<table>
<thead>
<tr>
<th><strong>PI:</strong> Podlesny, Erin Eileen</th>
<th><strong>Title:</strong> Synthesis of Bisanthraquinone Natural Product and BINOL-type Chiral Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Received:</strong> 08/11/2009</td>
<td><strong>FOA:</strong> PA09-209</td>
</tr>
<tr>
<td><strong>Competition ID:</strong> ADOBE-FORMS-A</td>
<td><strong>Council:</strong> 01/2010</td>
</tr>
<tr>
<td><strong>FOA Title:</strong> Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research</td>
<td></td>
</tr>
<tr>
<td><strong>1 F31 GM093515-01</strong></td>
<td><strong>Dual:</strong> AT, CA, DK, MH</td>
</tr>
<tr>
<td><strong>IPF:</strong> 6463801</td>
<td><strong>Accession Number:</strong> 3220080</td>
</tr>
<tr>
<td><strong>IPF:</strong> 6463801</td>
<td><strong>Organization:</strong> UNIVERSITY OF PENNSYLVANIA</td>
</tr>
<tr>
<td><strong>Former Number:</strong></td>
<td><strong>Department:</strong> Chemistry</td>
</tr>
<tr>
<td><strong>IRG/SRG:</strong> ZRG1 IMST-D (29)L</td>
<td><strong>AIDS:</strong> N</td>
</tr>
<tr>
<td><strong>Subtotal Direct Costs</strong></td>
<td><strong>New Investigator:</strong> N</td>
</tr>
<tr>
<td><em>(excludes consortium F&amp;A)</em></td>
<td><strong>Early Stage Investigator:</strong> N</td>
</tr>
<tr>
<td><strong>Animals:</strong> N</td>
<td></td>
</tr>
<tr>
<td><strong>Humans:</strong> N</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Trial:</strong> N</td>
<td></td>
</tr>
<tr>
<td><strong>Current HS Code:</strong> 10</td>
<td></td>
</tr>
<tr>
<td><strong>HESC:</strong> N</td>
<td></td>
</tr>
<tr>
<td><strong>Senior/Key Personnel:</strong></td>
<td><strong>Organization:</strong> University of Pennsylvania</td>
</tr>
<tr>
<td>Marisa Kozlowski</td>
<td><strong>Role Category:</strong> Other (Specify)-Sponsor</td>
</tr>
<tr>
<td>Erin Podlesny</td>
<td><strong>University of Pennsylvania</strong></td>
</tr>
<tr>
<td></td>
<td><strong>PD/PI</strong></td>
</tr>
</tbody>
</table>

**Reference Letters**

[Redacted]
APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

1. * TYPE OF SUBMISSION

☐ Pre-application  ☑ Application  ☐ Changed/Corrected Application

2. DATE SUBMITTED

08/11/2009

3. DATE RECEIVED BY STATE

4. Federal Identifier

5. APPLICANT INFORMATION

* Legal Name: University of Pennsylvania

Department: Chemistry  Division: 

* Street1: 

Street2: 

* City: 

* State: PA: Pennsylvania  County: 

* Country: USA: UNITED STATES  * ZIP / Postal Code: 19104-6205

Person to be contacted on matters involving this application

Prefix: * First Name: Pamela  Middle Name: 

* Last Name: Caudill  Suffix: 

* Phone Number:  Fax Number: 

Email: 

6. * EMPLOYER IDENTIFICATION (EIN) or (TIN):

7. * TYPE OF APPLICANT:

O: Private Institution of Higher Education

Small Business Organization Type ☐ Women Owned  ☐ Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:

☐ New  ☐ Resubmission  ☐ Renewal  ☐ Continuation  ☐ Revision

If Revision, mark appropriate box(es).

☐ A. Increase Award  ☐ B. Decrease Award  ☐ C. Increase Duration  ☐ D. Decrease Duration

☐ E. Other (specify): 

* Is this application being submitted to other agencies? Yes ☐ No ☑

What other Agencies?

9. * NAME OF FEDERAL AGENCY:

National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

Synthesis of Bisanthraquinone Natural Product and BINOL-type Chiral Ligands

12. * AREAS AFFECTED BY PROJECT (cities, counties, states, etc.)

N/A

13. PROPOSED PROJECT:

* Start Date  * Ending Date

01/01/2010  12/31/2012

14. CONGRESSIONAL DISTRICTS OF:

a. * Applicant  b. * Project

PA-002  PA-002

15. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: * First Name: Erin  Middle Name: 

* Last Name: Podlesny  Suffix: 

Position/Title: Graduate Student

* Organization Name: University of Pennsylvania

Department: Chemistry  Division: 

* Street1: 

Street2: 

* City: 

* State: USA: UNITED STATES  County: 

* Country: USA: UNITED STATES  * ZIP / Postal Code: 

* Phone Number:  Fax Number: 

* Email: 

OMB Number: 4040-0001
Expiration Date: 04/30/2008

Tracking Number: GRANT10396266
Funding Opportunity Number: PA-09-209 Received Date: 2009-08-11T15:56:58-04:00
**16. ESTIMATED PROJECT FUNDING**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. * Total Estimated Project Funding</td>
<td></td>
</tr>
<tr>
<td>b. * Total Federal &amp; Non-Federal Funds</td>
<td></td>
</tr>
<tr>
<td>c. * Estimated Program Income</td>
<td></td>
</tr>
</tbody>
</table>

**17. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?**

- a. YES
  - □ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
  - DATE: 
- b. NO
  - ☑ PROGRAM IS NOT COVERED BY E.O. 12372; OR
  - ☑ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

**18. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)**

- ☑ * I agree

* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

**19. Authorized Representative**

- Prefix: 
- * First Name: Leona
- Middle Name: 
- * Last Name: Joseph
- Suffix: 
- * Position/Title: Associate Director
- * Organization: University of Pennsylvania
- Department: Chemistry
- Division: 
- * Street1: 
- Street2: 
- * City: 
- County: 
- * State: 
- Province: 
- * Country: USA: UNITED STATES
- * ZIP / Postal Code: 
- * Phone Number: 
- Fax Number: 
- * Email: 

- * Signature of Authorized Representative
- * Date Signed

**20. Pre-application**

- Add Attachment
- Delete Attachment
- View Attachment

**21. Attach an additional list of Project Congressional Districts if needed.**

- Add Attachment
- Delete Attachment
- View Attachment

**OMB Number:** 4040-0001  
**Expiration Date:** 04/30/2008
# 424 R&R and PHS-398 Specific

## Table Of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF 424 R&amp;R Face Page</td>
<td>1</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>3</td>
</tr>
<tr>
<td>Performance Sites</td>
<td>4</td>
</tr>
<tr>
<td>Research &amp; Related Other Project Information</td>
<td>5</td>
</tr>
<tr>
<td>Project Summary/Abstract (Description)</td>
<td>6</td>
</tr>
<tr>
<td>Public Health Relevance Statement (Narrative attachment)</td>
<td>7</td>
</tr>
<tr>
<td>Bibliography &amp; References Cited</td>
<td>8</td>
</tr>
<tr>
<td>Facilities &amp; Other Resources</td>
<td>10</td>
</tr>
<tr>
<td>Equipment</td>
<td>11</td>
</tr>
<tr>
<td>Other Attachments</td>
<td>12</td>
</tr>
<tr>
<td>Diversityeligibilityltr</td>
<td>12</td>
</tr>
<tr>
<td>Refereelist</td>
<td>13</td>
</tr>
<tr>
<td>Sponsorplan</td>
<td>14</td>
</tr>
<tr>
<td>Research &amp; Related Senior/Key Person</td>
<td>19</td>
</tr>
<tr>
<td>Biographical Sketches for each listed Senior/Key Person</td>
<td>20</td>
</tr>
<tr>
<td>PHS Fellowship Supplemental Form</td>
<td>26</td>
</tr>
<tr>
<td>Specific Aims</td>
<td>29</td>
</tr>
<tr>
<td>Background and Significance</td>
<td>30</td>
</tr>
<tr>
<td>Preliminary Studies/Progress Report</td>
<td>33</td>
</tr>
<tr>
<td>Research Design and Methods</td>
<td>35</td>
</tr>
<tr>
<td>Respective Contributions</td>
<td>39</td>
</tr>
<tr>
<td>Selection of Sponsor and Institution</td>
<td>40</td>
</tr>
<tr>
<td>Responsible Conduct and Research</td>
<td>41</td>
</tr>
<tr>
<td>Goals for Fellowship Training and Career</td>
<td>42</td>
</tr>
<tr>
<td>Activities Planned under this Award</td>
<td>43</td>
</tr>
<tr>
<td>Doctoral Dissertation and Other Research Experience</td>
<td>44</td>
</tr>
</tbody>
</table>
RESEARCH & RELATED Project/Performance Site Location(s)

