CHEM4710

Project in Chemistry or Biochemistry

2021/2022 Project Presentations

April 9th, 2022

University of Manitoba
205 Armes Building

University of Manitoba

Program:

9:30 am	**Introduction**	Dr. Mario Bieringer (course coordinator)	
	Opening Remarks	Dr. Steve Whyard (Associate Dean Research)	

Time	Presenter	Title	Page	Supervisor
Session 1:				
9:40 am	Matthew W. Kirby	*The in silico Study of Aryl Hydrocarbon Receptor Activation* ABSTRACT	*2*	Dr. J. Stetefeld
10:00 am	Arqum Shami	*Optimization of Electrode Formulation for Lithium Sulfur Batteries* ABSTRACT	*3*	Dr. C. Kuss
10:20 am	Kaitlin A. Isfeld	*Developments in the Remote Functionalization of Conjugated Carbonyl Compounds through Radical Bromination* ABSTRACT	*4*	Dr. R. Davis
10:40 am		**Coffee Break**		
Session 2:				
11:00 am	Rodrigo Unat	*Biophysical analysis of salt effects on the folding of Paratox, a Group A Streptococcus prophage protein* ABSTRACT	*5*	Dr. M. Khajehpour
11:20 am	Amelia Kacperkiewicz	*Synthesis and Characterization of Divalent Group 10 Metal Complexes Supported by Benzannulated N^N^O⁻-Coordinating Ligands* ABSTRACT	*6*	Dr. D. Herbert
11:40 am	Andrew L. Laluk	*The Synthesis of Adenylyl Cyclase 6 (AC6) Selective Forskolin Analogues for the Treatment of Persistent Pulmonary Hypertension of the Newborn (PPHN)* ABSTRACT	*7*	Dr. J. Sorensen
12:00 pm		**Lunch Break**		
Session 3:				
1:00 pm	Alex Prefontaine	*Towards the Metabolic Usage of Fluorinated Proline* ABSTRACT	*8*	Dr. N. Budisa
1:20 pm	Hajrah A. Ata	*Synthesis of Isocoumarin Analogues* ABSTRACT	*9*	Dr. J. Sorensen
1:40 pm	Quinn Neale	*Structure-Activity Relationships of Lipid Modifications on Polycationic Adjuvants* ABSTRACT	*10*	Dr. F. Schweizer
2:00 pm	Spare slot			
2:20 pm		**Closing Remarks**		
2:30 pm		**End of Event**		

The *in silico* Study of Aryl Hydrocarbon Receptor Activation

Matthew Kirby (Stetefeld Group)

The Aryl hydrocarbon receptor (AhR) is a ligand binding transcription factor of the Per-ARNT-Sim (PAS) superfamily known to function as a sensor of xenobiotic ligands. The AhR has the ability to bind and respond to a variety of environmental pollutants, chief among these are polycyclic aromatic hydrocarbons (PAHs) and halogenated aromatic hydrocarbons (HAHs). These compounds pose a serious risk to not only human health but also aquatic organisms and ecosystems through the activation of AhR mediated pathways[1,2]. Here, we report on the establishment of an *in silico* pipeline to discriminate between AhR active and inactive compounds in zebrafish. This pipeline combines homology modeling of the AhR ligand binding domain, a rigid body batch docking protocol, and anisotropic thermal diffusion (ATD) simulations in order to make these discriminations. The results generated by the pipeline allowed for insights to be made into the activation mechanism of the AhR as well as the actions of specific classes of compounds by way of a clustering analysis. These results contribute towards a deeper understanding of AhR-ligand interactions paving the way for the design of AhR modulating drugs as well as predictive models of AhR based environmental toxicity.

References

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Optimization of Electrode Formulation for Lithium Sulfur Batteries

Arqum Shami (C. Kuss Group)

The development of future advanced energy-storage systems must fulfill several requirements. They must be low cost, have a high energy density, high power, long cycle life, safe operation, and be environmentally benign. Lithium-sulfur batteries have long since been believed to be a cheaper, suitable alternative to Lithium-ion batteries, checking all the previous requirements. Lithium-sulfur technologies however are plagued with their own set of issues, such as low sulfur loading content, poor conductivity, and the polysulfide shuttle effect which causes slow reaction kinetics, short cycle life, and poor battery stability[1,2]. To improve upon these shortcomings, conventional auxiliary materials such as battery binders and conductive additives, which are performance bottlenecks, are being explored. Binders must strongly adhere to and maintain a connection of cathode active material to the current collector all while providing mechanical stability, while conductive additives improve the conductivity of electrode active material[3]. Herein this presentation we introduce electrode formulations to improve upon the existing Lithium Sulfur technology. Electrode slurries were prepared with a wide range of sulfur, carbon, and binder content. Slurries were then cast and tested using contact angle measurements, wetting tests, impedance spectroscopy, and electrochemical methods. The application of a conducting polymer, cellulose-based binder within Lithium-Sulfur cells was also explored.

