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Professional Development (Undergraduate Research)

Reactivity Profiling of Relevant Natural Products

Relevant natural products, as defined here, are naturally occurring compounds that show increased incidence and significance in the current biotechnology literature. Biotech scientists desire comprehensive reactivity data on relevant natural products (RNPs – such as those shown in Figure 1), however stringent timelines and focused synthetic targets often prevent systematic reactivity profiling of these compounds. Undergraduate research provides the ideal environment to explore the panoply of modern organic reactions on these RNPs. In addition, this research will offer extensive "learn by doing" student training and the opportunity for publication.

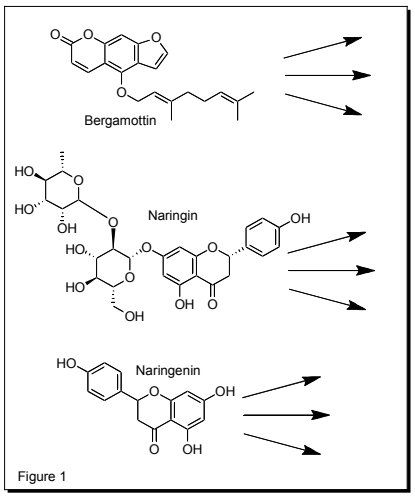


Figure 1

Whether in preparation for industry or graduate school, Cal Poly students need research projects which are: conducive to hands on laboratory experience, provide extensive team building environments, and are suitable for varying levels of experience. Reactivity profiling is much like reaction methodology except that the reagents are varied instead of the starting materials. The reactions used to profile these compounds will focus on the most modern oxidations, alkylations, and metatheses, etc. Not only will students become educated in the newest organic reaction methodologies, but also in the isolation and characterization of the products. In addition, the project lends itself to a "research team" environment because each student contributes a portion of the reactivity profile to the overall picture. Common starting materials should create open scientific communication amongst all team members. As far as student abilities in the lab, advanced students can focus on more complex reactions (e.g. metathesis or in-situ coupled reactions) while less experienced students can start with easier, less complicated reactions (e.g. EAS, substitutions).

Although reactivity profiling of RNPs is considered basic research, the products of the individual reactions are desired in applied biological research. For example, the Molecular Libraries Small Molecule Repository (MLSMR), which is a component of the Molecular Libraries Program of the NIH Roadmap, acquires and maintains diverse chemical compounds with known and unknown biological activity for use in high-throughput screening of biological assays.[1] Specifically, specialty sets of pharmacologically active compounds and derivatives of natural products are highly sought after by the MLSMR from the general scientific community. The products of the undergraduate research described here are perfect candidates for acceptance into the MLSMR. The benefits of submitting these compounds to the MLSMR include (as summarized by the NIH):

1) PubChem, the public database that identifies the structure and the bioassays for each of the compounds in the MLSMR, will identify the source of each compound (thereby increasing the public visibility of Cal Poly's research program).
2) Bioactive hits on PubChem may stimulate collaborations between biologists and chemists leading to new research projects and new opportunities for grant funding.
3) Submitting a compound to the MLSMR will contribute to the unprecedented investigation of gene product function.

Proposed implementation of undergraduate research at Cal Poly

1. Define the most exciting natural products that are relevant to the scientific community and accessible to Cal Poly. Bergamottin, naringin, and naringenin are proposed to be the first three RNPs to be profiled. Bergamottin is a known agonist for the TSH stimulating receptor (an activator of intracellular cAMP), a known inhibitor of cytochrome P450 1A2, 2D6, 2C9, and 2C19, and an inhibitor of β-lactamase.[2-4] A cost effective route to obtain multi-gram quantities of bergamottin is shown in Scheme 1. Naringin and naringenin are potent inhibitors of cytochrome P450 3A4 and 1A2 and are known specific membrane transport inhibitors.[5]

2. Individual research students will be assigned a portion of the total reactions needed to develop the profile of a particular RNP. Students will be responsible for isolating, purifying, and characterizing the products. Products will be purified to a level consistent with the MLSMR acceptance criteria. Examples of reactivity experiments for bergamottin and naringin are shown in Figure 2 and Figure 3, respectively.

3. Once a sufficient number of successful and informative reactions are completed, the knowledge of the RNP reactivity profile will be compiled and submitted for peer review publication.

4. Isolated products from the reactivity profile will be submitted to the MLSMR.

Scheme 1. Although most RNPs are chosen in part for their affordability, the following synthesis will yield multigram quantities of bergamottin at a reasonable price.

