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Green Research Group

**Overview**. The Green Research Group works at the intersection of Chemistry, Biology and Physics and provides extensive training and collaborative opportunities for students in our program. The Green Research Team, led by PI Kayla N. Green, employs organic and inorganic synthetic methods along with spectroscopic/analytical techniques to target current challenges in biomedicine and chemical industry. Collaborations complement this work and include cellular biology, physical inorganic methods, and imaging techniques. Our studies grow from the foundation of developing a fundamental physical organic and inorganic understanding of the properties and chemical reactivity of modified pyridinophanes. Current applications of our work include the development of small molecules that can target diseases that involve oxidative stress and/or metal-ion mis-regulation, such as Alzheimer's. Another interest is the development of a new class of metal-based complexes that can be used to study and ultimately optimize C-C and C-H transformations in organic chemistry. We are also exploring routes to make new pyridinophanes apply this to producing antioxidant biomimetics and polymer materials. We currently have funding from the **NIH** (NIGMS), **ACS PRF**, and **Welch Foundation** to support this work.

## Expanding the Structural Scope of the Pyridinophane Scaffold

The 12-membered tetra-aza pyridinophane $^{H}$**PyN$_3$** (1=1,4,7,10-tetraaza-2,6-pyridinophane, Figure 1) has been in the chemical literature for over 30 years.[1-2] Metal complexes derived from $^{H}$**PyN$_3$** and substitutions on the secondary amines are abundant and have been studied extensively in catalysis, imaging (PCTA), and therapeutics. Advantages of using pyridinophanes include water solubility, biocompatibility, stability, and strong interactions with earth abundant metal-ions.

**The Green Research Group works along the central theme that the full potential of pyridinophanes is not yet realized given that substitutions to the pyridine have not been systematically explored.**

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Modifications to the pyridine ring of 12-membered $PyN_3$ pyridinophanes *were* limited to one example in the chemical literature when we started work in this area but have since been expanded to $^{CH3O}$**PyN$_3$**, $^{p\text{-}OC6H4Br}$**PyN$_3$**, and $^{Br}$**PyN$_3$** by others.[3-4] We added $^{OH}$**PyN$_3$** and $^{OH}$**Py$_2$N$_2$** as potential therapeutics for neurodegenerative diseases involving oxidative stress, (discussed below). We observed that the majority of 12-membered, 4-substituted $PyN_3$ pyridinophanes reported up to 2019, with the exception of $^{Br}$**PyN$_3$**, were limited to electron donating functionalities, which can be attributed to the synthetic challenges associated with the electrophilic character at the 4-position of the pyridine ring. However, we were able to strategically overcome these challenges and engineer synthetic pathways to access pyridinophane congeners with electron withdrawing groups: $^{NO2}$**PyN$_3$**, $^{CN}$**PyN$_3$**, $^{Cl}$**PyN$_3$**, $^{CF3}$**PyN$_3$**, (*J. Org. Chem*. **2020**, *85*(7), 4988–4998). We have also recently produced $^{I}$**PyN$_3$**, $^{Cl}$**Py$_2$N$_2$**, and $^{I}$**Py$_2$N$_2$** *en route* to using pyridinophanes for a new area of exploration that we hope to report on soon. As a means of methods development, we also produce the N,N,N-type pincers of each pyridine substitution (*Dalton Trans.* **2020**, *49*, 2356-2363). We compliment the synthesis of these molecules with fundamental studies of the p$K_a$ and log $\beta_{Mn(II)L}$ (M = Mn, Fe, Ni, Cu, Zn) to delineate the impact of substitutions to the pyridine ring (*Dalton Trans*. **2019**, *48*, 12430-12439).

