoles as Fluorescent Chemosensors" poster presentation at the 2023 Creighton CURAS Summer Undergraduate Research Fellowship Poster Symposium, Creighton University, September 6, 2023.

   4. Connor Price and James T. Fletcher. "Chelating Aminopyridyltriazoles as Fluorescent Chemosensors" poster presentation at the 2023 American Chemical Society Midwest Regional Meeting SciMix poster event, St. Louis, MO, October 18, 2023.

   5. Connor Price and James T. Fletcher. "Chelating Aminopyridyltriazoles as Fluorescent Chemosensors" poster presentation at the 2023 Ferlic Fellows poster event, Creighton University, October 24, 2023.

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

   Graduate School in Chemistry (organic)

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

   8 semesters

8. **Anticipated graduation date**

   May 2024

Chemosensing Properties of Tridentate Aminopyridine Click Chelators

Background

Heavy metal contamination has been an environmental issue in the U.S. for decades, including here in Omaha where soil lead levels were recently among the highest in the nation. Lead overexposure is associated with adverse effects on child development, alongside a host of other negative health risks.[1] The toxicity of heavy metals raises the need for new practical methods of detection that do not involve the use of expensive, elaborate instrumentation or extensive training in the field. Chemosensors are small molecules that produce a physical and observable change when exposed to their target analytes.

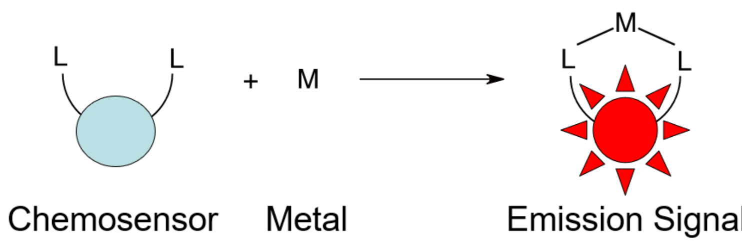

Figure 1. Example of a chemosensor mechanism

Chemosensors operating via chelation mechanisms are known for toxic metals such as lead, cadmium, and mercury,[2] but there is an ongoing need to develop new chemosensing tools with improved selectivity, sensitivity, and portability. Ideally, a chemosensor for a toxic metal would be selective, effective at concentrations relevant to its toxicity in the environment, and its output could be read by eye using a simple setup.

Previous Work

My previous work in the Fletcher lab involved extensive research into bidentate triazole chelators. Forty-nine analogs were synthesized and screened against seventeen different metals. This

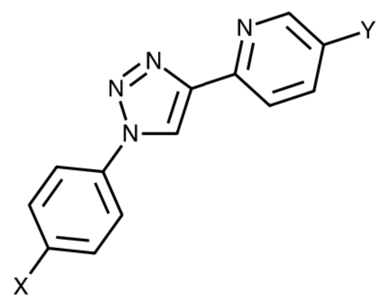

Figure 2. A bidentate chelator with X and Y representing possible functional group modification sites. A metal can bind between the nitrogen atoms, analogous to the example in Figure 1, causing an increase in fluorescence.

high-throughput method allows compounds of interest to be "found" much more efficiently than they could be designed and studied one at a time.[3,4] These screenings led to the determination of several highly selective iron cation fluorescent-based chemosensors, shown in green in Table 1. It also revealed relationships between the structure of triazole chelators and how they fluoresce when chelated with a metal.

Table 1. All synthesized bidentate chelator analogs. Highly selective and sensitive chemosensors for iron cations are shown in green, moderate chemosensors in yellow, and poor chemosensors in red.

Y Group	X Group
H	H
H	NH_2
H	OCH_3
NH_2	H
NH_2	NH_2
NH_2	OCH_3
OCH_3	H
OCH_3	NH_2
OCH_3	OCH_3
NH_2	Cl
NH_2	CH_3
NH_2	$COCH_3$
NH_2	CH_2CH_2OH
NH_2	SO_2NH_2
NH_2	$CO_2CH_2CH_3$
CO_2CH_3	H
CO_2CH_3	NH_2
CO_2CH_3	OCH_3
NO_2	H
NO_2	NH_2
NO_2	OCH_3
NH_2	$OCH_2CH_2OCH_3$
NH_2	OEtOEtOMe
CO_2Et	H
CO_2Et	OCH_3
NH_2	Naphthalene (C1)
NH_2	Naphthalene (C2)
COOH	H
COOH	OCH_3
NH_2	COOH
H	Pyrene (C1)

