Applied Pharmaceutical Chemistry

2023

Thursday, June 8

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ORGANIZERS' WELCOME

Welcome to the 2023 Applied Pharmaceutical Chemistry Conference.

Our organizers have gathered another excellent group of speakers for the fourteenth annual APC conference. The program is arranged to incorporate extensive audience participation and discussion. We encourage attendees to take full advantage of the opportunity to engage in discussion in order to receive the maximum benefit from the APC experience.

Thank you for your participation.

ORGANIZING COMMITTEE

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Conference Chair: Kenneth Boy, BMS

Conference Chair Elect: Pedro Garcia Barrantes, Vertex

Committee Members

Susan Ashwell, Civetta Therapeutics
Eamon Comer, Kymera Therapeutics
David Ebner, Pfizer
Baudouin Gerard, Nuvalent Inc.
Catherine Jorand Lebrun, Ananke Therapeutics
Benoit Moreau, Remix Therapeutics

APC 2023 CONFERENCE AGENDA

Thursday, June 8

8:00 - 9:00	**Registration & Breakfast**
9:00 - 9:05	**Conference Opening** Kenneth Boy, BMS
9:05 - 9:10	**Speaker Introduction** Eamon Comer, Kymera Therapeutics
9:10 - 9:45	**Protein Editing using Small Molecules** Amit Choudhary, Harvard Medical School/B&W's Hospital
9:45 - 9:50	**Speaker Introduction** David Ebner, Pfizer
9:50 - 10:20	**Discovery of the MC4R Antagonist PF-07258669 as Potential Treatment for Appetite Loss** Michelle Garnsey, Pfizer
10:20 - 10:25	**Speaker Introduction** Sue Ashwell, Civetta Therapeutics
10:25 - 10:55	**From Platform to Clinic: Leveraging a MonoART-Focused Chemical Library to Advance PARP7 and PARP14 Inhibitors as Novel Therapeutics** Nicholas Perl, Ribon
10:55 - 11:15	Break
11:15 - 11:20	**Speaker Introduction** Baudoin Gerard, Nuvalent
11:20 - 11:50	**Holistic Drug Design for Small Molecule Drug Discovery** Lewis Pennington, Kymera
	VENDOR SHOWCASE
11:50 - 11:55	**Plenary Speaker Introduction** Kenneth Boy, BMS

11:55 - 12:40 **PLENARY: The Invention of Fipravirimat, An Inhibitor of HIV-1 Maturation**
Nicholas Meanwell, The Baruch Blumberg Institute (formerly Vice President, Head of Discovery Chemistry Platforms, Bristol-Myers Squibb)

12:40 - 1:55 Lunch

1:55 - 2:00 **Speaker Introduction**
Pedro Garcia Barrantes, Vertex

2:00 - 2:30 **Discovery and Preclinical Characterization of Brain-penetrant, Orally Bioavailable LRRK2 Inhibitors for Parkinson's Disease**
Mitch Keylor, Merck

2:30 - 2:35 **Speaker Introduction**
Kenneth Boy, BMS

2:35 - 3:05 **Engineering Permeability Beyond the Rule of Five: A Case Study in KRAS-Targeting Peptides**
Matthew Mitcheltree, Merck

3:05 - 3:25 Break

VENDOR SHOWCASE

3:25 - 3:30 **Speaker Introduction**
Benoit Moreau, Remix Therapeutics

3:30 - 4:00 **RAPID – a Next-Generation Chemoproteomics Technology Enabling the Discovery of Reversible Binders to Pre-specified Targets in Living Cells**
Justin Rettenmaier, Jnana Therapeutics

4:00 - 4:05 **Closing Plenary Speaker Introduction**
Catherine Lebrun, Ananke Therapeutics

4:05 - 4:50 **PLENARY: Chemical Approaches to Edit Post-translational Modifications in Cells**
Christina Woo, Harvard University