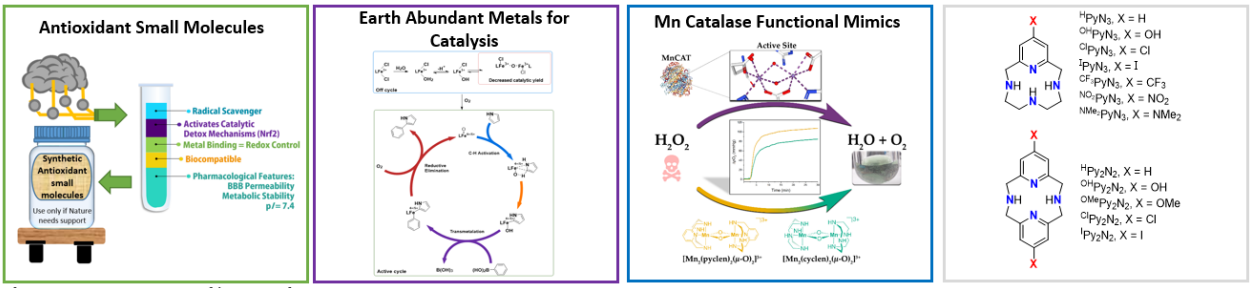


**Figure 1**. Recent areas of interest for our team.

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## Development of Chemistry to Combat Oxidative Stress

The Green Lab specializes in developing small molecules that uniquely target oxidative stress from multiple pathways (Figure 2). Molecules resulting from this work are currently being explored as potential therapeutics for **Alzheimer's** and other neurodegenerative diseases. For example, molecules $^{H}$**PyN$_3$** and $^{HO}$**PyN$_3$** disrupt and prevent the Cu(II)-induced formation of beta-amyloid plaques *in vitro* by binding copper ions (***ACS Chem. Neurosci***. **2012**, *3*, 919-927; ***Chem. Commun***. **2013**, *49*, 2712-2714). New molecules with potential to treat neurodegenerative diseases continue to be reported as well (***Metallomics***, **2014**, *6*, 2072-2082). Our most recent molecule ($^{HO}$**Py$_2$N$_2$**) exhibits both positive pharmacological features and potent antioxidant activity due to direct (radical quenching, N-oxide formation, and metal binding) and catalytic antioxidant mechanisms (activation of the Nrf2 pathway) (***Inorg. Chem.*** **2019**, *58*(24), 16771–16784). We are also now working with Dr. Hongli Wu (UNTHSC) and seeing very positive results in diseases of the eye (**cataracts** and **age-related macular degeneration**) as well. Publications from this new avenue of focus are forthcoming.

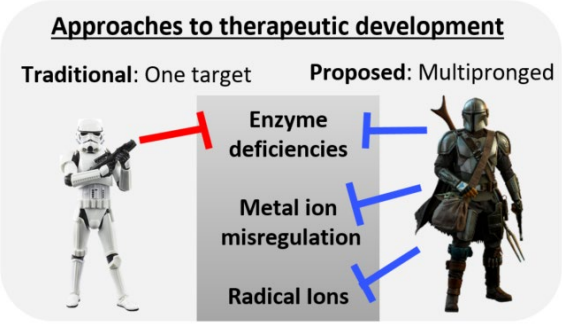


**Figure 2**. We aim to use synthetic chemistry and analytical and biological methods to identify small molecules that can rebalance ROS using a multipronged approach.

## Turning Chemical Catalysis Green

The Green Lab is working to develop 'greener', versatile earth abundant transition metal catalysts that transform hydrocarbons into usable chemicals with oxygen or hydrogen peroxide as oxidants. This approach would result in catalytic processes with lower toxicity and safety concerns, decrease in overall costs, and improved efficiency compared to current catalytic hydrocarbon manipulations. Specifically, PI Green showed that a series of iron pyridinophane complexes could catalyze C-C coupling reactions (***Inorg Chim Acta*** **2018,** *478*, 139-147). In a collaborative project, The Green Group and Dr. Tim Hubin's Team (SWOSU) defined key characteristics (Figure 3) that provided increased yields in C-C coupling reactions (***Inorg. Chem.***, **2018**, *57* (15), 8890–8902). A direct correlation between catalytic yields and the iron(III/II) redox potential of the C-C coupling catalyst was observed along with the need for two open coordination sites, something previously unrealized in the chemical catalysis community for this type of chemistry. We are building on this work through details related to the coordination chemistry (***RSC Adv*****, 2020**, *10*, 31165-31170) and mechanistic studies related to the C-C coupling reaction as well (manuscript submitted). In this latter work, it is clear that Fe-O-Fe dimers serve as off-cycle species that detract from the catalytic cycle. Mechanistic studies related to the C-C coupling reaction have also been elucidated very recently (***Organometallics***, **2021**, *40(*15), 2467–2477) as well.

