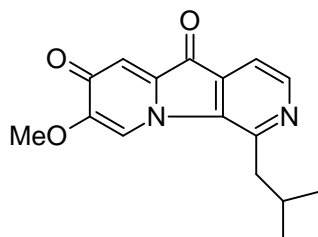


Introduction: There is always a need for a new anti-cancer drug and there are several ways of discovering a new drug. One of them is a natural product based drug discovery process. Organic molecules are isolated from natural sources (a plant or an animal source) and are tested against several biological targets (cancer cells or bacteria) to see whether they have any medicinal activity. Once a molecule is identified as having a medicinal activity, the next step is to enhance its activity by making some modifications to the natural product's structure. As the modified structures are tested against the biological targets, we learn more about the relationship between the structure and the activity of the natural product. This knowledge should lead to a new structure, which will have better activity than the original natural product structure.



Pterocellin A (1)

The target of interest for this project is Pterocellin A, a marine natural product, isolated in 2003 by Yao *et al.*¹ Pterocellin A possesses a novel cyclic structure and exhibits potent anticancer (P388 IC₅₀ = 477 ng/mL) and antimicrobial activity *in vitro*² but modest activity *in vivo*.³

Goals set by the Proposal: The goal of this project is the synthesis of the structural analogs of natural product Pterocellin A in order to (1) understand the relationship

¹ Yao, B.; Prinsep, M. R.; Nicholson, B. K.; Gordon, D. P. *J. Nat. Prod.* **2003**, *66*, 1074-1077.

² *in vitro* refers to the technique of performing a given experiment in a test tube, or, generally, in a controlled environment outside a living organism.

³ *in vivo* refers to experimentation done in or on the living tissue of a whole, living organism as opposed to a partial or dead one. Animal testing and clinical trials are forms of *in vivo* research.

between its structure and activity, and (2) enhance its *in vivo* anti-cancer / antimicrobial activity which may lead to a new drug discovery. Since this is a long term project, we will achieve only part of the first goal in the time frame of this grant. The first goal requires us to synthesize a minimum of 20 structural analogs of Pterocellin A to understand the relationship between the structure and activity. As we proceed in the project, we may be required to synthesize even more analogs depending on the feedback we get from the activity results of the first batch of analogs. The synthesis of each analog should take about 4-5 weeks in experienced hands. Therefore, the specific goal for the period of this grant is the synthesis of 3-5 analogs by me and an undergraduate student over the spring and summer. The results of this research will be presented at national and regional conferences and will be submitted for publication when it is completed.

What is Accomplished?: Even though Pterocellin A has been synthesized⁴ (Scheme 1) under my guidance before and it was proposed to use that published synthesis, we decided to design a new, shorter, safer, and a better (environmentally) synthetic pathway which will serve better for our goals set by the proposal. Therefore, this new goal set back some of the goals we put forward in our proposal, such as synthesis of analogs. However, with the new synthesis, we can accomplish those currently un-met goals faster in a safer manner.

Our original synthetic design is shown in Scheme 1, which includes nine steps with overall 2% yield. The current design, which is developed during the grant time, is shown in Scheme 2, which includes 5 steps with expected overall yield of 15%. It took two years to accomplish the original synthesis and, compared to that, the completion of the new synthesis less than a year is big accomplishment, especially when the work is

⁴ O'Malley, M. M.; Damkaci, F.; Kelly, R. *Org. Lett.* **2006**, *12*, 2651-2652.

done solely by an undergraduate student. This is a great accomplishment in both cutting the number of steps in half and increasing the yield. We already accomplished the synthesis of compound **4**, **5**, and **6** (shown in Scheme 2) and currently, we are working on the synthesis of compound **7**. Once the synthesis of compound **7** is accomplished, the new synthetic design can be published in a peer-reviewed journal. The new design, then, will be used to produce analogs of the natural product in order to understand the structure-activity relationship as described in the proposal. We are hoping to finish the synthesis according to new design during spring semester and continue on the synthesis of analogs through summer and next year.