4:50 - 4:55 **Closing Remarks**
Pedro Garcia Barrantes, Vertex

4:55 - 5:55 **Reception**

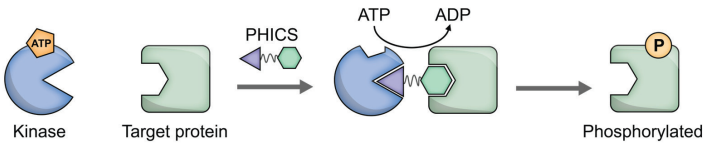
ABSTRACTS

Protein Editing Using Small Molecules

Amit Choudhary, Harvard Medical School/B&W's Hospital

My laboratory focuses on applying chemistry-based approaches to propel the development of molecular and cellular modalities for various disorders. I will briefly introduce our efforts in cellular engineering using CRISPR-based technologies and the development of zinc-based prodrug systems, but my presentation will focus on Phosphorylation-Inducing Chimeric Small molecules (PHICS). Small molecules have been classically used to inhibit enzyme function (i.e., loss-offunction), but several new classes of small molecules are emerging that endow neo-functions to enzymes via proximity-mediated effects. I will describe the development and applications of PHICS, which can induce phosphorylation of a given target protein by forcing proximity between a kinase and the target protein (Scheme 1).

Scheme 1.



Platform development: The first-generation PHICS were formed by joining the target binder via a linker to a non-inhibitory kinase binder, which are scantily available. I will describe linkers based on addition-elimination reactions that enable the generation of PHICS using kinase inhibitors (abundantly available), allowing rapid development of PHICS for > 30 kinases (and their isoforms). Beyond PHICS, these linker chemistries may accelerate the development of chimeric molecules that induce/remove other post-translational modifications.

Novel bioactivities of PHICS: I will describe various activities of PHICS, including induction of phosphorylations that trigger signal transduction or phase separation, and induction of neophosphorylations (unobserved endogenously and potentially immunogenic) that adversely affect the target protein's ability to interact with negatively charged biomolecules. For example, PHICSmediated phosphorylation disrupted the ability of KRAS, a GTPase that translocates to the membrane, to interact with GTP/phospholipids. "Homo-PHICS" (i.e., a dimer of kinase binder) efficaciously inhibited the kinase by inducing ATP-binding pocket's phosphorylation that disrupts further ATP loading. This novel mechanism of action allowed PHICS to efficaciously kill cancer cells resistant to known drugs (e.g., Imatinib/Asciminib for CML, Ibrutinib for CLL).

In summary, we have developed bifunctional molecules that exhibit novel MoA via neophosphorylation and a linker technology that will enable rapid development of bifunctional molecules that induce/remove other posttranslational modifications.

Discovery of the MC4R Antagonist PF-07258669 as Potential Treatment for Appetite Loss

Michelle Garnsey, Pfizer

The melanocortin-4 receptor (MC4R) is a centrally expressed, Class A GPCR that plays a key role in the regulation of appetite, food intake, and energy expenditure. Deficiencies in MC4R signaling, due to either the loss of receptor function or the loss of production and processing of endogenous agonist peptides, result in hyperphagia, increased linear growth, and increased body mass in humans. Antagonism of MC4R signaling has the potential to mitigate decreased appetite and body weight loss in the setting of anorexia or cachexia due to underlying disease. We will report on the identification of a series of orally bioavailable, small-molecule MC4R antagonists using a focused hit identification effort and the optimization of these antagonists for potency, brain penetration, and ADME attributes leading to the identification of PF-07258669 as a clinical candidate.

From Platform to Clinic: Leveraging a MonoART-Focused Chemical Library to Advance PARP7 and PARP14 Inhibitors as Novel Therapeutics

Nicholas Perl, Ribon Therapeutics

Ribon Therapeutics has a longstanding interest in studying the 17-member poly[adenosine diphosphate (ADP)-ribose] polymerase (PARP) family of enzymes. A subset of the family, the monoARTs, utilize NAD+ to catalyze the transfer of a monomer of ADP-ribose (MAR) onto a substrate (MARylation).

