COLLEGE OF PHARMACY
MEDICINAL CHEMISTRY
UNIVERSITY OF MICHIGAN

Public Oral Examination
For the Degree of Doctor of Philosophy

Yuning Shen

"High Throughput Experimentation Facilitated Development of Amine-Acid Cross Coupling Reactions"

Monday, February 27, 2023 at 10:00am
North University Building Room 2548

Zoom option:
https://umich.zoom.us/j/94333726279
Meeting ID: 943 3372 6279
Passcode: medchem

Committee Members:

Dr. Tim Cernak (Chair)
Dr. John Montgomery
Dr. Peter Scott
Dr. Andy White

Abstract:

High throughput experimentation (HTE) is an important technique which can expedite the hit-to-lead process in drug discovery. The first chapter of this thesis reviews reported applications using HTE in medicinal chemistry research and provides the basics of establishing HTE capabilities including software, hardware, and data analysis. Especially we have demonstrated the establishment of an HTE platform in our lab. HTE could leverage areas like machine learning, cheminformatics, and reaction prediction. With an interest in bridging these areas, we have reported an algorithm to map chemical space of the amine–acid coupling system, which utilizes two of the most significant building blocks for medicinal chemists. The scientific rationale in connecting amine–acid coupling with physicochemical properties is discussed in Chapter 2. With the interest in developing novel methodologies for amine–acid coupling, and to showcase the HTE capabilities we established, we have identified a unique amine–acid C–O bond formation applying carboxylic acids and arenediazonium salts as an activated form of anilines. Chapter 3 discusses the development of this copper catalyzed amine–acid C–O esterification and discusses in detail ultraHTE screen, where reactions are performed in 1,536 wellplates, for the miniaturized general substrate scope investigation. While the C–O bond formation is not ultimately the single aim of expanding amine–acid coupling system, we also explored metallaphotoredox catalysis for deaminative–decarboxylative C–C bond formation. In Chapter 4, the discovery and optimization of the novel method to couple redox active esters with triazenes are discussed. The unique substrate pairs also showed the possibility to form decarboxylative–deaminative coupling products and decarboxylative amination products, which again, showcased the strong connection between transformation and properties. This work, as a whole, demonstrates the significance of HTE in the search for novel reactivity, and demonstrates the significance of the amine–acid coupling system, evidenced by developing amine–acid C–O, C–C, and C–N bond formation.

Publications:

1. **Shen, Y.,** Mahjour B. and Cernak, T., Development of deaminative esterification using high-throughput experimentation. *Commun. Chem.*, **5**, 83 (2022). https://doi.org/10.1038/s42004-022-00698-0

2. **Shen, Y.,** Borowski, J.E., Hardy, M.A., Sarpong, R., Doyle, A.G. and Cernak, T., Automation and computer-assisted planning for chemical synthesis. *Nat. Rev. Methods Primers*, **1**,1-23 (2021).

3. Mahjour, B., **Shen, Y.** and Cernak, T., Ultrahigh-Throughput Experimentation for Information-Rich Chemical Synthesis. *Acc. Chem. Res.*, **54**, 2337-2346, (2021).

4. Lin, Y., Zhang, Z., Mahjour, B., Wang, D., Zhang, R., Shim, E., McGrath, A., **Shen, Y.,** Brugger, N., Turnbull, R. and Trice, S., Reinforcing the supply chain of umifenovir and other antiviral drugs with retrosynthetic software. *Nat. Commun.*, **12**, (2021).

5. Mahjour, B., **Shen, Y.,** Liu, W., & Cernak, T. A map of the amine–carboxylic acid coupling system. *Nature*, **580**, 71-75 (2020).

Patents:

Cernak, T., Mahjour, B., **Shen, Y.,** McGrath, A. and Zhang, R., University of Michigan, 2020. Property modulation with chemical transformations (US Patent).

Select Presentations:

1. Oral presentation at 2022 ACS Spring, San Diego
2. Oral presentation at 2022 ACS Fall, Chicago

Future Plans:

Yuning has accepted a position of Scientist at Octant Bio in San Francisco.