Synthesis of New Class of Enhanced Asymmetric Curcuminoids

Department of Chemistry & Biochemistry

University of Wisconsin – La Crosse

1. Proposal Narrative

A. Abstract

Curcumin has extensively exhibited biological and medicinal relevance in many instances, most notably in cancer and neurodegenerative diseases. With high promise, curcumin has significant faults concerning its low solubility resulting in minimal absorption. Curcumin-like molecules termed curcuminoids, display the ability to maintain and/or enhance the positive effects of curcumin by improving solubility. By using both synthetic and theoretical chemistry, asymmetric curcuminoids will be synthesized using acetylcyclohexanone. Our proposal will result in a new class of asymmetric curcuminoids with the intent of enhancing its medicinal potential.

B. Background/Statement of the Problem/Significance of the Project

Curcumin is a naturally occurring small molecule derived from a plant, *Curcuma longa*. Curcumin has been gaining attention in the medicinal community due to its discovered anti-oxidizing[1], anti-inflammatory[2-5], anti-aging[6-7], and neuroprotective effects[8], all of which have been supported through laboratory and clinical studies. Prominently, curcumin has shown to have positive effects on notable complications such as cancer and dementia. Due to its biological relevance, curcumin has been used to study its medicinal effects and displays positive results.

However, natural curcumin has poor water solubility causing a limitation on the potential biological impact of curcumin.

Our proposal focuses on the synthesis of curcumin-like molecules, termed curcuminoids, to target various chemical features with the intent to enhance the biological properties found in curcumin. Our goal is to synthesize a variety of asymmetric curcuminoids and create an effective procedure to modify curcuminoid properties efficiently. Preliminary research has shown asymmetric curcuminoids have demonstrated enhanced biological effects9. With this, unfortunately, the scope of the research is limited, and our project intends to expand the knowledge on asymmetric curcuminoids and create a new class of compounds never created before.

C. Objectives / Specific Aims

1. Expand the original microwave synthesis of curcuminoid to include additional aldehydes.

2. Synthesize asymmetric acetylcyclohexanone-based product with central asymmetric piece and two different aldehydes, referred as an ABC and CBA types to indicate difference in the point of attachments (Appendix I).

3. Conduct theoretical calculations of starting materials, relevant transition states, and anticipated products.

4. Perform analysis of obtained experimental and computational data (in collaboration).

D. Methods

Due to the nature of our synthetic project, our methods section has been split into three

different aspects: synthesis of desired compounds, characterization of products, and computational calculation of relevant structures. Each of these sections are completed independently, yet when combined, they offer comprehensive chemical assessment.

Synthesis

All reactions will be conducted primarily through a Biotage Initiator+ Microwave reactor, a single point microwave reactor. Microwave synthesis will be used because it reduces the reaction time from hours to minutes, while still retaining adequate yield and product purity. In this proposal, our synthesis will consist of aldehydes (labeled for simplicity as A and C), our side pieces, and a diketone, our central piece (labeled for simplicity as B). The microwave reaction parameters, including the reaction time, temperature, and ratio of reagents, will be based on the general procedure we had previously established in Fall 2019. In the first part of our synthetic, the side pieces, aldehydes, will remain identical on both sides of our central piece generating ABA type curcuminoids.

After expanding our aldehyde selection, we will attempt to synthesize a product with different side pieces, referred to as ABC or CBA types. The purpose is to eventually gain complete control of where each piece will attach to the central piece. To obtain this understanding, we will modify our general procedure by adjustments of ratios, the order of additions, temperature, and time.

Characterization

To determine the identity and purity of our products as well as progress of reactions and potentially reaction mixtures' composition, proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) will be utilized. ^{1}H NMR allows us to determine

the molecular structure based on the different molecular environments the hydrogens (protons) are in. The key feature of our product is the presence of trans-coupling signals of a very unique appearance in a particular region of the ^{1}H NMR spectrum. This will not only allow us to gauge the success of the reaction quickly but also will allow us to relatively easily determine product ratios obtained. ^{13}C NMR will be used to provide a full characterization of all new compounds required for publication. Thin-layer chromatography (TLC) will be utilized routinely to monitor reaction purity and provide a preliminary assessment of products' purity.

When the desired products are synthesized, two main experimental methods will be performed: (1) X-ray crystallography and (2) Elemental Analysis. Both techniques are widely used in synthetic studies to absolutely determine the product is precisely what we have discovered with the techniques listed above. These two techniques will be completed as they are necessary for publication in synthetic chemistry journals.

Computational

The purpose of combining theoretical calculations with synthetic organic chemistry is to use highly supported chemistry theories to hypothesize chemical properties within molecules before creation. The synthetic work requires a substantial time commitment and usage of chemicals. If the desired product does not fit into the category of desired properties, this implies wasted hours/days and money. The combination of theoretical data and synthetic efforts will allow us to provide promising new curcuminoids with the ultimate efficiency. In addition to our project, the combinations of methods will help us understand the best reaction schemes to increase the likelihood of synthetic success. As a result, we will be able to reduce chemical waste, making our research considerably more environmentally friendly. Additionally,

theoretical calculations allow us to develop products specifically to enhance bioactive properties; once again, this will enable us to avoid mere trial and error.