MonoART enzymes are of interest due to their role in regulating fundamental cellular processes, including gene expression, protein degradation, and cellular stress response. We have built a collection of assays and selective, small molecule inhibitors to interrogate the biology of the monoART enzymes, leading to the advancement of two first-in-class monoART inhibitors into clinical trials. The first, RBN-2397, is a potent and selective NAD+-competitive inhibitor of PARP7, a monoART that is a negative regulator of nucleic acid sensing in tumor cells. Inhibition of PARP7 after oral dosing restores the Type I interferon (IFN) signaling response in mouse models of cancer, leading to tumor regression by both direct inhibition of cell proliferation and activation of the immune system within the tumor microenvironment. RBN-2397 is currently being evaluated in the clinic as a single agent in multiple tumor types (NCT04053673) and in combination with anti-PD-1 therapies (NCT05127590). The second monoART inhibitor that we have advanced into the clinic, RBN-3143, is a potent NAD+-competitive inhibitor of PARP14, a macrodomain-containing monoART that is induced by all three types of interferon and has been shown to modulate tissue inflammation through Th2/Th17 signaling. Oral dosing of RBN-3143 in multiple mouse models of inflammatory disease leads to broad suppression of disease features. RBN-3143 is currently being tested in a Phase I study in normal healthy volunteers and patients with atopic dermatitis (NCT05215808).

Holistic Drug Design for Small Molecule Drug Discovery

Lewis Pennington, Kymera

Modern small molecule drug discovery requires rapid and simultaneous multiparameter optimization in a wide variety of assays. To improve the efficiency of multiparameter optimization and increase the chance for success in small molecule drug discovery, holistic drug design is needed, which entails the strategic and integrated use of orthogonal, complementary, or synergistic drug design approaches based on the goal and stage of the drug discovery program, the quantity and quality of data for analyses, and the availability and accuracy of predictive models. This talk will discuss the evolution of small molecule drug design and discovery over the past 30 years, introduce the concept of holistic drug design as a way of strategic thinking enabled by a new conceptual framework, and then highlight three exemplary case studies.

PLENARY TALK

The Invention of Fipravirimat, An Inhibitor of HIV-1 Maturation

Nicholas A. Meanwell, The Baruch Blumberg Institute

The betulinic acid derivative bevirimat provided clinical proof-of-concept for inhibition of HIV-1 virion maturation as a therapeutic approach to control infection. However, the antiviral effect was compromised by the presence of pre-existing polymorphisms in the spacer peptide-1 (SP1) of the Gag polyprotein that amounted to almost 50% of the population, reflecting a similar percentage of non-responders in the Phase II clinical trial. GSK-3532795 (BMS-955176) was identified as a second generation HIV-1 maturation inhibitor that expanded potent inhibitory activity toward the polymorphic variants insensitive to bevirimat. The discovery of GSK-3532795 (BMS-955176) and the Phase II clinical efficacy data will be discussed followed by a description of the campaign to further embellish the antiviral profile of HIV-1 maturation inhibitors which resulted in the identification of fipravirimat (GSK3640254, BMS-986173), a compound currently in clinical trials sponsored by ViiV Healthcare.

Discovery and Preclinical Characterization of Brain-penetrant, Orally Bioavailable LRRK2 Inhibitors for Parkinson's Disease

Mitch Keylor, Merck

Inhibition of leucine-rich repeat kinase 2 (LRRK2) represents a genetically-supported, chemically-tractable, and potentially disease-modifying mechanism by which to treat Parkinson's disease. In this presentation, vignettes from the discovery and optimization of ATP-competitive small molecule inhibitors of LRRK2 kinase activity will be shared. Examples of the application of property- and structure-based design approaches will be shown in the context of pharmacokinetic profile improvement and kinome selectivity optimization, respectively. Additionally, tactics successful in mitigating efflux transporter liabilities and preclinical safety concerns will be described.