## Pyridinophane Scaffolds Can Support and Control Mn(CAT) Reactivity

Examples of manganese containing metalloenzymes include manganese catalase (MnCAT), superoxide dismutase, and the oxygen-evolving complex within photosystem II. The relevance of these enzymes to the energy industry and medicinal interests has been inspiration for studies of the many manganese small molecules in the chemical literature.[5] Binuclear manganese-oxo ($Mn_2O_2$) bridged species with a range of manganese oxidation states provide a rich history as models for the oxygen-evolving complex in photosystem II, many of which utilize N-rich tetra-aza macrocycles as ligands. However, a smaller subset of manganese complexes have been isolated and reported to catalyze the $H_2O_2$ disproportion reaction in a monomeric form; only a few of the examples function in aqueous solution and in a range of pH values.[6-9] Interest in these types of complexes remains high due to their potential to serve as antioxidants for the treatment of diseases involving excess ROS and inflammation.

Recent reports of mononuclear 12-membered Mn(II)**Py$_2$N$_2$** complexes that were functional mimics of

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MnCAT for the decomposition of $H_2O_2$ motivated the synthesis and study of Mn(cyclen) and Mn(**$PyN_3$**) complexes (***Inorg. Chem. Front*. 2020**, *7*, 1573-1582). We found them to be moderate MnCAT functional mimics in aqueous solutions. The pH dependent TON and TOF achieved with the two structures suggested that electronic differences in the ligand may play a role in the catalytic cycle, with the pyridine containing systems being superior – a point we are now exploring in depth. Moreover, we observed through spectroscopic methods that the catalyst is likely a μ-oxo species such as $[Mn_2(\mathbf{PyN_3})_2(\mu\text{-}O)_2][ClO_4]_3$ (Figure 1) but decomposes over time. PI Green would ultimately like to expand this work to oxidation catalysts and will use the foundational knowledge from this system to lay the groundwork for those future studies.

## Outlook

We have invested heavily in developing synthetic methods that allow access to pyridine modified 12-membered tetra-aza pyridinophanes. With this foundation, we can now make a strong pivot toward application focused chemistries. We will continue our focus on therapeutics for oxidative stress but are expanding our opportunities through collaboration to include diseases of the eye in addition to the brain. Moreover, our interests in biomimetic chemistry (MnCAT) are now growing and preliminary results for reactivities of other protective metalloenzymes are exciting to our team.

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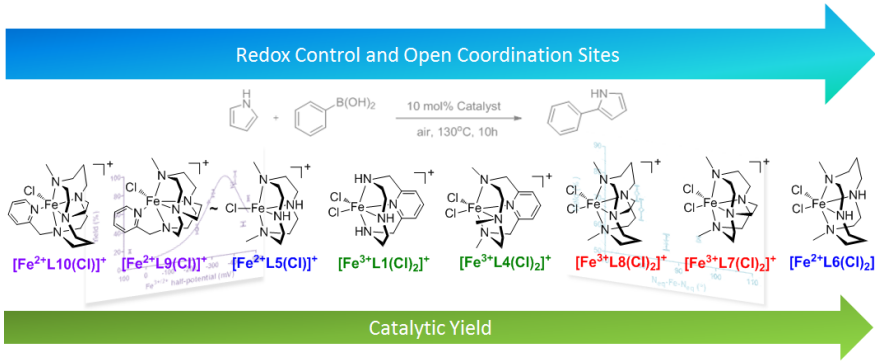


**Figure 3**. C-C coupling by non-heme iron catalysts can be controlled with redox tuning and coordination chemistry.