

PUNDS 2026 — Presentation Assignments

Oral Presentations

Name	University	Abstract
Kyle Faivre	Purdue	Mitigating Aspartimide Formation in the Automated Synthesis of Secretin Family Hormones The Secretin/Glucagon superfamily of hormones represents a therapeutically rich source of alpha helical peptides that target various class B G-protein coupled receptors. Analogs of said peptides include successful therapeutics such as semaglutide and tirzepatide as well as emerging drug candidates such as glepaglutide. Despite their biomedical importance, many members of the secretin family remain challenging synthetic targets owing to their proclivity to form aspartimide during solid phase peptide synthesis. This work will describe practical strategies that enable discovery scale synthesis of secretin family hormones using automated peptide synthesizers. Strategies to minimize aspartimide formation, including optimization of protecting groups and deprotection conditions, will be discussed. Additionally, new analogs of secretin family hormones displaying long-range sequence effects to aspartimide formation will also be discussed. Taken together, these findings provide an efficient route to synthesis of secretin class hormones as well as providing new insights into factors promoting aspartimide formation.
Felix Adulley	Notre Dame	Title: Therapeutic targeting of Grp94: A paradigm shift in glaucoma treatment Abstract: The 90 kD heat shock proteins (Hsp90) are molecular chaperones responsible for the maturation of proteins that are directly associated with cancer and/or metabolic diseases. Consequently, > 20 small molecule N-terminal inhibitors of Hsp90 have entered clinical trials and manifest pan-inhibitory activity against the four Hsp90 isoforms. Unfortunately, Hsp90 pan-Inhibitors appear to be disadvantageous as several toxicities have been reported including the induction of the heat shock response (HSR). Therefore, the development of Hsp90-isoform selective inhibitors represents an alternate therapeutic strategy that may circumvent some of the deleterious effects. Glucose regulated protein 94 (Grp94) is an ER-specific Hsp90-isoform that folds/trafficks and stabilizes client proteins/receptors. Interestingly, Grp94 is non-essential in mature cells, and inhibiting its N-terminal domain does not induce the HSR. Furthermore, the N-terminal domain of Grp94 contains a unique binding pocket ("site 2"), which allows for the design of selective inhibitors over the other three isoforms. Previous generation of inhibitors designed in our lab demonstrated selective inhibition of Grp94 as supported by in vitro data, and the degradation of integrins. In fact, in cellulo inhibition of Grp94 also reduces intracellular levels of mutant myocilin, which contributes to primary open angle glaucoma (POAG). Current studies are focused on the synthesis and biological evaluation of improved analogs to minimize entropy and increase inhibitory activity towards Grp94 to target myocilin-associated glaucoma.
Ana-Teresa Mendoza	Notre Dame	N-Amino peptide-derived pyridinium salts as precursors to sactionine linkages Sactipeptides are a class of ribosomally-synthesized and post-translationally modified peptides (RiPPs) containing unique thioether bonds formed between cysteine residues and the α-carbon of acceptor amino acids (sactionines). Several sactipeptides possess potent and selective antimicrobial activity, highlighting the need for efficient and general synthetic approaches. Existing methods to access sactionine linkages through chemical synthesis include alkylation of cysteine with electrophilic glycine derivatives, Lossen rearrangement of N-hydroxy amino acid derivatives, and catalytic addition of thiols to dehydroamino acids. Late-stage sactionine bond formation would improve efficiency and provide a route to new and diverse thioether-bridged peptide macrocycles. Here, we leverage the reactivity of backbone N-aminated peptides to generate pyridinium salts that readily undergo elimination across the Cα-N bond in the presence of a mild base. The resulting N-acylimines are trapped by cysteine and serine nucleophilic side chains in situ to generate cyclic N-amidoacetals and thioacetals. The connectivity of the newly-formed heterocycles was confirmed by 2D NMR. Our methodology features late-stage cyclization of crude linear precursors and requires only a final HPLC purification to afford sactipeptide products. We further apply this method to the synthesis of a 12-membered sactionine ring found in the naturally occurring RiPP streptosactin. These results show that N-amino peptides are versatile substrates for the incorporation of sactionine bridges, and enable further synthetic studies targeting sactipeptide antibiotics and their congeners.

Name	University	Abstract
Kylie Wells	Kentucky	Discovery of a Novel Synthetic Opioid with Improved Safety Profile Kylie Wells 1, Dan Luo 1,2, Suresh Narva 1, Loan Vu 1, Marissa C. Hessing 1, Warren J. Alilain 4,5, Jill R. Turner 1, Michael T. Bardo 3, and Thomas E. Prisinzano 1,2,* 1 Department of Pharmaceutical Sciences, University of Kentucky, Lexington KY 40506, United States 2 Center for Pharmaceutical Research and Innovation, College of Pharmacy, University of Kentucky, Lexington KY 40506, United States 3 Department of Psychology, University of Kentucky, Lexington KY 40536, United States 4 Spinal Cord and Brain Injury Research Center (SCoBIRC), College of Medicine, University of Kentucky, Lexington KY 40536, United States 5 Department of Neuroscience, University of Kentucky, Lexington KY 40536, United States Atoxifent is a potent, biased mu-opioid receptor (MOR) agonist that produces antinociception with reduced respiratory depression. Structurally, it contains a conformationally constricted piperazine core. We sought to explore the importance of the piperazine core as the unconstrained precursor acts as an antagonist. This indicates that the piperazine core is a key modulatory feature that can be used to gain further insight into ligand recognition at the MOR. The size and position of the bridge were explored on the piperazine core to modulate the angle of the substituents on the core and alter the distance between the basic nitrogen and other key interactions in the binding pocket. These variations resulted in mostly equipotent MOR agonists, in reference to Atoxifent, however varying levels of B-arrestin recruitment as well as differing kappa and delta opioid receptor activity were observed in-vitro. Further modification led to the discovery of KSW-88, a G-Protein biased MOR agonist with fentanyl-like antinociception that was reversible with naltrexone in mice. In rats, KSW-88 demonstrated reduced levels of respiratory depression compared to fentanyl and maintained the righting reflex. These results indicate a novel synthetic opioid class that provides a more favorable safety profile compared to fentanyl. Acknowledgements: This work described was supported by the National Institute on Drug Abuse (U01 DA051377), National Institute of General Medical Sciences (P20 GM130456), and the Kentucky Medical Services Foundation Endowed Chair in Pharmacy (T.E.P.). The authors thank the College of Pharmacy PharmNMR Center for analytical support. PharmNMR is supported in part by NIH grants S10 OD28690 and P20 GM130456. The content is the sole responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
Xue Zhao	Purdue	Discovery of Macrocyclic γ-AApeptide Insulin Receptor Agonists by Combinatorial Screening The insulin receptor (IR) is a key regulator of glucose and lipid metabolism, and impaired IR signaling contributes to diabetes and related metabolic disorders. To develop synthetic alternatives to insulin, we explored macrocyclic γ-AApeptides as chemically stable receptor agonists. A one-bead-two-compound (OBTC) library containing more than 500,000 macrocyclic γ-AApeptides was screened against the extracellular domain of IR to identify novel receptor-binding ligands. Hit compounds were subsequently optimized through structure-guided design and bioconjugation. Optimized γ-AApeptides demonstrated specific IR binding and robust activation of downstream AKT signaling in vitro, while the unnatural peptide scaffold provided enhanced proteolytic stability. These findings establish macrocyclic γ-AApeptides as promising scaffolds for synthetic insulin mimetics and demonstrate the utility of OBTC combinatorial screening for the discovery of functional IR agonists.