As, it was stated in the proposal, this project is a multi-year project and may result more than one publication. The current results already presented in the 2nd annual Sigma Xi Conference and in the seminars given in department of chemistry.

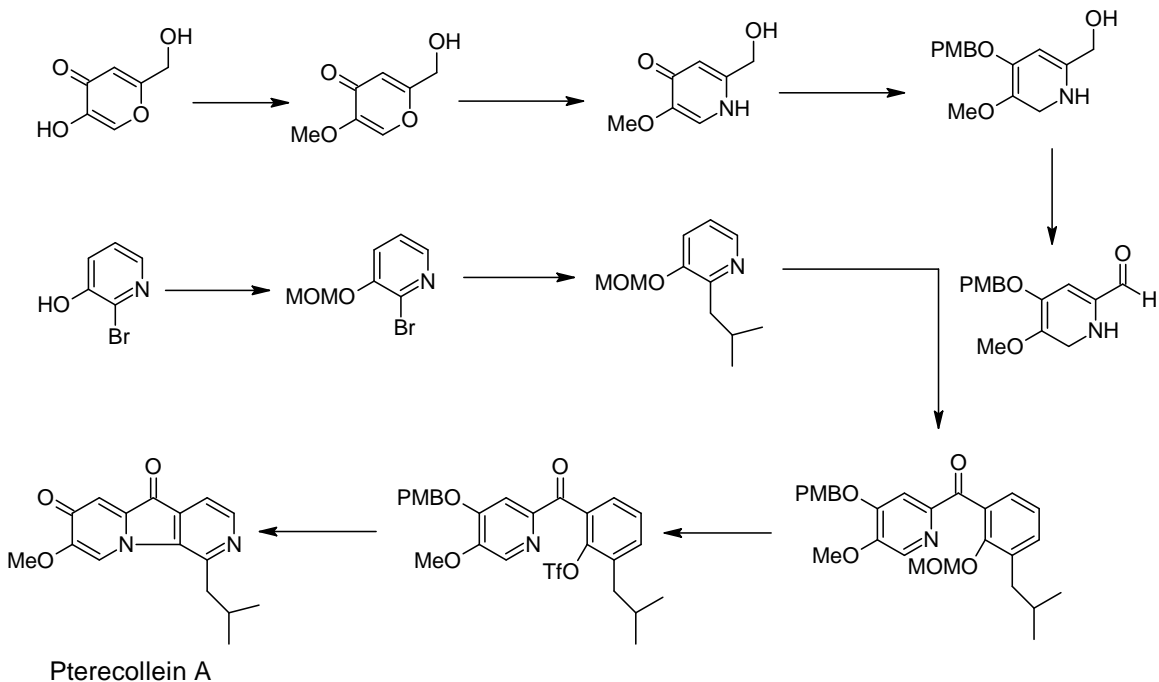
Budget Spending:

Student assistant: The proposal asked for \$2,000 as a summer stipend by a full-time student researcher. The money is given to Adam Stinger (senior, graduating in December) who worked on the project during summer and fall semesters. He worked 10 weeks over the summer and stayed on campus. Voluntarily, he worked more than 40 hours per week which moved the project further than expected timeline.

Supplies and Equipment: The proposal asked for \$1000 to be used mainly for the purchase of organic reagents, which was used daily basis for performing reactions and purifying the mixtures of the products obtained from those reactions. Here are some chemicals purchased: Kojic acid (3 orders) (10 g, \$102x3 = \$306), oxone (5g, \$18), pyridinium dicarboxymate (2orders) (5g, \$36 x2 = \$72), Dimethyl sulfate (500 mL, \$20), various broken glassware replacements, purchase of common laboratory consumables (solvents, gloves, etc.)

I would like to thank to ORSP office, SCAC committee members, and administrators who supported our work and make it happen. The future publications related to this project will be forwarded to ORSP and Provost's office.

Scheme 1: Original synthetic design proposed to be used.



Scheme 2: New synthetic design developed with the grant.

