Empowering Women in Organic Chemistry Conference 2026

Poster Abstract Booklet

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The posters will be displayed in two sessions on Friday, June 26, 2026 from 5:00–6:30pm.

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Please do not photograph or record the poster presentations, unless you have the explicit permission of the presenter.

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4	Jeanine Yacoub	Synthesis of psychedelic-adjacent tryptamines
5	Anika Monga	Development and Mechanistic Investigation of 1,5-Hexadiene-Enabled Nickel-Catalyzed Reductive Cross-Coupling Reactions
6	Cameron Berlin	Total Synthesis of Dimeric Clausenawalline Natural Products
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20	Laila Aiad	Allosteric-Allosteric Bivalent CDK2 Inhibitors for Anticancer Therapy and Non-Hormonal Male Contraception
21	Anna-Lee Thompson	INVESTIGATING ACYL CARRIER PROTEIN SELF-ACYLATION WITHIN TYPE I AND TYPE II POLYKETIDE SYNTHASES
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26	Divya Chennamadhavuni	SYNTHESIS OF CARBOHYDRATE AND CERAMIDE MODIFIED ANALOGS OF ALPHA -GALACTOSYLCERAMIDE FOR BIASED CYTOKINE RESPONSE
27	Masiel Belsuzarri	SF5–[1.1.1]Bicyclopentane (SF5–BCP) "Hybrid" Bioisosteres: Synthesis and Evaluation
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Poster Abstracts for Session 1 (5:00 – 5:45pm)

METHODOLOGY DEVELOPMENT TO ACCESS ENANTIOENRICHED N-SPIROCYCLE THROUGH ENZYMATIC CATALYSIS AND OPTIMIZATION OF Ir-PORPHYRIN TRANSPORTER SYSTEM

Nicole (Jingtong) Xu, Ami Serrano-Palacios, Brandon J. Bloomer, John N. Brunn, Andrew P. Quest, Sukriyo Chakraborty, Joseph E. Schneider, Douglas S. Clark, John F. Hartwig*

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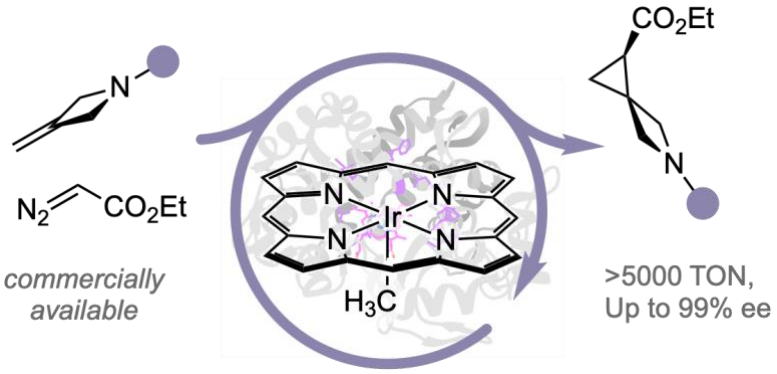
Nitrogen-containing heterocycles are ubiquitous in nature and are important motifs in drug design due to the ability of the nitrogen lone pair to interact with biological targets. In particular, conformationally constrained N-spirocyclic cores can increase structural complexity and diversity in drug screening libraries. However, the stereoselective synthesis of N-spirocycles typically requires chiral ligands and specialized reagents, highlighting the need for more direct methods. Artificial cyclopropanase enzymes have been used to catalyze carbene transfer to unconjugated 1,1-disubstituted alkenes. Here, we report the stereoselective cyclopropanation of methylene-substituted saturated heterocycles using an iridium-containing artificial metalloenzyme (Ir-ArM) assembled *in vivo*. Rational mutagenesis of the enzyme active site identified variants that form spiroazetidines, spiropyrrolidines, and spiropiperidines with up to 99% enantioselectivity. This work provides an efficient route to rigid, sp^3-rich scaffolds for drug discovery and enables access to complex nitrogen-containing pharmacophores.[1]

The *in vivo* assembly of Ir-ArM relies on efficient transport of the Ir-porphyrin across the cell membrane and periplasm, enabled by a haem transport system encoded by the *hug* operon. Building on prior work, we optimized the plasmid harboring the *hug* operon by varying the origin of replication, introducing operon variants, and testing different host strains. These optimizations improved transformation efficiency and cell growth for strains co-expressing the HUG system, thereby facilitating more efficient screening.



[1] Xu, J.; Bloomer, B. J.; Brunn, J. N.; Quest, A. P.; Chakraborty, S.; Schneider, J. E.; Clark, D. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2025**, *147*, 28875– 2888

MILD DIRECT REMOTE HYDROXYLATION OF ENALS IN AIR

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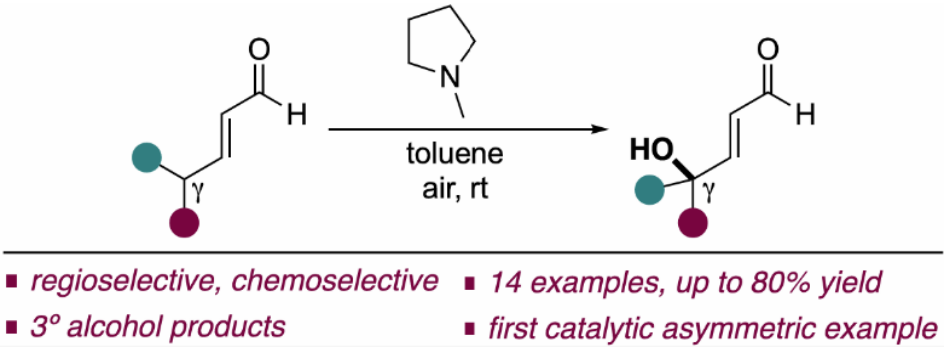
γ-Hydroxyenals are versatile molecules that can be widely used for the synthesis of medicinal compounds. Accessing tertiary alcohols directly from *α,β*-unsaturated aldehydes via remote oxygenation is an ideal method to obtain such valuable structures. In this project, we successfully developed a mild metal-free method to synthesize *γ*-hydroxyenals in up to 80% yield requiring only a stoichiometric amount of tertiary amine that acts as both a base and a reductant. This method also proved to be regioselective and chemoselective.[1] Additionally, we discovered that by subjecting the *α,β*-unsaturated aldehydes to reaction conditions including a copper catalyst in the presence of a chiral secondary amine catalyst, the *first example of a catalytic enantioselective* *γ*-hydroxylation of enals was achieved. These conditions enabled the synthesis of natural compounds e.g., *R*-boivinianin A and *R*-gossonorol, and generated *γ*-hydroxyenals in up to 87% ee. Further studies are being conducted in our laboratory to improve this reaction.



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[1] Liu, F.; Vicidomini, A.; Brenner-Moyer E., Stacey. *J. Org. Chem*. **2026**, *91*, 12, 4516–4520.

SYNTHESIS OF DICARBONYL SUBSTRATES FOR THE SELECTIVE ACCESS OF α-ACYLOXY CARBONYL SCAFFOLDS

Claire P. Martinez, Reagan P. Carter, Sandra M. Simmons, Wahab A. Badmus, Meagan E. Hinze*

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The Baeyer-Villiger oxidation is a reaction used to transform ketone functional groups into esters. Traditional chemical methods often employ strong reagents such as peroxyacids, but these synthetic strategies may require excess reagents, increasing safety risks at high concentrations, and create environmentally hazardous by-products. To address these concerns and offer a greener alternative, we aim to investigate a biocatalytic strategy utilizing flavin-dependent Baeyer-Villiger Monooxygenases (BVMOs). BVMOs are versatile enzymes that exhibit the ability to perform oxidations with regio-, chemo-, and stereoselectivity. Furthermore, BVMOs offer an eco-friendly solution due to their utilization of molecular oxygen, mild reaction conditions, and creation of non-hazardous by-products. To broaden the synthetic utility of this class of biocatalysts, we aim to construct a diverse substrate library composed of dicarbonyl scaffolds. Substrates incorporating β-keto esters and symmetrical diketones would provide access to α-acyloxy carbonyl motifs. Preliminary results will compare chemical and enzymatic oxidation outcomes across our substrate library. Orthogonal synthetic routes for the α-acyloxy carbonyl standards are also described.

SUPRAMOLECULAR CATALYSIS WITH SELF-ASSEMBLED CAGE HOSTS

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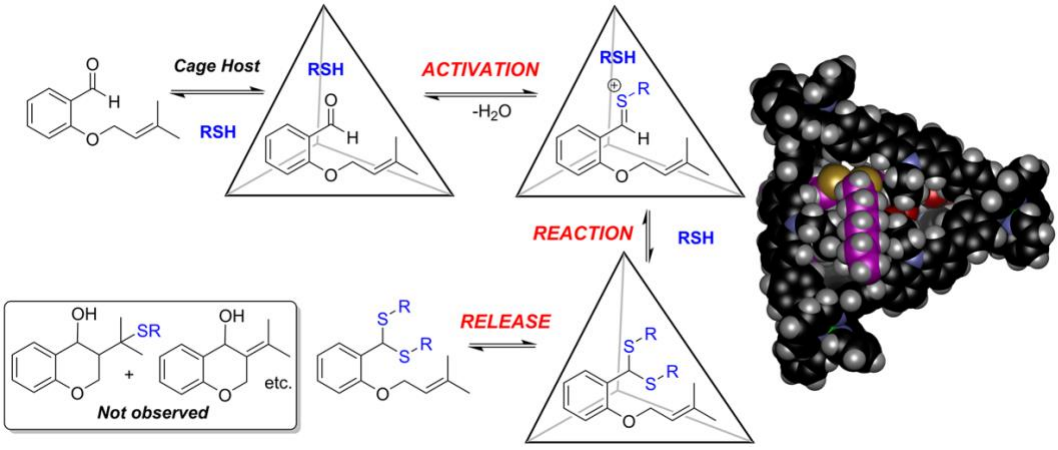
Self-assembled metal-ligand cage complexes are now widely used in selective catalysis, sensing, cargo transport and myriad other applications that center around their properties as hosts, i.e. their ability to perform selective molecular recognition. When substrates are confined within the cavities of these cage complexes, the increased effective concentration can facilitate biomimetic catalysis. Herein, we show that a self-assembled Fe_4L_6 cage complex can catalyze the formation of dithioacetals under mild, selective conditions. The reaction can be performed with 5% cage and no product inhibition is observed, and the process is remarkably selective for dithioacetal formation, with no need to remove water to drive the equilibrium. The cage-catalyzed process is significantly accelerated, compared to small molecule sulfonic acid catalysis, and is selective for dithioacetal formation with fragile allyl-functionalized aldehydes that can otherwise undergo fragmentation and rearrangement. Substrate recognition in the internal cavity controls the reaction rate, and both size and shape-selectivity is seen. The selectivity is determined by a complex balance of multiple equilibria, and the size and shape of both electrophile and nucleophile factors into the selectivity.[1] A new series of functionalized Fe_4L_6 cage complexes have also been synthesized, exploiting lipophilic groups at the pyridyl termini to confer solubility in a range of solvents, and studied the effects of solvent and internal functionality on the molecular recognition properties of the cages.[2] Binding studies and cage catalysis in non-polar environments highlights the importance of solvent selection in optimizing reaction conditions.



[1] Sharma, K.; Kim, T.; Hooley, R. J. *Chem. Eur. J.*, **2026**, e70849.
[2] Woods, C. Z.; Sharma, K.; Chen, C.; Yang, L.; Chen, J.; Wu, Yu-C.; Farooqi, N. S.; Zhang, J.; Julian, R. R.; Hooley, R. J. *J. Org. Chem.* **2025**, *90*, 240-249.

EXPLORING THE REACTIVITY OF TWO BAEYER-VILLIGER MONOOXYGENASES FOR SYNTHETIC APPLICATIONS

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Oxidation reactions play a critical role in small molecule synthesis through functional group conversions or by increasing molecular complexity. However, traditional chemical oxidations may require harsh conditions and generate harmful byproducts. More recently, biological catalysts have received significant attention due to the potential to access more moderate conditions, simpler procedures, and greener byproducts. While the function and scope of many families of oxidation biocatalysts, such as Cytochrome P450s, have received significant attention, other enzyme classes have been underexplored. Baeyer-Villager Monooxygenases (BVMOs) are a class of flavin-dependent enzymes that have the potential to generate a variety of oxidized scaffolds with regio-, chemo-, and stereo-selectivity. The preliminary data disclosed will examine the reactivity and selectivity of two BVMOs: TfPAMO from *Thermobifida fusca* and $BVMO_{AFL838}$ from *Aspergillus flavus*.

Photochemical Oxidative Functionalization of C(sp^3)–H Bonds Adjacent to Heteroatoms on Saturated Heterocycles

Suha Yacoob,[1] Rachel Rew,[1] Jenya Semenova,[2] Matthew Webster,[2] Eric Voight,[2] and Shannon S. Stahl[1]

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[2]AbbVie, Global Pharmaceutical R&D, 1 North Waukegan Road, North Chicago, Illinois 60064, United States

C(sp^3)–H functionalization adjacent to heteroatoms is an increasingly important strategy in the synthesis of bioactive molecules and drug-like scaffolds. These α-heteroatom C(sp^3)–H bonds are uniquely hydridic and possess relatively accessible bond dissociation free energies, enabling selective activation to rapidly increase molecular complexity from simple precursors. Traditional approaches rely on strong single-electron or hydride-transfer oxidants to generate iminium or related heteroatom-stabilized electrophilic intermediates, enabling α-functionalization, but often limiting functional-group compatibility due to direct substrate oxidation. Milder α-hydrogen-atom abstraction strategies have recently expanded the synthetic landscape, yet many existing methods continue to require solvent-level substrate loadings, harsh oxidants, or apply only to specific heteroatoms. Herein, we report a photochemical method that leverages a mild stoichiometric oxidant to promote α-hydrogen-atom abstraction on saturated heterocycles and deliver alkoxylated and hydroxylated products, with a central focus on nitrogen-containing heterocycles due to their dominant prevalence in the pharmaceutical industry. The resulting carbon-centered radical is trapped by a halogen radical and subsequently undergoes nucleophilic substitution with alcohols to deliver a versatile synthetic linchpin. Multiple trapping reagents can be employed depending on substrate class and various ring sizes can be tolerated. This room-temperature method is general across several heteroatoms—including O, N, and S—and operates at 0.2 M substrate concentration, avoiding solvent-quantity conditions. Comparison with the electrochemical Shono oxidation on nitrogen heterocycles shows improved substrate oxidation yields, and a robustness screen demonstrates significantly enhanced functional-group tolerance compared to the Shono screening conditions. Several pharmaceutically relevant molecules have been oxidized in good yields with high substrate generality observed for subsequent nucleophilic addition reactions. This methodology underscores significant promise for late-stage α-functionalization to heteroatoms in medicinal chemistry.

A Photoredox-Catalyzed Deaminative Approach Towards Benzylic Quaternary Carbon Centers

Holly Hutchinson,[†] Samantha L. Goldschmid,[†] Trevor C. Sherwood,[‡] Candice L. Joe,[§] Eric R. Welin,[#] Tomislav Rovis*[,†]

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[‡]*Discovery and Development Sciences, Bristol Myers Squibb, Princeton, New Jersey, USA*
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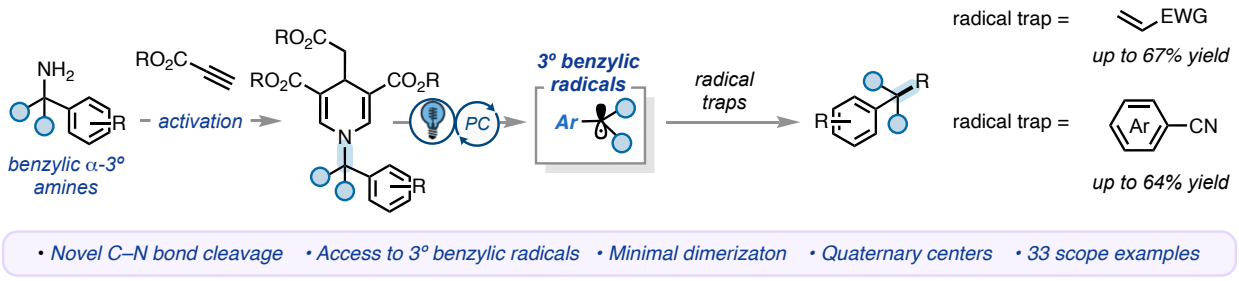
Primary amines are widely found in natural products, synthetic building blocks, and therapeutics. Accordingly, their structural diversity and low cost render them highly attractive building blocks in organic synthesis. Recent advances in deaminative functionalization methodologies, particularly those that leverage redox-active Katritzky salts and redox-active imines, have revitalized interest in C–N bond activation. While these methods have been highly enabling for developing valuable bond forming reactions, methods that liberate and functionalize tertiary benzylic radicals in a controlled and selective fashion remain elusive. Herein, we report the C–N bond cleavage of 1,4-dihydropyridines, a substrate class readily synthesized from primary amines, to generate tertiary benzylic radicals for selective radical trapping. Using photoredox catalysis, this method serves as a valuable strategy for constructing quaternary carbon centers.[1] Scope studies and mechanistic investigations that support the cleavage of the C–N bond via single-electron oxidation of the 1,4-dihydropyridine will be presented here. Additionally, comparison of this method to other deaminative methods will illuminate the substrate tolerance and mechanistic nuances between amine activation platforms.



(1) Hutchinson, H. L.; Goldschmid, S. L.; Sherwood, T. C.; Joe, C. L.; Welin, E. R.; Rovis, T. *ACS Catal.* **2026**, *16* (3), 2588–2595.

REMOTE STEREOCONTROL IN ARYL/ALKYL C–H INSERTION REACTIONS OF RHODIUM CARBENES: ASSEMBLY OF PSEUDORIGIDOLS A AND B

Linda Ung, Sarah N. Dishman, Sophia Zhang, James C. Fettinger, Jared T. Shaw*

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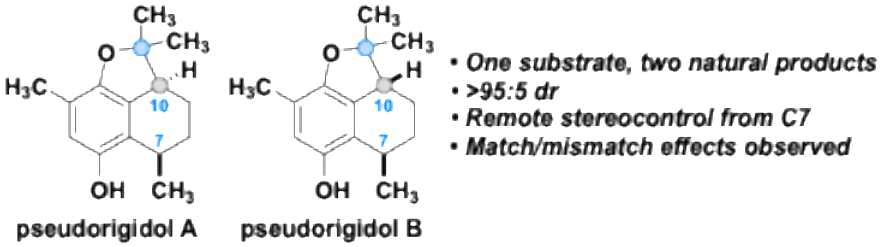
Intramolecular C–H insertion reactions using donor/donor dirhodium carbenes have proven useful in synthesizing molecules with high enantio- and/or diastereoselectivity.[1-3] This method can provide asymmetric access to a variety of natural products containing a benzodihydrofuran ring, including pseudorigidol A and pseudorigidol B. To assemble these cadinane natural products, the starting material contains a remote stereocenter. The aim of this research is 1) to complete the first total syntheses of pseudorigidols A and B, and 2) to investigate the influence of remote stereocenters on aryl/alkyl C–H insertion reactions, studies on which have yet to be reported in the literature. The completed syntheses of pseudorigidol A and pseudorigidol B, along with the dirhodium catalyst screen results, will be presented.



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[1] Soldi, C.; Lamb, K. N.; Squitieri, R. A.; González-López, M.; Di Maso, M. J.; Shaw, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 15142-15145.

[2] Lamb, K. N.; Squitieri, R. A.; Chintala, S. R.; Kwong, A. J.; Balmond, E. I.; Soldi, C.; Dmitenko, O.; Castiñeira Reis, M.; Chung, R.; Addison, J. B.; Fettinger, J. C.; Hein, J. E.; Tantillo, D. J.; Fox, J. M.; Shaw, J. T. *Chem. Eur. J.* **2017**, *23*, 11843–11855.

[3] Dishman, S. N.; Laconsay, C. J.; Fettinger, J. C.; Tantillo, D. J.; Shaw, J. T. *Chem. Sci.* **2022**, *13*, 1030-1036.

PROGRESS TOWARDS ENANTIOSELECTIVE SYNTHESIS OF THE MEROTERPENOID RHODATIN

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Progress towards enantioselective synthesis of the meroterpenoid rhodatin and the related terpenoid rhodocorane L, both with unique oxidized acorane-type core structures, will be discussed. The 5,6-spirocyclic acorane core of each will be formed using asymmetric gold-catalyzed dearomative spirocyclization. This work towards rhodatin explores synthesis and reactivity of ene-diketones, which are rare understudied motifs, towards carbon nucleophiles.

FROM FEEDSTOCKS TO LINEAR AND CYCLIC UNNATURAL AMINO ACIDS

Mengfei Xu, Emma Yang, Vy M. Dong*

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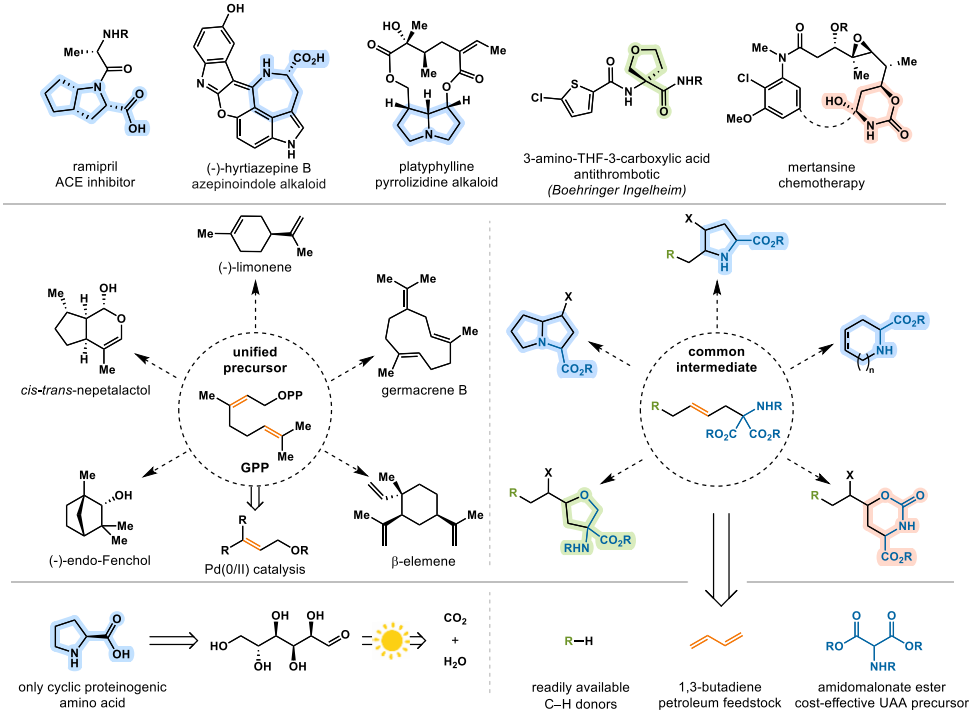
Both linear and cyclic unnatural amino acids (UAAs) play a central role in drug discovery but remain challenging to access from feedstocks. Inspired by terpene biosynthesis, we designed a simple and unified olefin precursor that can be diverged into constrained cyclic motifs, including prolines, azepanes, carbamates, ethers, and lactones. To access this olefin precursor, we exploit the emerging Pd(I/II) cycle and demonstrate a three-component coupling. This visible light-promoted transformation converts readily available C–H donors, 1,3-butadiene, and amidomalonate esters into functionally rich α-tertiary amino acid precursors. We further show how this achiral motif can furnish enantioenriched UAAs through Liu's dynamic kinetic resolution. In addition, we build a pyrrolizidine core found in various natural products from simple building blocks, including dichloroethane. Our approach represents a modern twist on the classic amidomalonate synthesis.



Note: Mengfei Xu and Emma Yang will be co-presenters of the poster.

NOVEL SPIROLACTAMS DISCOVERED FROM SUPRAMOLECULAR PROTECTING GROUPS (SPGs) STUDIES

Oluebube F. Ezenwafor, Jayden Jiang, Ken Shimizu*

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My first research explores a class of SPGs based on hydrogen bonding designed to achieve selective protection of dicarboxylic acids. In the study, new SPG_**1** was developed that can selectively protect dicarboxylic acids while enabling the preferential esterification of monocarboxylic acids with selectivity factor *s* = 72.[1] Building on this SPG strategy, an asymmetric SPG-**2** was designed and synthesized for the resolution of cis and trans diacids. However, while synthesizing SPG-**2**, a novel spirolactam was also formed. The formation of the spirolactam was identified during an attempted desilylation of a TMS-protected acetylenic amide. The reaction is hypothesized to proceed via an anionic cascade trimerization mechanism, involving two sets of sequential Michael and anti-Michael additions.