Computational work will be completed using two software: Avogadro and GAMESS, in collaboration with Dr. Joseph West (Winona State University). Avogadro will be used first to build the molecule of interest, and GAMESS will provide adjusted data output. In addition, I have recently received access to the Minnesota Supercomputing Institute, known as the MSI. This access will allow me to run much of my computational work more efficiently and serve as a storage site for my data acquired. If for some reason, MSI is not operating, I still maintain the necessary software to complete my computational work on my personal computer. Furthermore, this summer, I will be completing a computational online course from Schrodinger titled, "Introduction to Molecular Modeling in Drug Discovery." Even though I have previously completed computational work for approximately one year, this will further extend my training to various applications providing more diversity in my computational abilities.

E. Final Products and Dissemination

The expected outcome of this proposal is to submit our results for publication in a relevant journal and present at the UWL Research and Creativity Symposium in the Fall of 2020. In addition, our project is unique as our synthesized products will serve as a synthesis-based study **AND** be used by the following research groups:

- Dr. Kelly Gorres (Department of Chemistry & Biochemistry at UW-L) to study the impact of asymmetric curcuminoids on viruses
- Dr. Xinhui Li (Department of Microbiology at UW-L) to study the inactivation of

foodborne viruses with asymmetric curcuminoids

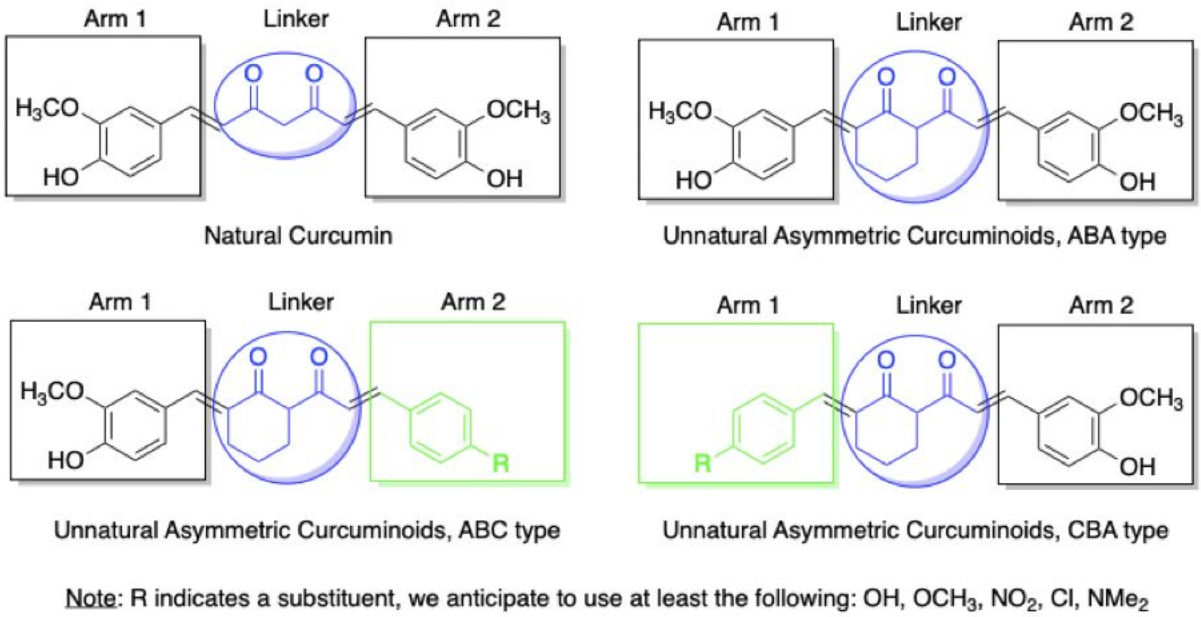
- Dr. Joseph West (Department of Chemistry at Winona State University) to synthesize vanadium, copper, and zinc metal complexes to study metal binding properties using asymmetric curcuminoids
- Dr. Emily Ruff (Department of Chemistry at Winona State University) to study the antimicrobial and bioavailability of synthesized curcuminoids

F. Budget justification

All reactions in this proposal will be conducted using a microwave reactor. The manufacturer of the particular instrument requires a single use of the microwave vessels to ensure the safe operation of these vessels under increased pressure and temperature. We also request the starting linker. In addition, X-ray crystallography and Elemental Analysis are requested for samples as they are necessary for publication. The remaining samples will be funded directly by Dr. Valeria Stepanova's funding.

#	Chemical name	Use	Supplier	Packaging	Price	Amount	Total
1	2-Acetylcyclohexanone	starting material	Aldrich	25 G	$36.50	3	$109.00
2	2-5 mL Microwave reaction vials	equipment	Fisher Scientific	100 ct.	$463.50	1	$463.50
3	X-Ray Crystallography	Equipment	N/A	N/A	$150.00	2	$300.00
4	Elemental Analysis	Equipment	N/A	N/A	$83.00	1	$83.00
						Total:	$956.00

Appendix



Scheme 1. Unnatural Asymmetric Curcuminoids – Targets of this Proposal

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