Engineering Permeability Beyond the Rule of Five: A Case Study in KRAS-Targeting Peptides

Matthew Mitcheltree, Merck

Membrane permeability is a central obstacle medicinal chemistry teams face, particularly when designing beyond the Rule of 5 (bRo5). Here we recount how bRo5 guidelines, modern analytical techniques, physics-based modeling, and QSAR prediction enabled our team to discover cell-active macrocyclic peptides targeting KRAS. We describe an evolving strategy for property optimization involving (1) cation-promoted cell penetration, (2) non-cationic, non-passive permeation, and (3) the engineering of metabolically stable, passively permeable peptides with potent on-target activity in mutant-KRAS cancer cell lines. For each approach, challenges and risk-mitigation strategies are presented that may enable discovery teams to accelerate the successful discovery of medicines in the bRo5 property space.

RAPID – a Next-Generation Chemoproteomics Technology Enabling the Discovery of Reversible Binders to Pre-specified Targets in Living Cells

Justin Rettenmaier, Jnana Therapeutics

RAPID is a new hit generation technology for identifying small molecules that bind reversibly to any target of interest in a living cell. RAPID identifies small-molecule binders irrespective of the fold or function of the target protein, delivering quality chemical matter for high-value targets.

First, RAPID leverages a proprietary library of photoreactive small-molecule fragments called "Reactive Affinity Probes" to identify druggable pockets on a target protein of interest inside of living cells. Unlike mass-spectrometry-based workflows that assess binding of one reactive probe to the entire proteome, RAPIDevaluates the binding of thousands of probes to a single protein target with >100X increased throughput. Next, once a reactive probe for a druggable pocket of interest is identified, RAPID's high-throughput detection technology enables screening hundreds of thousands of reversible, lead-like molecules for those that bind to the target in cells and thereby prevent binding of the reactive probe.

Driven by the RAPID platform, Jnana advanced a first-in-class allosteric inhibitor of a genetically validated target for PKU into the clinic in Q4'22. This seminar will introduce the RAPID technology and describe its application towards the discovery of the first described ligands for the transcription factor IRF3, which is the master regulator of the Type I IFN response downstream of cGAS/STING and RIG-I/MAVS.

PLENARY TALK

Chemical Approaches to Edit Post-translational Modifications in Cells

Christina M. Woo, Harvard University

Nature regulates many biological processes through post-translational modifications that modify protein activity and relay signals through protein networks. Interpretation of how nature uses these modifications will provide new insights to biological regulation, and open new frontiers in the design of therapeutic modalities that mimic nature to treat human disease. We combine the rational design of small molecules and proteins with chemical proteomics technology to tackle key challenges in decoding and editing post-translational modifications. Here, I will describe approaches to write and erase chemical signals on target substrates in cells that in combination with molecular mechanism of action studies have led to the discovery of new regulatory processes through post-translational modifications in biology.

BIOGRAPHIES

Amit Choudhary, PhD, Harvard Medical School/Brigham & Women's Hospital: Dr. Choudhary is an Assistant Professor of Medicine at Harvard Medical School, an Associate Biologist at Brigham and Women's Hospital, and an Associate Member at the Broad Institute. He performed his pre-doctoral studies in Chemistry at Indian Institute of Science-Bangalore and doctoral studies in Biophysics, where he elucidated a new force akin to the hydrogen bond in its quantum mechanical origin. Subsequently, he was appointed a Junior Fellow of the Harvard Society of Fellows. The efforts of Choudhary laboratory have been recognized by Burroughs Wellcome Fund's Career Award at the Scientific Interface, NIH Director's Transformative Research Award, DARPA's Safe Genes and HEALR awards, Vilcek Prize for Creative Promise, ICBS Young Chemical Biologist Award, and Juvenile Diabetes Research Foundation's Innovation Award. Dr. Choudhary is a scientific founder of Photys Therapeutics that leverages the group's findings on bifunctional molecules that induce or remove post-translational modifications.