Project/Performance Site Primary Location

Organization Name: University of Pennsylvania

* Street1: 
Street2: 
* City: County: 
* State: Province: 
* Country: USA: UNITED STATES * ZIP / Postal Code: 

Project/Performance Site Location 1

Organization Name: 

* Street1: Street2: 
* City: County: 
* State: Province: 
* Country: USA: UNITED STATES * ZIP / Postal Code: 

Additional Location(s) 

OMB Number: 4040-0001
Expiration Date: 04/30/2008
**RESEARCH & RELATED Other Project Information**

1. * Are Human Subjects Involved?  
   - [ ] Yes  
   - [x] No  

   1.a. If YES to Human Subjects  
       - Is the IRB review Pending?  
         - [ ] Yes  
         - [x] No  
       
       IRB Approval Date:  
       Exemption Number:  
       Human Subject Assurance Number:  

2. * Are Vertebrate Animals Used?  
   - [ ] Yes  
   - [x] No  

   2.a. If YES to Vertebrate Animals  
       - Is the IACUC review Pending?  
         - [ ] Yes  
         - [x] No  
       
       IACUC Approval Date:  
       Animal Welfare Assurance Number:  

3. * Is proprietary/privileged information included in the application?  
   - [ ] Yes  
   - [x] No  

4. * Does this project have an actual or potential impact on the environment?  
   - [ ] Yes  
   - [x] No  

4.a. If yes, please explain:  
4.b. If yes, please explain:  
4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed?  
   - [ ] Yes  
   - [x] No  

4.d. If yes, please explain:  

5.a. * Does this project involve activities outside the U.S. or partnership with International Collaborators?  
   - [ ] Yes  
   - [x] No  

5.b. If yes, identify countries:  
5.c. Optional Explanation:  

6. * Project Summary/Abstract  
   - ProjectSummaryAbstract .pdf  
   - [ ] Add Attachment  
   - [ ] Delete Attachment  
   - [ ] View Attachment  

7. * Project Narrative  
   - projectnarrative.pdf  
   - [ ] Add Attachment  
   - [ ] Delete Attachment  
   - [ ] View Attachment  

8. Bibliography & References Cited  
   - ReferencesCited.pdf  
   - [ ] Add Attachment  
   - [ ] Delete Attachment  
   - [ ] View Attachment  

9. Facilities & Other Resources  
   - facilities.pdf  
   - [ ] Add Attachment  
   - [ ] Delete Attachment  
   - [ ] View Attachment  

10. Equipment  
    - Equipment.pdf  
    - [ ] Add Attachment  
    - [ ] Delete Attachment  
    - [ ] View Attachment  

11. Other Attachments  
    - [ ] Add Attachments  
    - [ ] Delete Attachments  
    - [ ] View Attachments
Project Summary/Abstract

Synthesis of Chiral Bisnaphthoquinones and Bisanthraquinones: Natural Product Synthesis and Utility in Asymmetric Catalysis

This project will result in total synthesis of a group of axially chiral bisanthraquinone natural products that has not been synthesized previously, providing material for biological study. The reported biological activity and physical properties of some of these compounds affects a variety of public health issues including treatment of cancer (suppression of tumor cell growth), diabetes, hepatitis, and depression. Also, antioxidant properties have been reported, which may have potential in protecting skin against the effects of UV radiation. Still, a great deal of information is lacking for the activity of many of these bisanthraquinones, cited a need for more biological studies. An efficient synthesis of these molecules is central to achieving these goals. Specifically, the generation of the compounds will be achieved via a concerted synthesis that diverges from the same chiral bisnaphthoquinone intermediate (1a). This versatile bisnaphthoquinone intermediate will be synthesized from a 2-naphthol via an enatioselective oxidative biaryl coupling reaction, followed by oxidation to 1. Tandem Diels-Alder/aromatization reactions between 1a and various vinyl ketene acetals (2) will provide the bisanthraquinone structure and subsequent transformations will afford natural products (3-7).

In addition, a new class of BINOL-type chiral ligands (8a-b) will be generated from a simpler bisnaphthoquinone precursor (1b). The synthesis of these ligands is important because they could positively impact asymmetric catalysis. Catalytic asymmetric synthesis is important to scientific research because it provides an important means of structural control in synthesis. The synthesis of a specific enantiomer or diastereomer is important in both pharmaceutical and materials chemistry because enantiomers of a particular therapeutic agent may have dissimilar biological activity or materials may have different properties. Following analysis of the stability of these molecules via NMR and HPLC, assessment of their effectiveness in asymmetric catalysis will be explored. Specifically these BINOL analogs will be compared to BINOL, H-b BINOL, perfluoro-BINOL and other electron deficient BINOLs via comparison of yield and enantiomeric excess in a variety of known reactions. Other more hindered derivatives (extended from the quinone moiety) will also be synthesized and analyzed.

Bisnaphthoquinone natural products

![Bisnaphthoquinone natural products diagram]

BINOL analogs

![BINOL analogs diagram]
The synthesis of bisanthraquinone natural products is relevant to public health because their biological activity may impact a variety of health issues, including treatment of cancer, diabetes, hepatitis, depression, and use as an antioxidant. An efficient synthesis of these molecules is central to a complete analysis of their activity. In addition, a new class of chiral BINOL analogs may positively impact asymmetric catalysis, which is an important method in pharmaceutical chemistry and development of therapeutic agents for treatment of disease.
Bibliography and References Cited


(21) Hashimoto, T.; Maruoka, K. "6,6'-Substituent Effect of BINOL in Bis-Titanium Chiral Lewis Acid Catalyzed 1,3-Dipolar Cycloaddition of Nitrones" Org. Biomol. Chem. 2008, 6, 2263-2265.


Facilities and Other Resources:

Room 4002 of the Vagelos Laboratory serves as the office of the principal investigator.

The principal investigator’s laboratory consists of 3 four-person laboratories (10 hoods) in the Vagelos Laboratory outfitted with standard organic laboratory glassware, vacuum systems, etc., an instrument room, and a computer room. A computer controlled Agilent HP-6850 GC with 8-turret autosampler and a computer controlled Agilent HP HPLC with autosampler capable of analytical separations. A 12 year old double station Vacuum Atmospheres He-453 Glove Box is also present.

Within the research group, three computers are dedicated to theoretical calculations: a SGI Octane (Unix, R10,000) and two Pentium IV PCs (WinXP Pro, 1GB, 300GB-HD). Available software includes MacroModel, Chem3D, ViewerPro, Spartan, DivCon, Jaguar, Gaussian98, GaussView, FUNMAP, CAVEAT, QM-QSAR, G-QSAR, and MAPLE as well as a variety of standard commercial math libraries (IMSL, NAG, NR), databases, and compilers to support our program development efforts.

For more time consuming calculations (HF, B3LYP, MP2, large QSAR runs, etc.) two additional resources are available: (1) University of Pennsylvania Chemistry Department Computer Facility with several SGI machines including a 4 processor SGI Origin 200; (2) a 64 node with 2 CPU/node Beowulf Linux Cluster in the Department of Chemistry at the University of Pennsylvania (purchased with a multi-PI NSF CRIF grant).
**Equipment:**

The central spectroscopic facilities of the Chemistry Department are available for this project. Mass spectral facilities: two high resolution spectrometers (VG 70/70 Micromass capable of ESI or CI), a walk-on Micromass Platform LC/MS in low resolution electrospray mode, and a walk-on Agilent GC/MS. NMR facilities: 9 Bruker Fourier transform NMR spectrometers (one 200-MHz, one 250-MHz, one 300-MHz, one 360-MHz, four 500-MHz, one 600-MHz) and three dedicated SGI (O2 or IRIX) workstations for advanced processing. X-ray facility: Rigaku Mercury CCD area detector system equipped with X-stream 2000 low temperature device. Software includes Rigaku/MSC CrystalClear package for area detector data processing and Rigaku/MSC CrystalStructure package for structure solution and refinement.