Name	University	Abstract
Alaa Abdelazziz	Notre Dame	Targeted Degradation of EB1 as a Chemical Approach to Modulate Microtubule Organization Microtubules (MTs) are essential components of the cytoskeleton that regulate cell division, migration, intracellular transport, and cellular organization. Because of their central roles in these processes, MTs are important therapeutic targets, particularly in cancer. However, clinically used MT-targeting agents such as paclitaxel (Taxol) act directly on tubulin and broadly disrupt MT function, which can result in significant toxicity. An alternative approach is to target proteins that regulate MT behavior rather than tubulin itself, potentially allowing more selective pharmacological control of MT-dependent cellular processes. MT behavior is regulated via a group of proteins known as plus-end tracking proteins (+TIPs). End-Binding Protein 1 (EB1) is a +TIP that regulates MT dynamics and recruits numerous proteins to the growing MT ends. Here, we investigate a proteolysis-targeting chimera (PROTAC) designed to induce targeted degradation of EB1 using immunofluorescence microscopy and biochemical approaches to characterize its effects on EB1 abundance and MT-associated proteins. In cultured cells, PROTAC treatment produced a concentration- and time-dependent reduction in EB1, with substantial effects following 0.3 μM short-term treatment and overnight treatment at concentrations as low as 1 nM. Reduced activity at higher concentrations was consistent with the characteristic PROTAC hook effect. Functionally, Targeted EB1 degradation resulted in a significant increase in cell migration, a significant decrease in tubulin signal, and a significant decrease CLASP I signal which is one of the +TIPs. These findings demonstrate that PROTAC-mediated EB1 degradation produces measurable changes in MT-associated cellular behavior and supports the use of this PROTAC as a chemical tool for investigating EB1 function. Finally, This EB1-directed PROTAC provides a chemical biology tool for investigating how EB1 coordinates MT organization and +TIP recruitment and establishes a foundation for evaluating EB1 degradation in disease-relevant cellular models such as breast cancer where EB1 is upregulated and acts as an oncogene driving tumor proliferation and malignancy.
Kylie Castator	Purdue	Synthesis of γ-butyrolactone and lactam Signaling Molecules from Streptomyces Species

Poster Session Group 1

Name	University	Poster	Group	Abstract
Monica Stefaniak	Notre Dame	1	Group 1	Discovery of novel benzothiophenes targeting penicillin-binding proteins in gram-positive bacteria Rising antibiotic resistance, coupled with diminishing investment in antibiotic development, has led to limited treatment options for multidrug-resistant bacterial infections. Penicillin-binding protein 2a (PBP2a) is a key determinant of resistance to many β-lactam antibiotics in methicillin-resistant <i>Staphylococcus aureus</i> (MRSA), while overexpression of PBP4 mediates resistance to fifth-generation cephalosporins. We previously identified the benzothiophene compound NDM-335 as a potential inhibitor of PBP4 that overcomes PBP4-mediated resistance to ceftobiprole. We conducted a structure–activity relationship study on the NDM-335 scaffold to identify compounds that overcome oxacillin resistance, with the lead compound lowering the minimum inhibitory concentration 32-fold at 5 μM. Further development of this adjuvant lead could potentially deliver a new combination therapy for treating MRSA infections. In parallel, we report the discovery of NDM-552, a novel antibacterial with potent activity (MIC = 1–2 μg/mL) against a range of gram-positive pathogens, including MRSA, methicillin-sensitive <i>S. aureus</i>, and <i>Enterococcus faecium</i>. NDM-552 exhibits bacteriostatic behavior, favorable therapeutic indices, and in vivo efficacy comparable to ceftobiprole in a murine wound infection model. Binding studies using biochemical and biophysical assays indicate interaction with PBP2 and secondary affinity for PBP4, supporting a mechanism targeting bacterial cell wall biosynthesis. Together, these findings highlight benzothiophene scaffolds as promising platforms for both antibiotic adjuvant development and direct antibacterial discovery, providing a foundation for future optimization against multidrug-resistant gram-positive pathogens.
Yu Yu Win	Purdue	2	Group 1	Name: Rational design of sulfonyl-r-AA peptides as cMyb mimics for disruption of cMyb-KIX interaction. Abstract: cMyb, 75-89 kDa, is a transcription factor essential for blood cell development. Its abnormal activity is linked to leukemia through interaction with the KIX domain of CBP. Targeting this interaction is a potential therapeutic strategy. We designed sulfonyl-r-AA peptides to disrupt cMyb/KIX binding. These mimics show strong binding, good cell permeability, and induce similar shifts in KIX as wild-type cMyb, suggesting as a promising antileukemic agents.
Evelyn Hance	Notre Dame	3	Group 1	Name: Structure Function Study of 2-Aminobenzimidazole Compounds to Combat Salmonella Biofilms Abstract: <i>Salmonella enterica</i> serovar Typhi is the causative agent of typhoid fever, an acute systemic infection that affects major organs, such as the liver and gallbladder. A major challenge in treating typhoid fever is the emergence of multidrug resistant (MDR) and extensively-drug resistant (XDR) <i>Salmonella</i> Typhi (<i>S. Typhi</i>) strains, along with the capability of <i>S. Typhi</i> to form biofilms. Bacteria in a mature biofilm state are ~1000-fold more tolerant to conventional antibiotics compared to planktonic bacteria, making them particularly hard to eradicate. We aim to provide alternative treatments for <i>S. Typhi</i> infections through the development of antibiotic adjuvants; small molecules that are non-toxic to the bacteria alone yet enhance the activity of an antibiotic through disruption or blockage of bacterial resistance mechanisms. The use of anti-biofilm agents has been reported as a promising strategy in minimizing bacterial carriage in the gallbladder via a murine model. Herein, we describe the design and synthesis of a library of derivatized small molecules based upon a previously identified scaffold that inhibits and disperses <i>S. Typhi</i> biofilms: M4. Synthesized derivatives are designed to decrease hydrophobicity and lower cLogP values, in order to mediate unfavorable interactions with the human Ether-a-go-go (hERG) channel. Structure activity relationship (SAR) studies are still ongoing to further investigate derivatization of M4.
Jess Bay	Purdue	4	Group 1	Title: Preparation of SuFEx Probes via Late-Stage Electrochemical Fluorination of Sulfones Abstract: Sulfonyl fluorides are a privileged functional group due to their electrophilic nature. They are useful as site selective, covalent protein modifiers that can engage important nucleophilic residues. Sulfonyl fluorides are noted for their aqueous stability, in vivo activity and reactivity to a variety of protein residues, and when installed on complex, biologically active molecules, the biocompatibility and reactivity make them a powerful tool for chemical biology and drug discovery. Despite being such a powerful tool, many of the current methods do not allow for late-stage installation of sulfonyl fluorides. Therefore, new methods that allow for late-stage installation are required to selectively install these electrophilic warheads on a wider range of substructures.

Name	University	Poster	Group	Abstract
Luke Cowart	Notre Dame	5	Group 1	Title : Further Optimization of the IMD-0354 Scaffold Generates Potent Colistin Adjuvants with Reduced Eukaryotic Toxicity that are Active In vivo. Abstract : The development of novel therapeutic approaches to combat infections that stem from extensively drug-resistant (XDR) gram-negative bacteria remains an area of significant unmet need. One such approach is the use of adjuvants, molecules that have little/no standalone antimicrobial activity but overcome antibiotic resistance mechanisms. Currently, colistin (polymyxin E) is used as the antibiotic of last resort for the treatment of XDR gram-negative bacterial infections. However, resistance to this critical antibiotic is on the rise. Previously, we reported a series of adjuvants based on the salicylanilide IκB kinase-β inhibitor IMD-0354 that overcome colistin resistance in several gram-negative pathogens. However, this scaffold exhibits unfavorable eukaryotic toxicity, thought to arise from the salicyl moiety. Herein, we investigate the structure-activity relationship (SAR) of second-generation m-hydroxybenzanilide analogs of IMD-0354, to uncover compounds with reduced eukaryotic toxicity and IκB kinase-β inhibitory properties while maintaining colistin adjuvant activity. Through analog synthesis, we have identified new leads that lower the colistin minimum inhibitory concentration (MIC) upwards of 2048-fold against highly colistin-resistant <i>Acinetobacter baumannii</i> (AB) and <i>Klebsiella pneumoniae</i> (KP) strains possessing chromosomally encoded polymyxin resistance, as well as strains harboring the plasmid borne mobile colistin resistance-1 (mcr-1) gene. Lead compound NDM-622 exhibits reduced HepG2 toxicity compared to IMD-0354, with an IC₅₀ of 124.5 ± 0.05 μM and a therapeutic index of ≥50. NDM-622 also exhibits reduced inhibition of IKKβ activity relative to IMD-0354, with IC₅₀s of 20.40 μM and 2.02 μM, respectively. In a murine peritonitis model using a highly colistin-resistant <i>K. pneumoniae</i> strain, the combination of NDM-622 and colistin effected a decrease in colony forming units (CFUs) compared to treatment with either colistin alone or vehicle controls. Preliminary mechanism of action studies suggest that m-hydroxybenzanilides act via a mechanism distinct from the salicylanilides, evidenced by the absence of lipid A modification reversal, and no observable increase in reactive oxygen species generation, iron binding, or increased membrane permeability.
Isaac Frederique	Purdue	6	Group 1	Title: Covalent modification of a conserved cysteine for inhibition of Plasmodium PI4K enhances antimalarial profile Abstract: Malaria is a life-threatening infectious disease caused by Plasmodium parasites, with <i>P. falciparum</i> and <i>P. vivax</i> being the most significant contributors to global mortality. The World Health Organization estimated that there are over 250 million malaria cases which cause over 600 thousand deaths yearly. Over the years these parasites have gained resistance to multiple treatment options including chloroquine, mefloquine and even the currently used artemisinin-based combination therapy. Although new and potentially effective treatments are being developed, the risk of drug resistance is recurring. To address this critical challenge, identifying covalent inhibitors that bind selectively and irreversibly to essential proteins in the parasite offers a promising strategy to reduce the likelihood of resistance development. Through an initial covalent fragment screen, we successfully identified a scaffold with an acrylamide warhead that targets a recently discovered kinase that is essential in Plasmodium. Notably, the scaffold forms a covalent bond with a residue that has minimal potential for mutation—an important feature, as resistance is often driven by mutations in the binding site. Optimization of the identified scaffold has led to potent derivatives that exhibit IC₅₀ values in the low nanomolar range. These compounds demonstrated irreversible inhibition of the target protein and effective parasite clearance. The successful development of these covalent inhibitors could lead to novel malaria treatments with a significantly reduced risk of resistance development.