Spirolactams are prominent spirocyclic motifs found in numerous natural and bioactive compounds and have been reported to showcase diverse pharmacological activities such as antimicrobial, anticancer, and antivomiting activities.[2] Given the broad importance of spirolactams across multiple areas of chemistry, extensive efforts have been devoted to developing efficient synthetic approaches, ranging from classical β-lactam synthesis to modern catalytic and cascade methodologies.[3] Notably, none of these previously reported synthetic methods include a cascade trimerization reaction involving sequential Michael and anti-Michael addition reactions, highlighting the novelty of our approach. The discovery, scope, and the plausible mechanism of the cascade trimerization reaction will be presented.

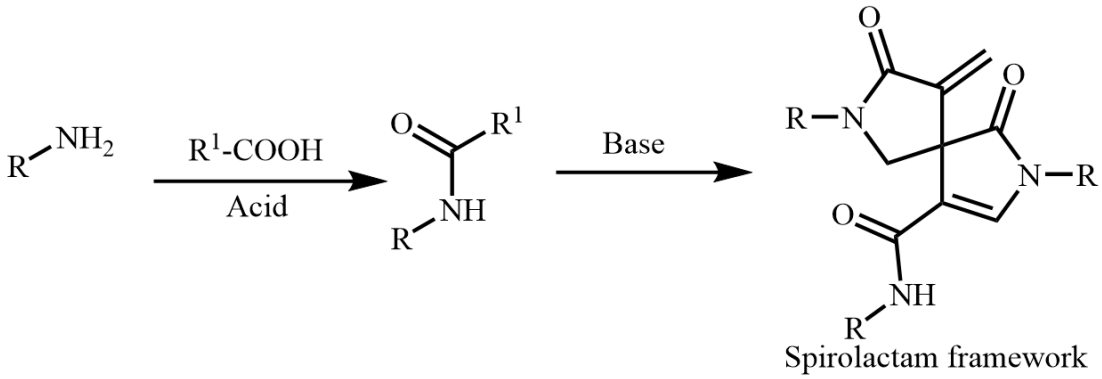

Fig.1. Schematic representation for the synthesis of the novel spirolactam

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Structure-Activity Relationship of *N,N*-Dimethyltryptamine Analogs for Elucidation of Molecular Mechanisms of 5-HT2AR

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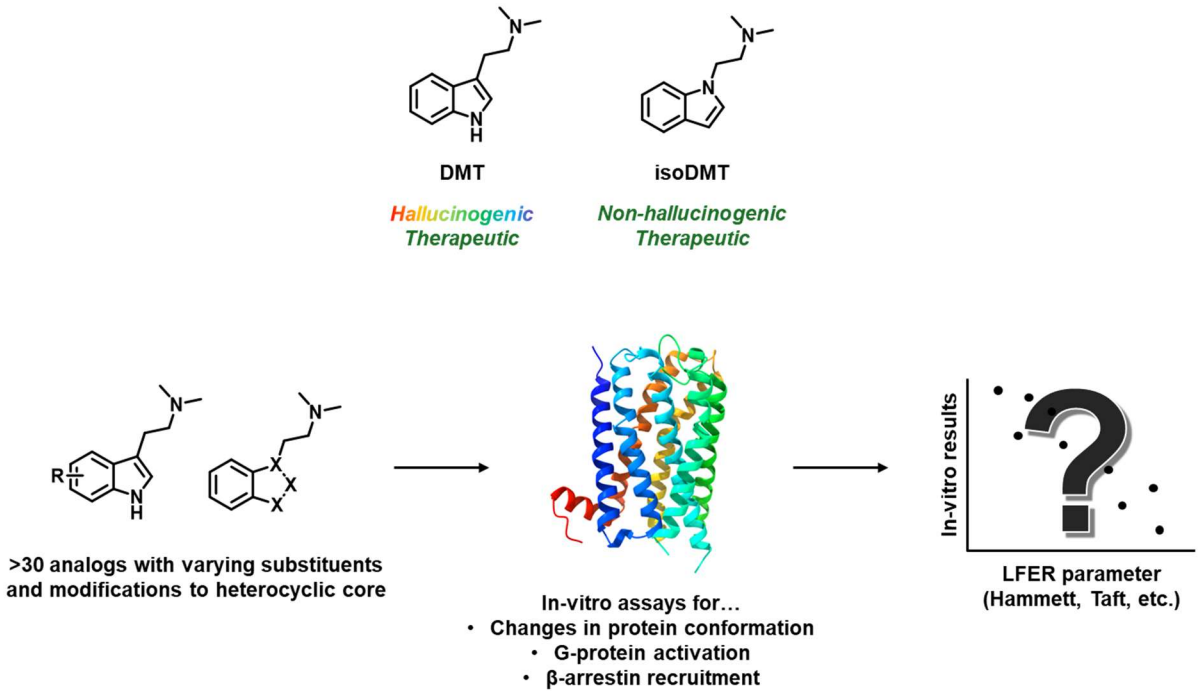
The 5-HT2AR (5-hydroxytryptamine 2A receptor) is one of several canonical receptors for the neurotransmitter serotonin, and appears to be the main receptor through which psychedelics elicit both therapeutic and hallucinogenic effects. However, the molecular mechanisms that differentiate hallucinogenic and non-hallucinogenic 5-HT2AR agonists are still unclear. For example, *in-vivo* studies suggest that *N,N*-dimethylisotryptamine (isoDMT) is non-hallucinogenic despite its striking structural similarity to the parent psychedelic, *N,N*-dimethyltryptamine (DMT). This suggests that subtle changes to the core tryptamine structure of serotonergic psychedelics lead to drastic differences in receptor conformation and intracellular function. In light of this, we designed and synthesized a library of DMT analogs with linear free energy relationship (LFER) parameters in mind to correlate how modifications in chemical properties of the core psychedelic result in differences in 5-HT2AR active state conformation, G protein activation, and β-arrestin recruitment in this structure-activity relationship study.



EFFORTS TOWARD AN ALTERNATIVE SYNTHESIS OF AVIBACTAM

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As the number of bacterial infections rises, so too does the number of multi-drug resistance cases. This has especially become a problem when considering β-lactam antibiotics for the treatment of complicated bacterial infections. In order to combat this, β-lactamase inhibitors have been developed to work in conjunction with β-lactam antibiotics. Avibactam is one of the most prevalent β-lactamase inhibitors currently on the market. Avibactam is a non-β-lactam β-lactamase inhibitor that was first approved for use by the FDA in early 2015. Since its approval, many attempts have been made to develop the most efficient, cost-effective method to synthesize avibactam. Most syntheses utilize expensive starting materials and/or have no or little room for late-stage analog development. We are developing a convergent synthesis that utilizes inexpensive starting materials and leaves room for late-stage analog development in the future.

Darwinollidae Alkaloids: Asymmetric Total Synthesis of Oxeatamide and Analogs

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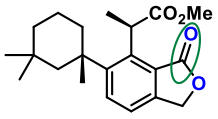
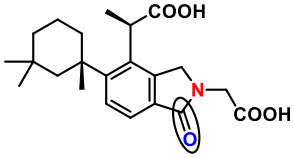
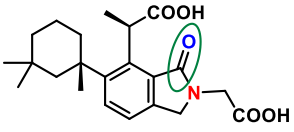
The ***Darwinollidae*** alkaloids, including the oxeatamide family, represent a structurally intriguing class of marine natural products with promising biological activity, yet their complex structures have limited both synthetic access and biological exploration. Building on our recently developed total asymmetric synthesis of membranolide, we are leveraging the strategies and key bond constructions established in that route to pursue the first asymmetric total synthesis of the oxeatamides and selected analogs. Early studies have enabled the preparation of key nitrogen-containing intermediates and validated the viability of our synthetic strategy, while also revealing challenges related to protecting-group compatibility and late-stage functionalization. Ongoing efforts aim to refine and extend this route to additional oxeatamide family members and to generate structurally diverse analogs. Access to these compounds will facilitate expanded biological evaluation, including their potential as MRSA biofilm-eradication agents, and will support future mechanistic studies and probe development to better understand their modes of action.



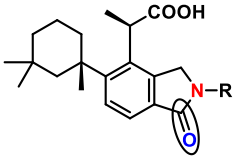
Membranolide



Oxeatamide A



Iso-oxeatamide A



Oxeatamide B-G

DISCOVERY AND DEVELOPMENT OF A NEW FIRST IN CLASS ANTIMALARIAL DRUG CANDIDATE

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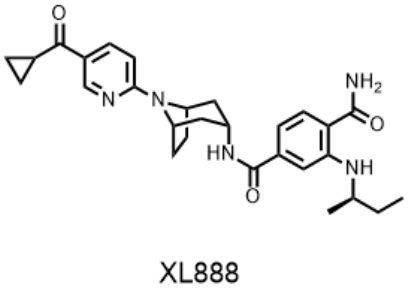
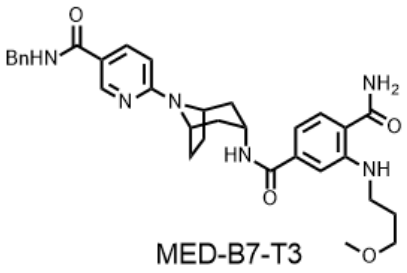
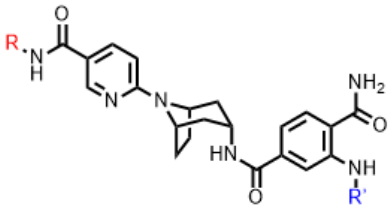
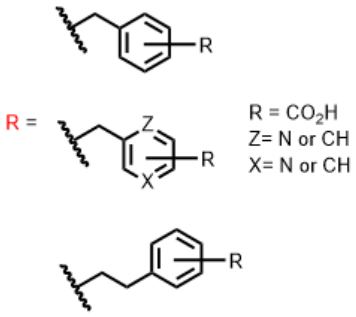
Nearly 40% of the global population is at risk of malaria, with 597,000 deaths annually. Plasmodium falciparum is a parasite that causes 99.7% of malaria-related fatalities. With antimalarial drug resistance on the rise, finding alternative solutions is critical to ensuring effective treatment & preventing the spread of resistant strains. Heat shock protein 90 (Hsp90) is a molecular chaperone, which is essential for the stabilization of protein complexes via ATP-driven folding processes. P. falciparum (Pf)Hsp90 has been shown to play an essential role in the liver and blood stages of the parasite's life cycle. However, targeting parasitic Hsp90 versus human (Hs)Hsp90 presents a significant challenge due to their high structural and functional similarities. One putative HsHsp90 inhibitor, XL888, which has been safely used in human clinical trials for the treatment of cancer, has been identified to have a 4.8-fold affinity towards PfHsp90 over HsHsp90. We have developed analogs of XL888 with improved selectivity, with a goal of advancing one of these as a first in class drug candidate for the treatment of malaria.









Convergent Total Synthesis of Varilactones A and B

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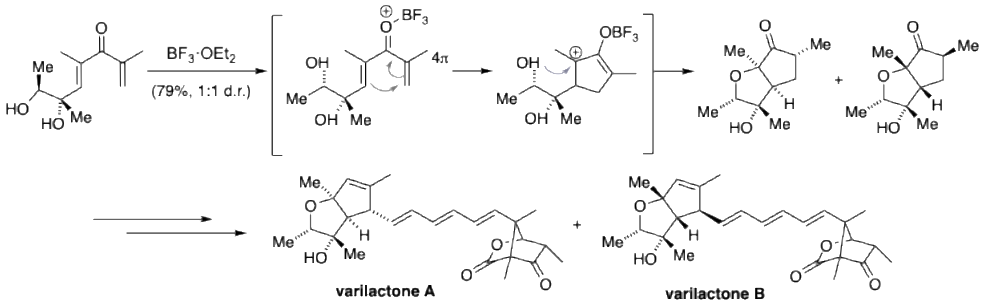
This work presents efforts towards the first total synthesis of varilactones A and B, a pair of polyketide natural products isolated from the fungus *Penicillium variabile.* These compounds are characterized by a unique "dumbbell" structure composed of oxabicyclo[3.3.0]octane and oxabicyclo[2.2.1]heptane rings connected by a triene unit. Inspired by the proposed biosynthesis, this convergent route features a novel hydroxy-interrupted Nazarov cyclization to forge a fused tetrahydrofuran ring system. Other key synthetic transformations include a highly chemo- and enantioselective Sharpless dihydroxylation, an acid-catalyzed dehydrative cyclization of a β-ketolactone, and a Horner-Wadsworth-Emmons olefination to unite the two halves of the dumbbell. Completion of this total synthesis will allow for further exploration into the reactivity of extended polyenyl cations and provide access to related polyketides with potent biological activities.



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[1] *Arch. Pharm. Res.* **2018**, *41* (1), 57-63.

GENERAL ACCESS TO C-GLYCOSIDES VIA REDOX-NEUTRAL RADICAL CROSS-COUPLING OF GLYCOHYDRAZIDES

Yiheng Li[1†], Yinliang Guo[1†], Benedikt Buchberger[1‡], Yixin Liu[1‡], Carla Capone[1], Tapas Adak[2], Shubham Ojha[2], Jasper L. Tyler[2], Philipp Neigenfind[1], Molhm Nassir[1], Yu Kawamata*[1], Varinder K. Aggarwal*[2], Phil S. Baran*[1]

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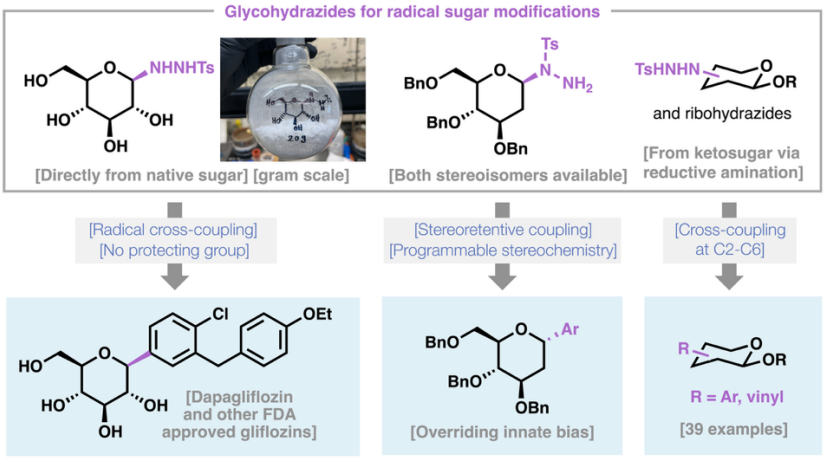
[†]These authors contributed equally to this work.

[‡]These authors contributed equally to this work.

C-Aryl glycosides are privileged motifs in medicinal chemistry, exemplified by blockbuster SGLT2 inhibitors for type 2 diabetes. However, their synthesis is often limited by lengthy sequences, poor selectivity, and extensive protecting-group manipulation of sugar derivatives. Herein, we report a practical and scalable approach to C-aryl glycosides using glycosyl sulfonyl hydrazides as redox-neutral radical precursors. These reagents are prepared on decagram scale directly from unprotected native sugars by treatment with sulfonylhydrazine in acetic acid, followed by simple crystallization. Under mild nickel-catalyzed cross-coupling conditions, they provide direct access to glycosyl radicals for highly stereoselective C-aryl glycoside synthesis. The utility of this platform is demonstrated by the two-step synthesis of dapagliflozin in 88% yield with excellent anomeric selectivity (β:α > 19:1). In addition, four FDA-approved SGLT2 inhibitors were synthesized through this unified strategy, highlighting the broad applicability of the method. Beyond anomeric functionalization of unprotected sugars, this platform enables C–C bond formation at multiple positions on carbohydrate scaffolds and supports stereoretentive radical coupling that can override inherent stereochemical biases. Overall, this work establishes glycosyl sulfonyl hydrazides as practical and versatile reagents for carbohydrate functionalization, providing streamlined access to carbohydrate-derived therapeutics and chemical probes from readily available starting materials.



Application of Chiral Lithium Amides in Divergent–convergent Total Synthesis of Indole Alkaloids

Yu (Ivy) Liang, Yang Li, Erika E. Chambers, Elena Paola, Armen Zakarian*

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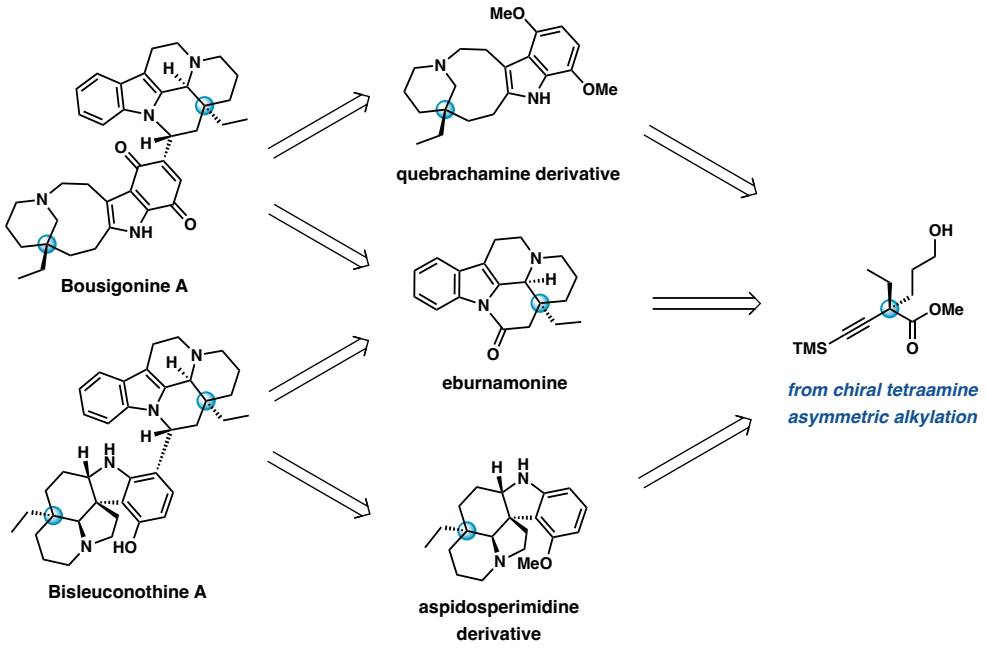
The complex structure of *Aspidosperma* alkaloids makes them appealing targets for total synthesis, due to their structural intricacy and notable pharmacological potential. Within this family, dimeric alkaloids have demonstrated significantly higher bioactivity compared to their monomeric counterparts. Notably, the bisindole alkaloids bousigonine A and bisleuconothine A exhibit remarkable anticancer and anti-proliferative effects. Herein, we present a modular and divergent total synthesis of three alkaloids, centered around a key intermediate: an enantioenriched quaternary carbon center generated via a method we developed using chiral lithium amides as non-covalent chiral auxiliaries.[1] This work outlines our efforts to implement a convergent-divergent approach for accessing these complex and underexplored bisindole alkaloids. This strategy highlights the applicability of our methodology and enables access to a range of natural products within the *Aspidosperma* family.



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SYNTHESIS OF NEXT-GENERATION COVALENT INHIBITORS OF ACID CERAMIDASE WITH IMPROVED DRUG-LIKE PROPERTIES

Miracle O. Olatunde[†], Xisto Neto[‡], Elizabeth Medearis[†], Johnson Ung[‡], Su-Fern Tan[‡], David Feith[‡], Thomas P. Loughran[‡], & Jetze J. Tepe[†*]

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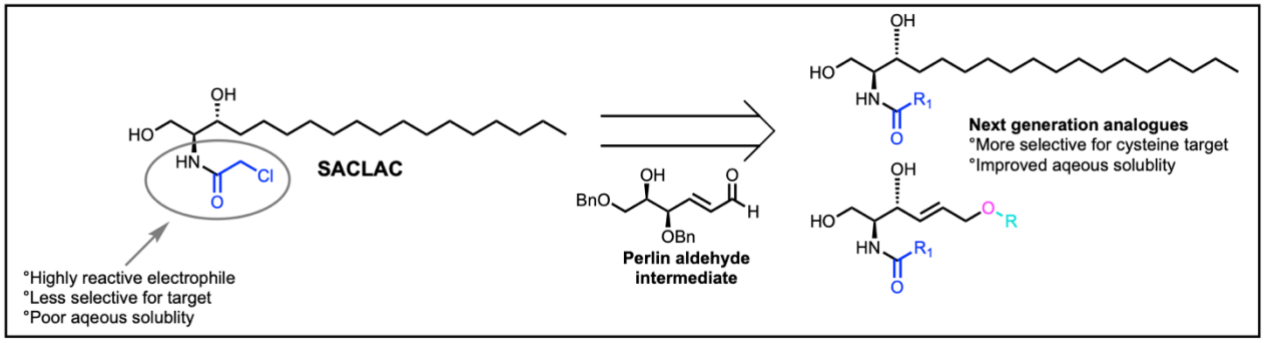
Acute Myeloid Leukemia (AML) is an aggressive hematologic malignancy with approximately 20,000 new cases annually in the United States and a 5-year survival rate below 30%, underscoring the need for improved therapeutic strategies. Acid ceramidase (AC), a cysteine hydrolase that regulates the ceramide–sphingosine-1-phosphate (S1P) rheostat, is a compelling therapeutic target, as its inhibition promotes pro-apoptotic ceramide accumulation.

SACLAC, a covalent AC inhibitor, exhibits potent anti-leukemic activity but is limited by poor aqueous solubility, rapid clearance, and an overly reactive α-chloroacyl warhead that may compromise pharmacological control. To address these limitations, we replaced the α-chloroacetyl electrophile with a panel of α,β-unsaturated amide warheads to tune covalent reactivity and improve selectivity for the cysteine active site of AC while maintaining target engagement. In parallel, we utilized a synthetic strategy centered on Perlin aldehyde as a versatile intermediate, enabling late-stage incorporation of polar functionality into the lipid scaffold. This platform enables systematic exploration of structure–activity and structure–property relationships, while preserving key pharmacophores and allowing independent optimization of electrophilicity and physicochemical properties.

The resulting compounds retain potent AC inhibitory activity and demonstrate functional efficacy in AML cellular models, including reduced cell viability and confirmed target engagement in AC activity assays. Notably, select analogues exhibit improved kinetic aqueous solubility relative to SACLAC. Collectively, this work establishes a platform for engineering polarity and tuned covalent warheads into lipid-like scaffolds, enabling improved pharmacokinetic properties while maintaining biological activity. These findings support the development of next-generation acid ceramidase inhibitors for AML therapy.



Reductive Trapping of Selected Acylated Emodin Derivatives

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Emodin is a natural product found in rhubarb and is commonly used in traditional Chinese medicine due to its anti-bacterial, anti-viral, anti-fibrosis, anti-cardiovascular, anti-diabetic, anti-cancer and anti-Alzheimer's effects. Emodin has an anthraquinone backbone, which upon single electron reduction produces reactive oxygen species (ROS) that damage DNA and cell membrane components. While ROS is beneficial when combating pathogens and cancerous cells, normal healthy cells are also damaged, and results in toxicity. This research is examining a method to avoid ROS generation in quinone-based drugs, by reducing the quinone and trapping the fully reduced hydroquinone to form a stable prodrug that retains biological activity but avoids unwanted ROS generation. In this study, we are developing methodology for creating acylated reduced emodin derivatives to investigate the bioactivity profiles of various prodrugs forms[1].

1. Tirado, K. Zinc-Mediated Reductive Acylation and Silylation of Various p-Quinones Derivatives. dissertation, 2023

Novel Fosmidomycin and FR900098 analogs as New Antimalarial Compounds

Griffin Klauder, Patrick Keane, Darean Bague, Kenneth Heidel, Spencer E. Bystrom, Timothy J. Scranton, Samuel Kirby, Audrey R. Odom John, Robin D. Couch, Cynthia Dowd

Plasmodium falciparum (Pf) is a species of parasite causing the deadly infection malaria. Left untreated, malaria can lead to multi-organ failure and inevitable death of the host. Over time, the use of antimalarial compounds has led to the development of drug-resistant strains of *Plasmodium falciparum* requiring novel treatments. *Plasmodium falciparum* reproduction and survival is dependent on the methyl erythritol phosphate (MEP) pathway. The MEP pathway is responsible for synthesizing the isoprenoids isopentenyl diphosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), both necessary for Pf survival in human red blood cells. The MEP pathway is a prime target for drug discovery due to its importance in Pf and lack of a human equivalent, minimizing off target effects. Our work focuses on synthesizing inhibitors of 1-deoxy-D-xylulose-5-phosphate reducto-isomerase (DXR), the first committed step of the MEP pathway. Natural product fosmidomycin has been examined as an antimalarial in the past, however facile recrudescence prompts a need for drugs with improved bioavailability. Prior work showed that α, β-unsaturation and prodrug moieties improved activity of these fosmidomycin and related analog FR900098. Our current work focuses on varying substituents on the benzoyloxymethylene (BOM) prodrug of N-formyl, N-acetyl, and N-benzoyl substituted molecules. The biological data from these compounds will provide important information to guide the synthesis of future antimalarials.