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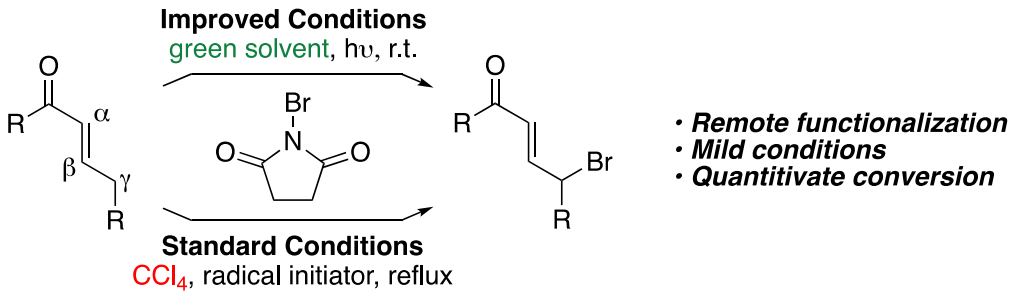
Developments in the Remote Functionalization of Conjugated Carbonyl Compounds through Radical Bromination

Kaitlin Isfeld (Davis Group)

Highly functionalized carbonyl compounds are direct precursors to a range of biologically relevant small molecules, yet methods for the functionalization of unsaturated carbonyl compounds at remote positions remain limited. By taking advantage of the allylic nature of the γ-position of α,β-unsaturated carbonyls, the radical Wohl-Ziegler bromination reaction can be employed to accomplish this transformation using N-bromosuccinimide (NBS). Despite traditional procedures for the Wohl-Ziegler reaction being both harsh and toxic, the method remains commonly utilized. In this research, a greener, room-temperature, photochemical bromination procedure has been developed and the scope of the optimized reaction conditions assessed on a range of unsaturated carbonyl compounds. To achieve a greater understanding of the observed reactivity, both computational and mechanistic studies have been completed.



Biophysical analysis of salt effects on the folding of Paratox, a Group A *Streptococcus* prophage protein

Rodrigo Unat (Khajehpour Group)

The ability of salts to induce effects on the stability and folding of proteins has been well known. However, a complete description on why various salts have distinct effects on biomolecules still eludes modern researchers. In this project we have investigated Hofmeister salt effects observed in the folding thermodynamics of a prophage protein called Paratox (Prx). Prx is a highly conserved bacteriophage protein that is encoded adjacent to a toxin or virulence gene of *Streptococcus pyogenes* (Group A streptococcus or GAS)[1]. It serves as a negative regulator of ComRS, a quorum-sensing system responsible for the exogenous DNA uptake machinery in streptococci bacteria. Using steady-state fluorescence spectroscopy, we have monitored the conformational changes of paratox in the presence of different Group1 and 2 chloride salts via measuring the intrinsic fluorescence of the tryptophan residue in a mutant F31W strain. The change in free energy (ΔG) was also calculated based on spectrophotometric data. It has been determined that the Prx folds into its monomeric state in a salt-specific manner; that is, different salts within the same group have different effects on the folding of paratox.

Interestingly, we have observed for the first time that paratox assembles into large amyloid aggregates when subjected into high divalent salt concentration. This finding is compelling because amyloids are commonly observed in bacterial inclusion bodies, a compact structure of accumulated misfolded proteins known to have intrinsic cytotoxic property to its bacterial host[3]. In order to observe *in vitro* folding of Prx from its native monomeric state into fibril aggregates, we used a fluorescent probe called thioflavin-T (ThT).