Name	University	Poster	Group	Abstract
Tyler Friedlander	Purdue	7	Group 1	"Toward Structure-Guided Design of Non-Opioid Analgesics: Localizing AC1-Selective Inhibitor Binding with AC1/AC2 Chimeras" Opioid analgesics relieve pain primarily by activating μ-opioid receptors (MORs), which suppress adenylyl cyclase 1 (AC1) activity and reduce cAMP signaling in pain-relevant circuits. This pathway is central to opioid analgesia, but opioids also activate β-arrestin and other MOR-dependent pathways responsible for tolerance, dependence, and respiratory depression. Directly targeting AC1 offers a way to engage the analgesic pathway without triggering these MOR-mediated side-effect pathways, providing a mechanistically grounded, non-opioid strategy for chronic pain. All known AC1-selective small molecules, including ST034307, D411-0524, and AC10142A, were derived from unbiased screening approaches. Compounds were optimized through SAR without structural guidance, since no AC1 structure exists. Thus, rational, contact-guided inhibitor design has not been possible, and medicinal chemistry efforts have proceeded essentially blind to the molecular determinants of isoform selectivity. Without knowing where AC1-selective inhibitors bind or what features of AC1 confer this selectivity, designing next-generation compounds with improved potency, selectivity, or drug-like properties remains difficult. To begin addressing how these inhibitors interact with the enzyme, we first profiled their behavior across multiple activation states. All three compounds responded differently as stimulation shifted from CaM-dependent to forskolin-dependent activation, indicating distinct mechanisms of engagement with AC1. Since these effects were not attributable to direct competition with forskolin, we turned to domain-swap chimeras to pinpoint the structural origin of AC1 selectivity. AC1/AC2 chimeras were tested under matched stimulation conditions. Chimeras retaining AC1 character from the N-terminus through C1b (AC1-2xC2a, AC1-2xCoil2, and AC1-TM2) produced full AC1-like concentration-response curves (CRCs) for the AC1-selective inhibitors. In contrast, chimeras with AC2 character in this same region (AC2-1xC2b and AC2-1xC2a) behaved identically to AC2 and failed to respond. Conversely, the AC2-selective inhibitor AC20002 inhibited AC2 and the AC2-derived chimeras, but not AC1 or the AC1-derived chimeras. Together, these results localize AC1-selective inhibitor engagement to the N-terminal-to-C1b region. Gain-of-function potency increases observed in some chimeras suggest altered conformational accessibility, but do not alter this domain-mapping conclusion. Ongoing work includes testing all constructs under a unified physiological stimulus (PGE$\blacksquare$) and generating additional chimeras (AC1-2xC1b and AC1-2xC1a) to further refine the binding region, potentially aligning with computational predictions of C1a-adjacent binding. AC1 is a promising non-opioid pain target, but its selective inhibitors (ST034307, D411-0524, AC10142A) were developed through blind screening with no structural guidance, leaving their binding site unknown. Using domain-swap AC1/AC2 chimeras, this work localizes their site of action to the N-terminal-to-C1b region. These studies report the first structural mapping of AC1-selective inhibitor engagement and serve as a starting point for structure-guided drug design going forward.
David Wilson	Notre Dame	8	Group 1	Optimization of an Hsp90β-selective Inhibitor via Exploration of Hsp90 N terminal ATP-binding Pocket The 90-kDa heat shock protein (Hsp90) promotes the maturation of >400 client protein substrates, many of which are implicated in the development/progression of cancer. Although 22 Hsp90 N-terminal inhibitors have undergone clinical evaluation, the toxicities that arose from pan-inhibition have hindered their development as chemotherapeutic agents.

Name	University	Poster	Group	Abstract
Aditi Bhatt	Notre Dame	9	Group 1	Targeting TAK1 in Mutant KRAS Pancreatic and Colorectal Cancers Aditi Bhatt¹, Desmond Akwata², Asmita Asmi² and Herman O. Sintim^{2,3} ¹Department of Biological Sciences, ²Department of Chemistry & Biochemistry, ³Harper Cancer Research Institute, University of Notre Dame, Notre Dame, IN 46556 KRAS is mutated in about 90% of pancreatic ductal adenocarcinomas (PDAC) and 40% of colorectal cancers. A few KRAS inhibitors (KRASi) have been approved for clinical use but while many patients initial respond to KRASi, resistance emerges in the majority of cases. Therefore there is a need for alternative strategies for treating KRAS-mutant PDAC and colon cancers. TAK1 (also called MAP3K7) is synthetic lethal to KRAS dependency. TAK1 is required for KRAS-dependent colon cancer cell viability, sustains KRAS-driven NF-κB signaling in pancreatic cancer, and protects pancreatic cells from programmed cell death. We have developed a series of novel imidazopyridazine-containing TAK1 inhibitors, which are orally bioavailable, and hypothesized that these compounds would be active against KRAS-dependent cancers. To identify inhibitors that retain potency across KRAS backgrounds, we measured GI50 values for a panel of our TAK1 inhibitors in five KRAS-mutant lines spanning three alleles and two tumor types: MIA PaCa-2 (G12C), PANC-1 and AsPC-1 (G12D), and SW620 and SK-CO-1 (G12V). The most potent compound differed between lines, indicating that potency is background-dependent rather than fixed. HSMK632 was the exception, ranking in the top five in every line, with GI50 values of 15 to 105 nM, and outperforming gemcitabine (GI50 0.56 μM) in PANC-1 and 5-fluorouracil (1.53 μM) in SK-CO-1. These results identify HSMK632 as a TAK1 inhibitor (TAK1i) with consistent activity across pancreatic and colorectal models, supporting our TAK1i as potential therapeutics for KRAS-mutant cancers.
Huapeng Li	Purdue	10	Group 1	Synthetic Biology and Genetics Approaches towards Understanding Histone Histaminylations Histone histaminylation, a transglutaminase-mediated covalent attachment of histamine to glutamine residues, has recently emerged as a novel epigenetic mark with important implications on cancers and neuronal diseases. Building upon the discovery of histone H3Q5 histaminylation (H3Q5His) and additional histaminylated sites across core histones, this work develops synthetic biology and genetic approaches to investigate the transcriptomic and biological consequences of histone histaminylation. First, a sortase-mediated ligation (SML) strategy was employed to install H3Q5His onto chromatin in live cells and uncovered direct transcriptomic impacts. Second, the H3.3 Q5H mutation was shown to recapitulate key biochemical effects of H3Q5His, including the disruption of WDR5 binding and suppression of H3K4 trimethylation (H3K4me3). Preliminary data also demonstrated the oncogenicity of H3.3 Q5H, implying a novel mechanism by which histone mutation drives cancer development. This research establishes versatile experimental toolboxes for dissecting the mechanisms of histone histaminylation and its effects on gene regulation. These approaches not only advance understanding of an emerging epigenetic modification but also create broadly applicable platforms for investigating diverse histone PTMs and their roles in human disease.
Sophia Elena Gregory	Notre Dame	11	Group 1	Structure-Activity Relationship Analysis and hERG Liability Assessment of Second-Generation Antibiofilm Compounds Active Against Salmonella Typhoid fever is a systemic, life-threatening illness caused by <i>Salmonella enterica</i> subspecies <i>enterica</i> serovar Typhi. The gallbladder is the most implicated organ in chronic carriage and host transmission due bacterial biofilm formation on gallstones. Biofilms facilitate chronic infection because the bacteria in biofilms are less susceptible to antibiotic treatment than non-biofilm associated, or planktonic bacteria. Previously, we reported compounds that disrupt biofilms of <i>Salmonella enterica</i> serovar Typhimurium, a serovar closely related to <i>S. Typhi</i>, in vitro and in vivo. This work extends the development of <i>Salmonella</i> antibiofilm agents through the further exploration of the parent scaffold. Lead anti-biofilm compounds were tested for human ether-a-go-go-related gene (hERG) channel inhibition, from which we report new lead compounds with improved anti-biofilm activity and reduced hERG channel inhibition.