BINDING KINETICS AND CELLULAR TARGET ENGAGEMENT OF HDAC4 INHIBITORS

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Histone deacetylases (HDACs) are important regulators of gene expression and play a critical role in various cellular processes. The HDAC family consists of 18 isoforms, which are classified into several classes according to their sequence homology and catalytic activity: class I (HDAC1, 2, 3 and 8), class IIa (HDAC4, 5 ,7 and 9), class IIb (HDAC6 and 10), class III (sirtuins 1-7) and class IV (HDAC11). HDACs catalyze the removal of acetyl groups from lysine residues located on histone tails, resulting in increased chromatin compaction and subsequent repression of transcription. This posttranslational modification plays a crucial role in tumor pathology and several other diseases.[1] Compared to class I HDACs, class IIa HDACs exhibit significantly lower catalytic activity due to the replacement of a catalytically essential tyrosine residue by a histidine residue. Consequently, their primary function is thought to involve the regulation transcription mediated by *myocyte enhancer factor* 2 (MEF2), although additional interactions and functions cannot be excluded.[2]

Within class IIa, HDAC4 was chosen as representative isoform. It plays an important role in cellular processes, including osteoblast differentiation, cardiac hypertrophy, certain cancers, and in progressive neurodegenerative diseases.[1,3] Despite their biological relevance, the molecular mechanism and the therapeutic potential of class IIa HDACs remain incompletely understood, making them attractive targets for drug discovery.[4] To date, the binding kinetics of HDAC inhibitors (HDACis) have been studied mainly for class I HDAC isoforms, while class IIa enzymes remain largely uncharacterized. In this work, we used a series of established class IIa selective HDACis to characterize their binding kinetics at HDAC4. Additionally, a suitable fluorescent tracer was designed and synthesized to establish a NanoBRET assay for assessing cellular target engagement of HDAC4 using an LgBiT-expressing HEK293$^{HDAC4\text{-}HiBiT}$ cell line. Combining biochemical kinetic characterization with NanoBRET cellular assays enabled a comprehensive evaluation of the binding properties of the selected HDAC4 inhibitors.

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TARGETING PIM KINASES FOR TACKLING CHEMORESISTANCE IN TRIPLE NEGATIVE BREAST CANCER

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Breast Cancer is the most frequent malignancy and the second leading cause of oncological mortality in women worldwide. Of all subtypes, triple-negative breast cancer (TNBC) is the most aggressive form and accounts for about 40% of breast cancer-related deaths. The intercalator and topoisomerase II inhibitor mitoxantrone is a chemotherapeutic drug for the treatment of metastatic TNBC. The therapy is often compromised by development of chemoresistance.[1] One potential mechanism contributing to resistance involves PIM kinases. The PIM family consists of three serin/threonine kinases and is involved in regulating cell cycle, survival, proliferation, and apoptosis.[2] Overexpression of PIM kinases has been found in hematologic malignacies, but also in solid tumors, such as prostate and breast cancer.[3] Notably, upregulation of PIM kinases is associated with invasiveness and drug resistance in TNBC. However, while PIM kinases are more thoroughly investigated targets in hematological malignancies, their role in TNBC is poorly explored.

In this project we aimed to characterize mitoxantrone resistant TNBC cells to investigate whether addressing PIM is a potential strategy to overcome resistance. Therefore, the cell lines CAL-51 and HCC1806 and their mitoxantrone-resistant subtypes were analyzed with respect to cytotoxicity of mitoxantrone alone or in combination with PIM and upstream JAK inhibitors. In functional assays, the impact on efflux transporter activity and further cellular respones has been elucidated.

Our findings revealed differences in the molecular basis of mitoxantrone resistance in the indicated cell lines. While inhibition of the JAK/PIM axis improved mitoxantrone activity significantly in HCC1806 cells and their resistant subtype, PIM inhibition had no effect in CAL-51 cells, whereas resistance in mitoxantrone resistant CAL-51 cells appears to be primarily mediated by increased efflux via BCRP. These results provide further insight into resistance mechanisms in TNBC and may contribute to the development of more effective combinational therapies.

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Synthesis of strained rings using palladium(0) carbenes

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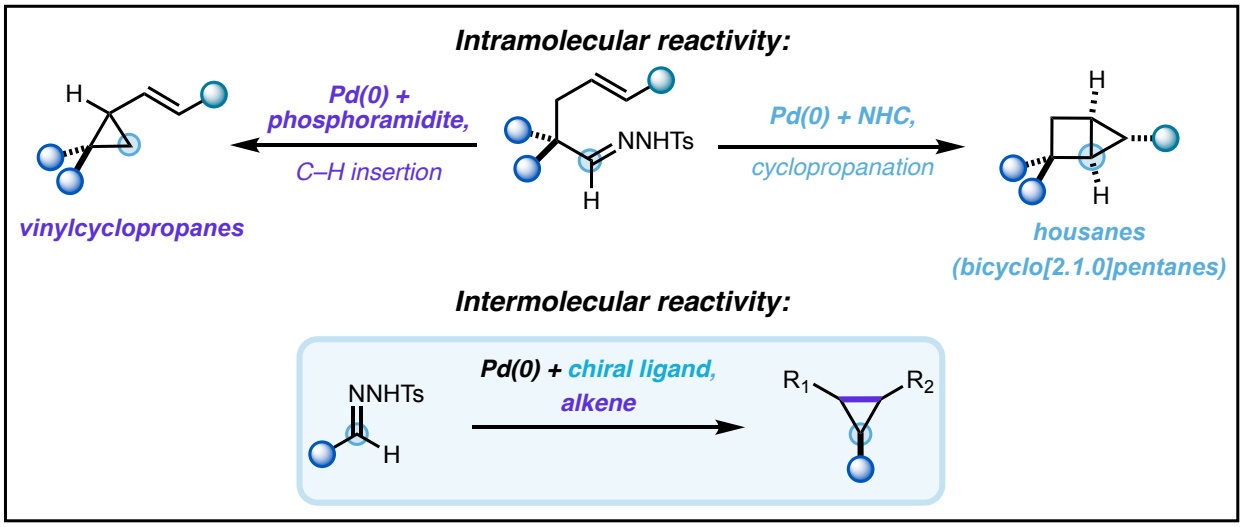
Cyclopropanes and other strained rings have been recognized as versatile and advantageous motifs in medicinal chemistry, due to their increased Fsp3 character, stronger C–H bonds, and rigid exit vectors. Despite this clear utility, the synthesis of cyclopropanes and other strained rings often relies upon the use of stabilized carbene precursors such as diazoesters or sulfoxonium ylides with transition metals such as rhodium or copper. The use of nonstabilized carbenes for cyclopropanation and C–H insertion reactions has historically been difficult due to unwanted side reactivity. Herein, we report the synthesis of bicyclo[2.1.0]pentanes and vinylcyclopropanes enabled through the ligand-controlled divergent reactivity of Pd(0) carbenes using hydrazones as bench-stable nonstabilized carbene precursors. Additionally, further development of the Pd(0)-catalyzed cyclopropanation reaction enabled an enantioselective intermolecular cyclopropanation through a proposed palladium carbene intermediate; to the best of our knowledge, this is the first example of such reactivity without the use of a chiral auxiliary.



A Single Reagent Enables Programmable Sulfur Functionalization

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Sulfur-containing compounds are indispensable in chemistry due to their diverse roles in biological systems, their ability to enhance the properties of pharmaceuticals, agrochemicals, and advanced materials, and their unique reactivity, which allows for the design of structurally and functionally complex molecules. In particular, the incorporation of sulfur-based functionalities and bioisosteres such as pentafluorosulfanyl (SF_5), known for its strong electron-withdrawing properties, high lipophilicity, and ability to improve metabolic stability and bioavailability while modulating drug-receptor interactions. Despite the promising potential of sulfur-containing compounds, versatile classes like sulfondiimines and sulfondiimidamides have remained underutilized due to limited synthetic routes, specifically lacking stereochemical control at the sulfur center. The development of an enantiopure bifunctional S(VI) transfer reagent (*t*-BuSF) has served as a chiral SuFEx template to asymmetrically access sulfoximines, sulfonimidoyl fluorides, sulfinamides, and sulfonimidamides. The methods presented herein expand the reagent platform to asymmetrically access over 30 sulfur functional groups, including chiral bis-aza S(VI) groups, as well as enabling SF_5 incorporation. Furthermore, the practical utility of this S-editing platform from *t*-BuSF was demonstrated to produce each sulfur analog on the pharmaceutically relevant celecoxib.

DIVERSE SYNTHETIC STRATEGIES TO ACCESS NOVEL MAIN-CHAIN PYRIDINIUM-FUSED POLY(NORBORNENE)S FOR ANTIBACTERIAL APPLICATIONS

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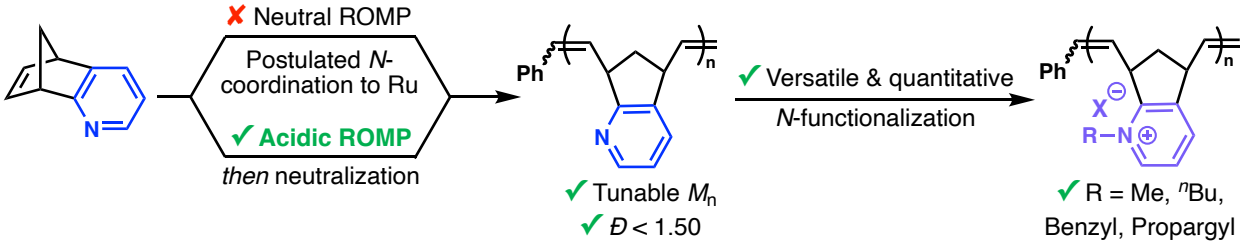
Abstract: Cationic polymers have emerged as a promising class of antibacterial materials that can induce bacterial cell death without significantly promoting antibiotic resistance. While polymers bearing side-chain cationic motifs are often targeted due to their straightforward synthesis, recent studies suggest that positioning cations closer to the backbone can enhance antibacterial efficiency and selectivity. This presentation will discuss our efforts toward developing a family of main-chain pyridinium-containing polymers synthesized either through direct polymerization of cationic monomers using a bespoke catalyst or via *N*-alkylation of a neutral pyridine-fused poly(norbornene) precursor. The synthesis of the pyridinium monomers relies on heteroaryne chemistry, followed by optimization of ring-opening metathesis polymerization (ROMP) conditions to achieve living characteristics[1]. We further demonstrate that the addition of acid enables successful ROMP of an unsubstituted pyridine-fused norbornene monomer by mitigating the deleterious *N*-coordination to the Ru center of the Grubbs third-generation catalyst, yielding a neutral pyridine-fused poly(norbornene) suitable for post-polymerization *N*-functionalization. Both synthetic routes afford main-chain cationic polymers with precise and tunable architectures. Finally, their antibacterial activities against *Escherichia coli* (*E.coli*) and *Methicillin-resistant Staphylococcus aureus* (MRSA), along with hemolytic assay data, reveal key structure–activity relationships for these novel polycationic macromolecules.



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MALDI-TOF MS for the Prioritization of Microbes Derived from Banana Slugs for Drug Discovery

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Marine and Microbial drug discovery have been transformed by advances in analytical instrumentation, including increased resolving power and the development of computational tools that facilitate the interrogation of large and complex datasets. Among these innovations, platforms such as IDBac enable rapid prioritization of bacterial strains through protein MS fingerprints and Metabolite Association Networks (MANs). Moreover, incorporating tandem mass spectrometry (MS/MS) directly from microbial colonies allows fragmentation-based structural characterization of microbial metabolites. Collectively, the MS data-driven approaches, both for prioritizing promising strains and dereplicating microbial natural products will ostensibly accelerate the discovery process. We hypothesize that integrating MS-based protein profiling, small molecule analysis, and MS/MS fragmentation within an understudied microbial habitat such as the mucus of *Ariolimax* spp. (banana slug), will provide a unique niche for microbial strains with therapeutic potential.

To date, one hundred and four microbial strains have been isolated. Individual colonies from isolated bacterial strains are directly transferred to a stainless steel MALDI target plate, overlaid with 70% formic acid, and analyzed using a MALDI-TOF-based workflow designed to generate three datasets per strain: a protein fingerprint on the MS1 level and a small molecule fingerprint at both the MS1 and MS2 levels. Protein MS1 data is acquired on a Bruker microflex LT in the 2 – 20 kDa mass range using sinapic acid as the matrix. Small molecule MS1 and MS2 data are acquired on a Bruker MALDI timsTOF fleX in the 0.2 – 2 kDa mass range, employing CHCA:DHB (1:1) as the matrix in the positive mode and 1,5-DAN in the negative mode.

Both protein and small molecule MS1 data are processed and visualized using IDBac to (i) generate a protein MS dendrogram to resolve protein-based phylogenetic relationships among isolates and the library, and (ii) build Molecular Association Networks (MANs) to assess shared and unique metabolite production across microbial isolates. Exploratory analysis resulting from the IDBac platform enabled the creation of a protein MS dendrogram from the protein MS data. Protein dendrogram allowed for the prioritization of 21 slime derived unique strains. This data revealed a cluster of four closely related strains defined by a cosine distance cutoff of 0.16. Additionally, IDBac facilitated the generation of a MAN from the small molecule data. This MAN indicated that these four strains share the production of a metabolite of interest, *m/z* 1653.2.

To confirm and further characterize this ions, MALDI MS/MS analysis was performed to obtain fragmentation patterns and compare them to public spectral libraries. Using the classical molecular network workflow in GNPS2, we confirmed the shared presence of *m/z* 1653.2, and other related fragment ions conserved across the strains clustered by the MS protein data. Moreover, the molecular network revealed mass shifts characteristic of amino acids losses, such as 156 Δ*m/z* (arginine) and 180 Δ*m/z* (tyrosine), indicating that this might be a peptide-based precursor. These findings strongly support the presence of a shared peptide product associated only with the four strains.

Given their distinct metabolic signature and MS protein-based similarity, these strains will be prioritized for downstream bioactivity testing.

Chemical Preparation and Reactivity of Acyl Phosphates under Prebiotic Conditions

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Pyruvate is a central biological metabolite that has also been previously detected in carbonaceous meteorites and hypothesized to have played an important role in protometabolic chemistry. It has been reported to participate in various networks of chemical reactions that could have helped generate compounds associated with primary metabolism, and possibly high-energy species such as acyl phosphates. One molecule of interest is methylsuccinic acid, a meteoritic compound that has been reported to form from the decarboxylation of a core pyruvate reaction network derivative. We aim to understand how similar prebiotic decarboxylation reactions may have driven the formation of high-energy species, such as acyl phosphates, analogous to how decarboxylation reactions drive metabolism in extant life. As a compound class, acyl phosphates are hydrolytically unstable species, but have been previously reported to be isolated or monitored *in situ*. We initially aimed to prepare methylsuccinyl phosphate, an acyl phosphate derivative of methylsuccinic acid, to aid in the exploration of our prebiotic experiments. This preparation was attempted through a phosphorylation reaction from methylsuccinic anhydride according to a literature protocol. However, isolation and complete spectral characterization of this compound remained challenging following that report. One of the identified challenges has been tied to the rapid reformation and subsequent hydrolysis of the five-membered anhydride ring under the phosphate reaction conditions. This was further supported by the differences observed from the *in situ* detection of glutaryl phosphate, a six-carbon acyl phosphate that was markedly more stable under the same reaction conditions. Additional preparation conditions were tested to isolate five-carbon chain acyl phosphates, starting with maleic anhydride as a reaction analog. Results highlighting efforts in the isolation and characterization of these promising prebiotic compounds will be presented. Overall, the characterization of acyl phosphates supports efforts to further understand prebiotic reactions within the pyruvate reaction network, a key step in uncovering the origins of life

Synthesis of Xanthurenic Acid Analogs to Interrogate Their Use in the Investigation of Plasmodium

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Malaria is a mosquito-borne infectious disease affecting humans and animals. It is transmitted to human beings by the *Plasmodium* parasite via a bite of an infected female Anopheles mosquito.

Plasmodium parasites have a complicated cycle and have developed a multi-drug resistance to currently available medications, which not only target the asexual symptom-causing parasitic forms, but the presence of transmissible gametocyte reservoirs, “the sexual stage”, in various asymptomatic individuals could potentially reintroduce malaria cases in areas where malaria has been fully eliminated.

Therefore, to fully eradicate malaria across the globe, it is imperative to develop either a viable drug or vaccine that could potentially block human-vector transmission by targeting different stages of the Plasmodium life cycle to discontinue the sexual developmental process. We envisioned blocking this transmission by synthesizing various new **Xanthurenic Acid**, a Gametogenesis-Activating Factor” analogs as our target towards new drug development.

SURFACE FUNCTIONALIZATION OF GOLD NANOSPHERES IN BIOLOGICALLY RELEVANT SOLUTIONS WITH DIVERSELY FUNCTIONALIZED PEPTOIDS

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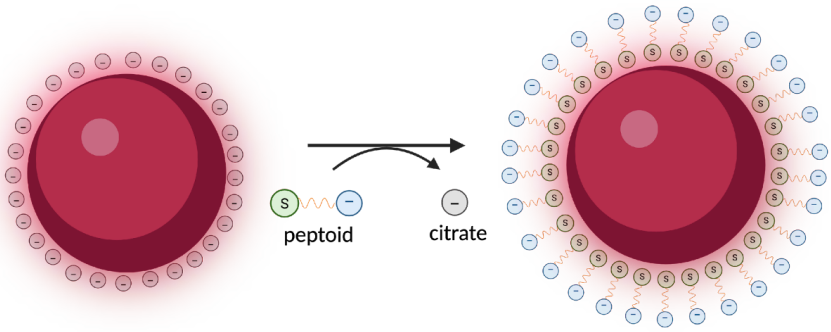
Colloidal gold nanoparticles (AuNPs) must be surface-functionalized with capping ligands to be utilized in aqueous environments. These ligands simultaneously maintain colloidal stability and apply a unique chemical identity to AuNPs. We will present our work employing peptoids, N-substituted glycine oligomers, as capping ligands for 10 nm gold nanospheres in aqueous dispersions. While both peptides and polymers have previously served this role, peptoid capping ligands offer several distinct advantages. Most notably, they can incorporate a wider diversity of functionality as side chains than peptides or polymers, including a wide range of charged groups that allow electrostatic repulsion of AuNPs. Peptoids also offer stability against proteolytic degradation which often limits peptide suitability in many biological applications. We will present our results correlating peptoid molecular structure with AuNP dispersion in varied aqueous solutions. We have further quantified peptoid-AuNP surface coverage and compared these to assess important molecular features for AuNP stabilization. Lastly, we will detail our characterization of the hydrodynamic radii, zeta potential measurements of peptoid-capped AuNPs.



Synthesis and Testing of Class II Selective Histone Deacetylase Inhibitors

Andrea Van Engen-Ver Beek and Mary Kay Pflum*

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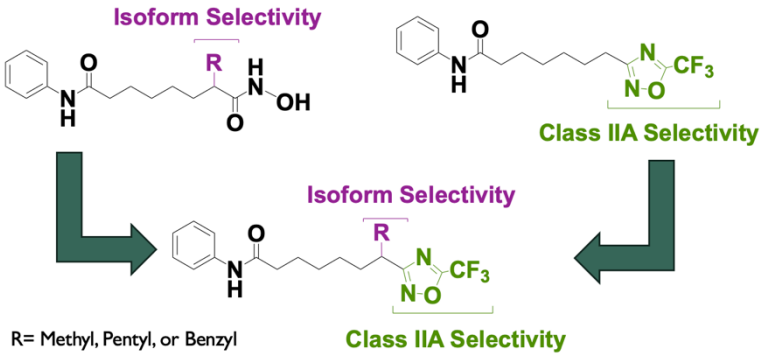

Histone deacetylase (HDAC) proteins involved in epigenetics, are unregulated in cancer, neurodegenerative disorders, cardiovascular conditions, and other diseases. Given their involvement in various pathologies, HDAC proteins have emerged as promising therapeutic targets. While current HDAC inhibitors (HDACi) show clinical promise, many lack selectivity. This project aims to assist in development of inhibitors for class IIa HDAC proteins (HDAC4, 5, 7, 9), and HDAC6 enhancing therapeutic precision. Our approach is divided into two specific aims: 1. Current class IIa HDAC inhibitors do not distinguish between HDAC4, 5, 7, and 9. To generate intra-class IIa selective inhibitors, two modifications will be applied to the existent HDAC inhibitor SAHA (Vorinostat): a. replacing the metal-binding group with a trifluoromethyl oxadiazole (TFMO)[1] to make class IIa selective. b. introducing a functional group at the C2 position of the linker[2] region to distinguish between class IIa isoforms. By combining modifications in two regions of the compound, we hypothesize that intra-class IIa selectivity can be achieved (Scheme). 2. Unlike other HDAC proteins, HDAC6 has two catalytic domains (CD1 and CD2)[3]. However, which domain existing inhibitors target is not yet known due to inefficient assays[4]. The current assays favor CD2 over CD1 resulting in a lack of information on CD1 potency. Thermal shift assay (TSA) will be developed to characterize the inhibition of each domain, facilitating the design of domain selective inhibitors. By developing selective inhibitors for class IIa HDAC proteins and a biological tool to study CD1 and CD2 in HDAC6, we seek to improve targeted therapeutic strategies for diseases associated with HDAC protein. Developing selective HDAC inhibitors not only advances fundamental understanding of HDAC biology but also supports the creation of safer, more effective therapeutics. This work aligns with my career goal of contributing to drug development in the pharmaceutical industry. With a strong foundation in chemistry, I aim to work within interdisciplinary teams to translate scientific discoveries into treatments that address unmet medical needs.

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Synthesis of Chiral Aromatic Heterocycles: Rhodium-Catalyzed Cyclization of Sulfonimidamides and Sulfondiimidamides

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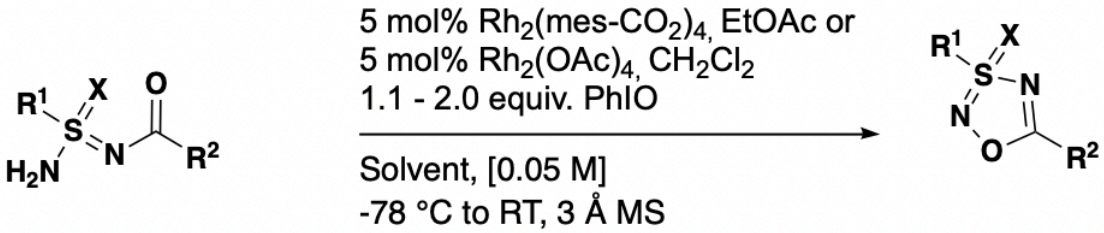
Since their turn of the century renaissance, sulfonimidamides (SIAs) have remained valuable motifs with various applications in medical chemistry, agriculture, and catalysis.[1] In addition to being able to possess a configurationally stable and stereogenic center, SIAs contain an imidic nitrogen which allows for a wider breadth of structural diversity and tunability compared to its oxy-analogue, sulfonamide.[2] Despite their known utility, there remains limited methodologies capable of accessing endocyclic SIAs. The diaza variant, sulfondiimidamides (SDAs), have fewer examples still in literature and industry.[3] Herein, we report the intramolecular cyclization of *N*-acylated SIAs and SDAs in the presence of a dirhodium catalysts and a hypervalent iodine oxidant to form novel five-membered aromatic heterocycles. Reaction optimization was performed on a para-toluene *S*-substituted SIA to determine the impacts of catalyst, oxidant, solvent, and temperature on cyclization through quantitative NMR. The influence of electronics, steric encumbrance, and the hybridization of SIA *S*-substituents on the cyclization was then investigated, with seventeen substrates displaying moderate to excellent yields (43% - quant.). Various SDAs, including alky (67-74%), *para*-trifluoromethyl (41%) and *para*-dimethylamino (quant.) substrates, were also successfully cyclized, demonstrating the robust nature of this methodology.