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Synthesis and Characterization of Divalent Group 10 Metal Complexes Supported by Benzannulated N^N^O$^-$-Coordinating Ligands

Amelia Kacperkiewicz (Herbert Group)

Divalent, Group 10 transition metal complexes with emissive and long-lived excited states have gained renewed interest over the past decade thanks to their potential use in a wide array of applications.[1-3] Due to the high spin-orbit coupling constant of Pt(II), the triplet excited state is more long-lived than in 3d transition metals,[4] but there are inventive applications emerging using 3d metal analogs.[5] Using effective ligand design, these photophysical properties can be enhanced. In this work, Pt(II), Pd(II), and Ni(II) complexes supported by novel tridentate, pincer-type σ-donor and π-acceptor ligands have been targeted, with the aim of extending charge-transfer excited state lifetimes. Namely, rigid Schiff base, phenanthridine-based *N^N^O(H)* ligands were synthesized and coordinated to metals. While analogous quinoline-based ligands[6] have been studied, benzannulation is anticipated to shift the emission thanks to the increased rigidity of the extended π-system.[7] The preparation and properties of a series of Pt(II), Pd(II), or Ni(II) complexes, including the formation of an unexpected paramagnetic octahedral species, will be discussed.

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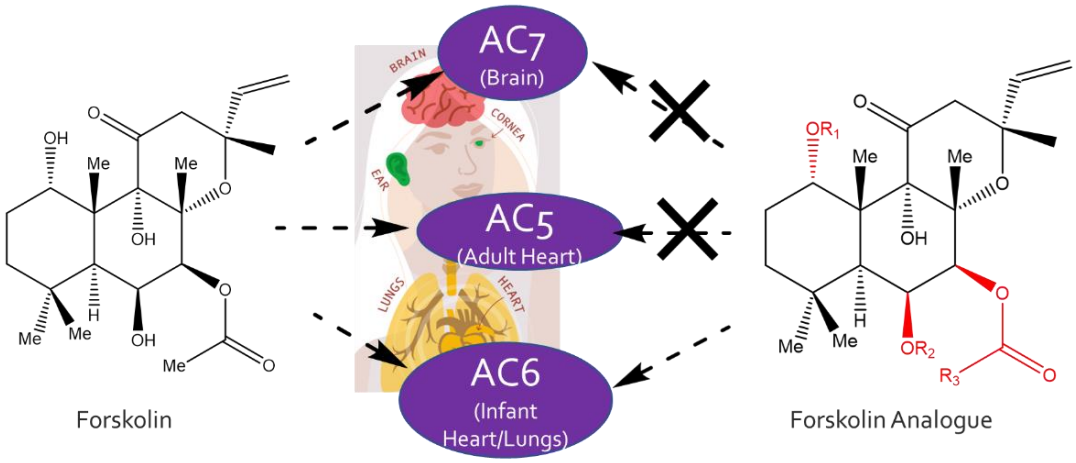
The Synthesis of Adenylyl Cyclase 6 (AC6) Selective Forskolin Analogues for the Treatment of Persistent Pulmonary Hypertension of the Newborn (PPHN)

Andrew Laluk (Sorensen Group)

Persistent pulmonary hypertension of the newborn (PPHN) is a disease that is characterized by hypoxic conditions in newborns arising from the failure of pulmonary blood vessels to dilate following birth, leading to developmental disorders and death. Despite affecting 0.1-0.6% of all live births[1], current treatments are either inconsistent (inhaled NO_2) or invasive (extracorporeal membrane oxygenation)[2], creating the need for a more consistent, less invasive alternative. Adenylyl cyclase 6 (AC6) is a transmembrane protein found primarily in infantile cardiac myocytes and vascular smooth muscle tissue in the heart and lungs which converts ATP to cAMP, causing pulmonary vasodilation and cardiac contraction[1]. Forskolin is a plant natural product that can bind to an allosteric site on AC6, increasing its activity. However, forskolin can also bind to the other 8 isoforms of human AC enzymes causing a wide range of side effects. This project focuses on the synthesis of novel forskolin analogues with increased selectivity for AC6. Specifically, we aim to improve the water solubility of novel forskolin analogues by the inclusion of an amine functional group. Our overarching goal is to make novel forskolin analogues that can serve as lead compounds for novel therapeutics.