Name	University	Poster	Group	Abstract
Shadwa Eldosuky	Purdue	12	Group 1	"Continuous Flow Synthesis of Aripiprazole Using High-Throughput Experimentation as a Guide" Aripiprazole is an essential third-generation antipsychotic drug primarily used for the treatment of schizophrenia. Its indication expanded owing to its favorable safety profile and efficacy to mood disorders like bipolar depression and pediatric irritability associated with autism spectrum disorders. Currently, it is also being investigated for its anticancer properties. Increased demand for the drug has triggered occasional market shortages, highlighting the importance of aripiprazole for clinical and research purposes. In this work, we have developed two different hybrid flow syntheses of aripiprazole from the readily available 1,2,3-trichlorobenzene precursor using insights from high throughput experimentation (HTE) to guide route scouting. Aripiprazole was produced in 29% overall yield over a three-step flow sequence in Route A. The overall synthesis times are significantly reduced compared to current batch methods from 38 hours to approximately 100 minutes for both routes.
Connor Winkelhake	Notre Dame	13	Group 1	"SAR and Development of Small-Molecule STING Inhibitors with Improved Pharmacokinetic & Pharmacodynamic Parameters" Aberrant cGAS-STING signaling drives chronic neuroinflammation and contributes to multiple human pathologies including Alzheimer's disease, Parkinson's disease, and systemic lupus erythematosus. However, no small-molecule STING inhibitor has reached the clinic due to poor drug-likeness, off-target toxicity, and inadequate blood-brain barrier (BBB) penetrability. Our group has previously identified substituted 3H-pyrazolo[4,3-f]quinolines as potent STING inhibitors via Povarov/Doebner multicomponent chemistry. Unfortunately, our lead scaffold HSKB142 (ClogP ~ 4.3) suffers from high lipophilicity, low aqueous solubility, and low BBB permeability (~ 5%). As such, we undertook an extensive SAR study (~ 40 analogs) across four ring positions of HSKB142 to further understand the scaffold. We then identified several compounds that retain or improve STING antagonism in murine macrophages that also promisingly lower logP and/or tPSA. Guided by these SAR trends and in silico validation (docking, MD), a combinatorial library was synthesized by pairing the highest-potency motifs to exploit additive gains in target engagement and reduce lipophilicity and tPSA to improve CNS penetrability. Lead compounds will then be pushed through a staged validation workflow to confirm adequate target engagement, evaluate BBB permeability, and determine their pharmacokinetic profile before we evaluate them in in vivo murine disease models of Alzheimer's disease and acute kidney injury.
Neeraj Maurya	Notre Dame	14	Group 1	Exploring Structural Diversification of the Solvent-Exposed Region of the Hsp90β ATP-Binding Pocket: Effects on binding affinity, antiproliferative activity, and solubility Cancer cells rely upon Hsp90 to maintain the conformational stability of mutated or overexpressed oncoproteins; this dependency has made the molecular chaperone an attractive target for anticancer drug discovery. However, pan-Hsp90 inhibitors have largely failed clinical trials due to on-target toxicities arising from non-discriminant inhibition of Hsp90α. To overcome these liabilities while retaining therapeutic efficacy, Hsp90β-selective inhibition is a promising alternative strategy. Building on our previous SAR exploration of the solvent-exposed region of the Hsp90β binding pocket, herein we describe the rational design and synthesis of additional analogs with "southern" handles that incorporate diverse three-dimensional moieties and/or various functional groups to further probe the pocket and improve drug-like properties. This study identified 2n as the most aqueous-soluble Hsp90β compound reported to date, with solubility of 13.4 μM and K_d values of >100 μM (Hsp90α) and 0.198 μM (Hsp90β), with selectivity >500-fold. These findings expand our understanding of the pocket for isoform-selective Hsp90β inhibitors and lay the foundation for future optimization towards a drug-like, clinically viable candidate.
Wendy Tang	Purdue	15	Group 1	Title: Exploring Sulfonyl-γ-AApeptide Analogues as Enhanced GLP-1 Agonists Abstract: Sulfonyl-γ-AApeptides are a versatile and productive peptidomimetic that combines an unnatural amino acid backbone with an ability to carry multiple different sidechains resulting in a small but mighty building block. The diversity of structure and sidechains allow for the creation of vast combinatorial libraries to find targets. Through this, we explore various Sulfonyl-γ-AApeptide structures built to mimic GLP-1 agonist in an attempt to create a more stable and effective mimic.

Name	University	Poster	Group	Abstract
Ritu Vrijender Mathuri	Purdue	16	Group 1	Title: Design and Development of Sulfono-γ-AApeptide Bac8c Mimic Analogs for Enhanced Stability and Antimicrobial Activity Abstract: Antimicrobial resistance (AMR) is a major global health challenge, necessitating alternative antibacterial strategies. Antimicrobial peptides (AMPs) have gained considerable attention due to their unique mechanisms of action, including membrane disruption. Bac8c, a short bacterenecin-derived AMP, exhibits potent broad-spectrum antibacterial activity but is limited by proteolytic instability, cytotoxicity, and other pharmacological challenges that hinder its therapeutic translation. Sulfonyl-γ-AApeptides are synthetic peptide mimics that incorporate non-natural backbones, offering enhanced resistance to proteolytic degradation and expanded chemical diversity compared with conventional peptides. Here, we explore sulfonyl-γ-AApeptides as peptidomimetic scaffolds for optimizing Bac8c. We designed and synthesized Bac8c-sulfonyl-γ-AApeptide hybrids and evaluated their antibacterial activity through structure-activity relationship studies. Several analogues demonstrated potent antibacterial activity, with the most active compound exhibiting a minimum inhibitory concentration (MIC) of 3.125 μg/mL against methicillin-resistant <i>Staphylococcus aureus</i> (MRSA). Further studies are underway to demonstrate the efficacy, stability, and mechanism of action of the lead peptide. Collectively, this work highlights sulfonyl-γ-AApeptides as a promising platform for optimizing natural AMP scaffolds and developing next-generation antimicrobial peptidomimetics.
Graham Thomason	Kentucky	17	Group 1	ShawShank Redemption: Differential Expression of Postsynaptic Scaffolding Proteins Underlie Morphological Changes to Pyramidal Neurons in the HIV-1 Transgenic Rat Approximately 40 million people worldwide live with HIV. Despite advances in combination antiretroviral therapy (cART), HIV-1 seropositive individuals still suffer from a number of chronic comorbidities, including neurocognitive impairments. The neuropathology of HIV is well characterized phenotypically; notable shifts in dendrite complexity and dendritic spine morphology are closely tied to cognitive function. However, the foundational molecular and cellular mechanisms are not well understood. We hypothesized that changes in expression of postsynaptic scaffolding proteins would underlie HIV-1-induced neuronal and dendritic spine dysmorphology in glutamatergic pyramidal neurons in the prefrontal cortex (PFC). The HIV-1 transgenic rat, which resembles HIV-1 seropositive individuals on cART, was used to recapitulate key aspects of HIV-1-associated neurocognitive disorders. Our results show both profound transcriptional and morphological alterations in the PFC, which largely occur in a sex-dependent manner. Quantitative PCR of tissue detected significant changes in expression of genes within the Shank (e.g., Shank2, Shank3) and Homer (e.g., Homer 1a, Homer 1b/c) families, which are key postsynaptic proteins that provide scaffolding and signal integration. Computational analysis of dendrite arborization and spine phenotype performed on ballistically labeled pyramidal neurons revealed major sex-dependent divergences in morphology between control and transgenic groups. Notably, ongoing statistical analyses are investigating if and/or how these transcriptional alterations mechanistically underlie dendritic spine dysmorphology and/or HIV-1-associated neurocognitive impairments. Elucidating the foundational molecular and cellular mechanisms underlying HIV-1-induced dendritic spine dysmorphology may identify novel therapeutic targets. Crucially, the marked sex differences indicate that discrepancies between females and males may arise in the efficacy of future HIV-1 therapeutics.
Emily Struck	Purdue	18	Group 1	Photocatalyzed Cyclization of gem-Difluoroalkenes with Alcohol Nucleophiles to Access Cyclic Difluorinated Ethers
Joey Wise	Purdue	19	Group 1	Deoxyfluoroalkylation of Cyclohexanones and Cyclohexenones Under Mild Photochemical Conditions Accesses Diverse Fluoroalkyl Arenes Fluoroalkyl arenes, particularly trifluoromethyl-substituted arenes, are valuable motifs in pharmaceuticals and materials but are challenging to synthesize due to harsh conditions and limited substrate scope in existing methods. Here we report a deoxyfluoroalkylation-aromatization sequence employing photoexcited 3⁺[DDQ] under mild conditions (35 °C, visible light irradiation), enabling efficient conversion of cyclohexan(en)ones to highly substituted fluoroalkyl arenes. This photochemical approach significantly broadens functional group tolerance and improves yields compared to prior thermal methods requiring high temperatures (120–140 °C) and the use of stoichiometric acid. The methodology accommodates diverse substrates, including heterocycles and acid-sensitive groups, and is scalable to decagram quantities. These findings provide a versatile and milder synthetic route to access complex fluoroalkyl arenes, facilitating their incorporation into advanced molecular architectures.