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LATE-STAGE INSTALLATION OF STRAIN-RELEASE WARHEADS FOR COVALENT INHIBITOR DEVELOPMENT

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Covalent inhibition has emerged as a powerful strategy in drug discovery. Expanding the diversity of covalent reactive groups (CRGs) is important for accessing new chemical space and expediting covalent inhibitor design. We report the development of a new class of cysteine-selective CRGs that leverage strain-release reactivity. To enable rapid exploration of this chemical space, we have developed novel reagents and synthetic methods that allow the installation of the CRG onto complex, heterocycle-rich pharmaceutical scaffolds through late-stage functionalization. Further diversification at a highly modular sulfur center, while preserving the reactive CRG, enables the tunability of the covalent inhibition. This platform provides efficient access to new covalent inhibitor candidates without requiring time-consuming de novo synthesis of each target molecule. Further studies introducing new CRGs with distinct σ-bonding character at sulfur, expanding the toolkit for covalent drug discovery and chemical biology, will be presented.

PHOTOCATALYTIC ALKENE HYDROFUNCTIONALIZATION UTILIZING ACRIDINE-LEWIS ACID COMPLEXES

Emily Jimenez, Daniel S. Brandes, Matthew R. Lasky, Olusayo J. Ogunyemia, Siqi Dong, Prof. Theodore Goodson III, Prof. Melanie S. Sanford*

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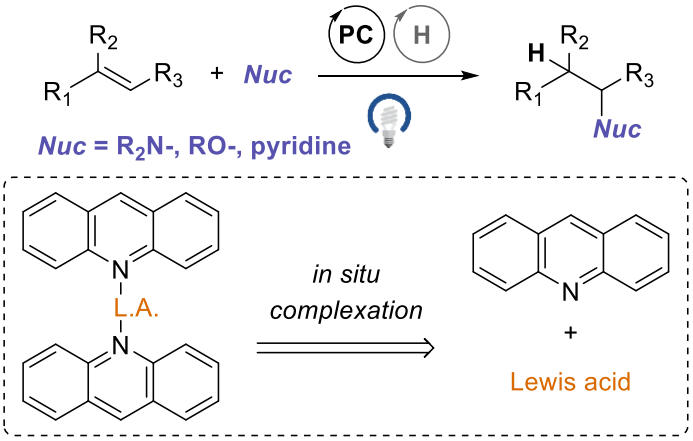
Photoredox catalysis has emerged as a mild and cost-effective approach for achieving organic transformation by harnessing energy from visible light and converting it to chemical energy. With the ability to access substrates that are otherwise unreactive, this methodology has been used in a wide range of fields. Acridinium photocatalysts with various substituents, including protonation at the *N*-position, have been widely explored and applied in many areas.[1,2] Our lab reported a novel class of photocatalysts composed of acridine derivatives and Lewis acids.[3] Compared to traditional acridine-based photocatalysts, these systems are both inexpensive and highly modular. Furthermore, they have excited state potentials of up to +2.65V vs SCE, thus enabling reactions with substrates that were previously low-yielding or completely inaccessible. The goal of this project was to explore the reactivity of these modular catalysts by applying them to the hydroetherification, hydration, hydropyridination, and hydroamination of alkenes. For each transformation, different catalytic systems have been optimized, taking advantage of the modularity of these catalysts by utilizing various Lewis acids in different combinations. Transient absorption studies have shown that differences in reactivity of these systems may be due to differences in the rate of formation of the key anethole radical cation intermediate. Future work will involve characterization of these catalysts, where we hypothesize that differences in reactivity will correlate to differences in photophysical properties. Overall, we are working toward developing a modular photocatalyst that can be quickly screened for any desired photophysical method or transformation.



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DESYMMETRIZATION OF BENZYLIC DIFLUOROMETHYLENE UNITS FOR THE CONSTRUCTION OF FLUORINE-CONTAINING STEREOCENTERS

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Organofluorine molecules are prevalent in a variety of industries and are particularly prominent amongst useful bioactive molecules; fluorocarbons comprise more than 20% of marketed pharmaceuticals and more than 50% of marketed agrochemicals.[1,2] Installing the small, electronegative fluorine atom can lead to prolonged metabolism and improved bioavailability while minimizing steric perturbation.[3] Despite the relevance of organofluorine molecules in pharmaceuticals, less than 1% of all fluorine-containing medicines feature a C–F stereocenter.[4]

An attractive fluorination site is the benzylic position, considered a "metabolic soft spot" in bioactive molecules because of the weak C–H bond.[5] Substitution here with fluorine may block deleterious metabolic pathways, impart beneficial pharmacokinetic properties, and allow for construction of fluorine-containing stereocenters. Current methods to form benzylic C–F bonds often rely on harsh reagents and directing groups to provide an enantioenriched product. We propose an alternate route to the enantioenriched, fluorinated benzylic position by desymmetrization of the aryl difluoromethylene through selective alkylation.

In 2020, the Hartwig group demonstrated the asymmetric alkylation of allylic *gem*-difluorides, utilizing an electron rich iridium catalyst and fluorophilic lithium to enact a "push-pull" strategy for mono-selective activation and substitution of the strong C(sp^3)–F bond (**Figure 1A**).[6] One example of benzylic desymmetrization was described, employing palladium catalysis. Herein, we report advancements in the optimization, scope, and mechanistic understandings of this transformation for the construction of enantioenriched fluorine-containing benzylic stereocenters (**Figure 1B**).

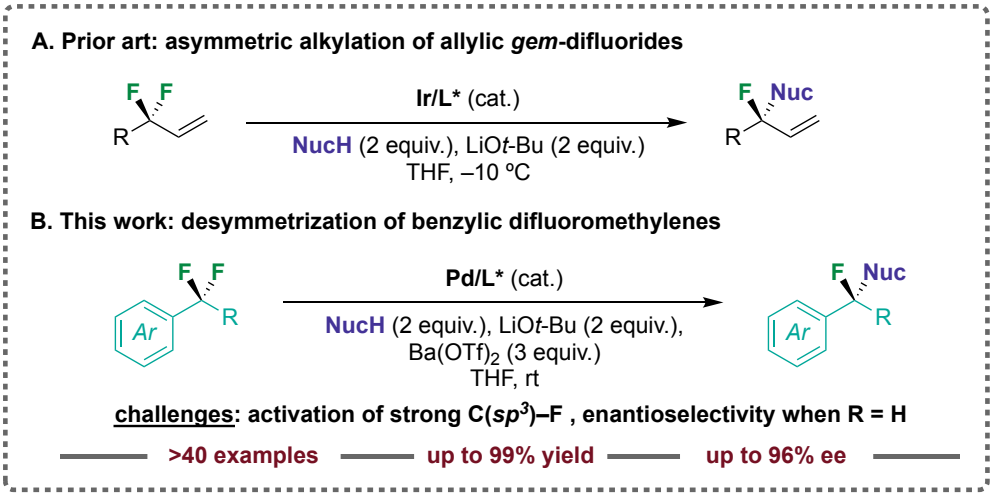

Figure 1. *Methods for desymmetrization of the difluoromethylene unit.*

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MINI-PROTEIN-MEDIATED DELIVERY OF GENE EDITING ENZYMES

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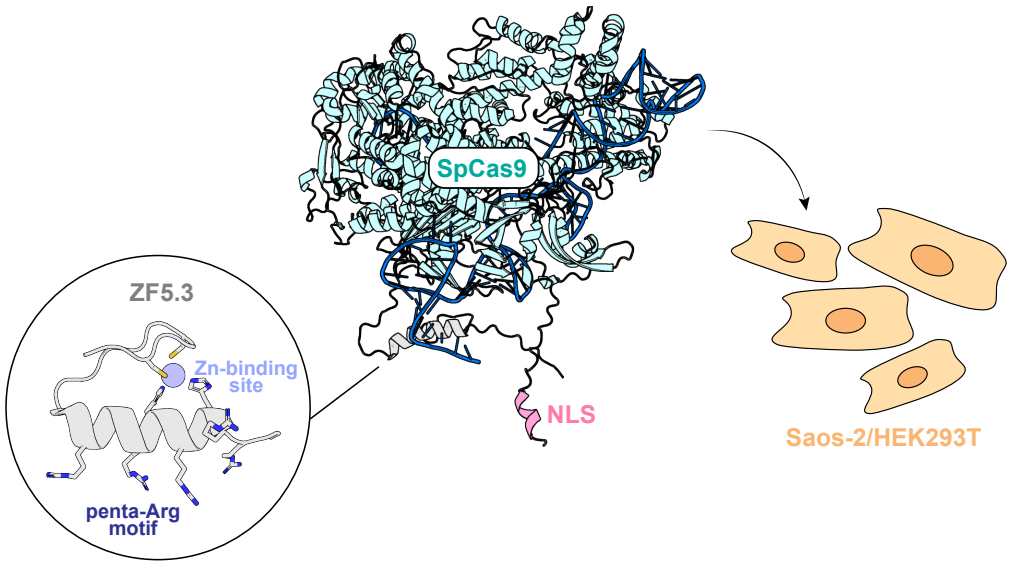
CRISPR-Cas technology is a precise and efficient genome editing tool which has considerable potential for treating genetic diseases. Delivery of CRISPR ribonucleoproteins (RNPs), which consist of a Cas enzyme and guide RNA (gRNA), has advantages over other delivery methods such as viral vectors, including accelerated editing and reduced off-target effects. However, effective delivery of RNPs remains challenging due to their substantial size, charge, and complex composition. Direct delivery by use of cell-permeant mini-proteins could provide a simple and broadly applicable therapeutic method. The Schepartz lab has designed a mini-protein called ZF5.3 which escapes from late endocytic vesicles and traffics protein cargo to the cytosol of mammalian cells. A penta-arginine motif aids in cellular uptake and endosomal escape, while a zinc-binding site participates in pH-dependent unfolding which is implicated in the escape mechanism. In addition, a re-designed mini-protein called AV5.3 contains an altered zinc-binding site which escapes from earlier endocytic vesicles at a higher pH. This allows for delivery of acid-sensitive cargo with preserved activity and maintained delivery efficiency. Here we aim to utilize ZF5.3 and AV5.3 to traffic gene editing agents to the cytosol and nucleus. Protein constructs were designed as fusions between ZF5.3 or AV5.3, SpCas9, and an NLS (nuclear localization signal), while gRNAs were designed for DNA cleavage activity assays. Trafficking to the cytosol and nucleus was measured by fluorescence correlation spectroscopy, and improved trafficking efficiency was demonstrated with mini-protein fusion RNPs compared to SpCas9 RNP. *In vitro* assays showed that the DNA cleavage activity of SpCas9 is not impaired by fusion to mini-proteins, and GFP expression disruption assays will be performed to determine whether delivery of RNPs as mini-protein fusions leads to greater gene editing activity in cells.



EFFORTS TOWARD AN ELEGANT SYNTHESIS OF HOMOTRYPTAMINES AS POTENTIAL SSRIs

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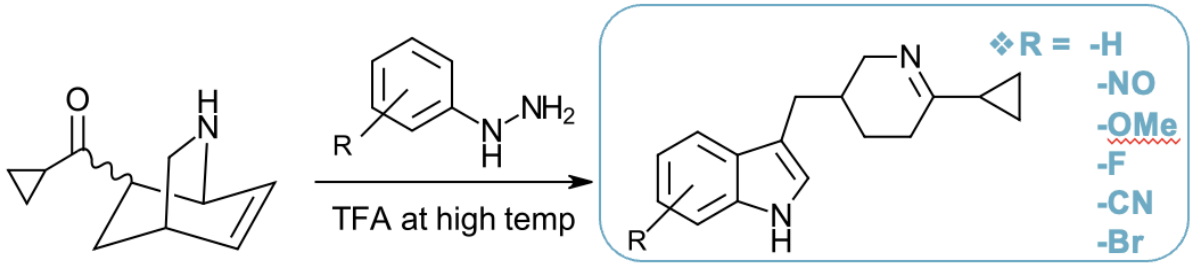
Several reports have assessed the anti-depressant like properties of the homotryptamine scaffold in serotonin transporter (SERT) inhibition assays. The serotonin transporter (SERT) is a monoamine transporter protein responsible for the reuptake of serotonin from the synaptic cleft back to the presynaptic neuron. Many selective serotonin reuptake inhibitor (SSRI) and tricyclic antidepressants work by binding to SERT thus reducing serotonin reuptake and increasing the amount of serotonin available in the synapse. Previous reports found that a more conformationally rigid propylamine chain increased potency in SERT inhibition activity of homotryptamine derivatives. We thus envisioned the synthesis of a library of rigid homotryptamine targets - both racemic and enantiopure - using a novel and complex rearrangement reaction. Current work is underway to efficiently synthesize and assess the therapeutic potential of our unique and rigid homotryptamine analogues.

- Key rearrangement reaction
- Will investigate various R groups and confirm endo vs exo mechanism



DESIGN, SYNTHESIS, AND ANTIBACTERIAL ACTIVITY OF NOVEL DERIVATIVES OF NATURAL PRODUCTS

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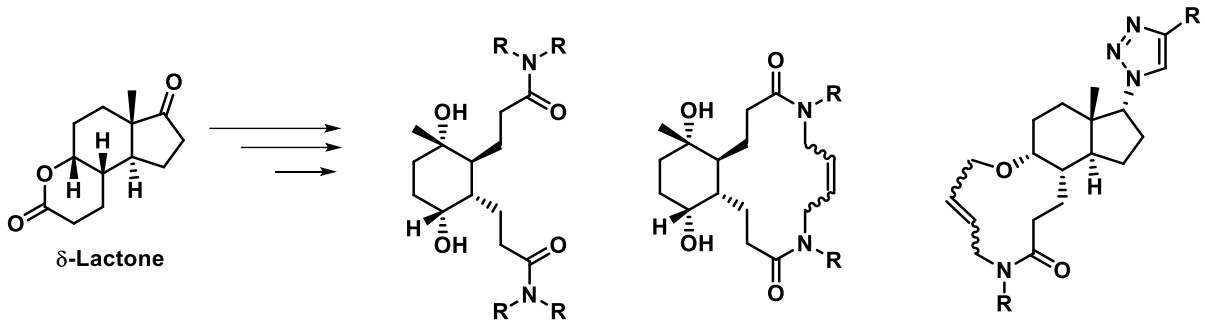
Natural products have long played a central role in drug discovery, particularly in infectious diseases. Their structural complexity and well-defined ligand–protein binding motifs make them valuable starting points for the design of bioactive molecules. However, the rate of discovery of new active natural products has declined in recent decades, with increasing instances of rediscovery of known scaffolds, particularly in antibacterial drug discovery, where natural products are extensively utilized. This limitation highlights the need for alternative strategies to access structurally diverse, biologically relevant chemical space.

Employing natural products as starting materials to create new scaffolds is an underexplored strategy that can offer structurally complex molecules with physicochemical properties analogous to those of natural products. These derivatives can be accessed as rapidly as synthetic compounds because natural products provide excellent frameworks for site-selective and stereoselective transformations. This approach adds further diversity to the complexity already installed by nature.

In this work, we investigate the non-traditional utilization of natural products by transforming compounds with little or no reported biological activity into potentially bioactive scaffolds. Specifically, δ-lactone, a steroidal natural product, and stevioside, a diterpene glycoside, are chemically modified to incorporate amide functionalities, triazole moieties, and macrocyclic architectures, enabling the generation of a diverse library of compounds.

The resulting derivatives are being evaluated for antibacterial activity against ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species), which are responsible for a significant proportion of multidrug-resistant infections. By introducing structural diversity into inactive natural product frameworks, this work aims to expand the accessible chemical space for drug discovery and identify new scaffolds with potential therapeutic relevance.



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CHALLENGES IN COMMERCIAL DEVELOPMENT OF A TELESCOPED TOSYLATION-CYCLIZATION REACTION FOR THE SYNTHESIS OF MEVROMETOSTAT

Amber M. Johnson*, Nicole Andersen, Michael Butler, Teri Hochdorfer, Sarai Lara-Boykin, Tyler Potter, Robert Pritchard, Sruthi Turaga, Matt Weekly

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One of the transformations in the synthesis of the oncology candidate Mevrometostat is a two-step one-pot alcohol tosylation followed by intramolecular cyclization. The transformation appears simple at first glance, relying on basic organic chemistry, but faced numerous challenges in development, including a challenging crystallization, a complex form landscape, and a poison impacting the catalyst in the subsequent step. Moving into production, the problem solving continued with identifying and mitigating new impurities and developing a deeper understanding of potential failure modes. The step was successfully scaled into commercial production to deliver metric tons of material.

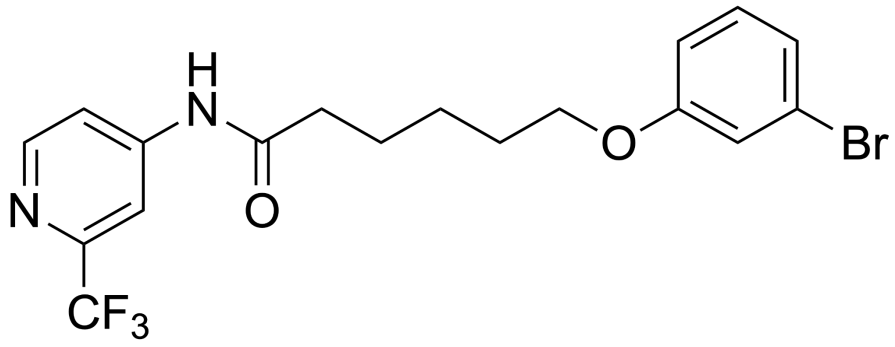
Poster Abstracts for Session 2 (5:45 – 6:30pm)

INVESTIGATION OF COLISTIN ADJUVANTS IN GRAM-NEGATIVE PATHOGENS

Angelina Lim, Laura Miller Conrad

Department of Chemistry, San José State University, San José USA, angelina.lim@sjsu.edu, laura.miller.conrad@sjsu.edu

Acinetobacter baumannii is an opportunistic and antibiotic resistant Gram-negative bacterium that targets immunocompromised patients as a secondary infection. Patients have limited options to clear the infection due to *A. baumannii*'s resistance to antibiotics. Our lab has previously reported antibiotic adjuvants that potentiate the activity of colistin in *Pseudomonas aeruginosa*, another Gram-negative bacterium.[1] Here we characterize the ability of the combination therapy to potentiate colistin activity in *A. baumannii* using static minimum inhibitory concentration assays. In the future, we seek to resensitize antibiotic resistant strains through the antibiotic-adjuvant combination as well as lower the concentration of antibiotic the patient needs to take.



(1) Zhang, Z.; Ortega, D.; Rush, A.; Blankenship, L. R.; Cheng, Z. J.; Moore, R. E.; Tran, M. L. N.; Sandoval, L. G.; Aboulhosn, K.; Watanabe, S.; Cortez, K. S.; Perlman, D. H.; Semmelhack, M. F.; Miller Conrad, L. C. Antibiotic Adjuvant Activity Revealed in a Photoaffinity Approach to Determine the Molecular Target of Antipyocyanin Compounds. *ACS Infect. Dis.* **2021,** *7*(3), 535–543.

STRUCTURE-ACTIVITY RELATIONSHIP AND BINDING MODE ANALYSIS OF A NEW CLASS OF RECEPTOR-INTERACTING PROTEIN KINASE 3 INHIBITORS

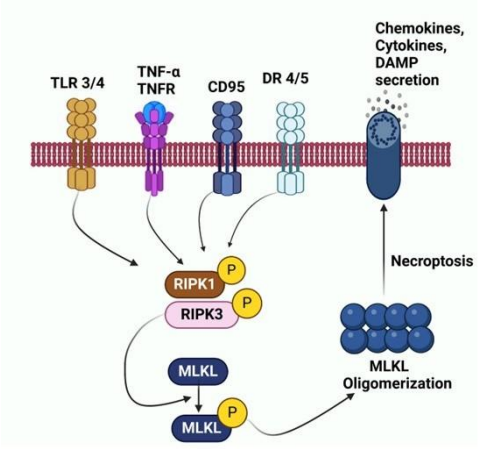
Manu Bala[1], Raghavender Boda[1], Anantha L. Duddupudi[1], Ghada Ali[1], Alexei Degterev[2], Siddharth Balachandran[3], and Gregory D Cuny[1*]

[1]Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX; [2]Department of Developmental, Molecular & Chemical Biology, Tufts University School of Medicine, Boston, MA; [3]Center for Immunology, Fox Chase Cancer Center, Philadelphia, PA.

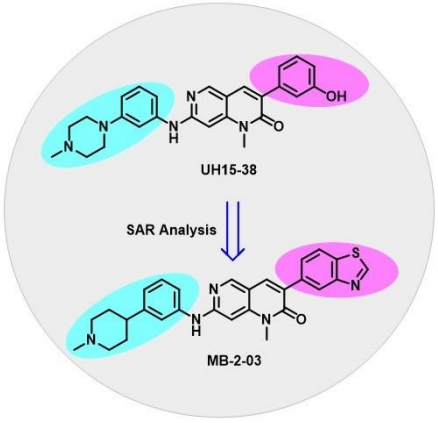
mbala@cougarnet.uh.edu

Abstract

Necroptosis is a programmed cell death triggered by death receptors when apoptosis fails. It has been linked to numerous diseases, such as cancers, liver diseases, cardiovascular diseases, neurodegenerative disorders, pancreatic diseases, lung diseases, and kidney diseases. Necroptosis is highly dependent on the protein receptor-interacting protein kinase 3 (RIPK3) and its substrate mixed lineage kinase domain-like (MLKL) pseudo-kinase, the fundamental players of the necroptotic pathway. Activated RIPK3 leads to MLKL phosphorylation, which results in MLKL oligomerization and translocation to the plasma membrane, triggering cell rupture and release of chemokines, cytokines, and damage-associated molecular patterns (DAMPs).



Molecular Mechanism of Necroptosis



Our previous studies identified UH15-38 as a potent inhibitor of RIPK3-mediated necroptosis (e.g., TNF-induced cell death in FADD-deficient JK cells), with an IC_{50} of 205 nM. Herein, we report a structure–activity relationship (SAR) and binding mode analysis of UH15-38 and its analogs. Substitution of the phenol ring with a benzothiazole moiety significantly enhanced RIPK3 inhibitory activity, yielding MB-2-03 with an IC_{50} of 49 nM. Additionally, derivatives with a piperidine substituent at the 3- or 4-positions of the solvent-exposed phenyl ring retained comparable potency. Molecular docking studies of the optimized compound MB-2-03 demonstrated a strong binding affinity to the DFG-in active conformation of RIPK3, consistent with the binding mode of the lead compound UH15-38.

From Acrylamides to Nickelacycles: A One-Pot, Ligand-Directed Strategy

Yashmeen[1] and Brad Carrow[1]*

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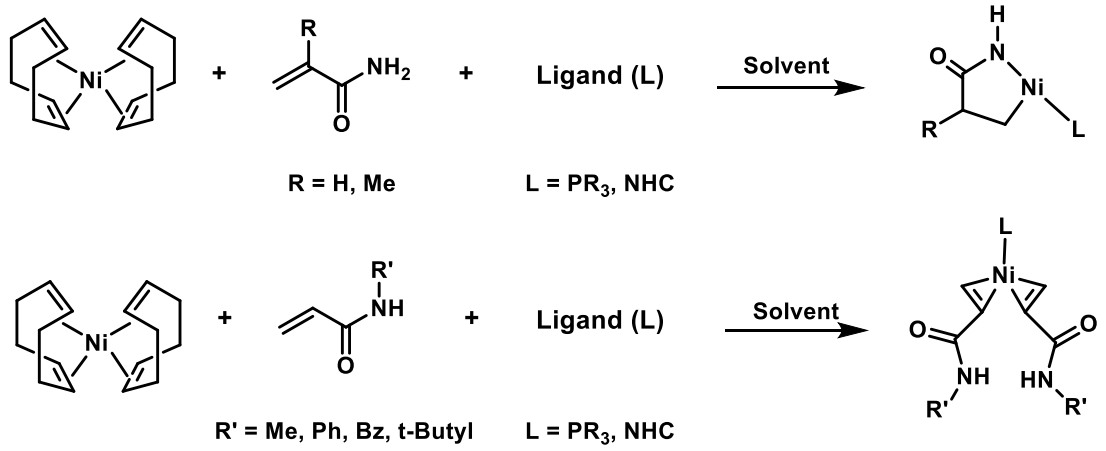
yyashmee@cougarnet.uh.edu

Nickelacycles are key intermediates in catalytic transformations involving carbon-carbon and carbon-heteroatom bond formation, including C–H functionalization, reductive coupling, and carbon dioxide activation. Conventional approaches to nickelacycles typically require multistep synthesis of well-defined Ni(0) complexes bearing phosphine or N-heterocyclic carbene (NHC) ligands, followed by oxidative cyclization of participating substrates.