Michelle Garnsey, PhD, Pfizer: Dr. Garnsey received her BS in chemistry from the University of New Hampshire and her PhD from Duke University from Prof. Don Coltart studying enolization methodology and its application to total synthesis. After completing a post-doctoral appointment with Prof. Larry Overman at the University of California, Irvine, Michelle started a position as a medicinal chemist at Pfizer in 2014. At Pfizer, Michelle has worked in both the synthesis and design groups focusing on a variety of targets in neuroscience and cardiovascular & metabolic indications. In her free time, Michelle enjoys spending time with her husband and two young children playing games such as "The Sneaky, Snacky Squirrel" and touring local playgrounds.

Mitch Keylor, Merck: Mitch Keylor joined the Merck Boston Discovery Chemistry team in January of 2018 after completing a Novartis-funded postdoctoral appointment under the joint advisorship of Dr. Kian Tan and Prof. Matt Sigman. During his postdoc, Mitch investigated method development and model build for catalyst-controlled selectivity in amine arylation reactions. Prior to this role, Mitch conducted his graduate studies under the tutelage of Prof. Corey Stephenson at the University of Michigan. His graduate work focused on the generation and study of persistent free-radical intermediates, and their application in the total synthesis of complex natural products. In his five-plus years with Merck, Mitch has contributed to neuroscience, oncology, and immuno-oncology programs from target ID and validation through lead optimization, and has co-authored six patents and two journal articles. Beyond the pipeline, Mitch contributes to talent acquisition as a Merck recruiting ambassador, and to employee growth and development as a people manager.

Nicholas A. Meanwell, PhD, The Baruch Blumberg Institute: Dr. Meanwell joined Bristol Myers Squibb in 1982 and retired in 2022 after having led drug discovery programs in the cardiovascular, neurosciences and virology therapeutic areas, work that resulted in the advancement of 33 clinical candidates. Nick and his team were involved in the design and development of flindokalner (MaxiPost®) (P3 for the treatment of stroke), the HIV-1 attachment inhibitor fostemsavir (RukobiaTM), the HIV-1 maturation inhibitors BMS-955176, fipravirimat and zegruvirimat, the HCV NS5A inhibitor daclatasvir (DaklinzaTM), the HCV NS3 protease inhibitors BMS-605339 and asunaprevir (SunvepraTM), and the HCV NS5B inhibitor beclabuvir, marketed in Japan as XymencyTM, a fixed dose combination with daclatasvir and asunaprevir.

Nick was the recipient of the 2015 Philip S. Portoghese Medicinal Chemistry Lectureship Award administered jointly by the *ACS Division of Medicinal Chemistry* and the *Journal of Medicinal Chemistry*. He was Inducted into the *ACS Division of Medicinal*

Chemistry Hall of Fame in 2015, was the co-recipient of a 2017 "Heroes of Chemistry" Award sponsored by the *American Chemical Society* and was the recipient of the 2022 Alfred Burger Award in Medicinal Chemistry sponsored by the *American Chemical Society*.

Nick received his Ph.D. degree from the University of Sheffield under the supervision of Dr. D. Neville Jones and competed a post-doctoral fellowship with Professor Carl R. Johnson at Wayne State University.

Matt Mitcheltree, PhD, Merck: Dr. Mitcheltree is a medicinal chemist at Merck Research Laboratories, where he has worked to discover new medicines for oncology, neuroscience, and immunology indications. Matt is a skilled designer with experience in small-molecule and peptide drug discovery, and has supported programs both in synthetic chemistry and modeling and informatics roles. Matt received a BS degree from Yale University studying with Seth Herzon, and earned a PhD degree with Andrew Myers at Harvard University with work culminating in the discovery of antibiotics overcoming bacterial multidrug resistance. Beyond science, Matt enjoys cooking, dancing, and making music.

