Synthetic organic chemistry has already had a significant impact on the fields of medicinal chemistry and drug discovery, with major advancements being applied towards developing new pharmaceutical therapies for the study and manipulation of biological systems. With this in mind, the future of synthetic organic chemistry will involve the development and application of innovative technologies in the field of organic synthesis as applied to the field of medicinal chemistry. My research interests are largely focused on drug discovery, and have an end goal of improving the process of drug development and facilitating innovation in medicinal chemistry and chemical biology. Specifically, I'm interested in developing novel flow chemistry techniques that will aim at enhancing current synthetic organic methodologies, and focus on lead generation and optimization in drug discovery. Additionally, my group also seeks to develop new synthetic methods using microwave techniques. New developments in synthetic methodologies using microwave and flow chemistry will replace existing techniques and avoid the need for the work-up, purification and manipulation required by current methods, making syntheses shorter and greener. My research entails the development and application of microwave and flow chemistry techniques towards solving some of the current limitations of organic synthesis, and also applying these techniques towards enhancing and accelerating medicinal chemistry programs. Recent advances will be presented.
Tobramycin-Cyclam Conjugates: Antibiotic Adjuvants against Gram-negative Pathogens.

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Gram-negative pathogens are often difficult to treat and resistant to many antibiotics because of their impermeable outer membrane. Recently, Gram-negative pathogens resistant to cephalosporins and carbapenems through metallo-beta-lactamases have become a major threat to public health. Antibacterial adjuvants are compounds which are able to increase the activity of these existing antibiotics or rescue them from resistance. In light of these problems and with insight gained from the outer membrane destabilizing effects of a tobramycin-hybrid scaffold established by our group, we synthesized novel tobramycin-cyclam conjugates with the goal of mitigating rising resistance in Gram-negative pathogens. Amphiphilic tobramycin is able to destabilize the outer membrane while cyclam is able to chelate Zn2+ needed for metallo-beta-lactamase activity. Here, we describe the synthesis of these tobramycin-cyclam conjugates linked by varying lengths of aliphatic tethers. Biological activity of the conjugates was evaluated against a panel of Gram-positive and Gram-negative clinical isolates including multidrug resistant strains. Synergistic studies were also performed for these conjugates with legacy antibiotics against multidrug and extensively drug-resistant Pseudomonas aeruginosa. Initial biological testing shows that tobramycin-cyclam conjugates are able to potentiate an array of legacy antibiotics including cephalosporins against P. aeruginosa.
Ferrocenium Boronic Acid Catalysed Coupling of Alcohols with Borate and Silane Nucleophiles.

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We have recently demonstrated that boronic acids can directly and catalytically activate various alcohols (allylic, propargylic, benzylic) for use as electrophiles in reactions such as Friedel-Crafts, [4+3] cycloadditions, and aza-Piancatelli rearrangements. Ferrocenium boronic acid salts have proven to be very effective in this regard. In search of further applications for this catalyst, we have developed methodologies for the preparation of C-2 functionalized pyrrolidines and tetrahydropyrans, as well as the direct functionalization of various other alcohols using sp and sp2 organotrifluoroborates and organosilanes as nucleophiles. The developed methodologies proceed under ambient conditions, with moderate to excellent yields. The development, scope, and mechanistic aspects of these reactions will be discussed.
Aquaporins are a family of polytopic transmembrane channel proteins that facilitate water and flux across cellular membranes in a large diversity of organisms from prokaryotes to humans. These proteins are exquisitely designed to facilitate the transport of small polar molecules while at the same time preventing ion transport that would alter membrane electrochemical potential difference. Understanding the substrate-specificity and ion selectivity of these channel proteins requires knowledge of the atomic dynamics of the proteins over a wide range of timescales. Nuclear Magnetic Resonance (NMR) spectroscopy is a powerful tool for studying atomic dynamics of proteins but its application to integral membrane proteins is problematic. Membrane proteins cannot be studied in their native bilayer by NMR but removal from the bilayer often leads to destabilization of the protein fold, protein precipitation, loss of activity and degradation of the quality of NMR spectra. Recently, lipid nanodiscs have been used to stabilize membrane proteins yielding high-quality NMR spectra. Nanodiscs are non-covalent assembled discoidal lipid bilayers stabilized by encircling amphipathic helical scaffold proteins termed membrane scaffold proteins (MSP). MSPs were genetically engineered based upon the human serum apolipoprotein A-1 (ApoA1), the primary protein component of high-density lipoprotein (HDL).