Herein, we report a one-pot, ligand-controlled strategy for the direct synthesis of nickelacycles from readily available acrylamides. In the presence of ancillary ligands, simple acrylamides undergo oxidative addition to Ni(0), affording nickelacycles in good yields without the need to pre-isolate ligand-supported Ni(0) precursors.

Sterics of ancillary ligand played a decisive role in controlling product nuclearity. Less hindered phosphines such as tricyclohexyl phosphine (PCy_3) and bulky N-hetrocyclic carbene (NHC) such as IAd favored oligomeric nickelacycles, whereas more sterically encumbered N-hetrocyclic carbene IMes, yielded asymmetric dimeric nickelacycle. In contrast, N-alkyl and N-aryl substituted acrylamides do not form nickelacycles, instead stable π-bound Ni(0) complexes were obtained.

Although substrate scope is currently limited, this operationally simple and tunable approach provides direct access to nickelacycles. Moreover, the observed ligand-dependent control over nuclearity suggests that further steric tuning may enable the isolation of monomeric nickelacycles, providing well-defined organonickel intermediates relevant to catalysis and mechanistic studies.

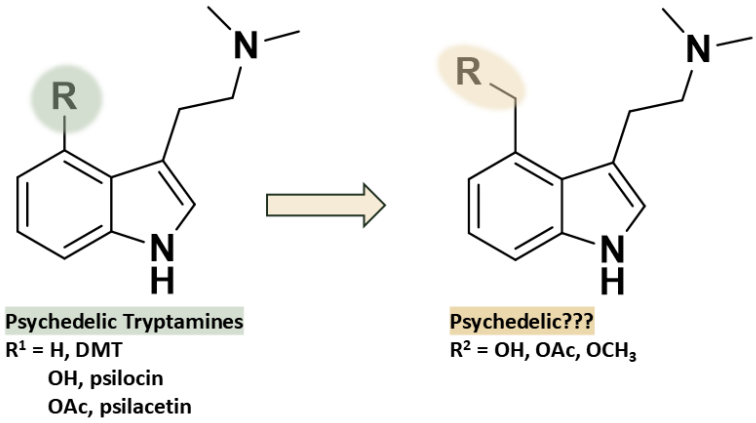


Synthesis of psychedelic-adjacent tryptamines

*Jeanine Yacoub[1,2], Elena Bray, Ph.D[2], Jacqueline von Salm, Ph.D.[2]
[1]Psilera, Inc., Tampa, FL
[2]Department of Chemistry, University of South Florida, Tampa, FL
Address: 4202 E. Fowler Ave, Tampa, FL 33620
Email: jyacoub@usf.edu

Abstract:
Classic psychedelics, including tryptamines like N,N-dimethyltryptamines (DMT) and psilocybin act as 5-HT_{2A} receptor agonists and have shown potential in treating central nervous system (CNS) disorders. Modifying the functionality at different positions of the indole core of tryptamines have led to new CNS medications, such as the triptan drug class. Recent efforts in exploring the functionality at the 4-position have led to new prodrugs, ethers, and/or salt forms of psilocin. However, these approaches only scratch the surface for potential derivatives of psilocin. We are developing novel compounds by expanding the diverse functionality at the 4-position on the tryptamine scaffold to identify new serotonergic agents with therapeutic potential. Herein we will highlight the synthesis of these new molecules and share preliminary biological data.

Graphical Abstract:



DEVELOPMENT AND MECHANISTIC INVESTIGATION OF 1,5-HEXADIENE-ENABLED NICKEL-CATALYZED REDUCTIVE CROSS-COUPLING REACTIONS

Anika Monga, John Montgomery*

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anikaa@umich.edu

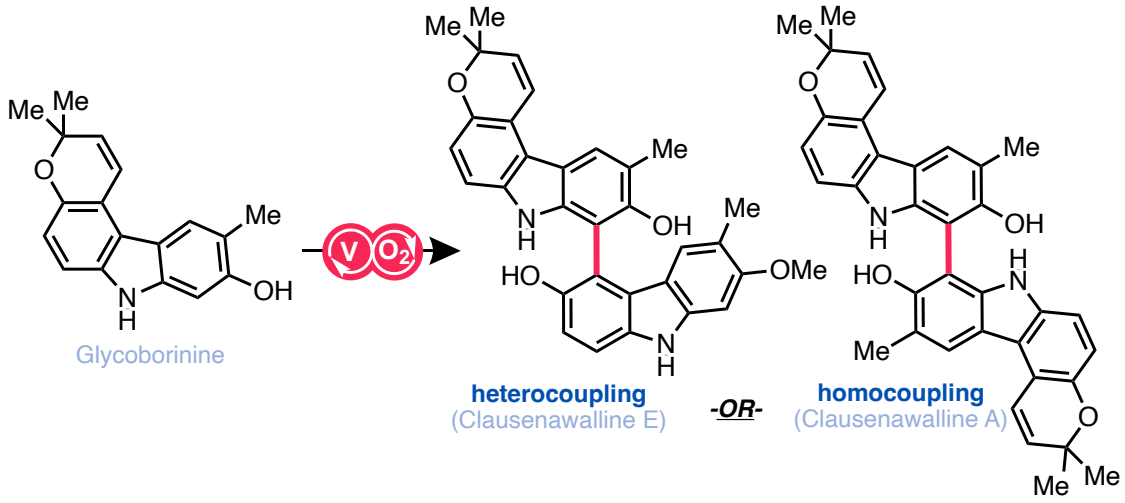
Olefin additives serve as valuable ligands in organometallic reactions, enhancing cross-coupling processes through their unique reactivity. In a nickel-catalyzed two-component coupling of aliphatic aldehydes with unactivated bromides, 1,5-hexadiene significantly improves heterocoupled product selectivity, with novel mechanistic studies revealing its critical role in directing reactivity. Extending this concept, the presence of an acrylate enables a three-component reductive coupling to access aldol products. Across both transformations, 1,5-hexadiene proves essential, highlighting its broad utility and providing new opportunities to broaden the scope of these transformations through an improved understanding.

TOTAL SYNTHESIS OF DIMERIC CLAUSENAWALLINE NATURAL PRODUCTS

Cameron B. Berlin, Hanna F. Roenfanz, Madeleine Salwen, Sai Nehete, Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States
email: cbberlin@berkeley.edu

The first total syntheses of glycoborinine, clausenawalline A, and clausenawalline E were achieved. The key step employed a vanadium-catalyzed oxidative coupling of two hydroxycarbazole monomers. High-throughput experimentation was used to identify conditions favoring selective heterocoupling of these monomers that possess similar redox potentials. A combination of a vanadium catalyst and 4-acetamido-TEMPO gives rise to greatly enhanced cross selectivity relative to the vanadium catalyst alone. Conditions to selectively form homodimer clausenawalline A or heterodimer clausenawalline E as the major product were found.[1]



[1] Berlin, C. B.; Roenfanz, H. F.; Salwen, M.; Nehete, S.; Kozlowski, M. C. *Org. Lett.* **2024**, *26(25)*, 5243–5247.

Accessing Novel Main-Group Organometallic Functional Groups using Bulky Ligand Scaffolds

Josiah Sánchez, John S. Wenger, Timothy C. Johnstone*

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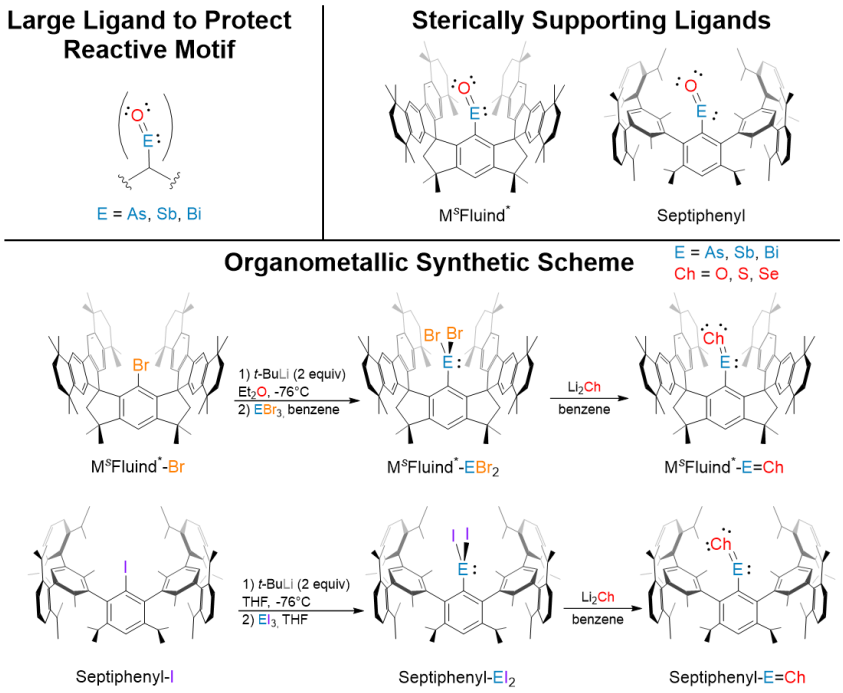
jsanc274@ucsc.edu

Abstract:

Expensive, Earth-scarce metals are frequently used to mediate important organic transformations. In addition to their cost, mining these elements is more energy-intensive and less sustainable compared to many Earth-abundant elements. Although the earth-scarce d-block metals frequently engage in chemistry inaccessible to p-block elements, new main-group organometallic motifs continue to be developed that achieve similar and/or unprecedented transformations compared to their transition-metal counterparts. Notably, highly polarized unsaturated bonds between heavy electropositive atoms and lighter electronegative atoms have demonstrated exceptional reactivity with a range of otherwise inert small-molecule substrates (e.g., C–F and Si–F bond activation). However, molecules featuring such polarized bonds are predisposed to oligomerize, thereby quenching their reactivity. This project focuses on isolating the first molecule featuring a terminal oxo group bound to antimony(III), and comparing its reactivity to other main group oxides. I employed a kinetic stabilization approach, using large bulky ligands (septiphenyl and M^{s}Fluind*) to prevent oligomerization. In preliminary studies, we have accessed terminal sulfides and selenides of antimony(III) using the M^{s}Fluind* scaffold.

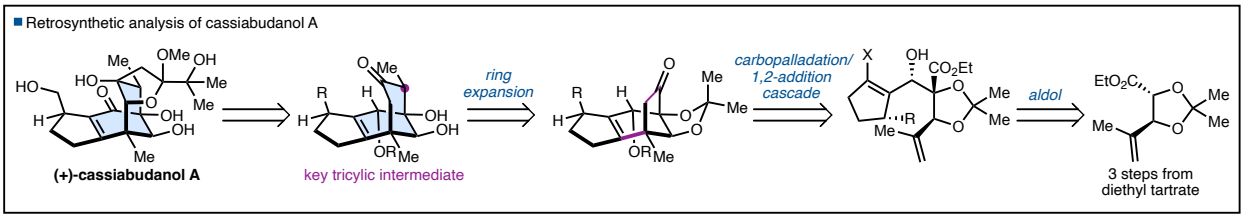


A Pd-Catalyzed Cascade Strategy Towards the Total Synthesis of (+)-Cassiabudanol A

Katelyn S. Gallagher, Jessica Wang, Sara Dibrell Zott, Priscila Marquez, Sarah E. Reisman*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California, USA
kgallagh@caltech.edu

(+)-Cassiabudanol A is a di*seco*-isoryanodane diterpenoid that exhibits potent immunostimulant activity.[1] It's highly oxidized 5/6/6/5 tetracyclic framework contains eight stereocenters, six of which are contiguous within the carbocyclic bicyclo-[3.3.1]-nonane core. Retrosynthetically, the molecule can be simplified to a key tricyclic intermediate via late-stage installation of the tetrahydrofuran ring. Ring expansion and palladium catalyzed carbopalladation/nucleophilic addition cascade allowed for swift access to the desired tricycle from a tartrate derivative. Through this cascade strategy, the bicyclic core of cassiabudanol A is accessed in just nine steps from (*L*)-diethyl tartrate. Ongoing synthetic efforts focus on tetrahydrofuran ring installation and completion of the natural product. Further investigations into this carbopalladation/nucleophilic addition cascade could provide a general approach towards the construction of similar carbocyclic bicycles present in bioactive molecules.



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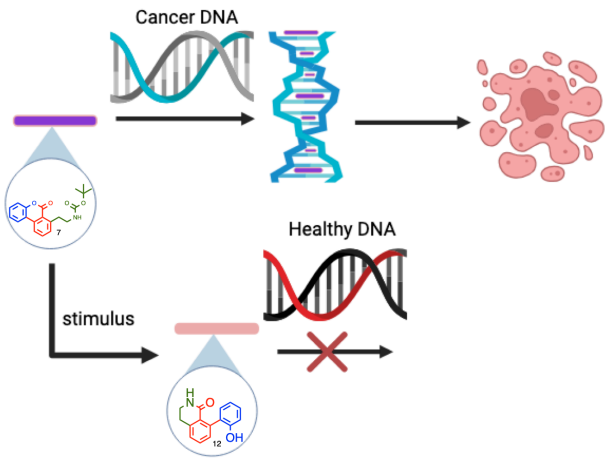
[1] Zhou, H.; Guoruoluo, Y.; Tuo, Y.; Zhou, J.; Zhang, H.; Wang, W.; Xiang, M.; Aisa, H. A.; Yao, G. Cassiabudanols A and B, Immunostimulative Diterpenoids with a Cassiabudane Carbon Skeleton Featuring a 3-Oxatetracyclo[6.6.1.0 ^{2,6} .0 ^{10,14}]Pentadecane Scaffold from Cassia Buds. *Org. Lett.* **2019**, *21* (2), 549–553. https://doi.org/10.1021/acs.orglett.8b03883.

Studies Towards the Synthesis and Evaluation of an Off-Switchable Anticancer Agent

Kathleen McIntyre and Dr. Herman Nikolayevskiy*

Department of Chemistry, University of San Francisco, San Francisco, California, USA
krmcintyre@dons.usfca.edu

Many current anticancer treatments do not have adequate selectivity between cancer cells and healthy cells, causing negative side effects that the patient has to endure. As a result, there is a need for drugs that can differentiate cancer cells from healthy cells. DNA intercalators are flat, planar molecules that bind noncovalently to DNA, altering its conformation and resulting in altered gene expression, inhibition of DNA replication, and can cause cell death. DNA intercalators that can be triggered to transform from planar (active) to nonplanar (inactive) when interacting with normal cells while maintaining planarity in cancer cells can increase the selectivity for this specific subset of anticancer drugs. An off-switchable benzochromenone intercalator was synthesized in 4 steps starting from a methyl ester using a Suzuki-Miyaura, Heck, Hydrogenation, and Curtius Rearrangement as key synthetic transformations. The synthesis of the nonplanar benzochromenone was completed using the same set of reactions, but in a different order. Future work will involve testing the synthesized DNA intercalators in Isothermal Titration Calorimetry (ITC) binding assays to see if they have different levels of DNA-binding, with the aim of eventually increasing the selectivity of anticancer drugs.



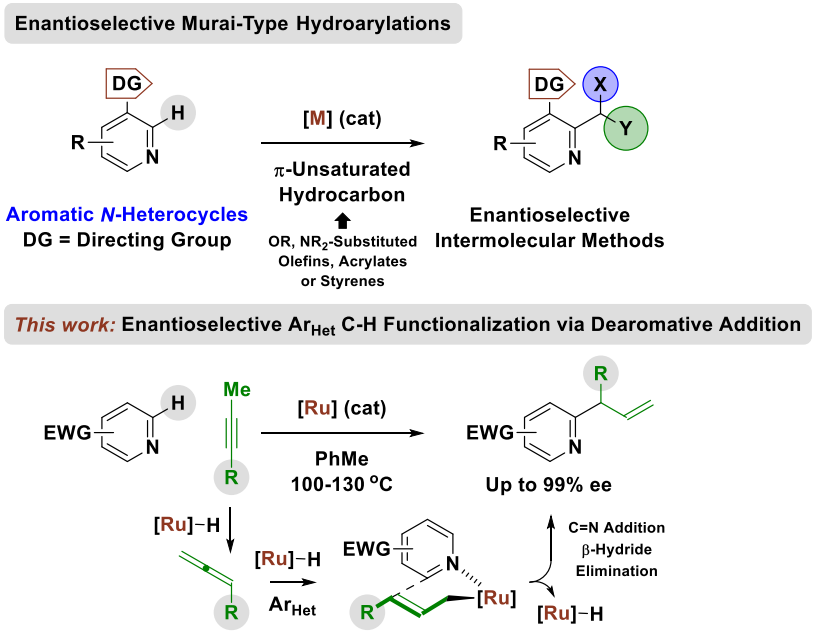
ENANTIOSELECTIVE *N*-HETEROARYL C–H FUNCTIONALIZATION FOR PIPERIDINE–AZINE CONJUGATION VIA DEAROMATIVE ADDITION-HYDROGEN AUTO-TRANSFER

Seoyoung Lee,[1] Yhin Sarah Teoh,[1] Pei-Pei Xie,[2] Erin M. McManus,[1] Brandon I. Gonzalez,[1] Tate A. Claggett,[1] Peng Liu,[2] and Michael J. Krische[1]*

[1] Department of Chemistry, University of Texas at Austin, Austin, Texas 78712, United States
[2] Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States
seoyoung27@utexas.edu

Piperidines, azetidines, and *N*-heteroarenes are privileged motifs in pharmaceutical chemistry, yet direct asymmetric C–C bond formation that links these fragments remains challenging, especially without premetalated reagents, directing groups, or Lewis acid activation. In contrast, hydrogen auto-transfer offers a catalytic strategy for C–C bond formation in which transient organometallic nucleophiles are generated in situ from π-unsaturated pronucleophiles, avoiding preformed organometallic reagents and stoichiometric metallic byproducts.

This work describes the first enantioselective *N*-heteroaryl C–H functionalization via dearomative addition-hydrogen auto-transfer. In this process, alkynes serve as latent allylmetal pronucleophiles, undergoing dearomative addition followed by β-hydride elimination to furnish products of C–H allylation. This strategy provides direct asymmetric access to piperidine–azine and azetidine–azine conjugates with high levels of enantioselectivity. Isolation of a dearomatized intermediate and DFT calculations support a dearomative pathway and show that the site of C–C bond formation is guided by the electronic structure of the *N*-heteroarene. Together, these studies establish alkynes as effective allylmetal pronucleophiles for enantioselective *N*-heteroaryl C–H functionalization.[1]



[1] Lee, S.; Teoh, Y. S.; Xie, P.-P.; McManus, E. M.; Gonzalez, B. I.; Claggett, T. A.; Liu, P.; Krische, M. J. *J. Am. Chem. Soc.* **2025**, *147*, 41946–41955.

EVALUATING THE FUNCTIONAL SELECTIVITY OF ENDOGENOUS D-AMINO ACID-CONTAINING NEUROPEPTIDES IN *APLYSIA CALIFORNICA*

Alisha Doda[1,2], Baba M. Yussif[1,2], James W. Checco[1,2]*

[1]Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE, 68588
[2]Nebraska Center for Integrated Biomolecular Communication (NCIBC), University of Nebraska-Lincoln, Lincoln, NE, 68588
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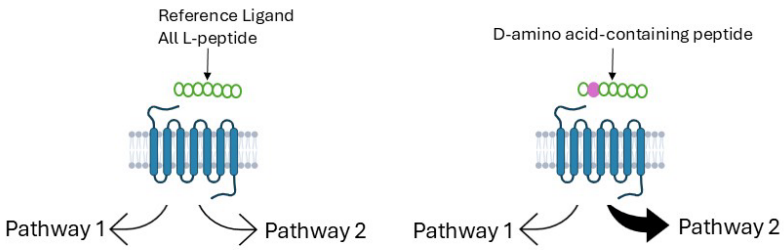
Some neuropeptides undergo a post-translational modification where an L-amino acid residue is converted into a D-amino acid residue. The resulting D-amino acid-containing peptides (DAACPs) have been found to have different biological functions as compared to the all-L-residue peptides. Despite the biological relevance, little is known about how endogenous L-to-D-residue isomerization in peptides impacts interactions with their cell surface receptors. Based on prior studies from our lab, we hypothesized that the isomerization of an L-amino acid residue to a D-amino acid residue in a peptide may lead to preferential activation of one signaling pathway over another, a naturally occurring form of functional selectivity. To test this hypothesis, we evaluated several signaling pathways for two of the known DAACP receptors, allatotropin-related peptide receptors 1 and 2 (*ap*ATRPR1 and *ap*ATRPR2) from *Aplysia californica*. We tested the activation of G protein-dependent pathways ($G\alpha_q$ and $G\alpha_s$), G protein-independent pathway, and phosphorylation of ERK (pERK) in transiently transfected HEK-derived (HTLA) cells using cell-based receptor activation assays to determine bias factors. For *ap*ATRPR1, the DAACP seems to be biased towards activation of $G\alpha_q$ pathway as compared to pERK and $G\alpha_s$ pathway. The DAACP also seems to preferentially activate G protein-independent pathway as compared to $G\alpha_q$ pathway for *ap*ATRPR1. For apATRPR2, the DAACP seems to show preferential activation of $G\alpha_s$ pathway as compared to $G\alpha_q$ pathway and $G\alpha_q$ pathway as compared to G protein-independent pathway. These results suggest that isomerization of the endogenous peptide ligands (all-L-peptide to DAACP) for receptors *ap*ATRPR1 and *ap*ATRPR2 leads to preferential activation of one signaling pathway over another for both receptors in HTLA cells. This research demonstrates how endogenous peptide isomerization can lead to functional selectivity and how nature utilizes isomerization to regulate downstream signaling pathways. Moreover, the presence of DAACPs across phyla suggests that cellular signaling involving peptide isomerization is not restricted to *Aplysia californica*, and the knowledge of functional selectivity could be relevant to other systems across the animal kingdom. This research provides a deeper understanding of the role of isomerization of peptides in regulation of neuropeptide-receptor signaling.

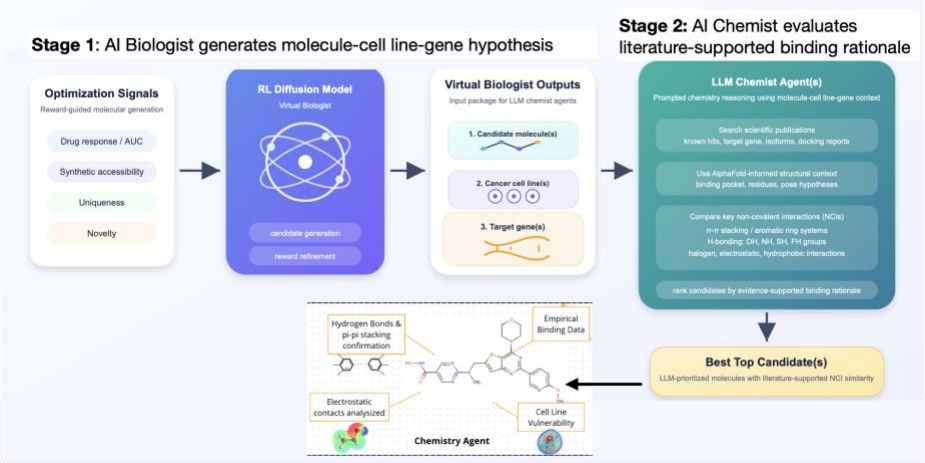


Reinforcement Learning-Guided Diffusion Models for Generation of Small Molecules with Biological Traits & Binding Rationale

Gisela A. González-Montiel, Brenda Nogueira, Olaf Wiest, Nitesh Chawla, Nuno Moniz*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana, USA
ggonzal6@nd.edu

We have implemented a latent-space framework for genotype-conditioned small molecule generation that extends a pretrained diffusional model[1] as a learnable perturbation reward with multi-objective optimization encompassing predicted drug response, physiochemical properties, and mechanistic binding signals. To incorporate biological plausibility, we extended our framework into a sequential three-agent large language model (LLM) pipeline that includes: BiologyAgent, ChemicalAgent, and ScoreAgent. The BiologyAgent extracts per-gene importance scores directly from the diffusion model's internal transformer attention weights, identifying cell-line-specific target genes from NeST ontology[2]. This jointly optimizes three reward axes – predicted sensitivity (AUC values), drug-likeliness (QED), and synthetic plausibility (SAS) – of which the latter two are non-differentiable due to discrete molecular SMILES decoding. Then the LLM ChemistryAgent produces a non-covalent interaction (NCI) analysis report. It retrieves literature on AlphaFold structure predictions and molecular docking studies specifically for the attention-grounded top genes. The report describes relevant chemical interactions—hydrogen bonds, π-π stacking, halogen bonds, electrostatic contacts, and hydrophobic interactions—between the candidate and the model-identified targets. Subsequently, the LLM ScoreAgent integrates the report to produce a structured JSON output with the final mechanistic plausibility score, a confidence estimate, key factors supporting the score, and flagged concerns. Together, our architecture introduces knowledge-driven reasoning grounded in the internal attention mechanisms of the diffusion model and real-world feedback loop. Ongoing work focuses on integrating our modular work across 15 evaluation cancer cell lines, enabling attention grounding in the LLM agents, which is critically design as a domain-agnostic, making it straightforwardly transferable to other generation problems.