Other research groups in the department have provided the part-time use of a Perkin-Elmer FTIR (G. Molander), a UV/Vis spectrophotometer (F. Gai), a Perkin-Elmer polarimeter (G. Molander), and a Kugelrohr distillation apparatus (J. Winkler).
August 13, 2009

To Whom It May Concern:

Please accept this letter as certification of eligibility for the Applicant Fellow, Erin Podlesny, for the Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research (PA-09-209).

Should you have any questions or concerns regarding this applicant, please feel free to contact me. We thank you for your time and attention.

Sincerely,

[Signature]

Marisa C. Kozlowski

Leona Joseph
Associate Director
Office of Research Services
University of Pennsylvania
pennaors@lists.upenn.edu
215-898-9984
List of Referees
Section II--Sponsor and Co-Sponsor Information:

1. Research Support Available

KOZLOWSKI, M. C.

ADC = annual direct costs
ATC = annual total costs
TDC = total direct costs (provided for instrumentation grants)
TC = total costs (provided for instrumentation grants)

ACTIVE

GOALI (Molander) 5/1/09 – 4/30/12 1.00 calendar
NSF $397,957(ADC) [MCK $40,000 ADC] $500,000 (ATC) [MCK $56,800 ATC]

“High Throughput Experimentation for Reaction Optimization”
In collaboration with Merck, the use of high throughput experimentation and design of experiment principles will be examined in range of new reaction methods.

R56 CA109164 (Kozlowski) 7/1/09 – 6/30/10 1.50 calendar
NIH/NCI - ARRA $131,845 (ADC), $196,173 (ATC)
"Synthesis of Novel Anticancer Agents”
Perylenequinone natural products and analogs will be synthesized and examined as anticancer photodynamic therapeutics.

CHE-0911713 (PI Kozlowski) 9/1/09 - 8/31/12 1.00 calendar
National Science Foundation $102,724 (ADC), $150,000 (ATC)
“Oxidative Methods for C-C and C-N Bond Formation”
New oxidative processes targeted for development include: phenol couplings, bisnapthoquinone and bisanthraquinone syntheses, and N-arylation reactions.

47616-AC1 (Kozlowski) 1/1/08 – 8/30/10 0.50 calendar

CHE-0616885 (Kozlowski) 9/1/06 - 8/31/09 1.00 calendar
National Science Foundation $94,072 (ADC), $139,000 (ATC)
“Oxidative Methods for C-C and C-N Bond Formation”
This study focuses on the mechanism of Cu catalyzed oxidative naphthol couplings and related oxidative reactions..
 CHE-0840438 (Lester) 2/1/09 – 1/31/12 0.10 calendar
NSF/CRIF $226,854 (TDC), $226,854 (TC)
“Purchase of an X-Ray Diffractometer”
Purchase of a departmental X-ray diffractometer to replace an aging instrument.

S10RR022442 (Smith) 9/30/06 – 9/29/08 0.10 calendar
NIH/NCRR $500,000 (TDC), $500,000 (TC)
“NMR systems: 2 Bruker Avance 500 Consoles”
Update of outdated user interfaces for NMR spectrometers critical for chemistry synthesis research.

2. Sponsor's/Co-Sponsor’s Previous Fellows/Trainees

Total previous predoctoral: 18
Total previous postdoctoral: 13

Representative trainees:
Erin DiMauro, predoctoral, B.A. Wesleyan Univ., Amgen, Research Scientist
Stephen Waters, predoctoral, B.S. Univ. Pittsburgh, postdoctoral with Sam Danishefsky at Sloan-Kettering, University of Vermont, Assistant Professor
V. Annamalai, predoctoral, B.S. Georgia Inst. Technology, postdoctoral with Laura Kiessling at Univ. Wisconsin
Michael Fennie, predoctoral, B.S. Canisus College, Sanofi-Aventis, Research Scientist
Barbara Jane Morgan, predoctoral, B.S. Kenyon College, postdoctoral at the Broad Institute
Bishwajit Ganguly, postdoctoral, Ph.D. Inst. of Science Bangalore, Central Salt and Marine Chemical Research Inst. India, Scientist E-1

3. Training Plan, Environment, Research Facilities

i) Ph.D. Candidacy Requirements: Ms. Podlesney has completed all the requirements for PhD candidacy at Penn including coursework, cumulative exams, and two semesters of teaching. Coursework consisted of organic chemistry mechanisms, organic synthesis, organometallic chemistry, heterocyclic chemistry, bioorganic chemistry, physical organic chemistry, organic materials chemistry, and chemistry literature/database searching.

ii) Meetings and Interactions: Joint group meetings between the Walsh (Organometallic Chemistry) and Kozlowski (Organic and Bioorganic Chemistry) groups are held weekly. After analyzing problems from the literature, one group member provides a formal presentation of their research from the last 6-9 months. Group discussion following the presentation provides a critique into the approaches taken and suggestions for further study. In conjunction, a written report is required, detailing the research from this time period. The reports are written in thesis format at a level of writing that would be appropriate for publication. Reports of this nature allow improvement of writing skills, self-evaluation of progress in the lab, and maintenance of satisfactory experimental records.

In addition, weekly Kozlowski group meetings will take place to review progress in the laboratory, troubleshoot problems, and identify new directions. As the total synthesis work draws to close, more time will be devoted to identifying the biological target(s) by meeting with collaborators in the Penn Medical School to develop further experiments. As the work on the chiral bisnaphthoquinones ramps up, opportunities for their use in materials chemistry will be explored via meetings with collaborators in Chemistry and the Laboratory for Research on the Structure of Matter (So-Jung Park, Andrew Feiring, Cheri Kagan).

iii) Seminars and Conferences: The University of Pennsylvania is at the hub of a vibrant region for science and research presenting an excellent environment for scientific discourse and numerous opportunities for continuing professional development. The Department of Chemistry alone maintains weekly seminar programs in four areas: Organic, Biological, Physical, and Inorganic Chemistry. In addition to academic speakers, speakers are drawn from local companies: Merck, Glaxo SmithKline, Wyeth, Bristol Myers Squibb, Aventis, Hoffmann LaRoche, etc., providing attendees with an appreciation of current biomedical topics of interest. Named and interdisciplinary lectureships from leaders in the field are held several times during the year. Students are also encouraged to attended seminars in their field outside of the Department Chemistry held at the Medical School, Wistar Institute, Laboratory for Research on the Structure of Matter, etc.

Ms. Podlesny is also a participant in the Chemical Biology Interface (CBI) program between the Department of Chemistry, the Department of Biology, and the Penn Medical School Biomedical Graduate Studies. The goal of the CBI training program is to provide students with the intellectual and technical skills required to solve important and complex biological problems that can be most effectively addressed by studies at the chemistry-biology interface and to create a group of graduating chemists and biologists who can effectively communicate and function successfully in multidisciplinary teams. The focus of the CBI training program will be mechanistic chemistry of proteins, which
is a theme that is of special interest to us with respect to the bisanthraquinone natural products. The CBI program includes coursework, monthly talks, and a twice annual mini-symposium centering on bioorganic chemistry. Even though Ms. Podlesney has completed the coursework required for the Ph.D. degree, she will take further courses in chemical biology, cell biology, and biochemistry to broaden her training and to be able to exploit the utility of her natural products.

Ms. Podlesney will attend national ACS meetings and NOS meetings on an annual basis to provide exposure to the broader scientific community. A further opportunity for professional development will be attendance of a Gordon Research Conference relative to her research interests in her fourth or fifth year to provide networking and prepare her for career after the Ph.D. degree. Finally, if her research moves into a specialized area (i.e. photodynamic therapy), then she will attend conferences or workshops in that area to gain further background and expertise.

iv) Research Environment and Facilities: The research community at Penn is vibrant. In Chemistry alone, there are ~190 doctoral students, ~70 postdoctoral fellows, and ~10 full-time scientific staff to support the ongoing research efforts. Approximately ~30 Ph.D. students graduate each year leading the School of Arts in Sciences at Penn. These students go on to high-profile postdoctoral, industrial, and academic positions. In addition, opportunities for interaction in the fields of biology and medicine abound with the School of Medicine, the Abramson Cancer Center, the Presbyterian Medical Center, and the Wistar Institute all located within a few blocks of the Chemistry department. For the chiral bisnapthoquinones as organic materials, the strong ties to the Laboratory for Research on the Structure of Matter, Chemical Engineering, Materials Science, and the Penn Regional Nanotechnology Facility are in place.

