LAKE SUPERIOR STATE UNIVERSITY

Return Report: Sabbatical Leave

R. Adam Mosey, Chemistry

Sabbatical Leave: AY 2019-2020

Title of Sabbatical Leave Proposal: NMR-Guided Reactivity Studies for New Reaction Methodology Development and Structure Activity Relationship Studies for the Development of Potent Proteasome Modulators

Sabbatical Aims

The aims of my sabbatical research were 1) to develop new chemical methodologies using Nuclear Magnetic Resonance (NMR) as a platform for reaction discovery and 2) to develop compounds for potential use as proteasome modulators for potential use in the treatment of aging related neurodegenerative diseases through collaboration with researchers at Michigan State University.

Sabbatical Outcomes

Research Findings

Expansion of reaction scope for the synthesis of C4-tertiary 3,4-DHQs. The synthesis of 3,4-dihyroquinazolines (3,4-DHQs) bearing a C4-tertiary center was a primary focus of my research prior to being awarded sabbatical leave, and this work was funded by an NIH R03 grant. DHQs are of interest in medicinal chemistry for their potential use in the treatment of a variety of diseases. Chemical methodology was developed in my lab to synthesize diverse molecules of this compound class, whereby simple commercially available materials (amides, amines, and aldehydes) could be assembled in a one-pot multicomponent reaction. The range and limitations of the chemistry were explored through the use of a variety of diverse starting materials in the reactions to produce a more complete understanding of the methodology. The key findings of these studies were published as a manuscript in *Organic and Biomolecular Chemistry* (2019) and were highlighted in *Synfacts* (2019), while additional findings are set to be disseminated in future manuscripts.

Methodology development for the synthesis of C4-quaternary 3,4-DHQs via a multicomponent reaction utilizing electron deficient ketones. The success of the C4-tertiary 3,4-DHQ synthetic methodology led to the exploration of an analogous synthesis of C4-quaternary 3,4-DHQs. The synthesis of quaternary derivatives of this compound class has been highly underexplored in the chemical literature, and the development of a simple multicomponent method such as the one developed for tertiary substrates would be a boon to this area of chemistry. Excitingly, new chemical methodology was successfully developed to access these quaternary compounds, with reaction parameters being rapidly optimized via NMR monitoring and NMR crude yield determination. Physical constraints typically limiting such a reaction, whereby a ketimine is generated from a ketone and an amidine *in situ* and consumed intramolecularly via a Pictet-Spengler-type annulation, were overcome through electronic tuning of the ketone component in the

reaction. The methodology afforded C4-quaternary adducts, wherein the C4 center was populated with a variety of groups, so long as one of the groups was electron deficient (e.g., an ester or ketone). The findings of this study were published as a manuscript in the *Journal of Organic Chemistry* (2020).

Synthesis of C4-quaternary 1,4-DHQs via regioselective functionalization. Whereas the synthesis of C4-quaternary 3,4-DHQs has been underexplored, there exist even fewer literature reports for the synthesis of C4-quaternary 1,4-DHQs (saturation at the 1 and 4 positions of the DHQ scaffold). C4-quaternary 3,4-DHQs synthesized through the new methodology described above were transformed to C4-quaternary 1,4-DHQs through a 2-step protocol involving N3 dealkylation followed by regioselective N1 funcionalization (both alkylation and acylation were performed), a process rapidly optimized via NMR monitoring. The source of regioselectivity was determined to arise from transition state energy differences between approach of functionalization agents towards the N1 and N3 atoms of the heterocyclic scaffold. Importantly, both 3,4- and 1,4-DHQ regioisomers may now be accessed from our chemistry, either directly from the 3,4-DHQ synthesis or indirectly after the dealkylation/functionalization sequence. The key findings of this study were published as a manuscript in the *Journal of Organic Chemistry* (2020).