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Towards the Metabolic Usage of Fluorinated Proline

Alexandre Prefontaine (Budisa Group)

One of the main research areas in synthetic biology is to expand the range of chemistry utilized by modern organisms to include foreign xenobiotics. Fluorinated compounds, such as fluorinated proline analogues, have been identified as particularly interesting candidates.[1] While fluorinated proline is usable by endogenous translation machinery, it generally seems to act as a toxin to cells. Obviously, this toxicity needs to be overcome to generate cells with widespread usage of the compound. Unfortunately, the genetic changes needed for cells to adapt to the use of xenobiotics are poorly understood and difficult to predict. Therefore, adaptive laboratory evolution (ALE) was chosen as the ideal method to generate a desirable phenotype without prior knowledge of the responsible genes. The process was based on the successful adaptation of *E.coli* to fluorinated indoles[2]. Briefly, *Escherichia coli* cells were serially cultured in an excess of fluorinated proline and an undersupply of standard proline. The goal of this experiment is to characterize the changes required for the adaptation to fluorinated prolines. This information will be used to gain a broader understanding of the mechanism of adaptation to xenobiotics.

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Synthesis of Isocoumarin Analogues

Hajrah Ata (Sorensen Group)

Lichen are associations between symbionts of fungi and algae (or cyanobacteria) that thrive in an extensive range of terrestrial habitats.[1] Lichen produce secondary metabolites known as polyketide natural products.[1,2] These natural products can serve as a promising sources of lead compounds for drug discovery programs, as these molecules have shown promising biological activities.[1,2] For instance, the Sorensen lab has discovered over 40 biosynthetic gene clusters in a single strain of the lichen, *Cladonia unicalis*.[3] These clusters, comprising anywhere from 2 to 10 (or more) genes, appear to each code for a unique natural product.[4] This research project aims to discover new biologically active molecules that can be used as lead compounds to design new pharmaceuticals. The newly identified gene cluster of particular interest from *C. uncialis* is proposed to produce a halogenated isocoumarin.[1] To better understand in the pathway coded by the gene cluster it was proposed that 6-hydroxymelinin is a biosynthetic precursor of the final isocoumarin natural product.[1] The goal of this project is to synthesize 6-hydroxymelinin as a probe for investigating the biosynthetic pathway. This presentation will discuss the synthesis of 6-hydroxymelinin and its characterization with the aid of ^{1}H-NMR spectroscopy.

References

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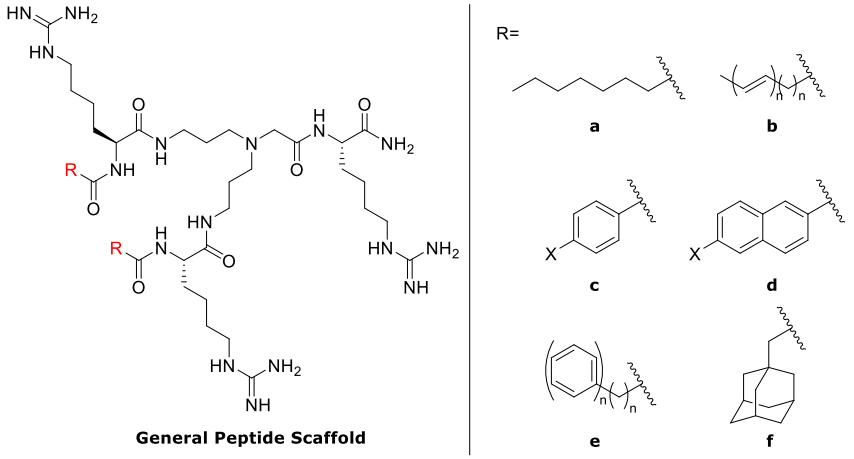
Structure-Activity Relationships of Lipid Modifications on Polycationic Adjuvants

Quinn Neale (Schweizer Group)

Antimicrobial resistance (AMR) is an ongoing problem making its way through society. In 2014, an estimated 700,000 deaths were caused by AMR infections, a number predicted to reach over 10 million within the next 30 years.[1] Comprising a number of these infections are Gram-negative bacteria (GNB) which evade antibiotics by consequence of their restrictive outer-membranes (OM).[2] In recent years, our lab has developed numerous peptide drug scaffolds with the ability to disrupt these OM structures, allowing for the passage of antibiotics which are normally restricted by the OM.[3-5] Herein, we present our development of a new peptidomimetic scaffold by monitoring the effect of different lipid structures on the potentiation of various antibiotics (scheme 1). In this study, we show that our new scaffold is able to rescue Rifampicin from resistance against *Escherichia coli* and *Acinetobacter baumannii* in both wild-type strains and clinical isolates.



Scheme 1. Structure of peptide scaffold and lipid moieties

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