[1] Kim, H., Bae, B., Park, M., Shin, Y., Ideker, T., & Nam, H. A genotype-to-drug diffusion model for generation of tailored anti-cancer small molecules. *Nat. Commun.* **2025**, *16*(1), 5628.
[2] Zheng, F., Kelly, M. R., Ramms, D. J., Heintschel, M. L., Tao, K., Tutuncuoglu, B., et al. Interpretation of cancer mutations using a multiscale map of protein systems. *Science* **2021**, *374*(6563):eabf3067.

Progress towards the synthesis of a trisaccharide from *Acinetobacter baumannii* ATCC19606

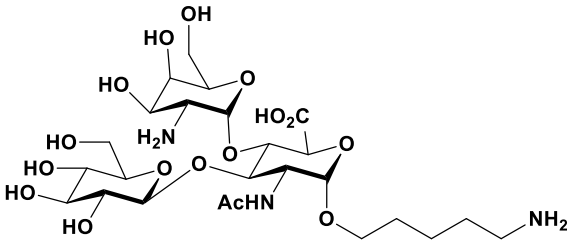
Helder Ombui[†], James M. Armstrong II[‡], Brandon Conrad[†], Justin Ragains[†*]

[†]*Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana, USA*

[‡]*Colonial Chemical Inc. South Pittsburg, Tennessee, USA*

hombui1@lsu.edu

Acinetobacter baumannii is a formidable pathogen in healthcare settings, known for its resistance to multiple antibiotics and its ability to cause serious infections in vulnerable populations[1]. Without treatment, infections can advance to septicemia and result in death. Over the years, this gram-negative pathogen has developed resistance towards some known antibiotics like carbapenem and therefore, there's an increasing demand for innovative preventative methods[2]. My research focuses on synthesizing oligosaccharides from the cell surface of *Acinetobacter baumannii* as a potential solution in the fight against infections it causes. The synthetic target lipooligosaccharide (LOS) is conserved in about 73% of *A. baumannii* strains[3]. We predict that a trisaccharide substructure of the LOS will be a useful tool in chemical immunology studies on *A. baumannii*. Herein I will report on progress towards the synthesis of this trisaccharide and other analogs of the LOS.



Synthetic target lipooligosaccharide (LOS)

[1] *Chem. Eur. J.* **2021**, *27*, 17444–17451
[2] *Org. Lett.* **2022**, *24* (19), 3461–3465
[3] *Microb. Genomics* **2023**, *9* (6)

A RADICAL MECHANISM FOR DIRECT CARBOXYLATION OF ELECTROPHILES *VIA* COOPERATIVE, TANDEM ELECTRON TRANSFER

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Department of Chemistry, University of California, Berkeley, California, USA
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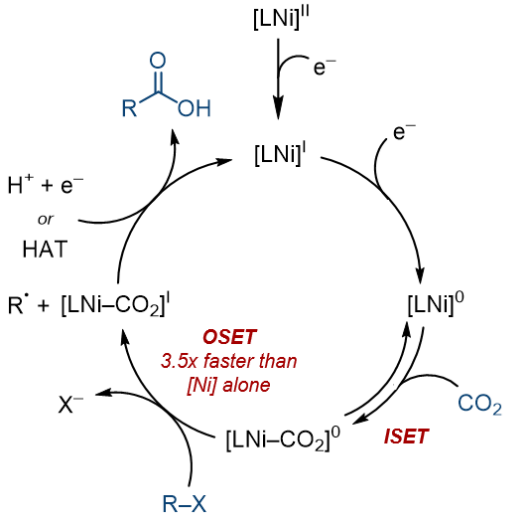
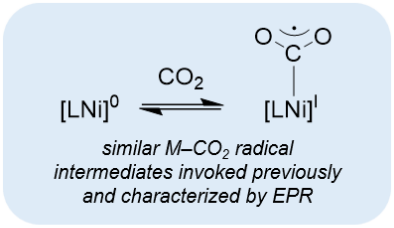
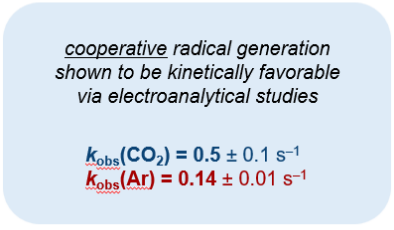
Cross-electrophile coupling (XEC) represents a powerful strategy for C–C bond formation from aryl and alkyl substrates, circumventing the need for a traditional transmetalation step or harsh chemical reagents.[1] Classical Ni-catalyzed XEC takes advantage of the distinct oxidative addition reactivity of C(sp^2)–X and C(sp^3)–X substrates, enabling high selectivity for the cross-coupled product. In complement to these methods, in this work, we demonstrate a unique Ni catalytic sequence in which binding and inner-sphere electron transfer (ISET) to one electrophile, in this case carbon dioxide, subsequently enables faster radical generation via outer-sphere electron transfer (OSET) from the second electrophile, an alkyl halide. [2,3]

Based on this cooperative strategy, we observe that a nickel-polypyridyl catalyst, Ni(tpyPY2Me), yields the carboxylation of alkyl iodides under reductive electrochemical conditions. Following binding and ISET from Ni(tpyPY2Me) to CO_2, which forms a $[Ni]^I$–CO_2 intermediate, radical generation *via* OSET to an alkyl iodide precursor is 3.5 times more rapid. Detailed mechanistic investigation of the reaction will be presented, including electroanalytical studies, to showcase the unique cooperativity of this tandem ISET-OSET sequence. Finally, we envision designing similar cooperative sequences which expand the scope of XEC between alkyl electrophiles and unorthodox coupling partners, harnessing the distinct catalyst-binding affinities and radical philicities of substrates predisposed to ISET—such as carbodiimides, silanes, and more.







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[1] *Chem. Rev.* **2024**, *124*, 13397–13569.
[2] *J. Am. Chem. Soc.* **2020**, *148*, 20489–20501.
[3] *J. Am. Chem. Soc.* **2021**, *143*, 6990–7001.

Development Of SLO3 and CatSper Inhibitors as Non-Hormonal Male Contraceptives

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ABSTRACT: Male contraceptive options are limited to condoms and vasectomy, both of which have drawbacks, including inconsistent efficacy or invasiveness and limited reversibility. Therefore, a non-hormonal, on-demand, reversible, orally available male contraceptive remains a critical unmet need. CatSper and SLO3, two sperm-specific ion channels, are crucial for sperm capacitation and hyperactivated motility. Genetic knockout of either channel in mice causes infertility, confirming them as contraceptive targets. A high-throughput screen of ~72,000 compounds identified six CatSper-inhibitor scaffolds. Among these, compound 4a showed strong activity and minimal off-target effects, prompting further structure–activity relationship studies. These studies led to EJ 3.148, a potent dual CatSper/SLO3 inhibitor. VU0546110 and VU6032735 are known SLO3 inhibitors. Our current research focuses on synthesizing analogs of these lead compounds and exploring new scaffolds that combine key structural elements. Candidate compounds will be evaluated using *in vitro* assays to confirm CatSper and SLO3 inhibition. Potent and selective compounds will then undergo ADMET profiling, followed by pharmacokinetic and mating studies. The goal is to improve ion-channel selectivity, physicochemical properties, and pharmacokinetics while minimizing off-target activity. The long-term aim is to develop safe, effective, orally-available and reversible non-hormonal male contraceptives.

The United States National Chemistry Olympiad Fostering Women's Success since 1984

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The United States National Chemistry Olympiad (USNCO), sponsored by the American Chemical Society (ACS), is a multi-tiered competition designed to identify talented high school chemistry students. Following a rigorous national selection process, twenty of the best performing students attend an intensive study camp at the University of Maryland, College Park, where four are ultimately selected to represent the United States at the International Chemistry Olympiad (IChO). The USNCO relies on the contribution of women at every level of involvement to make it a successful program that praises excellence in chemistry.

Since the United States' inaugural participation in 1984, the program has been led and administered by women. A total of 21 female mentors—comprising eight high school and thirteen college faculty members—have provided the pedagogical expertise necessary for high international achievement.

Most importantly, the USNCO does its best to support and promote female students. Between 1984 and 2025, 85 young women qualified for the study camp. Of these, 17 were selected to be in the final four-member national team, competing in 19 IChO events and receiving a total of 18 international medals. The long-term impact of the program is evidenced by the students' subsequent attendance of prestigious institutions, including the Massachusetts Institute of Technology, Harvard University, and the University of California, Berkeley. These results suggest that while more effort is needed to increase women's participation in science, the USNCO remains a steady and consistent catalyst of their accomplishments in chemistry.

Aminopyridine compounds as antibiotic adjuvants in Gram-negative bacteria

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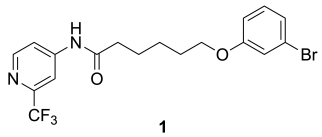
Gram negative bacteria pose a growing threat to public health, in particular to those with compromised immune functions and within hospital settings. There are few treatments available to combat infections with antibiotic-resistant strains, thus there is an urgent need for new treatments to disrupt pathogenicity and inhibit growth. A potential strategy is through the development of antibiotic adjuvants. Antibiotic adjuvants do not kill the pathogen themselves, but potentiate the activity of the antibiotic, allowing the drug to be effective at lower doses. Our lab has found that analog 1 is able to reduce the colistin only minimum inhibitory concentration (MIC) from 0.5 μg/mL to 0.25 μg/mL with 10 μM adjuvant.[1] In the presented work we aim to enhance the efficacy of the colistin-adjuvant combination therapy through the development of adjuvants with variable aminopyridine headgroups in a structure-activity relationship (SAR) study.



1
static MIC = 0.25 μg/mL

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(1) Zhang, Z.; Ortega, D.; Rush, A.; Blankenship, L. R.; Cheng, Z. J.; Moore, R. E.; Tran, M. L. N.; Sandoval, L. G.; Aboulhosn, K.; Watanabe, S.; Cortez, K. S.; Perlman, D. H.; Semmelhack, M. F.; Miller Conrad, L. C. Antibiotic Adjuvant Activity Revealed in a Photoaffinity Approach to Determine the Molecular Target of Antipyocyanin Compounds. *ACS Infect. Dis.* **2021,** *7*(3), 535–543.

CATALYST-FREE PHOTOINDUCED DEAMINATIVE FUNCTIONALIZATION OF AMINO ACIDS AND GLUTARIMIDE PRECURSORS

Tyler G. Chong[1], Julia R. Dorsheimer[2], Zixi Zhu[3], Trevor C. Sherwood[4], Candice L. Joe[2], Eric R. Welin[3], Tomislav Rovis[1]*

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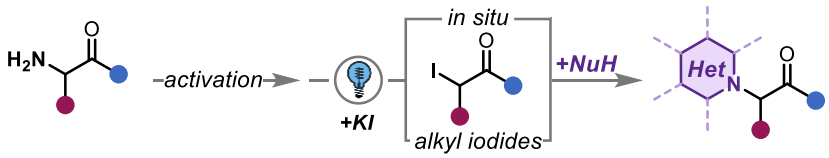
Functionalized *N*-heterocycles are found among a majority of pharmaceutical drugs, including targeted protein degraders that often employ the glutarimide motif. Typical strategies for synthesizing these scaffolds require individualized and multi-step routes, or alkylation with an α-haloglutarimide that is low yielding and limited by substrate availability. In contrast to alkyl halides, primary amines are abundant and commercially inexpensive, making them attractive coupling partners. We will present a generalizable pathway to forming these alkylated *N*-heterocycles from abundant primary amines derived from amino acids via a unique Electron Donor-Acceptor (EDA) complex. Irradiation with blue light induces the formation of a diradical species, which recombines to form traditionally unstable and often inaccessible alkyl iodides in situ, which are displaced by the introduction of an exogenous nucleophile. Overall, this transformation introduces an umpolung approach to heteroarylation by converting primary amines into electrophilic coupling partners. We will show that when employing glutamate and glutamine derivatives, this strategy can enable efficient late-stage introduction of glutarimides.[1]

Nucleophilic Functionalization of Amino Acids via* in situ *Deaminative Halogenation



- *Access to synthetically challenging alkyl iodides*
- *Generalizable pathway*
- *Strategy for late-stage glutarimide introduction*
- *39 examples*

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[1] Chong, T.G.; Dorsheimer, J.R.; Zhu, Z.; Sherwood, T.C.; Joe, C.L.; Welin, E.R.; Rovis, T. *J. Am. Chem. Soc.* **2026**, 148, 16, 17522–17529

COMPUTATIONAL INVESTIGATION OF LIGHT INDUCED [2π+2σ] CYCLOADDITION REACTION

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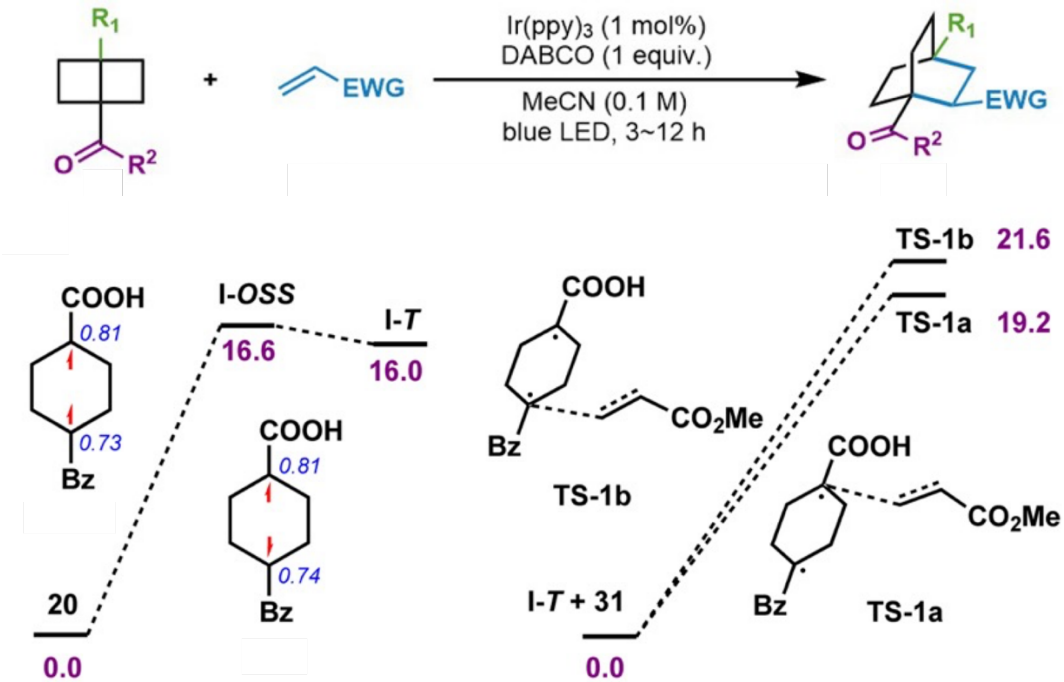
The unique highly strained structure of bicyclo[2.2.0]hexane offers high synthetic utility. These molecules act as a versatile reactants for [2π+2σ] cycloadditions with electron-deficient alkenes, forming a wide array of trisubstituted bicyclo[2.2.2]octanes as single regioisomers. Radical trapping experiments suggest a diradical transition state. Using density function theory (DFT), we investigated the reaction mechanism by computing the energetic barriers of the cycloaddition. The results elucidated the relative reactivity trends in this cycloaddition reaction, rationalizing the experimental findings. Spin density analysis provided the basis of the experimentally observed regioselectivity.



ALLOSTERIC-ALLOSTERIC BIVALENT CDK2 INHIBITORS FOR ANTICANCER THERAPY AND NON-HORMONAL MALE CONTRACEPTION

Laila Aiad[†], Maryam Nazari[‡], Kristen John[‡], Gunda Georg[‡*]

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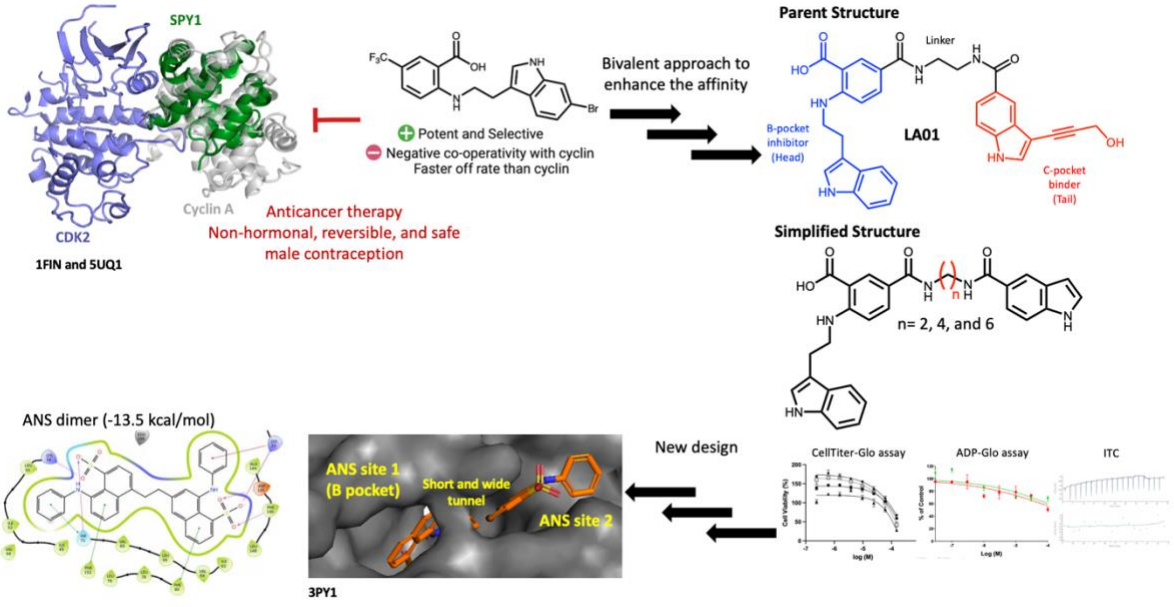
Cyclin-dependent kinase 2 (CDK2) is a serine/threonine kinase activated by different partner proteins during the cell cycle (cyclin E and A) and spermatogenesis (cyclin A and Spy1). CDK2 hyperactivation is associated with several cancer types, and CDK2$^{-/-}$ knockout mice are healthy but sterile, validating CDK2 as a target for chemotherapy and non-hormonal male contraception. However, developing selective inhibitors remains challenging due to the high structural similarity among kinases, particularly at the ATP-binding site. Our group has discovered a series of anthranilic acid-based allosteric inhibitors, bind to the B-pocket of CDK2, that are highly selective and potent against CDK2. However, these inhibitors demonstrate negative cooperativity with cyclin binding and exhibit faster off-rates compared to cyclins.[1] To overcome this, we are pursuing a new approach of targeting CDK2 using bivalent inhibitors. This involves the design, synthesis, and biological evaluation of bivalent inhibitors that simultaneously target two distinct allosteric pockets in CDK2. The initial design strategy involved linking two known allosteric binders: an anthranilic acid-based scaffold (**TW-8-67-2**) and a crystallographically validated fragment (Ludlow fragment). These scaffolds were connected via linear diamide linkers of varying lengths. Biological evaluation of these first-generation bivalent compounds showed weak activity in CellTiter-Glo assay, with IC_{50} values of approximately 150 µM. In ADP-Glo assay, the compounds exhibited weak inhibition with IC_{50} values ranging from 100 to 700 µM. Furthermore, isothermal titration calorimetry (ITC) showed no detectable binding, and X-ray crystallography screening failed to yield co-crystals under the conditions tested. Given these results, we are pivoting our strategy toward a new bivalent framework. Based on observations of two 8-Anilino-1-naphthalenesulfonic acid (ANS) molecules binding at distinct allosteric sites and docking simulations suggesting a favorable bivalent binding mode for an ANS dimer, we are currently exploring the design and synthesis of linked ANS-based bivalent inhibitors.



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INVESTIGATING ACYL CARRIER PROTEIN SELF-ACYLATION WITHIN TYPE I AND TYPE II POLYKETIDE SYNTHASES

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Polyketides are a structurally diverse and biologically active class of natural products synthesized by polyketide synthases (PKSs) in microorganisms. These biosynthetic enzymes are categorized primarily into type I and type II systems: Type I PKSs are large, multifunctional proteins with covalently linked modules that process substrates sequentially in an assembly-line manner, while type II PKSs consist of discrete proteins that act iteratively. Central to both type I and type II PKSs are acyl carrier proteins (ACPs), which shuttle intermediates and incoming extender units derived from malonyl-CoA or methylmalonyl-CoA via their reactive phosphopantetheine (Ppant) arm. While acyl transferases (ATs) are known to catalyze the addition of the malonyl-based units onto ACPs, recent studies suggest that some ACPs are capable of loading extender units independently, without enzyme assistance. This work investigates the conformational dynamics and structural underpinnings that enable self-acylation in some ACPs but not others. To explore this, we expressed, purified, and characterized the self-acylation activity of a diverse set of *holo*-ACPs from both type I and type II PKSs. We installed a thiocyanate probe onto the terminal thiol of each *holo*-ACP and employ IR spectroscopy to probe the local solvation environment of the Ppant arm—revealing whether it holds a sequestered or solvent exposed conformation. Additionally, we are developing a spectroscopic method for determining the pKa of the terminal thiol of a Ppant arm by tracking the Raman active thiol S-H stretching frequency. Here we present our efforts to understand how characteristics of ACPs such as Ppant arm conformation or pKa may correlate to self-acylation ability, with the goal of informing future biosynthetic engineering strategies that leverage ACP self-acylation to expand substrate scope and generate novel or derivative polyketides.

Synthesis of C3-derivatives of kojic acid via rhodium-catalyzed thia-Sommelet-Hauser rearrangement

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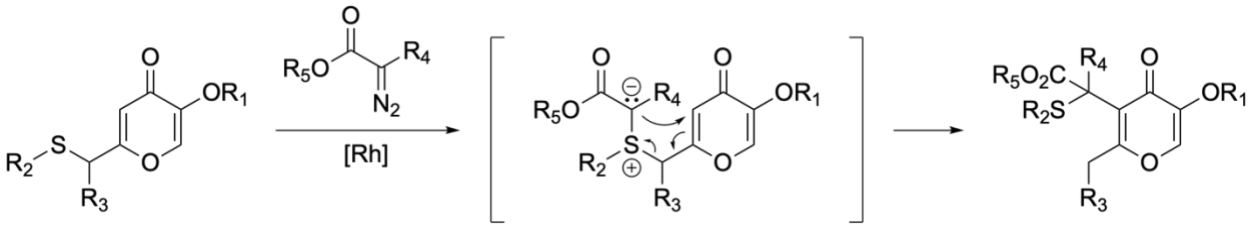
Substituted 5-hydroxy-γ-pyrones have shown promise in drug discovery as molecules with antibacterial and anticancer activity. Recent studies from the Jaudzems and Waldman groups demonstrated that 5-hydroxy-γ-pyrones can act as covalent inhibitors of bacterial Sortase A and TEAD proteins. Most screening efforts have focused on C2- and C5-derivatives of kojic acid, as these positions are more readily accessible synthetically. Reports of C3-derivatives of kojic acid remain limited to base-induced thia-Sommelet-Hauser rearrangements of unbranched sulfonium ylides. Here, we report an optimized rhodium-catalyzed thia-Sommelet-Hauser rearrangement of 5-hydroxy-γ-pyrones and an expansion of the substrate scope towards the formation of C3-derivatives. By varying protecting groups on the alcohol at C5, groups on the benzene of the thiophenol at C2, and a range of diazo compounds, we aim to provide a diverse scope of C3-derivatives of kojic acid upon rearrangement. The resulting method offers a new chemical entry point for the development of 5-hydroxy-γ-pyrones with enhanced antibacterial and anticancer activity.