Name	University	Poster	Group	Abstract
Md Eahsanul Karim Anik	Notre Dame	20	Group 1	High-Throughput Screening of FDA-Approved Drug Library to Identify Synergistic Combinations with Hsp90β-Selective Inhibitors in Breast Cancer. Md Eahsanul Karim Anik, Ian Mersich, Aktar Ali, Brian S. J. Blagg. Department of Chemistry and Biochemistry, Warren Center for Drug Discovery, University of Notre Dame, Notre Dame, IN Abstract: Breast cancer remains the most frequently diagnosed cancer in women worldwide and a leading cause of cancer-related mortality, with substantial global incidence and mortality across diverse populations [1]. Despite advances in surgery, chemotherapy, endocrine therapy, and HER2-directed treatments, therapeutic resistance and disease recurrence continue to limit long-term survival, particularly in aggressive breast cancer subtypes. Heat shock protein 90 (Hsp90) is an ATP-dependent molecular chaperone that stabilizes numerous oncogenic client proteins involved in tumor proliferation, survival, and metastasis, and pharmacological inhibition of Hsp90 promotes the degradation of these oncogenic drivers [2]. The constitutively expressed Hsp90β isoform plays a critical role in maintaining oncogenic signaling and proteostasis, making it an attractive and selective therapeutic target for cancer treatment [3]. However, breast cancer progression involves dysregulation of multiple parallel signaling pathways, highlighting the need for rational combination strategies to enhance therapeutic efficacy and overcome resistance [2]. To identify synergistic partners for Hsp90β inhibition, we performed high-throughput screening (HTS) of an FDA-approved drug library in combination with NDNB25, a selective Hsp90β inhibitor. Breast cancer cell lines were stratified based on HSP90AB1 dependency using DepMap CRISPR and RNAi datasets. MDA-MB-231 cells were selected as an Hsp90β-dependent (NDNB25-sensitive) model, while AU565 cells were selected as an Hsp90β-independent (NDNB25-resistant) model. Sensitivity classification was experimentally validated by determining NDNB25 IC$_{50}$ values across multiple breast cancer cell lines using CellTiter-Glo luminescent cell viability assay. The same assay was used for combination treatments (NDNB25 + FDA-approved drugs) during high-throughput screening. Synergistic interactions were quantified using the Bliss independence model by comparing observed and predicted additive effects. Combination screening identified 63 synergistic hits in MDA-MB-231 cells and 26 synergistic hits in AU565 cells. These synergistic combinations produced a greater reduction in cell viability compared to single-agent treatments. Identified hits were further categorized based on drug targets and signaling pathways to facilitate mechanistic interpretation and prioritization. Together, this HTS identified novel synergistic drug combinations that enhance the anticancer efficacy of Hsp90β-selective inhibition and provide a strong rationale for developing effective combination therapies in breast cancer. References: 1. Kim J, Harper A, McCormack V, Sung H, Houssami N, Morgan E, Mutebi M, Garvey G, Soerjomataram I, Fidler-Benaoudia MM. Global patterns and trends in breast cancer incidence and mortality across 185 countries. <i>Nature medicine</i>. 2025 Apr;31(4):1154-62. 2. Blagg BSJ, Kerr TD. Hsp90 inhibitors: small molecules that transform the Hsp90 protein folding machinery into a catalyst for protein degradation. <i>Medicinal research reviews</i>. 2006 May;26(3):310-38. 3. Chaudhury S, D'Amico T, Blagg BSJ. The Hsp90β isoform: An attractive target for drug development. <i>Medicinal Research Reviews</i>. 2025 Sep;45(5):1452-65.

Name	University	Poster	Group	Abstract
Alaa Abdelazziz	Notre Dame	21	Group 1	Targeted Degradation of EB1 as a Chemical Approach to Modulate Microtubule Organization Microtubules (MTs) are essential components of the cytoskeleton that regulate cell division, migration, intracellular transport, and cellular organization. Because of their central roles in these processes, MTs are important therapeutic targets, particularly in cancer. However, clinically used MT-targeting agents such as paclitaxel (Taxol) act directly on tubulin and broadly disrupt MT function, which can result in significant toxicity. An alternative approach is to target proteins that regulate MT behavior rather than tubulin itself, potentially allowing more selective pharmacological control of MT-dependent cellular processes. MT behavior is regulated via a group of proteins known as plus-end tracking proteins (+TIPs). End-Binding Protein 1 (EB1) is a +TIP that regulates MT dynamics and recruits numerous proteins to the growing MT ends. Here, we investigate a proteolysis-targeting chimera (PROTAC) designed to induce targeted degradation of EB1 using immunofluorescence microscopy and biochemical approaches to characterize its effects on EB1 abundance and MT-associated proteins. In cultured cells, PROTAC treatment produced a concentration- and time-dependent reduction in EB1, with substantial effects following 0.3 μM short-term treatment and overnight treatment at concentrations as low as 1 nM. Reduced activity at higher concentrations was consistent with the characteristic PROTAC hook effect. Functionally, Targeted EB1 degradation resulted in a significant increase in cell migration, a significant decrease in tubulin signal, and a significant decrease CLASP I signal which is one of the +TIPs. These findings demonstrate that PROTAC-mediated EB1 degradation produces measurable changes in MT-associated cellular behavior and supports the use of this PROTAC as a chemical tool for investigating EB1 function. Finally, This EB1-directed PROTAC provides a chemical biology tool for investigating how EB1 coordinates MT organization and +TIP recruitment and establishes a foundation for evaluating EB1 degradation in disease-relevant cellular models such as breast cancer where EB1 is upregulated and acts as an oncogene driving tumor proliferation and malignancy.
Dem Santiago	Purdue	22	Group 1	Title: Neuroprotective Effects of PACAP27 Against PD-related insults Abstract: The aggregation of α-synuclein into highly stable inclusions in Parkinson's disease (PD) impairs cellular clearance pathways and heightens oxidative stress. This insult drives mitochondrial dysfunction, characterized by disrupted fusion-fission dynamics, reactive oxygen species (ROS) overproduction, and elevated proton leakage resulting in genomic stress and DNA double-stranded breaks (DSBs). The neuropeptide PACAP27 engages neuroprotective cascades, including the cAMP/PKA pathway, to suppress pathological Drp1-mediated mitochondrial fission, stabilize mitochondrial membrane potential, promote antioxidant defenses, and upregulate anti-apoptotic and DNA repair factors. We are testing PACAP27 for its ability to attenuate neurotoxicity in primary cortical neuron cultures subjected to various PD-associated environmental exposures (paraquat, rotenone) and cellular insults (α-synuclein pre-formed fibrils). Evidence that PACAP27 mitigates PD-associated mitochondrial collapse and genomic stress would highlight its potential as a disease-modifying therapeutic agent for synucleinopathies.