The research facilities at Penn for this work include the standard facilities in Chemistry as well significant additional resources as conditions warrant from the institutes and centers listed above. The Chemistry facilities undergo constant renewal with recent instrumentation grants having updated the NMR, X-ray, and MS facilities. The Chemistry complex is comprised of four buildings with older facilities being renovated on a rotating basis. Our laboratory space is located in the 11-year old Vagelos Laboratories.

v) Additional Required Training or Technical Skills: Training in departmental instrumentation will continue to be provided by Dr. George Furst (Director, NMR Services), Dr. Rakesh Kohli (Director, MS Services), and Dr. Patrick Carroll (Director, Crystallographic Facility). Under the tutelage of Dr. Steven Johnson (University of Pennsylvania Medical School, Department of Hematology/Oncology), all of the necessary equipment and training for cancer cell assays is available. Should these assays prove encouraging, then Theresa Busch (University of Pennsylvania Medical School, Department of Radiation Oncology) will provide further training and guidance in testing of the photodynamic therapeutic properties of the bisanthraquinone natural products including clonogenic cell assays, animal toxicity studies, and animal tumor model studies. Both these collaborations are firmly established with our ongoing work using the perylenequinone natural products (J. Am. Chem. Soc. 2009, 131, 9413–9425).

vi) Applicant’s Career Goals: With strong interests in organic synthesis and a desire to pursue a career in basic research, an individual development plan will be devised and examined periodically with Ms. Podlesney. The current version combines strong training in the core area of organic synthesis combined with interdisciplinary training in biological chemistry and/or materials science. Regardless of the precise direction the research develops, Ms. Podlesney will emerge with the skills to solve complex chemical problems in a team environment.
4. Number of Fellows/Trainees to be Supervised During the Fellowship

Total predoctoral: 8
Total postdoctoral: 2

5. Applicant's Qualifications and Potential for a Research Career

Ms. Podlesny received her BS in Chemistry from Gettysburg College. She was an undergraduate researcher in two laboratories, one at Gettysburg and one at the University of Virginia.

This assessment is in line with her performance here at Penn. She has gotten off to an impressive start in her first year in the laboratory. For example, in Amos Smith's total synthesis class she was assigned one of the axially chiral bisanthraquinone synthetic targets that my group was considering (she is now moving forward with this synthesis following one of the plans she designed). For the class, two synthesis proposals were required, one utilizing enantioselective induction and one starting from commercially available chiral materials. While the first synthesis could be devised using our catalytic asymmetric oxidative naphthol coupling, the second was very challenging since axially chiral compounds are not abundant precursors (i.e. available from commercial sources at less than $1 per gram). She came up with a synthesis commencing from BINOL that was both clever and insightful. Prof. Amos Smith, Prof. Patrick Walsh, and I all commented on how innovative her proposal was as we had never seen any synthesis starting from BINOL, which is now relatively inexpensive (~35 cents per gram).

In her one year in my laboratory, Ms. Podlesny has made excellent progress in her project on the bisnapthoquinones and the corresponding bisanthraquinone natural products. She has been the most productive among the four students from her class in my group.

My philosophy toward student training is to provide a preliminary plan with missing details and important concepts. Ms. Podlesny has shown that she can manage such input and she has significantly developed the very preliminary project outline that I gave her. She has identified further natural products, developed completely new synthetic routes, and tackled significant difficulties in implementation of the research plan. Already, she is growing into the role of an interesting and innovative coworker vs a novice student. As she continues to mature, I will challenge her to develop new projects and new ideas based both on her current work and her developing interests via one-on-one meetings as well as group discussions. I find that this method may result in slower research progress initially since I do not lay out every experiment. However, the ultimate result is a well-developed, confident student who can identify important problems and develop plans for experimental implementation fully independently. Activities to foster this development will include writing manuscripts, identifying and researching new projects for younger coworkers and grant applications, supervising undergraduate students and junior graduate students, reviewing important literature topics for the group, and ultimately writing research proposal sections.

At this stage in her development, Ms. Podlesny compares to the best students that have come out of my lab. I am excited to work with her further to complete her development as an independent scientist.
**PROFILE - Project Director/Principal Investigator**

Prefix:  
* First Name: Erin  
* Last Name: Podlesny  
Suffix:  

Position/Title: Graduate Student  
Department: Chemistry  

Organization Name: University of Pennsylvania  
Division:  

* Street1:  
Street2:  
* City:  
County:  
* State:  
* Province:  
* Country: USA: UNITED STATES  
* Zip / Postal Code: 19104-6323  
* Phone Number:  
Fax Number:  
* E-Mail:  
Credential, e.g., agency login:  

* Project Role: PD/PI  
Other Project Role Category:  

*Attach Biographical Sketch*  
Attach Current & Pending Support

**PROFILE - Senior/Key Person 1**

Prefix:  
* First Name: Marisa  
* Last Name: Kozlowski  
Suffix:  

Position/Title: Professor  
Department: Chemistry  

Organization Name: University of Pennsylvania  
Division:  

* Street1:  
Street2:  
* City:  
County:  
* State:  
* Province:  
* Country: USA: UNITED STATES  
* Zip / Postal Code: 19104-6323  
* Phone Number:  
Fax Number:  
* E-Mail:  
Credential, e.g., agency login:  

* Project Role: Other (Specify)  
Other Project Role Category: Sponsor  

*Attach Biographical Sketch*  
Attach Current & Pending Support

**ADDITIONAL SENIOR/KEY PERSON PROFILE(S)**

**Additional Biographical Sketch(es) (Senior/Key Person)**

**Additional Current and Pending Support(s)**
NAME OF FELLOWSHIP APPLICANT
Erin E. Podlesny

eRA COMMONS USER NAME (credential, e.g., agency login)

POSITION TITLE
Predoctoral researcher

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gettysburg College</td>
<td>B.S.</td>
<td>05/2007</td>
<td>Chemistry; Biology minor</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>Ph.D.</td>
<td>2012</td>
<td>Organic Chemistry</td>
</tr>
</tbody>
</table>

A. Positions and Honors

<table>
<thead>
<tr>
<th>ACTIVITY/OCcupATION</th>
<th>BEGINNING DATE (mm/yy)</th>
<th>ENDING DATE (mm/yy)</th>
<th>FIELD</th>
<th>INSTITUTION/COMPANY</th>
<th>SUPERVISOR/EMPLOYER</th>
</tr>
</thead>
</table>

Academic and Professional Honors

Presidential Scholarship, Gettysburg College, 2003-2007
CRC Press Freshman Chemistry Achievement Award, Gettysburg College, 2004
Organic Chemistry Achievement Award, Gettysburg College, 2005
NSF REU Chemistry Fellowship, University of Virginia, 2006
ACS Undergraduate Award in Analytical Chemistry, Gettysburg College, 2006
Honorable Mention for NSF Graduate Research Fellowship, 2007
American Chemical Society certification, 2007
Society for Analytical Chemists of Pittsburgh Award, 2007
Stine Chemistry Prize, Gettysburg College, 2007
B.S. awarded with departmental honors, Summa Cum Laude, Valedictorian, 2007
Teaching assistant commendation, Chemistry Department, University of Pennsylvania, 2009
NIH Chemistry-Biology Interface Training Fellowship, 2009

Memberships in professional societies:
Phi Beta Kappa
Omicron Delta Kappa
American Chemical Society

B. Publications

Abstracts:

Reviews:
C. Scholastic Performance

<table>
<thead>
<tr>
<th>SCIENCE</th>
<th>YEAR</th>
<th>COURSE TITLE</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETTYSBURG COLLEGE</td>
<td>2003</td>
<td>Intro to Ecology and Evolution</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>Chemical Structure and Bonding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>Exploring the World of Fungi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Form and Function/Living Organisms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Chemical Reactivity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Genetics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Organic Chemistry I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>Cell Biology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>Organic Chemistry II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>Chem. Applications of Spectroscopy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>Instrumental Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>Advanced Organic Chemistry</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>Introductory Modern Physics I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Advanced Inorganic Chemistry</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Introductory Modern Physics II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Developmental Biology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Physical Chemistry I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Biochemistry I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Individualized Study-Research</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Individualized Study-Research (summer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>Biochemistry II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>Physical Chemistry II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>Individualized Study-Research</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER</th>
<th>YEAR</th>
<th>COURSE TITLE</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETTYSBURG COLLEGE</td>
<td>2003</td>
<td>Fundamental Spanish I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Calculus I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Fundamental Spanish II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Calculus II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Intermediate Spanish I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>Intermediate Spanish II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>Intro to Archaeology and Physical Anthropology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Gettysburg in History and Memory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Multivariable Calculus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>Intro to the Civil War Era</td>
<td></td>
</tr>
</tbody>
</table>

| UNIVERSITY OF PENNSYLVANIA       | 2007 | Organic Mechanisms                                |       |
|                                  | 2007 | Organic Reactions                                 |       |
|                                  | 2007 | Organometallics                                   |       |
|                                  | 2008 | Physical Organic Chemistry                        |       |
|                                  | 2008 | Advanced Organic Synthesis                        |       |
|                                  | 2008 | Topics in Organic Chemistry                       |       |
|                                  | 2008 | Topics in Organic Chemistry                       |       |
|                                  | 2008 | Topics in Organic Chemistry                       |       |
|                                  | 2008 | Independent Study                                 |       |
|                                  | 2009 | Independent Study                                 |       |

|                                  | 2007 | Organic Reactions                                 |       |

Except for the summer individualized study-research course, Gettysburg College courses were graded on a 4.33 scale with plus and minus grades (i.e. A+ is 4.33, A is 4.0). The summer individualized study-research course was graded on a satisfactory (S) or unsatisfactory (U). Satisfactory is a C– or better. Courses at the University of Pennsylvania were graded on a 4.0 scale (A/A+).

GRE Scores:
BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors. Follow this format for each person. DO NOT EXCEED FOUR PAGES.

NAME
Kozlowski, Marisa C.

eRA COMMONS USER NAME

POSITION TITLE
Associate Professor, University of Pennsylvania

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornell University, Ithaca, NY</td>
<td>BA</td>
<td>1989</td>
<td>Chemistry</td>
</tr>
<tr>
<td>U.C. Berkeley, Berkeley, CA</td>
<td>PhD</td>
<td>1994</td>
<td>Organic Chemistry</td>
</tr>
</tbody>
</table>

Please refer to the application instructions in order to complete sections A, B, and C of the Biographical Sketch.

A. Research & Professional Experience

Research Experience and Employment:
- NSF Postdoctoral Research Fellow, Mentor – Prof. David A. Evans, Harvard Univ. 1995-1997
- Assistant Professor, Chemistry Department, University of Pennsylvania 1997-2003
- Associate Professor, Chemistry Department, University of Pennsylvania 2003-2009
- Professor, Chemistry Department, University of Pennsylvania 2009-

Honors:
- Cornell Tradition Fellowship, Cornell University 1985-1989
- Merck Chemistry Award, Cornell University 1989
- Department of Education Fellowship, University of California at Berkeley 1989-1992
- Syntex Fellowship, University of California at Berkeley 1992-1993
- National Science Foundation Postdoctoral Fellowship, Harvard University 1995-1996
- DuPont Young Investigator Award, University of Pennsylvania 1998-2001
- National Science Foundation CAREER Award 2001-2006
- George Lesher Lecturer in Bioorganic and Medicinal Chemistry (RPI) 2001
- Alfred P. Sloan Research Fellow 2002-2004
- Kahn Award for Distinguished Teaching by an Assistant Professor 2002
- American Cancer Society Beginning Research Scholar 2002-2006
- ACS Travel Progress Award 2007

B. Selected Publications (54 of 72 total)


33) Kozlowski, M. C.; Diazadecalin Metal Complexes: Efficient Formation of Chiral 1,5-Diazadecalin Base" Organometallics 2003, 22, 850-855. http://dx.doi.org/10.1021/om0269759


C. Research Support
ACTIVE:

National Institutes of Health (NCI) R56 CA109164 Kozlowski (PI) 8/1/09 - 7/31/10
“Synthesis of Novel Anticancer Agents”
Synthesis and anticancer study of the photoactive perylenequinone natural products.

National Science Foundation CHE-0616885 Kozlowski (PI) 8/1/06 - 7/31/09
"Oxidative Methods for C-C and C-N Bond Formation"
New reactivity in C-C, C-O, and C-N bond formation is explored.

PREVIOUS (last 3 years)
NIH/NCI R01 CA109164 Kozlowski (PI) 7/20/04 – 5/30/08
“Synthesis of Novel Anticancer Agents”
Synthesis of the bisnaphthopyrone and perylenequinone natural products.

NIH/NIGMS R01 GM59945 Kozlowski (PI) 3/1/00 - 2/27/06
"Designing Ligands for Reactions Using Computational Techniques"

NSF CAREER Award Kozlowski (PI) 4/1/01 - 3/31/06
"Asymmetric Oxidative Methods for C-C Bond Formation"
### A. Application Type:

From SF424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated here for your reference as you provide the responses that are appropriate for this Fellowship application.

- [ ] New
- [ ] Resubmission
- [ ] Renewal
- [ ] Continuation
- [ ] Revision

### B. Research Training Plan

1. **Introduction to Application**
   (for RESUBMISSION applications only)

2. **Specific Aims**
   - FinalPlanSpecificAims.pdf

3. **Background and Significance**
   - Finalplanbackground.pdf

4. **Preliminary Studies/Progress Report**
   - FinalplanPrelim.pdf

5. **Research Design and Methods**
   - FinalplanMethods.pdf

6. **Inclusion Enrollment Report**
   (for RENEWAL applications only)

7. **Progress Report Publication List**
   (for RENEWAL applications only)

### Human Subjects

Please note. The following item is taken from the Research & Related Other Project Information form. The response provided on that page, regarding the involvement of human subjects, is repeated here for your reference as you provide related responses for this Fellowship application. If you wish to change the answer to the item shown below, please do so on the Research & Related Other Project Information form; you will not be able to edit the response here.

<table>
<thead>
<tr>
<th>Are Human Subjects Involved?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. * Human Subjects Involvement Indefinite?</td>
<td>[ ] Yes</td>
<td>[x] No</td>
</tr>
<tr>
<td>9. Clinical Trial?</td>
<td>[ ] Yes</td>
<td>[x] No</td>
</tr>
<tr>
<td>10. Agency-Defined Phase III Clinical Trial?</td>
<td>[ ] Yes</td>
<td>[x] No</td>
</tr>
</tbody>
</table>

11. **Protection of Human Subjects**
12. **Inclusion of Women and Minorities**
13. **Targeted/Planned Enrollment**
14. **Inclusion of Children**

### Other Research Training Plan Sections

Please note. The following item is taken from the Research & Related Other Project Information form. The response provided on that page, regarding the use of vertebrate animals, is repeated here for your reference as you provide related responses for this Fellowship application. If you wish to change the answer to the item shown below, please do so on the Research & Related Other Project Information form; you will not be able to edit the response here.

<table>
<thead>
<tr>
<th>Are Vertebrate Animals Used?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. * Vertebrate Animals Use Indefinite?</td>
<td>[x] Yes</td>
<td>[ ] No</td>
</tr>
</tbody>
</table>

16. **Vertebrate Animals**
17. **Select Agent Research**
18. **Resource Sharing Plan**
19. **Respective Contributions**
   - RespectiveContributions.pdf
20. **Selection of Sponsor and Institution**
   - SelectionofSponsorandInstitution.pdf
21. **Responsible Conduct of Research**
   - ResponsibleConductofResearch.pdf
C. Additional Information

Human Embryonic Stem Cells

1. * Does the proposed project involve human embryonic stem cells?  
   - Yes  
   - No  

   If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s), using the registry information provided within the agency instructions. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the Registry will be used:

   - Specific stem cell line cannot be referenced at this time. One from the registry will be used.  