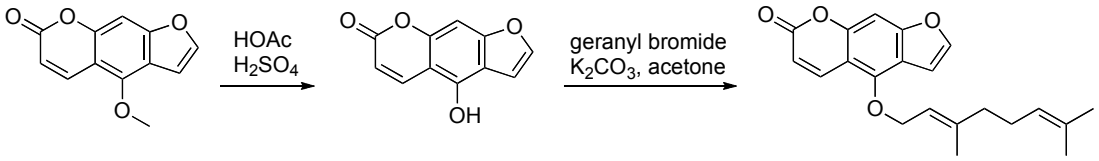
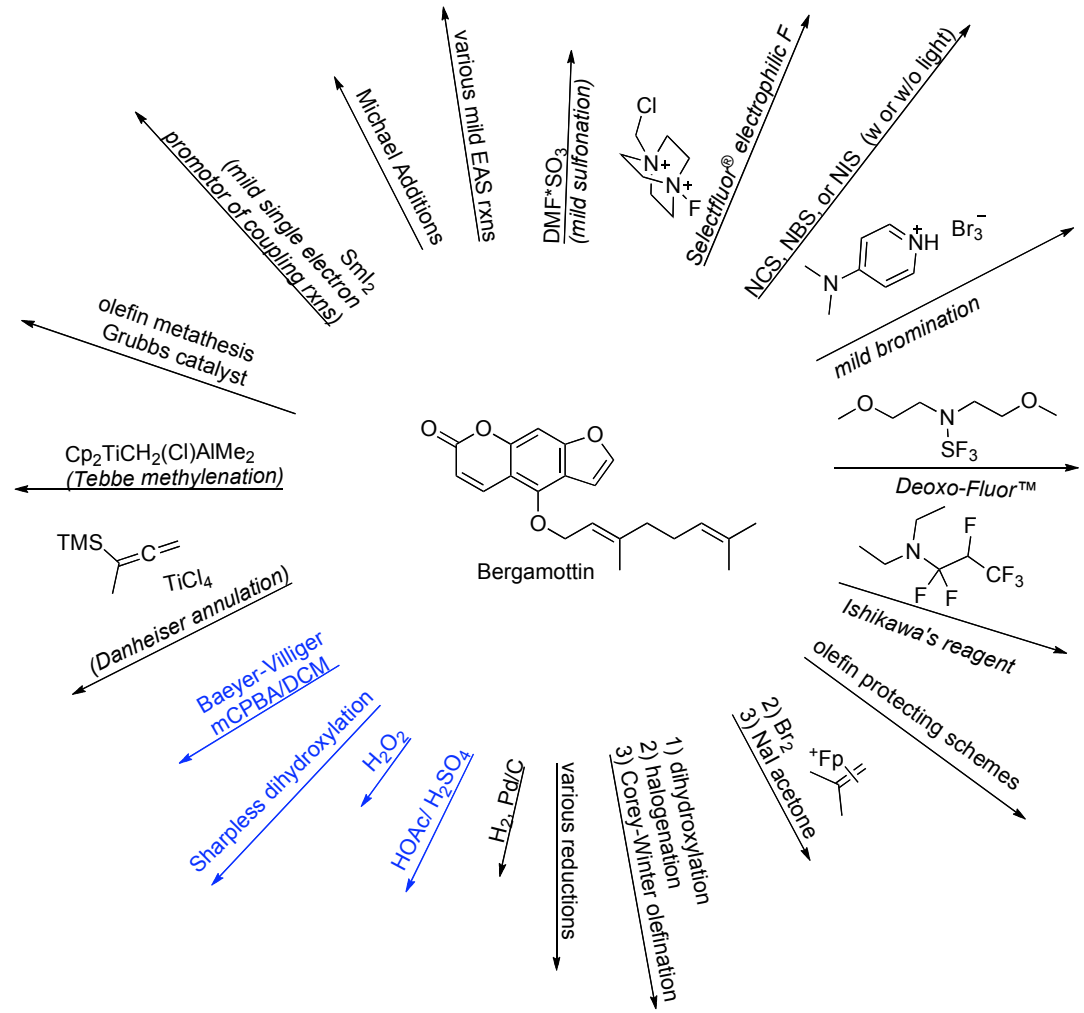