Poster Session Group 2

Name	University	Poster	Group	Abstract
Xiaoling Chen	Purdue	23	Group 2	Human brain assembloids reveal cortico-striatal circuit dysfunction and therapeutic rescue in SCN2A deficiency
Laura Hession	Notre Dame	24	Group 2	β-Arch proteomimetics of Pick's disease tau as models of pathogenic aggregation The dysfunction and aggregation of tau is a hallmark of neurodegenerative diseases termed tauopathies, which include Alzheimer's disease, Pick's disease, and several different types of dementias. Wild-type tau functions in the regulation of microtubule stability and dynamics in the brain. In brains affected by tauopathies, tau transitions from soluble monomers to insoluble, aggregated filaments which impede neuronal structure and function. Furthermore, pathological tau can propagate to healthy neurons from diseased neurons in a prion-like manner. Recent cryo-EM structures of patient-derived tau from post-mortem brain tissue have uncovered various conformational strains which vary between tauopathies. Despite these advances in structural characterization, we lack robust methods to recapitulate disease-associated tau misfolds using either recombinant or synthetic constructs. Here, we describe the design, synthesis, and conformational analysis of cyclic recombinant and synthesized proteomimetics inspired by core hydrogen bonds observed in β-arch motifs observed in Pick's disease tau. Cysteine mutations of hydrogen-bond partners, combined with diversity-oriented macrocyclization, provide cyclic compounds that can self-assemble into β-arch fibrils. These proteomimetics will serve as tools to study the contribution of various bond partners and motifs to self-assembly and seeding propensity, as well as potential future models to test drugs or generate binders. With our approach, we aim to reduce the reliance on patient-derived tau and enable further studies probing structure-function relationships of aggregation and seeding.
Felix Adulley	Notre Dame	25	Group 2	Title: Therapeutic targeting of Grp94: A paradigm shift in glaucoma treatment Abstract: The 90 kD heat shock proteins (Hsp90) are molecular chaperones responsible for the maturation of proteins that are directly associated with cancer and/or metabolic diseases. Consequently, > 20 small molecule N-terminal inhibitors of Hsp90 have entered clinical trials and manifest pan-inhibitory activity against the four Hsp90 isoforms. Unfortunately, Hsp90 pan-inhibitors appear to be disadvantageous as several toxicities have been reported including the induction of the heat shock response (HSR). Therefore, the development of Hsp90-isoform selective inhibitors represents an alternate therapeutic strategy that may circumvent some of the deleterious effects. Glucose regulated protein 94 (Grp94) is an ER-specific Hsp90-isoform that folds/trafficks and stabilizes client proteins/receptors. Interestingly, Grp94 is non-essential in mature cells, and inhibiting its N-terminal domain does not induce the HSR. Furthermore, the N-terminal domain of Grp94 contains a unique binding pocket ("site 2"), which allows for the design of selective inhibitors over the other three isoforms. Previous generation of inhibitors designed in our lab demonstrated selective inhibition of Grp94 as supported by in vitro data, and the degradation of integrins. In fact, in cellulo inhibition of Grp94 also reduces intracellular levels of mutant myocilin, which contributes to primary open angle glaucoma (POAG). Current studies are focused on the synthesis and biological evaluation of improved analogs to minimize entropy and increase inhibitory activity towards Grp94 to target myocilin-associated glaucoma.
Andrew Sayers		26	Group 2	Abstract not provided

Name	University	Poster	Group	Abstract
Jayani Dhanasinghe	Purdue	27	Group 2	Continuous Flow Synthesis of Indomethacin via Telescoped N-acylation Strategy Indomethacin is a potent non-steroidal anti-inflammatory drug (NSAID) that is typically used to treat severe pain. An expanding range of therapeutic applications has increased the demand for this agent, thus motivating the desire to develop a greener and efficient process for its synthesis. In this work, we report a 2-step route for the synthesis of indomethacin in flow, comprising indole ring formation followed by N-acylation. Each step of the process was first optimized under batch conditions before converting them to continuous synthesis conditions, with subsequent translation into a fully continuous telescoped flow sequence. Both reaction steps demonstrated significantly improved performance in flow compared to the corresponding batch reaction. Continuous acid–base extraction of the product generated in the telescoped continuous flow process, conducted with a liquid–liquid separator, achieved 98% recovery with 97% purity. The overall residence time for the telescoped continuous process was 53 minutes, thus demonstrating an efficient, protecting-group-free, two-step continuous flow synthesis of indomethacin.
Mengyao Lu	Purdue	28	Group 2	Ubiquitin C-terminal hydrolase L3 (UCHL3) is a deubiquitinating enzyme involved in DNA-damage-response pathways and has emerged as a potential target for cancer therapy. Although genetic studies have helped define its biological functions, progress has been limited by the lack of well-characterized, selective chemical probes. Here, we describe the identification and optimization of a new covalent scaffold that irreversibly inhibits UCHL3. Systematic structure–activity relationship studies identified the molecular features required for activity, while ligand-bound crystal structures confirmed covalent modification of the enzyme's catalytic cysteine. Cellular target engagement was demonstrated in two cell lines using ubiquitin activity-based probe competition and gel-shift assays. Together, these findings establish this scaffold as a useful starting point for developing chemical probes to investigate UCHL3 function in cancer and other biological settings.
Wumaierjiang Adilijiang	Notre Dame	29	Group 2	Pharmacokinetic Screening of Oxadiazoles for Treatment of Clostridioides difficile Infection
Lukman Abidemi Bello	Purdue	30	Group 2	Title: Diastereoselective Cascade Reactions of Mono- and Bidentate Aryl-Tethered Aldehydes and Dihydrofurans: A Modular Route to Tricyclic Benzocyclopentafurans and Benzocyclohexafurans. Abstract: A TiCl ₄ -mediated diastereoselective cascade reaction of Mono- and Bidentate aldehydes and Dihydrofurans has been developed to construct previously unexplored benzo-fused tricyclic ether frameworks. The cascade proceeds through carbonyl addition followed by Friedel–Crafts cyclization, giving 5/5/6 tetrahydro-benzocyclopentafurans from aromatic aldehydes and 5/6/6 hexahydro-benzocyclohexafurans from aryl-tethered acetaldehydes in good yields with moderate-to-excellent diastereoselectivity. Both reaction efficiency and diastereocontrol in the 5/5/6 series are governed by the ortho-methoxy group: aldehydes bearing it engage in bidentate coordination to titanium, driving higher reaction efficiency and selectivity than their monodentate counterparts. The ortho-methoxy group also drives product reactivity: the corresponding 5/5/6 tricyclic alcohol undergoes spontaneous rearrangement on silica gel to the thermodynamically more stable 5/5/6 scaffold, while the analog lacking it is unreactive under the same conditions. In the 5/6/6 series, tether length replaces chelation as the dominant factor governing regio- and stereochemical outcomes.