   Cell Line(s):
   

Candidate

2. Alternate Phone Number:  

3. Graduate Degree Earned (if applicable):

   Degree:  
   If "other", please indicate degree type:  
   Date Earned (month/year):

4. Degree Sought During Proposed Award:

   Degree:  
   PHD : Doctor of Philosophy  
   If "other", please indicate degree type:  
   Expected Completion Date (month/year):

5. * Field of Training for Current Proposal:  
   1770 Synthetic Chemistry

6. * Current Or Prior Kirschstein-NRSA Support?  
   - Yes  
   - No  

   If yes, please identify current and prior Kirschstein-NRSA support below:

<table>
<thead>
<tr>
<th>* Level</th>
<th>* Type</th>
<th>Start Date (if known)</th>
<th>End Date (if known)</th>
<th>Grant Number (if known)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. * Applications for Concurrent Support?  
   - Yes  
   - No  

   If yes, please describe in an attached file:

8. * Goals for Fellowship Training and Career

   GoalsforFellowshipTrainingandCare

9. * Activities Planned Under This Award

   ActivitiesPlannedUnderThisAward

10. Doctoral Dissertation and Other Research Experience

   OtherResearchExperience.pdf

11. * Citizenship:  
   - U.S. Citizen or noncitizen national  
   - Permanent Resident of U.S.  
   - Temporary Resident of U.S. (if a permanent resident of the U.S., a notarized statement must be provided by the time of award)  
   - Permanent Resident of U.S. Pending  
   - Non-U.S. Citizen with temporary U.S. visa
D. Budget

Senior Fellowship Applicants Only:

1. Present Institutional Base Salary:

<table>
<thead>
<tr>
<th>Amount</th>
<th>Academic Period</th>
<th>Number of Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Stipends/Salary During First Year of Proposed Fellowship:

   a. Federal Stipend Requested:

<table>
<thead>
<tr>
<th>Amount</th>
<th>Number of Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

   b. Supplementation from other sources:

<table>
<thead>
<tr>
<th>Amount</th>
<th>Number of Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

   Type (sabbatical leave, salary, etc.)
   
   Source
   

All Fellowship Applicants:

3. * Tuition and Fees:

<table>
<thead>
<tr>
<th>None Requested</th>
<th>Funds Requested:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1: 16,000.00</td>
</tr>
<tr>
<td></td>
<td>Year 2: 16,000.00</td>
</tr>
<tr>
<td></td>
<td>Year 3: 16,000.00</td>
</tr>
<tr>
<td></td>
<td>Year 4:</td>
</tr>
<tr>
<td></td>
<td>Year 5:</td>
</tr>
<tr>
<td></td>
<td>Year 6 (when applicable):</td>
</tr>
</tbody>
</table>

   Total Funds Requested: 48,000.00
Specific Aims

Specific Aim 1: Synthesis and Utility of Chiral Bisnaphthoquinones for Asymmetric Catalysis

The synthesis of chiral bisnaphthoquinones 1 will be explored (Scheme 1) with the purpose of generating a set of potentially useful BINOL analogs (2a-2b). These BINOL analogs will then be analyzed in the context of asymmetric catalysis. They will be compared to the parent BINOL ligand, H$_8$-BINOL, perfluoro-BINOL and other electron deficient BINOLs.

Scheme 1. BINOL Derivatives.

Specific Aim 2: Synthesis of Chiral Bisanthraquinone Natural Products

Five chiral bisanthraquinone natural products 4-8 will be synthesized via a concerted route from the same bisnaphthoquinone intermediate 3 (Scheme 2). Divergence from this common intermediary will occur via Diels-Alder reactions between the bisnaphthoquinone and various vinyl ketene acetals (10-11), affording the desired bisanthraquinones. The synthesis of the less complex 5,5'-bisoranjidiol 9 will follow a shorter but parallel route, from a simpler bisnaphthoquinone (1, Scheme 1).

Scheme 2. Bisanthraquinone Natural Products.
Background and Significance

Chiral Bisnapthoquinones (Specific Aim 1)

The synthesis of a novel set of chiral bisnapthoquinones for use as ligands is significant because they have the potential to positively impact asymmetric catalysis. Catalytic asymmetric synthesis is important to scientific research because it provides an important means of structural control in synthesis. The synthesis of a specific enantiomer or diastereomer is important in both pharmaceutical and materials chemistry because enantiomers of a particular therapeutic agent may have dissimilar biological activity or materials may have different properties.

One ligand regularly employed in a variety of enantioselective reactions is the axially chiral ligand BINOL or 1′-bi-2-binaphthol (12, Scheme 3). To date many BINOL derivatives have been synthesized, which offer improvements in yield or selectivity over BINOL for many reactions. A majority of these ligands possess a 3,3′-disubstituted scaffold with sterically influential groups at these positions, while another category of BINOL ligands have 6,6′-disubstituted frameworks. The bisnapthoquinones 1 are not only key intermediates to the bisanthraquinone natural products (see Specific Aim 2, Scheme 2), but they may also lead to potentially useful BINOL derivatives (2a-2b, 13-14, Scheme 3) for asymmetric catalysis. These novel BINOL analogs would have electron withdrawing groups (para-quinone) and the core bisnapthoquinone structure would enable facile production of derivatives at the 3,3′-positions or augmentation through the quinone moiety.

Scheme 3. Bisnapthoquinones as BINOL Analogs.

Chiral Bisanthraquinones (Specific Aim 2)

The symmetrical bisanthraquinones are a class of biaryl natural products possessing axial chirality (Scheme 2). Members include bisoranjidiol (9), skyrin (4), bislinutin (5), trachypone (6), and 7 and 8. The biological activity and physical properties that have been reported for some of these compounds encompass a wide spectrum: applications in tumor suppression, diabetes, hepatitis, depression, as well as possession of photosensitizing and antioxidant properties. An efficient synthesis of these molecules is important because it would not only provide significant quantities of all of the bisanthraquinone natural products for biological testing, but also make the synthesis and testing of analogs, or unnatural enantiomers possible.

Bisoranjidiol (9, Scheme 2) is the most recently isolated (2006) of these bisanthraquinones and is notably lacking the hydroxyl at the 4,4′-positions. The dimer is a prominent metabolite found in the leaves of Heterophyllaea pustula (genera Rubiaceae). This is a toxic shrub which grows in the mountains of Argentina and Bolivia. Due its phototoxicity, animals eating the shrub tend to suffer from photosensitization, expressed as dermatitis and/or blindness. Bisoranjidiol has been shown to possess photosensitizing properties. Specifically, it can interact with molecular oxygen to produce electronically excited singlet oxygen (1O2) as well as the ground state radical anion (O2−). Singlet oxygen is a very reactive species which can induce DNA damage and apoptosis of cells. This is the basis of photodynamic therapy (PDT), which is a cancer treatment that uses light to activate a photosensitizing agent to produce reactive oxygen species that cause cell death.

Skyrin (4, Scheme 2) is the oldest and most studied of these bisanthraquinones. It was first isolated from penicillium islandicum in 1954 and has since been found in a variety of other fungi and lichen. The interest in the molecule stems from its biological activity, as this emodin dimer is reported to suppress the growth of HeLa, Vero, K562, Raji, Wish, and Calu-1 and other tumor cell lines. A variety of other biological activities and physical properties have also been observed. For example, skyrin has been reported to interfere with the coupling of glucagon to adenylate cyclase independent of binding to the glucagon receptor. This could be useful for the treatment of diabetes. Recently, the antioxidant and radical scavaging ability of skyrin has...
also been studied. It was reported that the antioxidant behavior is similar to that of emodin (skyrin monomer) and comparable to vitamin C and E. These properties make skyrin useful, with possible applications in protecting skin against the effects of UV radiation.\textsuperscript{12}

Of the bisanthraquinones in Scheme 2, only prior syntheses of skyrin exist. This biomimetic synthesis of skyrin was achieved by the chemical oxidation of either emodin or emodinanthonrone in meger 0.28\% and 1.2\% yields, respectively.\textsuperscript{14} Two decades later, a fully methylated derivative was synthesized via an Ullman reaction of the brominated emodin.\textsuperscript{15} However, there is still much room for improvement as these syntheses are both inefficient and nonstereoselective. To date, no efficient nor asymmetric syntheses of these bisanthraquinones have been achieved. Also, while a variety of biological activities and physical properties have been reported, most of the focus has been on skyrin. The bisanthraquinones are all structurally related and potentially possess similar biological activity and properties. Information of this type is lacking for many of the other bisanthraquinones, citing a need for more biological studies. An efficient synthesis of these molecules is central to achieving these goals.