Methodology development for the synthesis of C4-quaternary 3,4-DHQs via hypervalent iodine mediated sp^3 C-H bond functionalization of C4-tertiary 3,4-DHQs. While the abovementioned chemistry permits installation of C4-quaternary centers into 3,4-DHQs bearing electron deficient features, it did not allow for the incorporation of electron rich groups. This shortcoming was addressed through investigation of the oxidation potential of tertiary 3,4-DHQs. Extensive reaction screening revealed hypervalent-iodine promoted conditions whereby these substrates could be oxidized to generate aromatic cations, and quenching of the cations with appropriate electron-rich nucleophiles was found to afford desired C4-quaternary 3,4-DHQs. These conditions complement our other method to allow synthetic access to quaternary 3,4-DHQs with a large variety of attached molecular functionalities. This emerging area of chemistry opens up a previously inaccessible swath of chemical space and will receive intense focus in near future studies.

Identification of 3,4-DHQs as proteasome modulators. Through collaboration with Professor Jetze Tepe and coworkers at MSU, several 3,4-DHQs have been identified for their role in proteasome modulation. This proteolytic modulation has implications for understanding and treating various neurodegenerative diseases. Our collaborative studies included initial evaluation of >80 compounds at multiple concentrations in high throughput assays to determine their efficacy as proteasome modulators (inhibitors and/or activators). Subsequently, a structure-activity relationship study was designed around many of the top "hits" from the initial screening, which involved the synthesis of new DHQ compounds and additional testing of these compounds for proteolytic inhibition and/or enhancement. Several structural features which are believed to lend to the activity of these molecules were identified, and new compounds bearing targeted features will be synthesized in our ongoing search for potentially more potent proteasome modulators. The initial report of our findings in this area has been submitted in the form of a manuscript for publication in *Organic and Biomolecular Chemistry* (2020).

Collaborations

An ongoing collaboration with the Tepe research group at Michigan State University continues to yield important biological data regarding compounds prepared in my lab. Additionally, collaboration with Alexei Iretskii of LSSU has added invaluable molecular modeling expertise to my studies, with the modeling being used to predict features of new chemical methodologies and to validate regiochemical outcomes in observed reactions.

Presentations

Michigan State University, Tepe Group, One-Pot Multicomponent Synthesis of 3,4-Dihydroquinazolines and Conversion to 1,4-Dihydroquinazolines, June 2019.

Scheduled spring and summer 2020 conferences where this work was to be presented were cancelled due to COVID-19.

Publications (*LSSU Undergraduate Researchers)

1. Magyar, C. L.*; Wall, T. J.*; Davies, S. B.*; Campbell, M. V.*; Barna, H. A.*; Smith, S. R.*; Savich, C. J.*; Mosey, R. A. Triflic Anhydride Mediated Synthesis of 3,4-Dihydroquinazolines: A Three-Component One-Pot Tandem Procedure. *Org. Biomol. Chem.* **2019**, *17*, 7995-8000.
    a. Article highlighted in *Synfacts*, **2019**, *15*, 1238.
2. Campbell, M. V.*; Iretskii, A. V.; Mosey, R. A. One-Pot Tandem Assembly of Amides, Amines, and Ketones: Synthesis of C4-Quaternary 3,4- and 1,4-Dihydroquinazolines. *J. Org. Chem.* **2020**, *85*, 11211-11225.
3. Fiolek, T.; Magyar, C. L.*; Wall, T. J.*; Davies, S. B.*; Campbell, M. V.*; Savich, C. J.*; Tepe, J. J.; Mosey, R. A. Dihydroquinazoline Analogs Enhance 20S Proteasome Activity and Degradation of IDPs Associated with Neurodegeneration. *Org. Biomol. Chem.* **2020**, *Submitted*.

Other

1. Participated on search committee to hire a replacement for Dr. Keller, Nov. 2019 – Mar 2020.
2. Attended MJBizCon expo in Las Vegas, NV with Dean Steven Johnson to develop new partnerships for the LSSU Cannabis Chemistry Program, Dec. 2019.
3. Completed ExtractionTek Certification training to operate cannabis hydrocarbon extraction equipment used in the Cannabis Chemistry program, Jan. 2020.
4. Assisted with curriculum development for the new Cannabis Production Certificate, May 2020.