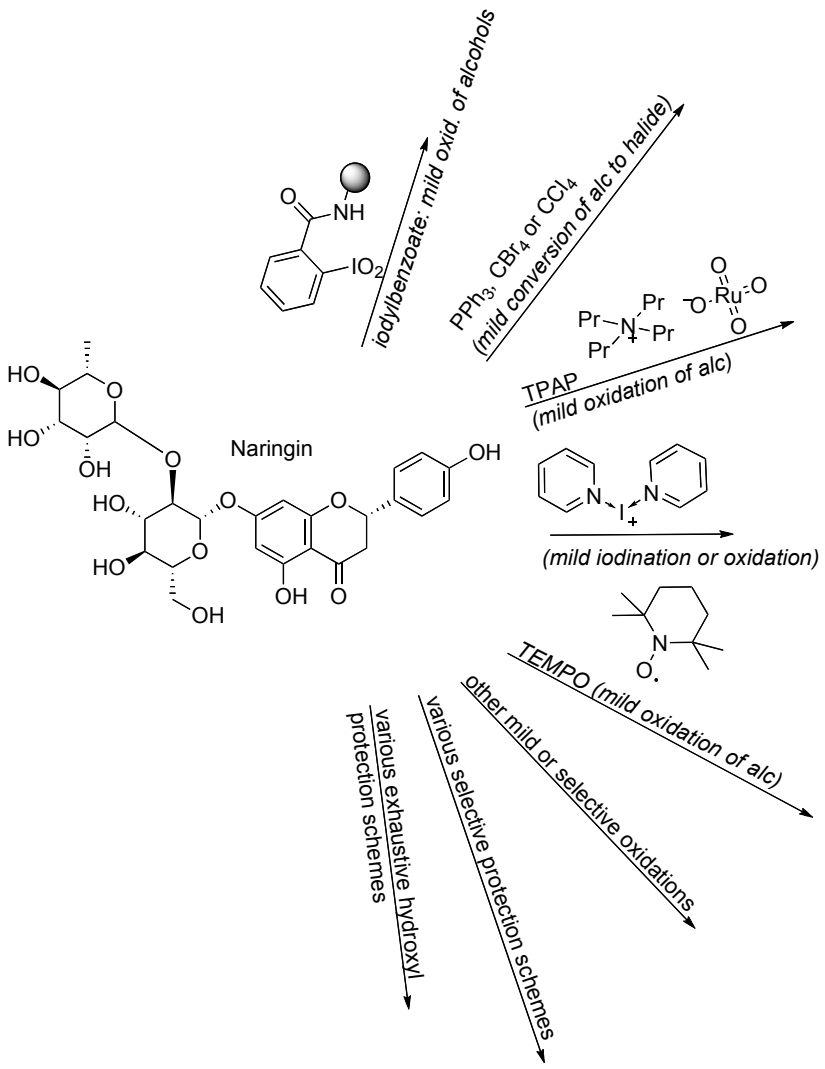
Figure 2. Examples of reactivity profiling methodologies to be attempted on Bergamottin. Bergamottin reactions reported in the literature are shown in lower left (blue).[6-9]



Potential coupled reactions to halogenated bergamottin products include:

1. Suzuki coupling
2. Negishi coupling
3. Buchwald cross-coupling

Figure 3. Although some reactions done on bergamottin can be repeated on naringin, additional methodologies will help to profile the reactivity of the carbohydrate moiety of naringin. Limited examples shown.



Summary

The reactivity profiling of three proposed RNPs, bergamottin, naringin, and naringenin, will serve as the foundation of this project. Profiling these pharmacologically significant RNPs should present excellent opportunities for publication and external funding. Furthermore, the potential for tangential projects or collaborations, as a result of the initial research, is highly probable given the focus on modern organic reaction methodologies. Most importantly, the students profiling the RNPs will learn essential lab and scientific communication skills in preparation for their future work as chemists in industry or graduate school.

References

1. http://mlsmr.glpg.com/MLSMR_HomePage
2. Jaschke *et al., J. Biol. Chem.* **2006**, 281(15), 9841-9844.
3. Cali, J. J. *et* al., Expert *Opin. Drug Metab. Toxicol.* **2006**, 2(4), 629-45.
4. Feng, B.Y.; Shoichet, B.K., *Nat. Protoc.* **2006**, 1(2), 550-3.
5. Hong, S.S.; Seo, K.; Lim, S.C.; Han, H.K., *Pharmaco. Res.* **2007**, 56(6), 468-73.
6. Bussey, C.; Lepoittevin, J. P.; Benezra, C., *Bioorg. Med. Chem. Lett.* **1993,** 3(6), 1283-6.
7. Row, E. C.; Brown, S. A.; Stachulski, A. V.; Lennard, M. S.,*Organic & Biomolecular Chemistry* **2006,** 4(8), 1604-1610.
8. Seemayer, R.; Liang, J. 2002-US31593, 2004037827, 20021022., 2004.
9. Seemayer, R.; Shi, Y. 2001-US27815, 2002095061, 20011220., 2002.