Name	University	Poster	Group	Abstract
Xiaotan Yu	Notre Dame	31	Group 2	Name: Vancomycin in Combination with Oxadiazoles as Spore Germination Inhibitors to Halt Recurrent Clostridioides difficile Infection Abstract: Clostridioides difficile infection (CDI) remains a major clinical challenge, characterized by high recurrence rates despite antibiotic treatment. While current therapies such as vancomycin effectively eliminate vegetative cells, they fail to eradicate dormant spores, which can persist in the gut and germinate to drive recurrent infection cycles. To address this limitation, we developed a dual-action strategy that combines traditional antibacterial treatment with inhibition of spore germination. We previously identified oxadiazole-based small molecules that selectively inhibit key enzymes (CspB and SleC) involved in the spore germination pathway, without disrupting the gut microbiota. However, the initial monomeric compounds were absorbed into the bloodstream, resulting in low concentrations in the gut. To overcome this, we designed and synthesized a series of oxadiazole dimers with polyethylene glycol linkers to decrease absorption. Among these, a PEG4-linked dimer demonstrated two-fold improved spore germination inhibition (IC 50 7.8 μM) and significantly reduced systemic exposure over the monomer in mouse pharmacokinetic studies. In a mouse model of CDI, co-administration of the oxadiazole dimer with vancomycin increased survival, reducing recurrence of infection compared to vancomycin alone, which correlated with higher compound concentrations in feces. These results highlight the potential of combining vegetative cell killing with targeted inhibition of spore germination as a promising therapeutic strategy to prevent CDI recurrence.
Max Perrino	Purdue	32	Group 2	"Designing Instability: Development of a Redox Active Protecting Group to Enable the Synthesis of Sulfonyl Fluorides" – The sulfonyl fluoride functional group is a privileged scaffold in medicinal and biochemistry. Synthesizing complex sulfonyl fluoride containing products is a challenge due to product decomposition, poor selectivity, the use of harsh reagents. This project seeks to address these challenges through use of a redox-active protecting group designed to be stable to most standard reactions but electrochemically labile. Installation of a sulfone bearing this protecting group is conducted early with use of a new, bench-stable reagent sulfinate reagent. Once installed, this protecting group enables structure diversification around the inert sulfonyl fluoride surrogate. Eventually, an electrochemical deprotection reaction cleaves the protecting group, generating a sulfonyl radical intermediate that abstracts a fluorine atom to deliver complex, late-stage, sulfonyl fluoride containing products.
Eric Woloshin	Kentucky	33	Group 2	Searching for Synthetic Opioid Rescue Agents. 2. Identification of an Ultra-Potent Synthetic Opioid Rescue Agent Ultra-potent synthetic opioids (UPSO) have become increasingly prevalent today, from being implicated in a mass casualty event to contaminating illicit drug supply across the country. These UPSOs are different than semi-synthetic and naturally derived opioids, in the sense that UPSOs have a much greater ability to cause opioid-induced respiratory depression (OIRD) and wooden chest syndrome (WCS), two medical phenomena that are essential in the lethality of UPS opioids. Here, we report the identification of a potential rescue agent (9) that is more potent than naloxone (NLX) in vitro and fully reverses fentanyl- and carfentanil-induced ventilatory depression and fentanyl-induced vocal cord closure in rats. Unlike naloxone, rescue agent 9 increases minute ventilation above normal in fentanyl- or carfentanil-treated rats and appears to have limited brain penetrance. Targeting peripheral opioid receptors offers a new strategy for reversing OIRD, and 9 offers a lead towards developing such an agent.

Name	University	Poster	Group	Abstract
Temitope Oropo	Purdue	34	Group 2	Activity-Based Characterization of Non-Ribosomal Peptide Synthetases Involved in Streptomyces Natural Product Biosynthesis Streptomyces species are prolific producers of structurally diverse bioactive natural products, many of which are assembled by non-ribosomal peptide synthetases (NRPSs) - large, modular enzymes with multiple domains each responsible for distinct steps in peptide assembly. Despite their pharmacological relevance, the large size and complex domain architecture of NRPSs makes functional characterization in native cellular contexts challenging. In particular, the effects of culture conditions on influence NRPS expression, activity, and subcellular organization in Streptomyces remain poorly understood. Here, we apply activity-based protein profiling (ABPP) to investigate the surugamide NRPS in Streptomyces albus. Leveraging the cognate amino acid recognition of the adenylation (A) domain, we utilize an acyl-adenosine vinylsulfonamide (AVS) probe that covalently traps active A-carrier protein (CP) interactions, enabling the detection of functionally engaged NRPS domains in complex proteomes. Labeled proteins are analyzed by fluorescence based detection or enriched via streptavidin pull-down following gel electrophoresis. We are currently evaluating how growth stage and culture conditions influence the detection of high-molecular weight NRPS complexes and their activity-dependent labeling. This work lays the groundwork for future studies on enzyme dynamics and subcellular localization in Streptomyces, with broader implications for understanding and engineering natural product biosynthesis.
Kelly Sprenkel	Notre Dame	35	Group 2	Synthesis of Novel Delavirdine Regulated Induced Proximity Targeting Chimeras to Promote HIV Cell Death Human immunodeficiency virus (HIV) persists as integrated proviral genomes within immune cells and currently does not have a cure. Antiretroviral therapies (ARTs) have demonstrated reduced mortality rate in people with HIV, but these therapies have limitations including decades-long treatment and adverse side effects which increase patient non-compliance. Delavirdine is an FDA approved non-nucleoside reverse transcriptase inhibitor (NNRTI). While delavirdine and other anti-HIV medications can decrease the chance of a patient developing acquired immunodeficiency syndrome (AIDS), there is a growing need for innovative therapies to eradicate HIV-1 infection. One approach to eradication is using chemical inducers of proximity (CIPs) to force two proteins together. Regulated induced proximity targeting chimeras (RIPTACs) is a class of CIPs that bridge target proteins and essential proteins required for cell survival via linker chains between target protein and essential protein ligands. A molecule similar to that of a RIPTAC could be used to induce selective HIV-infected cell death. In order to test this hypothesis, a library of novel delavirdine derived RIPTACs must first be synthesized, with JQ1 acting as the essential protein ligand. Since the sulfonamide of delavirdine does not participate in the binding pocket, the motif can be modified without negatively impacting the compounds binding affinity. Several novel compounds were synthesized and will undergo biological screening for activity in HIV cell lines.
Charles Nelson Kuedukey	Purdue	36	Group 2	Title: E6 Inhibition Through LxxLL Peptide Derivatives Abstract Human papillomavirus (HPV) is responsible for nearly all cervical cancers and a substantial proportion of anogenital and oropharyngeal malignancies. In addition to promoting degradation of the tumour suppressor p53 through recruitment of the E3 ubiquitin ligase E6AP, the HPV16 E6 oncoprotein suppresses innate antiviral immunity by binding interferon regulatory factor-3 (IRF3), thereby inhibiting type I interferon signalling. Recent structural studies indicate that E6 recognizes an LxxLL α-helical motif within IRF3, providing a potential target for therapeutic intervention. Here, we report the design and synthesis of IRF3-derived hydrocarbon-stapled peptides that mimic the E6-binding α-helical interface to competitively target HPV16 E6. To improve intracellular delivery, a series of conjugates incorporating proteolytically stable N-substituted glycine (NArg) cell-penetrating peptoids of varying lengths were synthesized using a combined peptide/peptoid solid-phase synthetic strategy followed by on-resin ring-closing metathesis to generate the hydrocarbon staple. The resulting library includes unstapled and stapled IRF3 peptides together with NArg$\blacksquare$-, NArg$\blacksquare$-, and NArg$\blacksquare$-conjugated derivatives, which were purified by RP-HPLC and verified by MALDI-TOF mass spectrometry. These molecules provide a chemically defined platform for future evaluation of E6 binding, inhibition of the E6-IRF3 interaction, cytosolic delivery, and restoration of antiviral signalling. This work establishes a foundation for the development of stapled peptide therapeutics that simultaneously target HPV-mediated immune evasion and oncogenic signalling.