From Bench to Classroom: Organic Synthesis and Functionalization of Subphthalocyanines and Porphyrins

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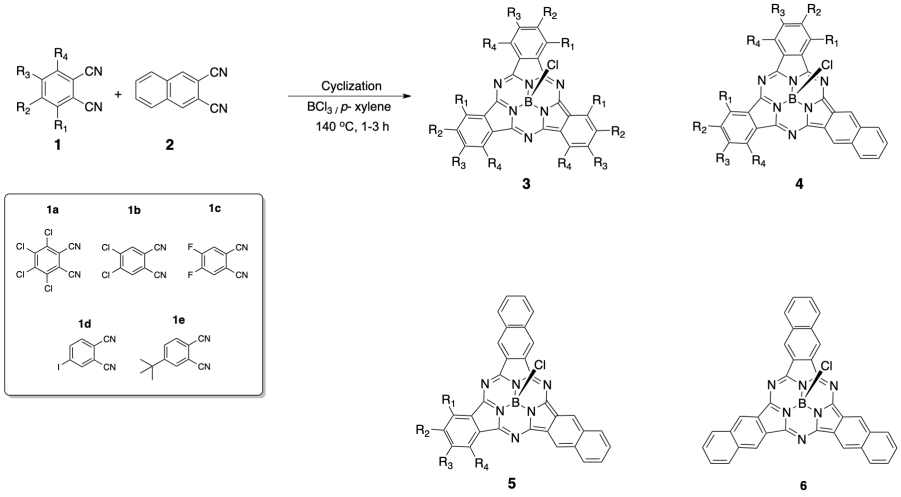
Subphthalocyanines (SubPcs) and Subnaphthalocyanines (SubNcs) are cone-shaped aromatic macrocycles with exceptional optical and electronic properties, making them attractive for applications in organic photovoltaics and photodynamic therapy[1]. We present three interconnected contributions spanning organic synthesis, functionalization, and chemical education. Novel hybrid SubPcs have been synthesized through strategic organic transformations to expand structural diversity and enable tunable optical properties. Nucleophilic substitution and covalent conjugation strategies have been employed to connect SubPcs with porphyrins, yielding donor-acceptor dyads exhibiting significant electronic communication and promise for light-harvesting applications[2]. The rich organic chemistry of these synthetically accessible macrocycles has also inspired their introduction into the undergraduate organic chemistry curriculum, providing students with hands-on experience in macrocycle synthesis and connecting classroom concepts to cutting-edge research. Together, these contributions highlight the versatility of SubPcs as platforms for both fundamental organic chemistry research and chemical education.



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DESIGNING TARGET-SPECIFIC DATA SETS FOR REGIOSELECTIVITY PREDICTION ON COMPLEX SUBSTRATES

Anjali Gurajapu[1], Jules Schleinitz[1], Alba Carretero Cerdán[1], Yonatan Harnik[2], Carolyn Ruan[1], Gina Lee[1], Amitesh Pandey[1], Anat Milo[2], Sarah E. Reisman[1]
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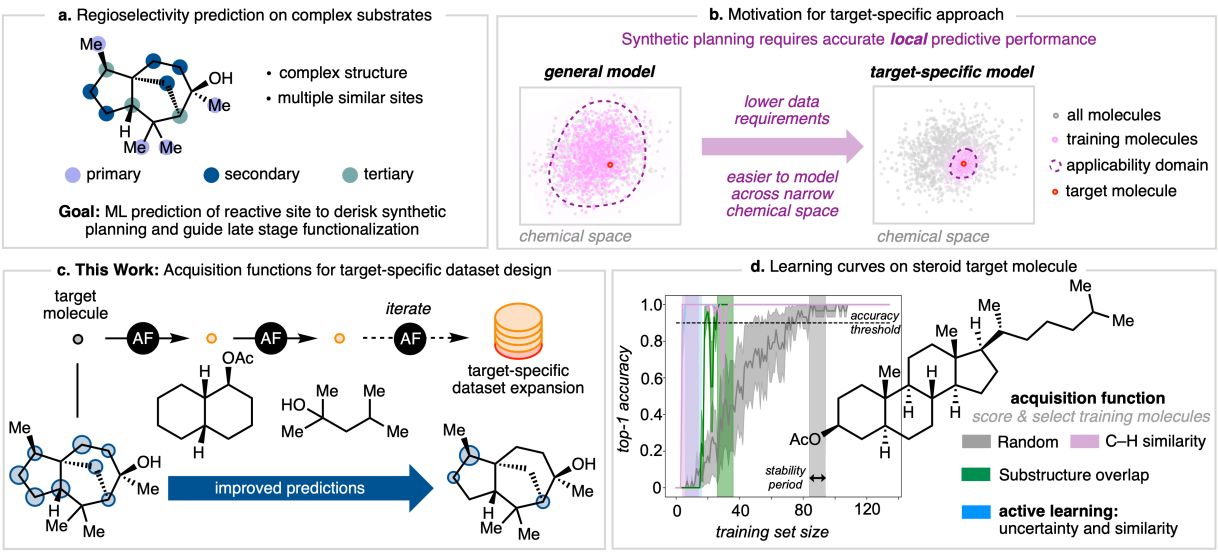
Predictive models for regioselectivity of undirected C–H functionalizations can de-risk these steps in synthetic planning and guide late-stage diversification. However, the difficulty of generating experimental regioselectivity data limits performance on complex intermediates that may be far from the training set distribution. We propose a target-conditioned active learning strategy for dataset design, motivated by the observation that synthetic planning requires accurate prediction on specific intermediates rather than global generalization.[1] This approach constructs compact, target-focused training sets using acquisition functions designed to balance model uncertainty and target similarity, thereby localizing learning to regions proximal to the target in descriptor space.

We develop a regioselectivity prediction model for dioxirane-mediated C–H oxidations. Evaluated on complex substrates, an active learning strategy leveraging both uncertainty and target similarity achieves accurate predictions at smaller dataset sizes than random, diversity-based, and similarity-only acquisition (~50 fewer data points on average than random selection; max. dataset size = 135). Moreover, target-focused models achieve accuracy on targets where larger, diversity-oriented or randomly selected datasets fail (62% top-1 accuracy vs. 38% and 40%, respectively). Similar gains in data efficiency are found on a C–H borylation dataset, suggesting broader applicability. We further validate the approach through prospective experiments on five complex substrates, identifying the major site of oxidation in 4/5 cases, and observing data efficiency improvements on all targets. Collectively, these results suggest that target-conditioned dataset design can improve data efficiency and accuracy for regioselectivity prediction on complex substrates.



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Orange Light-Mediated C(sp^2)-C(sp^3) Cross-Electrophile Coupling of Aryl and Alkyl Bromides

Defne Tuncaral[1], Katherine A. Xie[1], Chloe Park[3], Candice L. Joe[2], Trevor C. Sherwood[3], Christiana N. Teijaro[3], Anthony N. Cauley[3], Eric R. Welin[4], Sergey V. Kolotilov[5], Tomislav Rovis[1,*]

[1]*Department of Chemistry, Columbia University, New York, NY, USA*
[2]*Chemical Process Development, Bristol Myers Squibb, New Brunswick, NJ, USA*
[3]*Global Discovery Chemistry, Bristol Myers Squibb, Princeton, NJ, USA*
[4]*Global Discovery Chemistry, Bristol Myers Squibb, San Diego, CA, USA*
[5]*L.V. Pisarzhevskii Institute of Physical Chemistry, National Academy of Sciences of Ukraine, 31, pr. Nauky, 03028 Kyiv, Ukraine*

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Cross-electrophile coupling is a robust and modular method of building molecular complexity, achievable with photoredox catalysis to achieve wide substrate compatibility under mild reaction conditions. Herein, we report the development of a first-in-class low-energy (i.e., orange light-driven) cross-electrophile coupling paradigm to access synthetically valuable C(sp^2)-C(sp^3) bonds from unactivated and commercially available organic halide starting materials. This dual nickel/metallaphotoredox catalysis method demonstrates the use of a new Ir(III) photocatalyst and a new application of a feedstock trialkylamine reagent to generate alkyl radicals from alkyl bromides, indicating a cost-effective alternative to existing silane-based halogen abstracting agents. We report a wide substrate scope of both alkyl and aryl bromide coupling partners, demonstrating the synthetic utility of this method, with advantageous tolerance for photosensitive substrates unamenable to existing UV or blue light-catalyzed cross-coupling paradigms.

• 1°, 2°, 3° alkyl bromides • Broad substrate scope • 40+ examples

SYNTHESIS OF CARBOHYDRATE AND CERAMIDE MODIFIED ANALOGS OF α-GALACTOSYLCERAMIDE FOR BIASED CYTOKINE RESPONSE

Divya Chennamadhavuni, Noemi Alejandra Saavedra-Avila, Leandro J. Carreño, Weiming Yuan, Stewart K. Richardson, Steven A. Porcelli, and Amy R. Howell*

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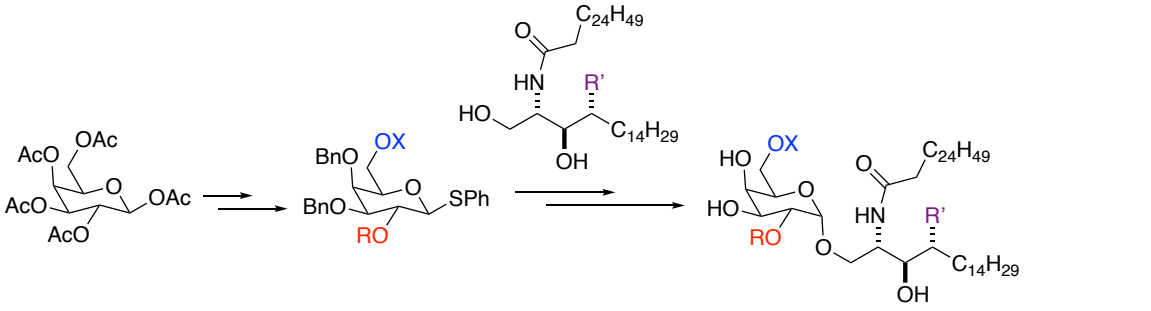
Invariant Natural Killer T (*i*NKT) cells are a subset of T cells that play a central role in regulating immune responses against cancer and infections. The glycolipid KRN 7000, an α-galactosylceramide (α-GalCer), stimulates these NKT cells but has had limited clinical success. Structure-activity relationship (SAR) studies on KRN7000 led to the development of various analogs with different immunostimulatory properties (Th1 or Th2) in mice, but these findings have not translated well to human *i*NKT cell responses. In this work, we describe the synthesis of a series of carbohydrate- and ceramide-modified analogs of α-galactosylceramides and report how these chemical modifications influence *i*NKT cell activation in both mice and humanized mice.[1]



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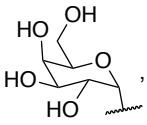
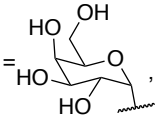
AH15-6, X = H, R =  , R' = H

AH15-5, X = $C(O)CH_2CH_2Ph$, R =  , R' = H

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Synthesis, Evaluation, and Context for Applications of SF_5-Containing [1.1.1]Bicyclopentane and [*2*]Staffane "Hybrid Bioisosteres"

Jón Atiba Buldt,[a] Masiel M. Belsuzarri,[a] Ansh Hiten Patel,[a] Yannick Kraemer,[a] Tyson Vu,[a] Riddhiman Banerjee,[a] Jake Anthony Olvera,[a] Dean Tantillo,[a,*] Lauren M. Holder,[b,*] Cody Ross Pitts[a,*]

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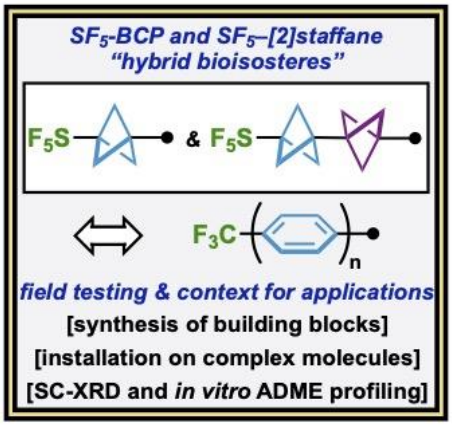
The pentafluorosulfanyl (SF_5) group is an emerging fluorinated group that has been historically underutilized in comparison to its congener, the trifluoromethyl (CF_3) group, due to limited reagent accessibility. Enabled by the recent increase in accessibility of the reagent SF_5Cl–a known source of SF_5 radicals – the Pitts laboratory developed a method for strain-release functionalization of [1.1.1]propellane in 2022 to make a novel pentafluorosulfanylated [1.1.1]bicyclopentane (BCP), i.e., SF_5–BCP–Cl. We envisioned that the SF_5–BCP motif could be of interest to medicinal chemists in the context of bioisosterism. On the one hand, the SF_5 group is an established bioisosteric replacement for the CF_3 group that has greater electronegativity, is more lipophilic, and has been shown in some cases to increase metabolic stability of the parent molecule. On the other hand, the BCP ring is a known bioisostere of a *para*-substituted phenyl ring. With the increased number of SP^3 bonds, replacing a Ph ring with a BCP ring can modulate lipophilicity and metabolic stability. Although both independent bioisosteres have been applied and evaluated, the combined effects of simultaneous replacement of a CF_3–Ph motif with a SF_5–BCP motif are currently unknown. We aim to explore the consequences of CF_3–Ph to SF_5–BCP hybrid bioisosteric replacement by synthesizing useful SF_5–BCP-containing building blocks that can be easily integrated into organic synthesis to make drug and agrochemical derivatives. Through collaborative efforts, we also explore the physicochemical properties of single (SF_5–Ph→ SF_5–BCP) and double bioisosteric replacements (CF_3–Ph→ SF_5–BCP) through *in vitro* ADME profiling.



Engineering Kainoid Synthases for the Efficient Biocatalytic Production of Non-Native Neuroactive Compounds

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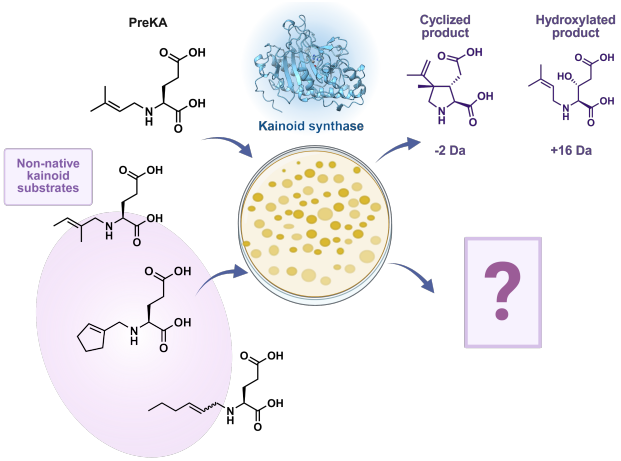
Kainoid synthases belong to a sub-family of non-heme iron α-ketoglutarate dependent oxygenases (Fe/αKGs), a diverse family of enzymes involved in both primary and secondary metabolism. Fe/αKGs use an Fe(II) cofactor, α-ketoglutarate as a co-substrate, and molecular oxygen to carry out several important transformations such as hydroxylation, halogenation, or cyclization via a radical-based mechanism. Kainoid synthases, derived from marine micro- and macroalgal species, catalyze the cyclization and/or hydroxylation of N-prenylated substrates with a glutamate backbone generating pyrrolidine-containing neuroactive compounds called kainoids. Kainoids are potent agonists/antagonists of ionotropic glutamate receptors that are implicated in neurodegenerative disorders such as epilepsy and schizophrenia; however, progress in studying these receptors has been hindered by the limited availability of chemical tools that can selectively modulate them. My research uses directed evolution strategies to enhance the production of receptor antagonists by kainoid synthase enzymes and to develop additional kainoid receptor-specific agonists and antagonists that would aid in the study and understanding of important neurological disorders and conditions. In collaboration with Prof. Laura Sanchez, we have recently developed a high-throughput rapid screening method that uses MALDI-TIMS-MS (matrix-assisted laser desorption/ionisation-trapped ion mobility mass spectrometry) to carry out direct colony-based measurements and assess large directed evolution libraries. By adapting the above MALDI-based method for substrate multiplexing assays, we have screened a library of non-native kainoid substrates against a number of kainoid synthase orthologs and ancestral enzymes and have identified putative cyclization/hydroxylation products. Our ongoing kainoid synthase engineering efforts will help further identify cyclized neuroactive kainoid receptor agonists/antagonists. Once identified, the assay will be optimized for scale-up to enable the characterization and validation of the putative 'hits'. These newly discovered kainoids will serve as valuable tools for probing the structure and function of ionotropic glutamate receptors and will further establish kainoid synthases as promising biocatalysts.



Enzymatic synthesis of site-selectively labeled nucleotides for the NMR investigations of oncomiR-1

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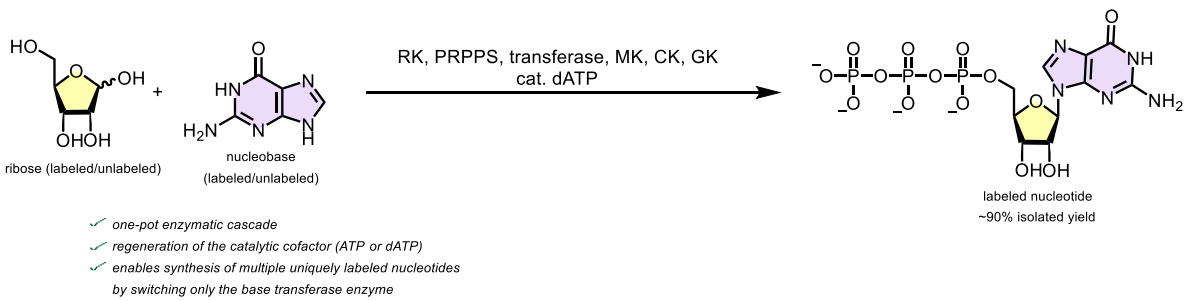
OncomiR-1 is an 827 nt long oncogenic primary microRNA transcript that possesses six component miRNAs and two non-precursor stem loop elements. The miRNAs from oncomiR-1 exist in different ratios as per the cellular conditions despite being present in the same amount within oncomiR-1. We hypothesize that structural dynamics in oncomiR-1 might be responsible for this differential miRNA processing and intend to understand this via NMR spectroscopy. We are using multiple site-selectively labeled nucleotides as NMR spectroscopy probes. Using a one-pot biocatalytic method, we were able to synthesize a site-selectively deuterated (commercially unavailable) guanosine triphosphate. This method enables the synthesis of various nucleotides by simply switching only the nucleobase and the enzyme catalyzing the base-transfer reaction in this cascade. Synthesis of additional labeled nucleotides as NMR probes for the structural studies of oncomiR-1 is underway.



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Development of the Commercial Manufacturing Process for Danuglipron

Nga M. Do on behalf of the Danuglipron Team

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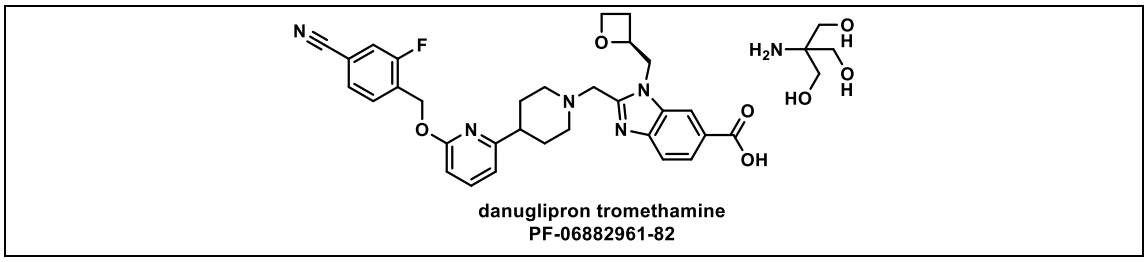
nga.m.do@pfizer.com

Danuglipron (PF-06882961) is a Glucagon-like Peptide-1 Receptor Agonist (GLP-1RA) previously under development for the treatment of chronic weight management and type 2 diabetes mellitus. Danuglipron is prepared in convergent fashion over 5 steps featuring a telescoped Pd-catalyzed C-O coupling and deprotection sequence, a C-N coupling to assemble the bonds of drug substance and a uniquely selective barium hydroxide mediated hydrolysis.



danuglipron tromethamine
PF-06882961-82

A MODULAR APPROACH TO (–)-ISODOCARPIN AND RELATED *ENT*-KAURANOIDS VIA C9–C10 BOND DISCONNECTION

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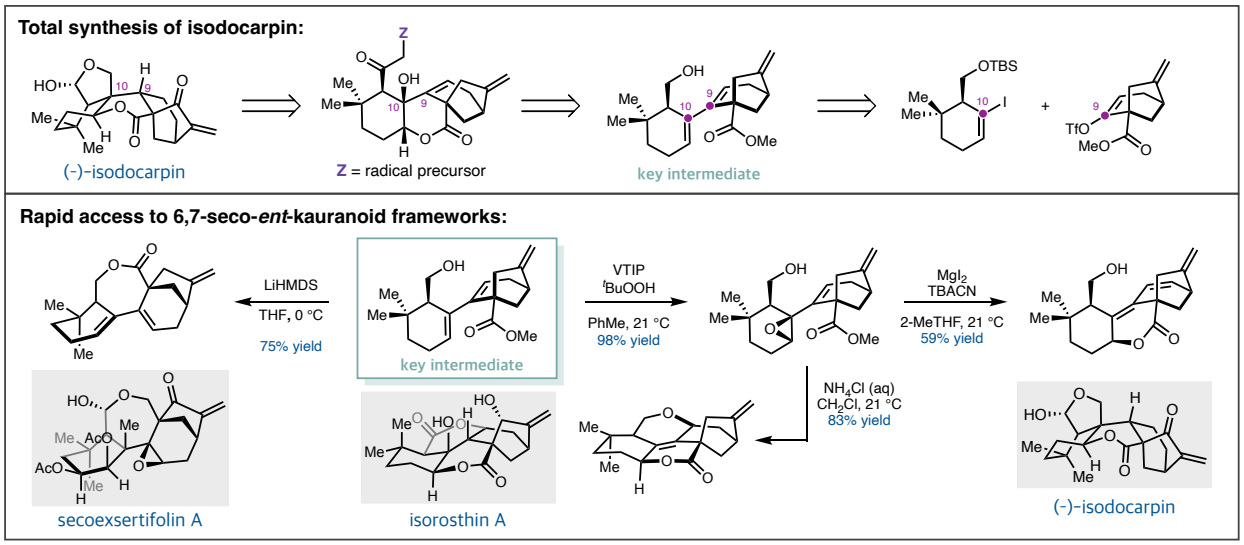
The 6,7-seco-*ent*-kauranoids encompass hundreds of diterpenoids with varying frameworks and notable antibacterial, anti-inflammatory, and anticancer bioactivities. To enable synthetic access to these architectures, we identified the C9–C10 bond as a strategic disconnection and pursued a modular approach toward a highly divergent building block and the total synthesis of (–)-isodocarpin. Formation of the C9–C10 bond was achieved via Ni/Pd dual-catalyzed cross-coupling of vinyl triflates with alkenyl iodides to furnish a diene substrate which supports access to multiple 6,7-seco-*ent*-kauranoid ring systems. Elaboration of this substrate has enabled entry to several underexplored scaffolds within this family. In studies towards (–)-isodocarpin, the central lactone has been constructed by leveraging a reactive epoxide intermediate. Progress has been limited by the pseudo-equatorial conformation of the tetracyclic product, which inhibits further manipulations. Current efforts focus on accessing an epimeric intermediate designed to bias the conformation towards productive radical cyclization to enable C20-installation and completion of the synthesis. Collectively, work thus far establishes a general, modular platform for accessing 6,7-seco-*ent*-kauranoids and lays the groundwork for the total synthesis of (–)-isodocarpin.