Proposal

During the end of the 2023 summer and this fall semester I have been exploring tridentate triazole chelators. These tridentate compounds contain a three-nitrogen binding pocket which allows for new metal interactions. I have taken the same high-throughput approach used for the bidentate chelators and applied it to tridentate chelators. Preliminary results show selective and sensitive

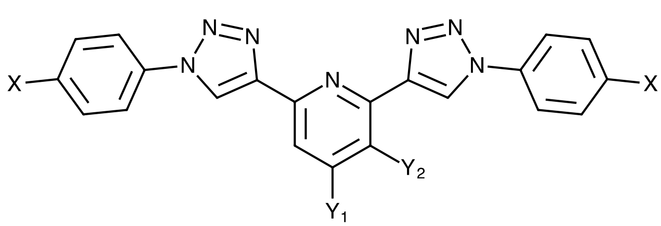

Figure 3. Tridentate chelator. An NH_2 is attached at either Y_1 or Y_2. X can be a variety of groups as outlined in Table 2.

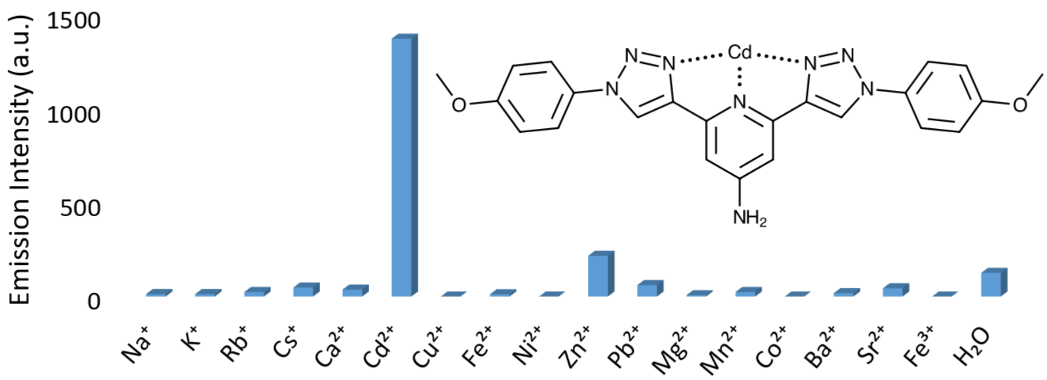

Figure 4. Fluorescence emission intensity at 350 nm of a tridentate chelator with NH_2 at the Y_1 position and OCH_3 as X. This analog serves as a cadmium chemosensor.

interactions with zinc and cadmium. Six proposed analogs for spring 2024 research are shaded grey in Table 2. These analogs were chosen because they have already been synthesized with a Y_1 NH_2 but not a Y_2 NH_2. Synthesis of the Y_1 NH_2 analogs was successful, and they were viable chemosensors for cadmium and zinc. Therefore, synthesis of the Y_2 NH_2 analogs should be successful, and they will hopefully serve as improved chemosensors. Overall, there are three separate reaction steps that must occur to create the desired tridentate chelators. First, a bromopyridine is reacted with TMS-acetylene to create a TMS-protected alkyne-functionalized pyridine in what is called a Sonogashira coupling.[5] Second, a Sandmeyer reaction takes place between an aniline and sodium azide to create an azide-functionalized arene.[6] Lastly, the alkyne and azide are clicked together using a paired click and deprotection reaction.[7] Once

