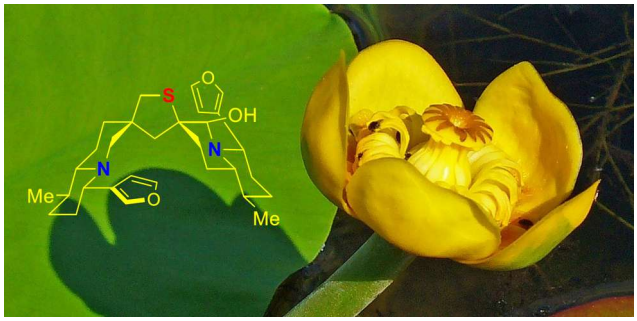
Total Synthesis and Biological Evaluation of the Nuphar Alkaloids

The hydroxylated dimeric nuphar alkaloids are found in the common yellow water lily. In particular, 6-hydroxythiobinupharidine induces apoptosis in human leukemia cell lines (U937) faster than any known small molecule. However, the only two studies concerning their biological mechanism of action are inconclusive. The first synthesis of any dimeric Nuphar alkaloid was reported in 2013 but was of an inactive compound. *This lecture will describe our work in accomplishing the first total syntheses of the biologically active, hydroxylated, dimeric nuphar alkaloids*.[1,2] We will also discuss novel methods for preparing the quinolizidine core,[3] as well as apoptosis data of several other compounds, including unnatural monomeric analogs previously unknown to nature.[4,5]



Leading References:

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(2) Li, H.; Korotkov, A.; Chapman, C. W.; Eastman, A.; Wu, J. Enantioselective Formal Syntheses of 11 Nuphar Alkaloids and Discovery of Potent Apoptotic Monomeric Analogues. *Angew. Chem. Int. Ed.* **2016**, *55* (10), 3509–3513. https://doi.org/10.1002/anie.201600106.

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(4) Li, H.; Cooke, T. J.; Korotkov, A.; Chapman, C. W.; Eastman, A.; Wu, J. Stereoselective Synthesis and Biological Evaluation of C1-Epimeric and Desmethyl Monomeric Nuphar Analogues. *J. Org. Chem.* **2017**, *82* (5), 2648–2655. https://doi.org/10.1021/acs.joc.6b03052.

(5) Mallick, D. J.; Korotkov, A.; Li, H.; Wu, J.; Eastman, A. Nuphar Alkaloids Induce Very Rapid Apoptosis through a Novel Caspase-Dependent but BAX/BAK-Independent Pathway. *Cell Biol. Toxicol.* **2019**, *35*, 435–443. https://doi.org/10.1007/s10565-019-09469-5.

Short Bio - Prof. Wu obtained his bachelor's degree from Princeton University in 1998 and then took a position as an associate chemist at Merck Process Research for two years before attending Harvard University where he obtained his PhD in chemistry from Prof. David Evans. Following this, he was an NIH postdoctoral scholar with Prof. Barry Trost at Stanford University. He began his independent academic career in 2007 at Dartmouth where he has been promoted to full professor. Research in the Wu group focuses on the development of new reaction methodologies in organic chemistry for enabling the synthesis of complex natural product targets and new compositions-of-matter that have potential therapeutic value.