INVESTIGATIONS INTO THE MECHANISM OF A NOVEL PHOTOCHEMICAL CYCLOPROPANOL SYNTHESIS

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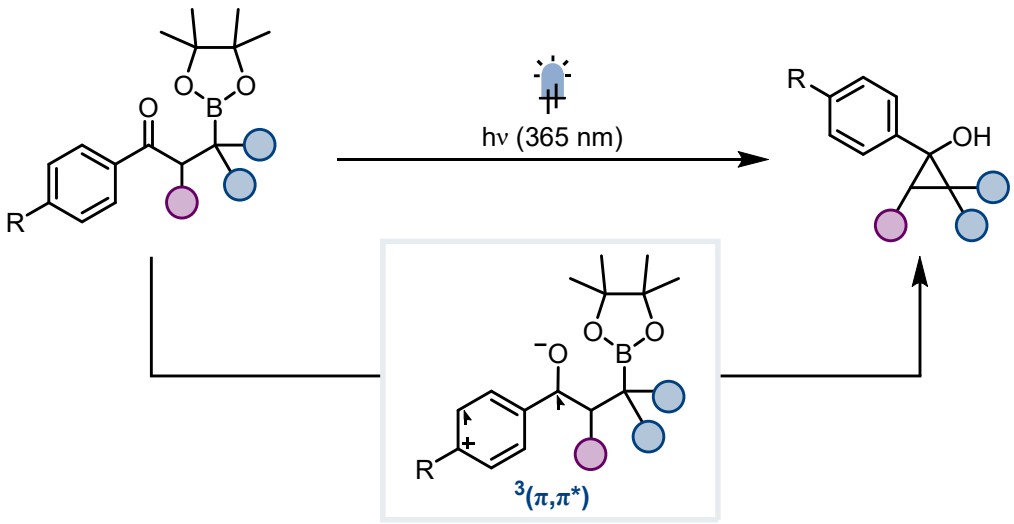
In the development of pharmaceuticals, cyclopropanols are valuable building blocks as they can undergo a variety of transformations, and the cyclopropane fragment itself is a prevalent motif in pharmaceuticals. Our group recently reported a method to synthesize cyclopropanols from β-boryl aryl ketones via direct photochemical excitation.[1] This method enables the synthesis of a diverse array of 1-aryl cyclopropanols, has excellent functional tolerance and great yields. Most notably, this reaction out competes 1,5-hydrogen atom transfer (HAT), a well-established photochemical reaction. In this presentation, the full mechanistic pathway of this transformation will be explored through a combination of computational and experimental work. With a deeper understanding of this reaction mechanism, powerful new transformations using this unique reactivity can be developed.



Boryl group transfer via $^3(\pi,\pi^*)$ state

[1] Pearson, J. W.; Dudra, S. L.; Palermo, A. F.; Chiu, B. S. Y.; Dang, J.; Gabbey, A. L.; Henson, B. A. B.; Hou, T. R.; Nabavi, N.; Rousseaux, S. A. L. *J. Am. Chem. Soc.* **2025**, *147*(40), 36890–36897.

Discovery of cyclin-dependent kinase 11 PROTAC degraders in breast and lung cancer cell lines

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Cyclin-dependent kinase 11 (CDK11) is a genetically validated but underexplored cancer driver involved in cell cycle progression, DNA repair, and apoptosis. In this work, we explored proteolysis-targeting chimeras (PROTACs) as a novel potential strategy against CDK11. Unlike classical inhibitors, PROTAC degraders eliminate both the enzymatic and non-enzymatic functions, offering a more durable and comprehensive therapeutic effect. We coupled OTS514[1], a potent CDK11 binder, with diverse E3 ligase ligands (thalidomide, pomalidomide, lenalidomide, and VHL032) and linkers of varying lengths and chemistries and evaluated their cytotoxicity in MDA-MB-231 (TNBC) and A549 (lung cancer) cell lines. Several compounds, BS-1-63 (amide-based) and BS-1-126/BS-1-129 (amine-based), demonstrated anticancer activity. We initially assessed CDK11 degradation by mass spectrometry and western blot analysis, but the results were inconclusive. We therefore confirmed the binding of BS-1-126 and BS-1-129 to cellular CDK11A using a NanoBRET live-cell assay, with IC_{50} values of 480 nM and 520 nM, respectively. In contrast, BS-1-63 showed poor binding to cellular CDK11A (IC_{50} >100 µM). A complementary CRBN fluorescence polarization assay confirmed effective E3 ligase binding by the analogs, with IC_{50} values of 21 nM for BS-1-63, 8 nM for BS-1-126, and 12 nM for BS-1-129. Finally, an HTRF-based ternary complex assay was performed to confirm ternary complex formation between CDK11 and the E3 ligase cereblon. The low S/N observed with the test compounds BS-1-126 (EC_{50} of 21 nM) and BS-1-129 (EC_{50} of 56 nM), and the absence of a signal for BS-1-63, underscore the challenge of inducing robust ternary complex formation for this CDK11:E3 ligase pair.

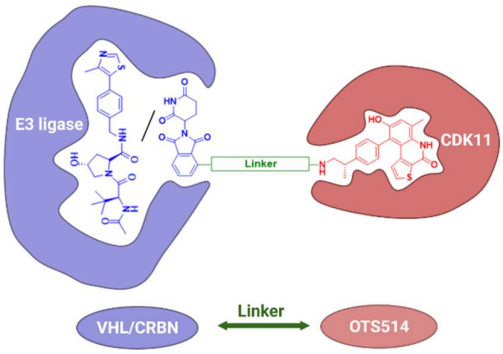

Figure 1: Design of PROTACs; a linker connects the E3 ligase ligand and the CDK11 ligand, OTS514. SAR library synthesis:12 amide-linked, 14 amine- linked. Linker lengths: 5-12 atoms.

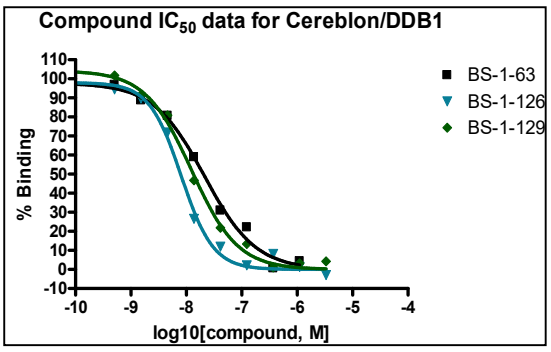

Figure 2: CRBN Fluorescence Polarization (FP) binding assay data. Compounds were tested in 10-concentration IC_{50} mode using 3-fold serial dilutions, starting at 10 µM.

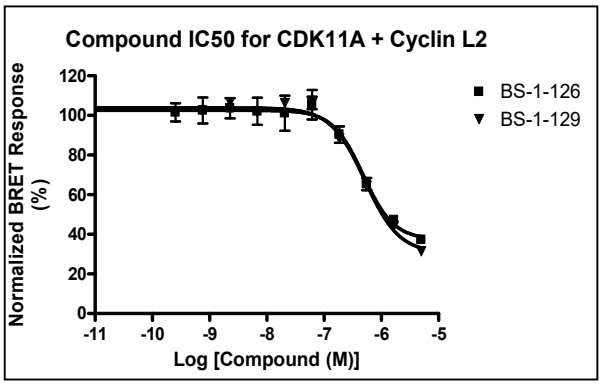

Figure 3: NanoBRET live-cell target engagement assay. The transfected cells were treated with the compounds (starting at 5 µM) and the reference compound (starting at 10 µM) in duplicate, 10 doses with 3-fold serial dilution.

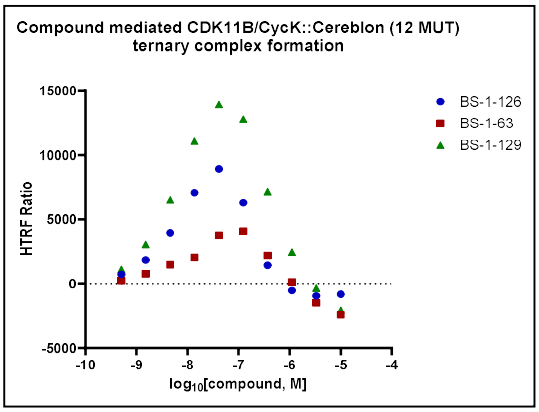

Figure 4: CDK11B/CycK::Cereblon Ternary Complex Assay. Ternary complex formation is observed in the presence of BS-1-126. No detectable signal for BS-1-63. Low S/N.

UNEXPECTED DIASTEREOSELECTIVITY AND COMPREHENSIVE MECHANISTIC STUDIES IN AN EPOXIDE-INITIATED ARENE-TERMINATED POLYENE CYCLIZATION

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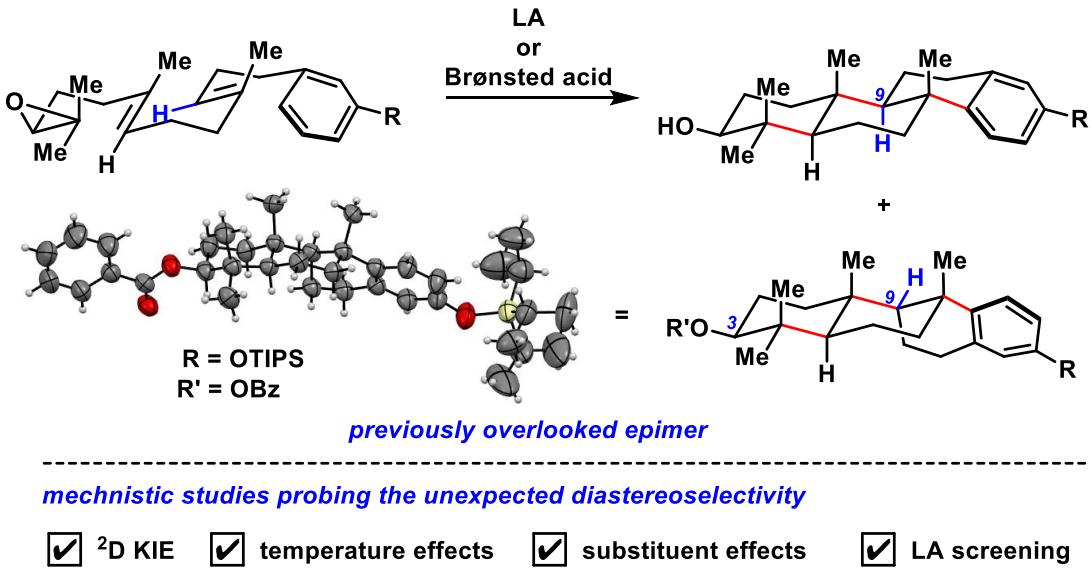
Inspired by the biosynthesis of terpenes, cationic polyene cyclization has been employed in natural product synthesis for more than 50 years as a powerful strategy to set multiple stereocenters simultaneously. Recently, we observed interesting diastereoselectivity during an epoxide-initiated arene-terminated polyene cyclization reaction, leading to the formation of epimers at C9. To date this selectivity issue has been overlooked in the literature, which prompted us to investigate this phenomenon further via experimental and computational mechanistic studies. Key mechanistic insights were derived via a modular decarboxylative olefination strategy for rapid assembly of various polyenes, enabling the elucidation of the extent of concertedness in the sequence of ring-closing events. This strategy allowed for the selective formation of the C9 epimer (9*α*-H) with *trans-anti-trans* stereochemistry through modulating substituent effects. To further decipher the origins of the observed selectivity we investigated the impact of temperature, isotopic labeling, choice of Lewis/Brønsted acids, as well as arene substituent effects on the C9 epimer ratio and their mechanistic implications.



Design, Synthesis and Optimization of a Series of Sulfonamides with Efficacy in Models of Kidney Injury.

Charity Ganskow, Hyojung Kim, Ros Paul, Kexin Xu, Rachel Forman-Rubinsky, Hazel Shanks, Neil Hukriede, Donna M. Huryn
Department of Chemistry, University of Pennsylvania
Department of Chemistry, University of Pittsburgh

Acute kidney injury (AKI), the sudden loss of renal function, is a common occurrence in patients in intensive care units, and with critical illnesses, sepsis or post-surgical complications. To date, despite its high prevalence, a thorough understanding of AKI, as well as methods to address the underlying causes or to hasten recovery, are limited.[1] Therefore, intervention and treatment of AKI is an ongoing unmet medical need. Our lab previously described **UPHH-207**, a promising lead that exhibits effects in multiple animal models of AKI.[2,3]

In order to further optimize this scaffold, we aimed to explore the chemical space of the alkyl chain in an attempt to not only improve potency, but also maximize metabolic stability. We applied various strategies, such as introducing conformational constraint and steric hindrance around the sulfur atom in an effort to retard metabolism. This poster will describe those designs, the methods developed for synthesis of optically pure analogs, as well as the biological activity of these novel analogs, several of which exhibit significantly improved activity in *in vivo* models compared to the original lead.

References

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[2] C. Ganskow, R. Paul, K. Xu, S. Subramani,[2] S. Joyasawal, R. Forman-Rubinsky, H. Shanks, R. Delgado, M. DeCaestecker, N. Hukriede, D. M. Huryn, Optimization of PTBA analogs as therapeutics for kidney disease, ACS Fall 2025 Meeting, August **2025** Washington, DC

Investigating CS585 as a Novel IP Receptor Agonist as the Next-Generation Antiplatelet Therapy

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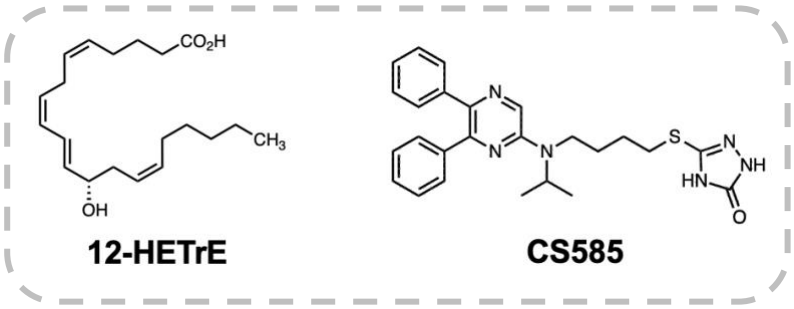
Platelets play a fundamental role in driving thrombus formation and are central to the progression of cardiovascular disease (CVD). Platelets regulate hemostasis and maintain blood flow; however, dysregulated platelet activation can lead to pathological thrombosis and vascular occlusion. Oxylipins are a diverse class of bioactive lipid mediators produced from polyunsaturated fatty acids (PUFAs) by lipoxygenase (LOX) enzymes and have emerged as a target for regulating platelet activation and vascular homeostasis. Recently, 12-hydroxy-eicosatrienoic acid (12-HETrE), an anti-thrombotic oxylipin derived from the oxidation of the fatty acid dihomo-γ-linolenic acid (DGLA), has been shown to attenuate platelet activation through prostacyclin (IP) receptor signaling. Although activation of the IP receptor is known to suppress platelet aggregation, the structural features that allow 12-HETrE and other IP receptor agonists to engage and activate this receptor remain poorly understood. CS585 is a synthetic analogue inspired by 12-HETrE that exhibits potent antiplatelet activity with improved stability and receptor selectivity compared to endogenous oxylipins. We aim to investigate the structure-activity relationship of CS585 analogues to identify IP receptor agonists with improved pharmacological properties. Metabolic stability and agonist potency will be optimized through modifications of CS585 and will be evaluated in established *in vitro* and *in vivo* platelet aggregation assays to quantify inhibition. CS585 will be leveraged as a chemical probe to elucidate how activation of the IP receptor regulates function, guiding the development of next-generation antiplatelet therapies.



Screening Modified RNA Libraries to Identify Motifs that Enable Site-Directed Editing with ADAR

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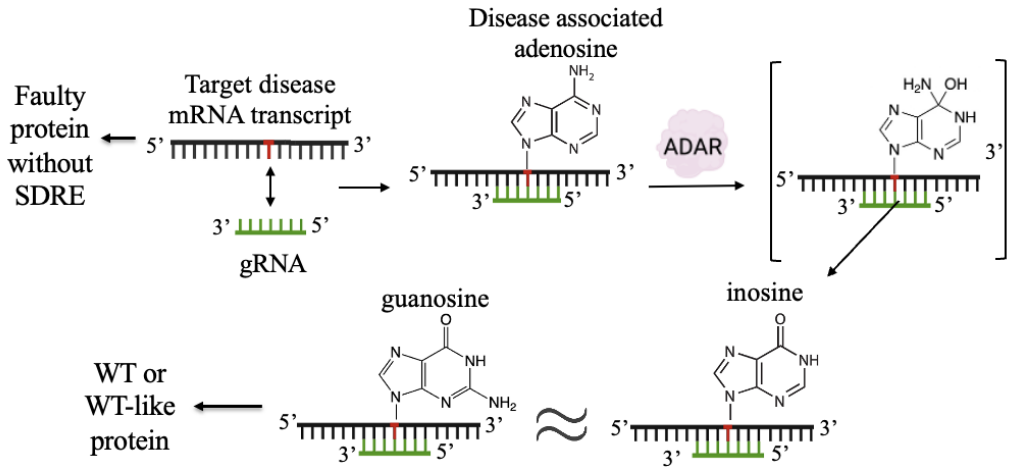
cbtang@ucdavis.edu

Adenosine deaminase acting on RNA (ADAR) is a family of enzymes that catalyze the hydrolytic deamination of adenosine to inosine in double stranded RNA (dsRNA). Inosine is read as guanosine by most downstream cellular machinery due to its preference to base pair to cytidine. We harness ADAR's capability to perform A-to-G edits by creating guide RNA (gRNA) that hybridize to therapeutically relevant adenosines. The efficiency of gRNAs that edit adenosines is sequence dependent and requires either backbone modifications or 2' sugar modifications for endonuclease resistance. Our library screening methodology allows for high-throughput screening of over one million gRNA with the necessary modifications to be considered for therapeutic application. We develop this methodology using a mutation, E198K, in the PPP25RD gene that is associated with the genetic disease Jordan's Syndrome.



1. Jacobsen, C.S., et.al., *ACS Chem Biol*. (2023) DOI: 10.1021/acschembio.3c00107

Photoproximity Protein Degradation Using Low Energy Light

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Targeted protein degradation (TPD) has emerged as a transformative strategy for the selective elimination of disease-associated proteins, particularly in cancer therapy. Current TPD technologies, including PROTACs, rely on recruitment of the cellular ubiquitin-proteasome system and are therefore limited by poor bioavailability, resistance mechanisms, unstable ternary complex formation, and dependence on endogenous degradation machinery.[1] To address these limitations, we propose a light-activated, non-enzymatic platform for selective protein degradation that operates independently of cellular degradation pathways.

This strategy combines deep red to near-infrared photoredox catalysis with proximity-directed chemical reactivity to induce localized peptide bond cleavage in target proteins. Osmium-based photocatalysts conjugated to protein-targeting ligands are activated by tissue-penetrant red light (600–800 nm), generating short-lived reactive intermediates selectively within the immediate protein environment. Upon activation, inert tagging molecules are converted into highly reactive carbodiimide or ketene species capable of modifying glutamate residues and promoting peptide backbone scission. By tuning the structure and lifetime of these intermediates, this system enables precise spaciotemporal control over degradation while minimizing off-target reactivity.

Building on advances in photoproximity labeling and red-light photocatalysis, this platform expands proximity-based chemistry beyond protein mapping toward direct protein ablation. This system is further applied toward degradation of the oncogenic phosphatase SHP2 through photocatalyst conjugation to the high-affinity inhibitor TNO155.[2]

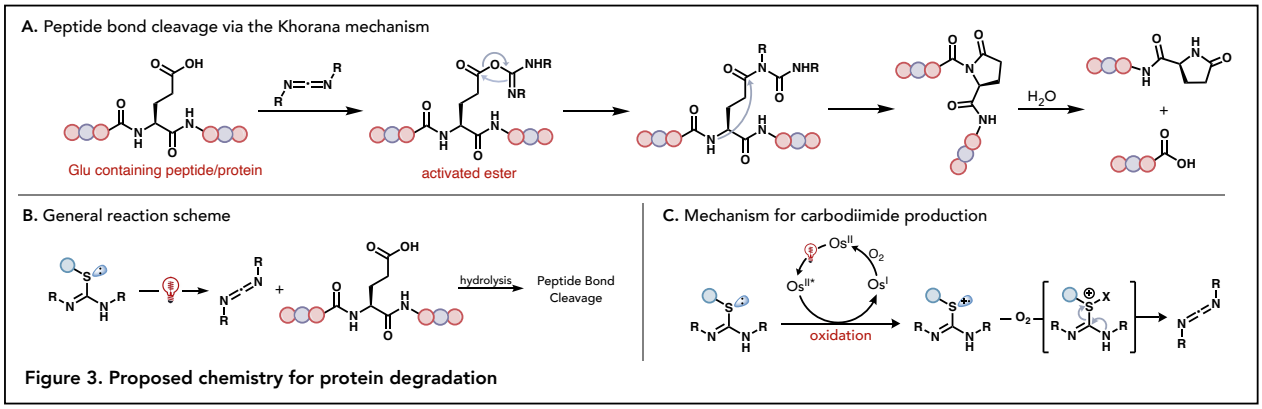

Figure 3. Proposed chemistry for protein degradation

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[2] Yang, X. et al. Eur. J. Med. Chem. 2021, 218, 113341.

Mechanistic Investigations of Cobalt Phthalocyanine in the Nickel-Catalyzed Atroposelective Reductive Synthesis of 2,2'-Bisphosphobiarenes

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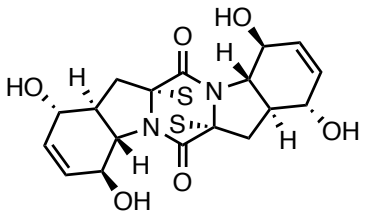
Recently, our lab disclosed one of the first general atroposelective reductive homocoupling of aryl halides to provide highly enantioenriched chiral biarenes. Interestingly, both yield and enantioselectivity in the reaction were found to be reliant on the additive cobalt phthalocyanine (CoPc). Ongoing mechanistic studies has focused on understanding the role of CoPc; however, the insolubility of CoPc has served as a barrier to an in-depth examination, making development of an organic-soluble CoPc derivative essential for these investigations. I have synthesized a large, bulky derivative of CoPc, $CoPc(O\text{-}aryl)_8$, and found it to be both active in the reaction and several orders of magnitude more soluble across a variety of organic solvents when compared to CoPc. I will describe this compound and preliminary studies into its role in reductive biaryl bisphosphine formation.

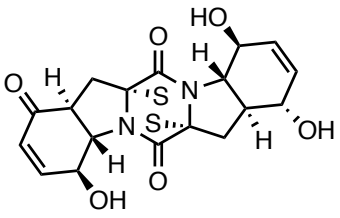
Brocazine Family of Natural Products: From Total Synthesis Efforts to Chemical Screening Library Construction

Vidya Nadar, Wasundara Hulangamuwa and Ryan J. Rafferty

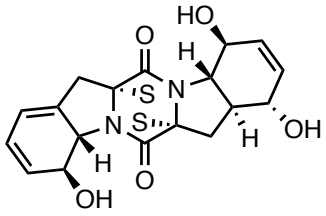
Natural products have been and continues to be one of the primary sources for discovery of pharmaceutically active compounds. Their total synthesis has given rise to multiple drugs that are primary treatment for numerous diseases. Our lab has been focusing on the brocazine family of natural products isolated from endophytic fungus derived from the marine mangrove plant *Avicennia marina* named *Penicillium brocae* MA-231by Wang and co-workers. Seven different brocazines (A-G) were isolated, and of those brocazine E showed the strongest activity against human pancreatic cancer cell line SW1990 (IC_{50} of 2.1 μM), whereas Brocazine F was shown to possess strongest activity against prostate cancer cell line DU145 (IC_{50} of 1.7 μM) and lung cancer cell line NCI-H460 (IC_{50} of 0.89 μM). Brocazine G showed strong activity against ovarian carcinoma cell line A2780 (IC_{50} of 0.664 μM), Cisplatin-resistant human ovarian cancer cells CisR A2780 (IC_{50} of 0.661 μM) and possesses strong and selective activity against human pathogen Staphylococcus aureus (MIC of 0.25 μg/mL). Other members possess different and interesting biological activity. All members of this family are composed of two unique, but structurally comparable units. Our lab has developed multiple routes to access each of the discrete units of the brocazine family. Coupling these units furnish the carbon framework of brocazine family members. We are currently in final stages to install the disulfide linkage to complete the first total synthesis of brocazine E, F and G. These synthetic efforts will be presented. Furthermore, the route developed allows accessing new targeted small molecule screening libraries. This can be achieved by derivatizing intermediates within the total synthesis route.



Brocazine E



Brocazine F



Brocazine G