Name	University	Poster	Group	Abstract
Ritu Vrijender Mathuri	Purdue	37	Group 2	Title: Design and Development of Sulfono-γ-AApeptide Bac8c Mimic Analogs for Enhanced Stability and Antimicrobial Activity Abstract: Antimicrobial resistance (AMR) is a major global health challenge, necessitating alternative antibacterial strategies. Antimicrobial peptides (AMPs) have gained considerable attention due to their unique mechanisms of action, including membrane disruption. Bac8c, a short bacterenecin-derived AMP, exhibits potent broad-spectrum antibacterial activity but is limited by proteolytic instability, cytotoxicity, and other pharmacological challenges that hinder its therapeutic translation. Sulfonyl-γ-AApeptides are synthetic peptide mimics that incorporate non-natural backbones, offering enhanced resistance to proteolytic degradation and expanded chemical diversity compared with conventional peptides. Here, we explore sulfonyl-γ-AApeptides as peptidomimetic scaffolds for optimizing Bac8c. We designed and synthesized Bac8c-sulfonyl-γ-AApeptide hybrids and evaluated their antibacterial activity through structure-activity relationship studies. Several analogues demonstrated potent antibacterial activity, with the most active compound exhibiting a minimum inhibitory concentration (MIC) of 3.125 μg/mL against methicillin-resistant <i>Staphylococcus aureus</i> (MRSA). Further studies are underway to demonstrate the efficacy, stability, and mechanism of action of the lead peptide. Collectively, this work highlights sulfonyl-γ-AApeptides as a promising platform for optimizing natural AMP scaffolds and developing next-generation antimicrobial peptidomimetics.
Milah Young	Notre Dame	38	Group 2	Resensitizing Highly Resistant <i>Klebsiella pneumoniae</i> via Histidine Kinase Inhibition The decline in novel antibiotics has fueled a rise in drug-resistant infections, creating an urgent need for alternative treatments. Antibiotic adjuvants offer a solution by blocking bacterial resistance mechanisms without killing the bacteria, which restores antibiotic sensitivity and slows down resistance evolution. In this study we screened a library of salicylanilides to determine their mechanism against colistin resistant <i>Klebsiella pneumoniae</i> (KP). Knowing that this library of compounds also targets the histidine kinases (HK) involved in colistin resistance in <i>Acinetobacter baumannii</i> we hypothesize they may also be targeting similar proteins involved in KP. Using in vitro phosphorylation assays several compounds were identified to target at least two of the three HKs involved in colistin resistance. There are still several studies ongoing to identify the in vivo effect of these inhibitors as well as studies to better visualize their potential binding site and affinity. Understanding the impact of salicylanilides on histidine kinases and their mechanism of interaction will lead to the development of more potent compounds that will serve as colistin adjuvant therapies for highly resistant gram negative infections.
Xiaosheng Jiang	Notre Dame	39	Group 2	Development of Hsp90 C-terminal inhibitors with noviomimetics that manifest anti-proliferative activities Heat shock protein 90 (Hsp90) is a dynamic protein that serves to ensure the proper folding of nascent client proteins, the regulation of transcriptional responses to environmental stress, and to guide misfolded and damaged proteins for degradation via the ubiquitin-proteasome pathway. Hsp90 is a homodimer with each monomer consisting of three components; an N-terminal ATP-binding domain (NTD), a middle domain (MD) wherein protein-protein interactions occur, and a C-terminal domain (CTD) that is responsible for dimerization. The development of Hsp90 C-terminal modulators (CTMs) have led to the alleviation of adverse on-target effects caused by induction of the heat shock response (HSR) via pan-inhibition of Hsp90 with N-terminal inhibitors. Moreover, Hsp90 CTMs are promising therapeutic agents that can manifest either antiproliferative or neuroprotective activity. However, the lack of a co-crystal structure of small molecules bound to the CTD has hindered their development. Therefore, structure-activity relationship (SAR) studies have been pursued for the development of such modulators. In order to investigate the size and nature of the C-terminal domain binding pocket, noviose sugar surrogates, also known as noviomimetics and analogs have been prepared. Herein, we report the synthesis and antiproliferative activities manifested by these Hsp90 C-terminal inhibitors.

Name	University	Poster	Group	Abstract
Abdulrahman Moursy	Purdue	40	Group 2	title "Synthesis and Development of Selective δ-Opioid Receptor Agonists" ; Abstract "Chronic pain is the leading cause of disability worldwide, and it affects at least 20.4% of adults in the United States. Opioids are among the most used classes for the treatment of chronic pain. However, opioids targeting μ-opioid receptors, such as morphine, are limited by many adverse effects and there has been an increasing overdose death associated with the abuse of these μ-targeting opioids. On the other hand, targeting DORs is also effective for treating chronic pain, but with much fewer side effects. Although several DOR agonists have been developed to this date, they have failed to reach the market for clinical use, either due to lack of efficacy, selectivity, or serious side effects, like convulsions. Studies carried out with DOR agonists have shown that agonists that recruit β-arrestin 2 lead to tolerance and convulsions. On the other hand, the non-convulsant DOR agonists have lower β-arrestin 2 recruitment. Therefore, a DOR-biased agonist that weakly or doesn't recruit β-arrestin 2, yet potently activates the G-protein, will be more clinically promising. (–)-TAN-67 is a potent DOR agonist with good DOR selectivity, and relatively low β-arrestin 2 recruitment efficacy. Moreover, in vivo studies in rat and mice showed analgesic properties without any observed convulsions. Therefore, (–)-TAN-67 represents a very good candidate for further investigation. On the other hand, the opposite enantiomer (+)-TAN-67 showed hyperalgesic activity and convulsions in mice which shows the importance of stereochemistry. This project aims to further enhance the potency of (–)-TAN-67 and decrease its β-arrestin 2 recruitment by a combination of SAR studies and computational drug design. The synthesis of (–)-TAN-67 is challenging and the reported syntheses are racemic and have various limitations. So, the main goal of the first phase of this project is to investigate the available racemic syntheses for this compound and to synthesize few derivatives. The second phase involves the development of the first enantioselective synthesis of (–)-TAN-67."
Mehdi Alikhani	Notre Dame	41	Group 2	Active metalloproteinases in Clostridiodes difficile infection
Brendan Veenstra	Kentucky	42	Group 2	Title: Maturation of Interneurons Derived from the Medial Ganglionic Eminence are Altered by Chronic Adolescent Oxycodone Self-Administration Abstract: Adolescence is a critical neurodevelopmental window characterized by prefrontal cortex (PFC) maturation and heightened vulnerability to substance use initiation. Chronic adolescent oral oxycodone (OXY) self-administration results in persistent neurocognitive deficits and synaptodendritic dysmorphology of excitatory cortical pyramidal neurons. To date, however, how adolescent oral OXY self-administration alters inhibitory interneurons in the PFC remains unexplored. To address this knowledge gap, the current study used quantitative polymerase chain reaction (qPCR) to investigate the central hypothesis that the long-term neurocognitive deficits following adolescent OXY self-administration are partially driven by disrupted maturation of medial ganglionic eminence (MGE)-derived interneurons in the PFC. First, evaluation of the core transcriptional cascade governing the maturation of MGE-derived interneuron function (<i>Dlx2</i>, <i>Lhx6</i>, <i>Sox6</i>, and <i>Mafk</i>) revealed a selective upregulation of <i>Dlx2</i> and <i>Mafk</i> in rodents with a history of adolescent OXY self-administration. Second, the MGE-derived interneuron markers <i>Sst</i> and <i>Pvalb</i> were upregulated in male, but not female, rats with a history of adolescent OXY self-administration. Third, GABAergic markers (e.g., cation-chloride cotransporters, presynaptic transporters and enzyme, and postsynaptic receptors) were profiled revealing a specialized, sex-dependent, transcriptomic state of GABAergic dysfunction. Crucially, ongoing analyses are exploring if and/or how transcriptomic alterations to GABAergic markers are associated with the persistent neurocognitive deficits. Collectively, results of the present study support aberrant development of MGE-derived interneurons following adolescent OXY self-administration; developmental alterations that may mechanistically underlie OXY-induced neurocognitive impairments.
Mengyao Lu	Purdue	43	Group 2	Ubiquitin C-terminal hydrolase L3 (UCHL3) is a deubiquitinating enzyme involved in DNA-damage-response pathways and has emerged as a potential target for cancer therapy. Although genetic studies have helped define its biological functions, progress has been limited by the lack of well-characterized, selective chemical probes. Here, we describe the identification and optimization of a new covalent scaffold that irreversibly inhibits UCHL3. Systematic structure–activity relationship studies identified the molecular features required for activity, while ligand-bound crystal structures confirmed covalent modification of the enzyme's catalytic cysteine. Cellular target engagement was demonstrated in two cell lines using ubiquitin activity-based probe competition and gel-shift assays. Together, these findings establish this scaffold as a useful starting point for developing chemical probes to investigate UCHL3 function in cancer and other biological settings.

Poster Session Group 2 — Continued

Name	University	Poster	Group	Abstract
Trevor Trombley	Purdue	44	Group 2	Title: On the Metabolic Stability of Fluorinated Small Molecules: A Physical Organic Chemistry Perspective The incorporation of fluorine and fluorinated motifs into medicinally relevant scaffolds can improve the metabolic and pharmacokinetic properties (DMPK) of drug molecules. Typically, this phenomenon is attributed to differences in C–H vs. C–F bond strengths, though such an explanation ignores accepted mechanisms of drug metabolism and how fluorine and fluorinated substituents perturb physicochemical properties of small molecules. Instead of relying on bond strengths alone, this poster discusses established mechanisms of Cytochrome P450 (CYP) mediated phase I oxidative processes (arene hydroxylation, radical rebound, N/O dealkylation) and phase II bioconjugation reactions (glucuronidation, glutathione conjugation) to provide mechanistic rationale and computational support for the improved metabolic profiles achieved by fluorinating drug candidates. In so doing, this poster connects observed trends in structure-metabolism-relationships with known mechanistic features of relevant drug-metabolizing enzymes, with the ultimate goal of improving medicinal chemistry decision-making.