Lewis D. Pennington, PhD, Kymera Therapeutics: Dr. Pennington is currently the Head of Platform Chemistry at Kymera Therapeutics. His research interests include drug discovery and defining strategies and tactics for multiparameter optimization in small molecule drug design. He previously served a variety of roles as a synthetic and medicinal chemist at Alkermes in Waltham, Massachusetts, Amgen in Thousand Oaks, California, Array BioPharma in Longmont, Colorado, and Eli Lilly & Co. in Indianapolis, Indiana. He earned a B.S. in Chemistry (with Highest Honors in Chemistry) under the guidance of Professor Masato Koreeda at the University of Michigan in Ann Arbor, Michigan, and a Ph.D. in Chemistry under the mentorship of Professor Larry Overman at the University of California in Irvine, California.

Nicholas Perl, PhD, Ribon: Dr. Perl completed his undergraduate studies at the University of Notre Dame and earned his Ph.D. from Columbia University, working on asymmetric reaction methodology with Professor James Leighton. After post-doctoral studies in natural product total synthesis in the labs of Professor David Gin at Memorial Sloan Kettering Cancer Center, he began his industrial career at Ironwood Pharmaceuticals. There he contributed to the advancement of two soluble guanylate cyclase stimulators, praliciguat and olinciguat, into Phase I clinical studies. After moving to Warp Drive Bio, he worked on drugging the GTP-bound form of KRAS-G12C using macrocyclic covalent molecular glues. Nick is currently a Director of Medicinal Chemistry at Ribon Therapeutics where he has served as chemistry lead on multiple programs, including their platform chemistry efforts.

Justin Rettenmaier, PhD, Jnana Therapeutics: Dr. Rettenmaier is Senior Director and Head of Early Discovery at the Boston-based biotech Jnana Therapeutics, where he leads the biochemistry, biophysics, assay development, and data science functions and co-leads the application and continued development of Jnana's platform. While at Jnana, Justin co-invented a ligand discovery technology called RAPID, which is a next-generation chemoproteomics platform that enables the identification of lead-like small molecule binders to any target of interest inside of a living cell. Jnana is leveraging RAPID to unlock historically difficult-to-drug targets, including transcription factors, phosphatases, molecular scaffolding proteins, and metabolite transporters. Prior to Jnana, Justin completed postdoctoral training in Discovery Biology at the Whitehead Institute with Susan Lindquist. He obtained his PhD in Chemical Biology working with Jim Wells at UCSF to discover small molecules targeting allosteric sites and protein-protein interfaces.

Christina M. Woo, PhD, Harvard University: Dr. Woo is an Associate Professor in the Department of Chemistry and Chemical Biology at Harvard University, and an affiliate member of the Broad Institute. Christina's research focuses on the design of chemical approaches to alter post-translational modifications and the signaling outcomes they produce in cells. She obtained a BA in Chemistry from Wellesley College (2008). She obtained her PhD in 2013 from Yale University under the guidance of Professor Seth Herzon as an NSF predoctoral fellow in the synthetic and chemical biology studies of diazofluorene antitumor antibiotics. In 2013, Christina joined the laboratory of Professor Carolyn Bertozzi at the University of California Berkeley as a Jane Coffins Child postdoctoral fellow and continued at Stanford University (2015) as a Burroughs Wellcome Fund postdoctoral fellow, where she developed a mass-independent chemical glycoproteomics platform for the identification of non-templated post-translational modifications. Christina joined the faculty at Harvard University in 2016. Her research has been recognized by the David Gin Young Investigator Award, Camille-Dreyfus Teacher-Scholar Award, Sloan Research Foundation, NSF CAREER, Bayer Early Excellence in Science Award, the NIH DP1 Avenir Award, and the Ono Pharma Foundation Breakthrough Science Award.

POSTER ABSTRACTS

Accelerating the hit to lead process using Flare™ Hit Expander and Flare FEP: discovery of CDK9 inhibitors

J. Brookes, L. Nelson, T. Cheeseright, M. Mackey
Cresset

The successful development of a compound within a drug discovery project can result from rapidly exploring the immediate chemical landscape around an initial hit compound. This case study demonstrates a workflow which combines the use of the new Hit Expander feature within Flare™ with relative free energy perturbation (FEP) calculations to rapidly identify the most promising putative ligands in a series, focusing here on CDK9 inhibitors.