The aim of my research project was to prepare GlpF that is amenable to study by high-resolution liquid NMR spectroscopy by incorporation into nanodiscs. I obtained the genes for 3 different His-tagged MSP proteins, transformed them into E. coli BL21(DE3), and purified all three proteins using Immobilized Nickel Affinity Chromatography. All of the proteins were analyzed by Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis (SDS-PAGE) and showed the correct molecular weight. Circular Dicroism (CD) spectra were obtained for all 3 proteins and they all showed strong α-helical signatures suggesting that the proteins were correctly folded. Analysis of the GlpF tetramer crystal structure determined that the transmembrane helix surface area is 3920 Å². On this basis MSP1E3D1 was chosen from among the three MSPs for further analysis based on its predicted diameter (12.1 nm) that should be able to accommodate the GlpF tetramer and associated lipid. Lipid-filled nanodiscs were formed with MSP1E3D1 and DMPC (Dimyristoylphosphatidyl choline). CD spectra showed that the MSP is helical in the lipid nanodisc. Differential scanning calorimetry (DSC) of the lipid-filled nanodiscs showed the gel-to-liquid crystal phase transition at 27°C and the unfolding of the MSP at 87°C. One attempt was made to incorporate GlpF into the lipid-filled nanodisc but no elevation of the GlpF melting point was observed casting doubt on the success of the preparation. In the future, optimization of the GlpF nanodiscs should be possible by optimizing the temperature, time, amount of hydrophobic sorbent, ratios of MSP, lipid, and GlpF. GlpF nanodisc formation will be confirmed by Small Angle X-ray Scattering.

References
Using standard solid state methods, Dy2ScNbO7, a member of a new series of pyrochlore oxides was synthesized. While the A-site is occupied by the magnetic Dy3+ cation, the B site is split into a mixture of disordered Sc3+ and Nb5+ cations. It appears that Dy2ScNbO7 has low temperature spin ice state that is similar to the titanate analogue, Dy2Ti2O7. Despite its similarities, Dy2ScNbO7 exhibits much faster spin dynamics than any other dysprosium spin ice candidate. Attempts to grow single crystals of Dy2ScNbO7 have been successful using the floating zone image furnace. Recent characterization results will be presented.
Design, Synthesis and Evaluation of a Tobramycin-Enoxacin Hybrid against Gram-negative Bacteria.

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Bacterial infections due to multidrug-resistant (MDR) *Pseudomonas aeruginosa* are associated with high mortality and morbidity. Treatment options are limited due to the organism’s intrinsic resistance to antibiotics, the lack of cell penetration and extensive efflux. Aminoglycosides are particularly active against several Gram-negative pathogens and are commonly used to treat severe *P. aeruginosa* infections. However, resistance to this important class of antibiotic as well as other antipseudomonal agents is escalating. The Schweizer group have previously reported heterodimeric agents that are composed of two clinically-used antibiotics that are covalently-linked together, termed antibiotic hybrids. The successful synthesis of antibiotic hybrids composed of the aminoglycoside tobramycin and either the fluoroquinolones ciprofloxacin or moxifloxacin revealed a potent adjuvant scaffold to synergize with existing antibiotics. For instance, it was shown that tobramycin-ciprofloxacin hybrids enhance the in vivo efficacy of minocycline, rifampicin and fluoroquinolone antibiotics against MDR *P. aeruginosa*. Herein, we present the synthesis and evaluation of a novel type of antibiotic hybrid that is composed of tobramycin and the fluoroquinolone enoxacin. The two clinically-used antibiotics are covalently linked by a 12-carbon long aliphatic tether. We hypothesize that this new antibiotic hybrid enhances, the adjuvant properties observed in our previously reported tobramycin-fluoroquinolone hybrids.