**Retrosynthetic Analysis: Bisanthraquinones**

From a retrosynthetic standpoint there are three key disconnections to form the bisanthraquinones (Scheme 4). In a departure from prior approaches, the anthracenyl ring system will be generated in my work after dimerization. Thus, the first disconnection is the Diels-Alder/aromatization reaction between a bisnaphthoquinone intermediate and the desired vinylketene acetal.\textsuperscript{16} Alkyl trimethylsilyl- or bis(trimethylsilyl)vinyl ketene acetals, also referred to as Brassard dienes,\textsuperscript{16} are typically employed though simpler dienes, such as Danishefsky's diene,\textsuperscript{17} have also been used. The bisnaphthoquinone could be formed via oxidation of a 8,8'-dihydroxy bisnaphthol. Finally, an enantioselective biaryl coupling reaction\textsuperscript{18,19} leads to the biaryl.

**Scheme 4. Retrosynthesis.**

**Asymmetric Naphthol Coupling**

The enantioselective oxidative coupling of naphthols to form the core binaphthol system is a key transformation for the formation of the bisanthraquinones and bisnaphthoquinones (see Scheme 4). This method of oxidative C-C bond formation was developed by the Kozlowski group\textsuperscript{18,19} and utilizes a diaza-cis-decalin copper catalyst (15, Scheme 5). This dianime copper catalyst can be used to couple a variety of functionalized 2-naphthols with C3 substitution. The best yields and enantioselectivities were observed with esters or phosphates at C3 (16a-d), attaining up to 85\% yield and 93\% ee (Scheme 5). Furthermore, highly functionalized substrates could also be coupled (16e-g).
Scheme 5. Enantioselective Oxidative Biaryl Coupling.

<table>
<thead>
<tr>
<th></th>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>R^4</th>
<th>R^5</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CO_2Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>85</td>
<td>91-93</td>
</tr>
<tr>
<td>b</td>
<td>CO_2Bn</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>79</td>
<td>90</td>
</tr>
<tr>
<td>c</td>
<td>CO_2&gt;Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>70</td>
<td>87</td>
</tr>
<tr>
<td>d</td>
<td>PO(OMe)_2</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>76</td>
<td>92</td>
</tr>
<tr>
<td>e</td>
<td>CO_2Me</td>
<td>OAc</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>72</td>
<td>≥ 90</td>
</tr>
<tr>
<td>f</td>
<td>CO_2Me</td>
<td>OAc</td>
<td>H</td>
<td>OMe</td>
<td>n-Pr</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>g</td>
<td>CO_2Me</td>
<td>OAc</td>
<td>H</td>
<td>OMe</td>
<td>I</td>
<td>80</td>
<td>&gt; 85</td>
</tr>
</tbody>
</table>
Preliminary Studies

Preliminary studies for this proposal have focused on the synthesis of a simple bisnaphthoquinone and investigations into the Diels-Alder reactions needed to form the bisanthraquinones. All preliminary research discussed in this section, except for the initial precedent of enantioselective coupling of 8-substituted 2-naphthols (Scheme 6), was accomplished by myself (fellowship applicant). All of these results are unpublished.

Specific Aims 1-2: Establishment of precedent for biaryl coupling and quinone formation

The enantioselective coupling with diaza-cis-decalin copper catalyst (R,R or S,S-15) is a proven method for the oxidative coupling of functionalized 2-naphthols, however, naphthols substituted at the C8 position had not been studied previously. A few years ago the Kozlowski group established precedent for the coupling of a simple naphthol with a methoxy moiety at the C8 position (Scheme 6). Using (R,R)-15, high enantioselectivity (90% ee) and moderate yield (59%) of bisnaphthol (S)-19 was obtained.

Scheme 6. Precedent for Biaryl Coupling of C8 Substituted Naphthols

I then began to investigate the synthesis of the bisnaphthoquinones. The racemate of 19 was synthesized in three steps from commercially available hydroxy naphthol 20 in 60% yield (Scheme 7). Subsequent deprotection of the 8,8′ methoxy substituents lead to formation of tetrrol 21 in 49% yield after esterification. Oxidation of 21 with salcomine (23) produced bisnaphthoquinone 22 in moderate yield (55%), with 19% of an unsymmetrical ortho/para-bisnaphthoquinone also forming.

Scheme 7. Synthesis of Bisnaphthoquinones Route 1.

Due to the inefficiency (incomplete reaction, hydrolysis, and solubility difficulties) of the demethylation step from 19 to 21 (Scheme 7), a new protecting group (benzyl) was chosen for the C8 phenol (Scheme 8). Starting from 7, esterification and selective benzylation provided naphthol 24 in good yield (72%, 2 steps). The use of CuCl(OH)TMEDA provided the racemate 25 in high yield (91%). When the (R,R) or (S,S)-diaza-cis-decalin copper catalyst (15) was used (S) or (R)-25 were produced, respectively, in moderate yield, but with high selectivity (95-97% ee, Scheme 8). The lower yields could be attributed to increased steric hinderance from the C8 substituent. Subsequent methylation, hydrogenation, and oxidation lead to (R)-26 in good yields, while retaining the enantiomeric excess (Scheme 8).
Scheme 8. Synthesis of Bisnaphthoquinones Route 2.

Specific Aim 1: Precedent for regiocontrol of Diels-Alder reaction

After preliminary Diels-Alder reactions with Danishefsky’s diene showed that a bisanthraquinone could be formed under thermal conditions, control of the regiochemistry of the Diels-Alder reaction via Lewis acid catalysis was examined (Scheme 9). When the Diels-Alder reaction between 26 and 10a was conducted in the presence of two equivalents of ZnCl₂, followed by exposure to silica and air, three bisanthraquinone isomers were isolated (Scheme 9). Two of these regioisomers are symmetrical (27 and 29) and the third unsymmetrical (28). When the Diels-Alder reaction between 26 and 10a was conducted in the presence of two equivalents ZnCl₂ (Scheme 9) the ratio of isomers observed was 4:3:1 of 27:28:29. However, when four equivalents were used, this ratio shifted towards the desired regioisomer in a ratio of <0.2:1:4.5 of 27:28:29 (Scheme 9).

Scheme 9. Control of Regioselectivity with Zinc Chloride.
Research Design and Methods

The synthetic transformations proposed in Specific Aims 1 and 2 will all be conducted and optimized first on racemic material before using enantiopure samples. The enantiomeric excess will be determined via chiral high-performance liquid chromatography (HPLC). The initial focus of this research will be the synthesis of the bisanthraquinone natural products. Generation of bisoranjidiol 9 will be explored first, as it required less steps and is structurally less complex than natural products 4-8. Concurrently, the simplest chiral bisanthraquinone BINOL analog could also be synthesized (Specific Aim 1), as the same intermediate is used to generate bisoranjidiol. Once bisoranjidiol has been synthesized, focus will shift to the five other bisanthraquinones. Knowledge gained from the synthesis of bisoranjidiol will prove useful for this route. Once all of the bisanthraquinones have been synthesized, accomplishing the objectives of Specific Aim 2, the focus will be placed on finishing the goals of Specific Aim 1.

Specific Aim 1: Synthesis of Chiral Bisnaphthoquinones

In preliminary studies, two different bisnaphthoquinones have already been successfully synthesized (Schemes 7, 8). From these versatile substrates, a variety of chiral BINOL analogs can be generated possessing either a disubstituted 3,3'-disubstituted skeleton with sterically influential groups at these positions, or extension through the quinone moiety. The simplest analog is 2a, which lacks functionality at 3,3'. It could be generated from precursor 1 via decarboxylation (Scheme 10). Once this ligand is obtained, the chemical stability and atropisomerism of the molecule will need to be assessed. The effects of acidic, basic, oxidative, reductive, and thermal conditions will be examined via NMR and HPLC. Metal complexes of the bisnaphthoquinone with titanium 30a and zirconium 30b will also be formed and characterized (Scheme 10).