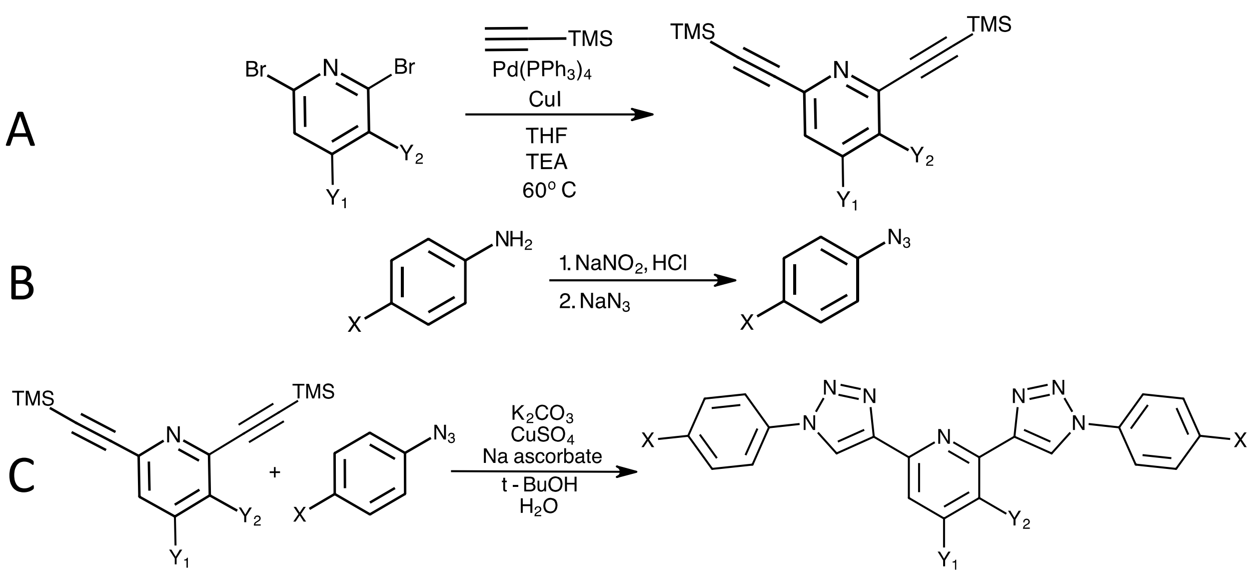

Figure 5. Sonogashira coupling (A), Sandmeyer reaction (B), paired click and deprotection reaction (C)

the six proposed analogs are synthesized using these methods, they will be purified using a CombiFlash NEXTGEN 100 chromatography instrument. One millimolar sensor solutions of the analogs will then be prepared and they will be chelated with ten millimolar metal solutions of Na^+, K^+, Rb^+, Cs^+, Ca^{2+}, Cd^{2+}, Cu^{2+}, Fe^{2+}, Ni^{2+}, Zn^{2+}, Pb^{2+}, Mg^{2+}, Mn^{2+}, Co^{2+}, Ba^{2+}, Sr^{2+}, and Fe^{3+} in a 2:1 metal to sensor ratio (200 µL of 1 mM sensor solution and 40 µL of 10 mM metal solution) in a 96-well plate. Fluorescence emission scans will be ran with excitations at 275 nm and 350 nm with emissions from 300-700 nm and 375-700 nm, respectively. Six sensors with seventeen metals with a water control will yield 108 unique results. Out of all these possible results, we hope to identify more selective and sensitive metal chemosensing molecules.

Table 2. Synthesized analogs of tridentate chelators. Shaded analogs are proposed.

NH_2 at Y position 1 or 2	X Groups
1	CH_2CH_2OH
1	CH_3
1	OCH_3
1	H
2	CH_2CH_2OH
2	CH_3
2	OCH_3
2	H
1	Cl
1	NH_2
1	COOEt
1	$OCH_2OCH_2OCH_3$
1	Napthalene (C1 attachment)
1	Napthalene (C2 attachment)
2	Cl
2	NH_2
2	COOEt
2	$OCH_2OCH_2OCH_3$
2	Napthalene (C1 attachment)
2	Napthalene (C2 attachment)

References

(1) Wodtke, G. T.; Ramaj, S.; Schachner, J. Toxic Neighborhoods: The Effects of Concentrated Poverty and Environmental Lead Contamination on Early Childhood Development. *Demography*. **2022**, *59*, 1275-1298.

(2) Kim, H. N.; Ren, W. X.; Kim J. S.; Yoon, J. Fluorescent and Colorimetric Sensors for Detection of Lead, Cadmium, and Mercury Ions. *Chem. Soc. Rev.* **2012**, *41*, 3210-3244.

(3) Cleemann, F.; Kum-Cheung, W. L.; Karuso, P. Combinatorial Synthesis of New Fluorescent Scaffolds using Click Chemistry. *Tetrahedron Letters*. **2022**, *88*, 153520.

(4) Christensen, J. A.; Fletcher, J. T. 2-(1,2,3-Triazol-4-yl)pyridine-containing Ethynylarenes as Selective "Turn-on' Fluorescent Chemosensors for Ni(II). *Tetrahedron Letters*. **2014**, *55*, 4612-4615.

(5) Chinchilla, R.; Nájera, C.; The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry. *Chem. Rev.* **2007**, *107*, 874-922

(6) Bräse, S.; Gil, C.; Knepper, K.; Zimmerman, V. Organic Azides: An Exploding Diversity of a Unique Class of Compounds. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240.

(7) Rostovtsev V. V.; Green L. G.; Fokin V.V.; Sharpless K.B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599.