Hit Expander makes small changes to a hit molecule via positional analog scanning (PAS). Many new designs are potentially created within a congeneric series which are highly suited for an FEP triage. By making small changes, Hit Expander facilitates the search of chemically interesting possibilities, leading to potentially large combinations based on learned SAR knowledge. Once created, the new compounds can then be easily explored using more computationally rigorous methods.

Relative FEP is used for triaging as the created dataset has small structural changes based on the initial reference compound. Given the close similarity to the reference molecule, high precision can be achieved using FEP with a relatively modest computational cost. Therefore, by starting with only one reference molecule with a known binding mode, along with a handful of known actives in a structure-based drug design project, a drug discovery problem can be quickly reduced from many suggestions to a few predictions with an assured high accuracy when using alchemical methods such as FEP.

A Novel and Efficient Synthesis Route for Glutarimide Ligands: Advancing CRBN Binders in Targeted Protein Degradation

Xinpeng Cheng

PURPOSE:

Targeted protein degradation has emerged as a promising therapeutic approach, harnessing the cell's own protein degradation machinery to selectively eliminate disease-causing proteins. One crucial aspect of this strategy involves recruiting E3 ubiquitin ligases, such as cereblon (CRBN), to facilitate the ubiquitination and subsequent proteasomal degradation of target proteins. Immunomodulatory drugs (IMiDs), including thalidomide, pomalidomide, and lenalidomide, have been recognized for their ability to bind CRBN and serve as key components in targeted protein degradation. However, the traditional synthesis of IMiDs poses several challenges, involving a stepwise process with numerous purification stages. The formation of the hydrolytically unstable glutarimide ring in these compounds further complicates synthesis and purification.

In light of these limitations, the purpose of this study is to develop an improved and more efficient synthesis route for glutarimide ligands. By addressing the challenges in traditional IMiD synthesis, this study aims to facilitate advancements in drug discovery and the broader application of targeted protein degradation as a therapeutic strategy.

METHODS:

To address the instability of the glutarimide ring, we employed 2,6-bis(benzyloxy)pyridine as a surrogate for glutarimide. 2,6-bis(benzyloxy)pyridine analogs are commercially available or can be readily synthesized from 2,6-bisfluoropyridine and benzyl alcohol through SnAr reaction. By employing a palladium-catalyzed coupling/hydrogenation cascade, 2,6-bis(benzyloxy)pyridine can be efficiently converted into glutarimide ligands. We assessed the scope and application of this approach in constructing C-C and C-N bonds, as well as its feasibility for large-scale synthesis.

RESULTS:

The synthesis of glutarimide ligands commences with the bromination of 2,6- bis(benzyloxy)pyridine, offering a versatile synthetic handle for functionalization. C-N bonds can be readily formed through Buchwald amination, accommodating various functional groups such as esters, amides, alcohols, and heterocycles. C-C bonds can be established either directly via Suzuki coupling reactions or through Miyaura borylation followed by Suzuki coupling, exhibiting good tolerability toward diverse heterocycles. The resulting molecules can be efficiently converted into glutarimide ligands through Pd-catalyzed hydrogenation with high yields. This strategy's practical application is exemplified by the 30 g synthesis of an indazole glutarimide ligand.

CONCLUSION:

In summary, our strategy provides a pathway to access diverse glutarimide ligands with exceptional functional group tolerability, circumventing the need for strong nucleophiles or preinstallation of an uncyclized glutarimide, which are commonly encountered in traditional IMiD synthesis methods. The development of this innovative synthesis approach may facilitate progress in novel CRBN binder synthesis and contribute to advancements in the field of targeted protein degradation.

Thank you to all of our Organizers, Speakers, Sponsors and Delegates! Without your dedication, support and participation APC 2023 would not be possible. We greatly value your comments regarding APC 2023 as well as thoughts or suggestions for improving future conferences. Please take the time to fill out our survey when we send it to you next week.

Sincerely,

The Boston Society