References


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Exploring the Effects of Conjugating Bioactive Peptides to the Fluoroquinolone Levofloxacin

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As multidrug-resistant bacteria become widespread, and the development of new antibiotics stagnates, we are steadily approaching a “post-antibiotic era” in which common bacterial infections may again result in patient mortality. The highly restrictive outer membrane of Gram-negative bacteria presents a significant challenge for the development of new antimicrobial agents. Existing antibiotics are able to enter the outer membrane by several mechanisms, including nonspecific porin channels as seen in fluoroquinolone (FQ) antibiotics or through a “self-promoted uptake” mechanism seen in some cationic antimicrobial peptides. One of the key structural features of these peptides is their amino acid side chains (such as amines or guanidines) which are protonizable at physiological pH and confer cationic character. These positively charged groups are able to interact with negatively-charged lipopolysaccharides studded on the outer membrane of Gram-negative bacteria, displacing the divalent cations that are responsible for the overall structural integrity of these lipopolysaccharides. This would result in destabilization of the outer membrane that would consequently facilitate a self-promoted uptake of the antimicrobial peptide. We hypothesize that the antibacterial activity of FQ antibiotics may be enhanced by covalently adding these cationic amino acids, thereby allowing the FQ to penetrate the cell through porins (FQ’s native mode of cellular entry) as well as through the self-promoted uptake mechanism that the cationic peptides may bestow. In addition, bacteria develop resistance to FQs by expelling them out of the cell via efflux pumps, and we hypothesize that these new structural modifications may serve to prevent efflux. Overall, we expect an increased membrane penetration and intracellular accumulation of the FQ derivatives. In this talk, we present the preparation of twelve derivatives of levofloxacin, which is a clinically used FQ, by incorporating varying amounts of amino acids via solid-phase peptide synthesis. Moreover, their antibacterial activity against multidrug-resistant pathogens will be discussed.
Study of the electron-transfer processes in novel 2,4-diferrocenyl-1H-pyrroles.

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Preparation of nanometer-scale molecular systems with controllable redox or electronic conductivity properties is of great interest for modern technology. Because of their well-defined redox properties and robust structure, mono- and poly(ferrocene)-containing compounds were proposed as candidates for potential application in molecular photonics, (opto)electronics, redox-driven fluorescence markers, and sensors for toxic ions. Among these organometallic platforms, compounds with strong metal-metal coupling are particularly interesting from fundamental and practical points of view. The novel 2,4-Diferrocenyl-1H-pyrrole was synthesized in five steps (Scheme 1) starting from commercially available ferrocene and characterized by 1H, 13C NMR, UV-Vis, and high-resolution mass spectrometry methods. Redox properties of this molecule were examined using cyclic voltammetry, differential pulse voltammetry, as well as spectroelectrochemical techniques. Absorption spectrum of this molecule was correlated with TD DFT-calculation.

Influence of Freezing and Cold Temperatures on Phosphorous Release from Manitoba Soils under Flooded Conditions.

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In Southern Manitoba, anaerobic conditions in flooded soils can develop with soil submergence during spring runoff. As a result of these conditions, enhancement of phosphorus release from soil can occur. To date, little work has been done to study the effect of phosphorous release under spring snow melt conditions that occur annually in Manitoba. In this study we examine the effects of cold temperatures on phosphorous release for five alkaline soils from Manitoba. For these experiments, soils were packed in incubation vessels and kept flooded for 28 days. A Pt electrode was used to measure soil redox potential over time. Samples of surface and pore water were also taken to determine Fe, Mn, pH as well as dissolved reactive phosphorous (DRP).
Development of a Novel Sulfonylation Reagent

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Sulfonamides are an important functional group in medicinal chemistry. Although widely used in therapeutic agents, methods for synthesis of sulfonamides is somewhat limited. The classic reaction between an amine and a sulfonyl chloride is the most common method to make sulfonamides. This reaction is not always practical as sulfonyl chlorides are very reactive and incompatible under certain reaction conditions. This work will be focused on development of a new sulfonylation reagent, and its application to the synthesis of a variety of sulfonamides. Finally, this report will address future application of our new reagent or its derivatives to become a novel zinc binding group used in for the inhibition of zinc containing enzymes and proteins.

Our new sulfonylation protocol is applicable with a variety of amines; primary, secondary, aryl and with amino acids. The new method required 1.1 equivalence of reagent, 1.0 equivalence of amine, and 2.0 equivalence of base with high purified yields.