# ORGANIC SEMINAR

## Tuesday, April 23, 2024

## 4:30 PM, WTHR 104

# *"High Throughput Experimentation for Reaction Optimization"*


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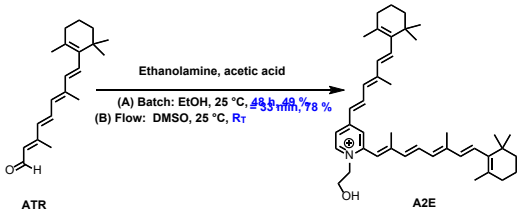
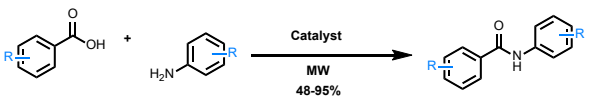
Abstract: High Throughput Experimentation (HTE) allows for the grouping of common operations so that a series of experiments can be rapidly performed in parallel at microscale. This approach also allows for the automation of procedures, such as liquid handling and data analysis, so that hundreds of experiments can be executed simultaneously and analyzed using quantitative techniques such LC-MS or semi-quantitatively by DESI-MS. Two projects will be presented leveraged by the use of HTE.


**Part 1. Continuous Flow Synthesis of A2E Guided by Design of Experiments and High-Throughput Studies:** Synthetic A2E is often used for inducing the accumulation of lipofuscins within the lysosomes of RPE cells in culture as an in vitro surrogate of retinal lipofuscin buildup, providing insights into the mechanisms of eye conditions such as Stargardt's disease, cone-rod dystrophy and Best's macular dystrophy. Many reports describing the use of synthetic A2E employ material that has been prepared using a one-pot reaction of all-trans-retinal (ATR) and ethanolamine at room temperature for 48 h. We have revisited this synthesis by performing a design of experiments (DoE) and HTE workflow that was tailored to identify the most productive combination of the variables for optimization of A2E yield. This revised method enabled a more efficient production of material, from a reaction time of 48 h to a residence time of 33 min, with an accompanying yield improvement from 49 to 78%.




**Part 2. High Throughput Experimentation as a Tool to Guide the Microwave Assisted Catalytic Amidation of Aryl Amines with Aryl Acids:** The formation of amides is one of the most essential transformations in the pharmaceutical industry, but most synthetic procedures include the use of either stoichiometric poor atom economy reagents or demands are compounded when condensing aryl amines with aryl acids due to their inherently low reactivity. To overcome such hurdles, we utilized high throughput experimentation to screen 640 different reaction conditions to find a suitable catalyst and solvent for benzamide formation. Based on those initial findings, we developed an efficient catalytic transformation of aryl amines with aryl acids into benzamides. Our method shows that even sterically hindered amines and carboxylic acids can be converted to the corresponding benzamides as well as previously reported unreactive aromatic and secondary amines. This approach follows the principles of green chemistry, aiming at atom economy by using catalysts, a green solvent, high substrate loadings, and efficient microwave heating.

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