Scheme 10. Generation of Chiral Bisnaphthoquinones and Metal Complexes.

After this point, the performance of these molecules as ligands will be ascertained by direct comparison with other BINOL analogs possessing electron-withdrawing groups as shown in Scheme 11. Specifically, the yield and enantiomeric excess with bisnaphthoquinone 2a as a ligand will be compared to BINOL analogs in three different reported reactions employing zirconium (a, aldol-type reaction),20 titanium (b, 1,3-dipolar cycloaddition),21 and hydrogen bonding catalysts (c, allylboration).22

Scheme 11. Test reactions for Comparison with BINOL Analogs.

Many other BINOL analogs can be generated from bisnaphthoquinone 2. For example, analogs with sterically influential groups near the metal center such as 2b, or BINOLs extended through the quinone moiety via Diels-Alder reactions (31) or ketalization (33, Scheme 12). Compound 33 could be more hindered than H8-BINOL (32). The utility of these novel ligands would also be compared against BINOL in the same manner.
Other uses of this type of chiral molecule will also be explored, such as its use together with air as a chiral catalytic oxidant for dearomatization reactions.

Scheme 12. Extended BINOLs.

Specific Aim 2: Synthesis of Chiral Bisanthraquinones

Retrosynthetic analysis of bisanthraquinones 4-9 (Scheme 2) reveals three key synthetic transformations (Scheme 4). These are 1) Diels-Alder/aromatization reaction between a bisnaphthoquinone intermediate and vinylketene acetal, 2) oxidation of a 8,8'-dihydroxy substituted bisnaphthol to selectively form the para-bisnaphthoquinone, and 3) the enantioselective biaryl coupling reaction to form the bisnaphthol. While bisanthraquinones 4-9 (Scheme 2) all share these key steps to their synthesis, there exists two structural differences between bisoranjidiol 9 and the other bisanthraquinones 4-8, requiring different synthetic routes and approaches. These routes will be discussed separately. The first architectural difference is that bisoranjidiol (9) lacks the 4,4'-hydroxy functionality shared by all bisanthraquinone phenols of the biaryl. The desired naphthol for 4-8 would necessitate formation of the naphthol ring system via synthetic means. The desired naphthol for 9, however, can be easily generated from a commercially available naphthol (20, Scheme 8). The second difference is with the left-hand rings of the bisanthraquinones. Compounds 4-8 share substitution at 5,5' and 7,7', while 9 has an ortho relationship (5,5' and 6,6').

Synthesis of 5,5'-bisoranjidiol

The proposed synthesis of bisoranjidiol 9 takes advantage of efforts already made in the synthesis of chiral bisnaphthoquinones, discussed in Specific Aim 1. Specifically the bisanthraquinone framework could be accessed directly from bisnaphthoquinone 26 through a Diels-Alder reaction of diene 11 (Scheme 13). This would be followed by acid formation and decarboxylation to give compound 9.

Scheme 13. Synthesis of 5,5'-Bisoranjidiol.

Synthesis of 4,4'-substituted bisanthraquinones

Naphthols, with a hydroxyl at C4, are a necessary intermediate for the synthesis of natural products 4-8 (Scheme 2). This hydroxyl could be generated from the appropriate phenylacetic acid through a four step sequence. Functional group tolerance is limited for this sequence. A benzyl protected phenol, which coincides with a benzoxyl group at the C8 position of the resulting naphthol is not stable to these conditions. A methoxy group is stable, however, due to the potential difficulties of deprotection of the 8,8’ phenols of the biaryl species as was experienced with 19 (Scheme 7), this route was not pursued further. Halogens are stable to the cyclization conditions and 2-chlorophenylacetic acid (34) could be used as a starting point (Scheme 14). Once the bisacetate compound 35 has been successfully synthesized, a selective deprotection of the 2-hydroxyl with base generates the desired coupling precursor. Enantioselective naphthol coupling would give the biaryl.
system 37. After protection of the 2,2'- and 4,4'-hydroxyls as methyl ethers, a Buchwald-Hartwig palladium catalyzed cross-coupling could be used to directly install the oxygen functionality at 8,8'. Salcomine oxidation should proceed similarly as with 26, likely forming both the desired para/para-bisnaphthoquinone and the ortho/para-bisnaphthoquinone. From this versatile intermediate 40, reaction with the desired ketene acetal should give the bisantraquinone. Subsequent protecting group manipulations followed by either reduction of the ester groups to methyls or conversion to acids and decarboxylation would quickly provide five natural products. If regioselectivity is modest for the Diels-Alder reaction, another means of controlling the regioselectivity is via an “internal Lewis Acid,” namely, H-bonding between the 4,4'-hydroxyl and the 5,5'-carboxyls effectively act as Lewis Acids (43, Scheme 15). Due to inherent difficulties of conducting two Diels-Alder/aromatization reactions on the same molecule, optimization of yield, and Lewis acid employed for control of regioselection will be conducted on a model system (Scheme 16). This also easily allows for comparison of substrates containing unprotected phenols (44a) with their fully protected counterparts (44b).


Scheme 15. “Internal Lewis Acid.”
Summary

This project will result in total synthesis of a group of natural products that has not been synthesized previously, resulting in material for biological study. This aspect of the project is expected to take 1.5 years. In addition, a new class of BINOL-type chiral ligands will be generated. Examination of the many possibilities of these compounds will be the focus of the remainder of the fellowship period.
The research training plan submitted for this application was written solely by myself (the applicant) then reviewed by my sponsor for editing purposes and suggestions. While the core idea behind this plan was not original, I have modified and expanded the plan to its present form. This was accomplished following results and observations from the preliminary research that I have already conducted. These modifications were both original as well as the result of discussions and suggestions received during our weekly group meetings. To illustrate this, for example, have extended the project’s natural product targets to include 5-5’-bisoranjidiol, I have modified the route for accessing the five complex bisanthraquinone natural products to include a palladium catalyzed coupling reaction, proposed an alternate and shorter route for accessing the bisnaphthoquinones (incorporation of a C8 benzyl protected naphthol). I expect to accomplish the proposed research independently while under the supervision of my sponsor. My sponsor will provide guidance and suggestions for the research.
Selection of Sponsor and Institution

I chose the University of Pennsylvania for my graduate education because the chemistry department has a very good reputation. In particular the chemistry department has a very good program for training in organic synthesis. This is what I’m interested in. Besides its respected reputation, which can play an influential factor in my career, I thought the University of Pennsylvania (Penn) offered more diverse and interesting opportunities in chemical research than any of the other institutions I had considered. As such, there were several professors at Penn I was interested in working for. In making my decision, I established a set of criteria for my education and research training. These goals are as follows:

1. As I am very interested in organic synthesis, I wanted a group that was interested in some synthetic projects.
2. I have always held an interest in the interface between chemistry and biology. I wanted to have an opportunity to work on a project with this multidisciplinary aspect, while still maintaining my focus in organic chemistry. I was interested in this because the research could have the potential to impact medicine and public health through therapeutics or otherwise.
3. I also wanted the opportunity to diversify and gain perspective in areas other than just total synthesis, such as methodology or biological studies.

These goals were a major factor in my decision to choose Dr. Marisa Kozlowski as my dissertation advisor and sponsor for this application. I feel she is my best opportunity to accomplish these goals and those specific aims outlined in the research training plan. To briefly illustrate, the research in her group is quite diversified with much of it focused on the development of new methods. These methods are then applied to the synthesis of natural products and derivatives with interesting biomedical implications. Upon completion of the synthesis, analysis was taken one step further to biological testing. A good example of this is the perylenequinone natural products. Using our methodology these molecules were synthesized by our group and the inhibitory effects on protein kinase C (PKC) were also assessed.
Upon entering graduate school, instruction was received in the Responsible Conduct of Research during orientation week. A student handbook on ethics and original research was given to all graduate students, and the contents of which were discussed. Topics included academic integrity, plagiarism, paraphrasing, proper citation of sources, etc. Also, as part of our Chemical Information course taken the second semester of our first year, we discussed several ethics case studies taken from *On Being a Scientist: Responsible Conduct in Research*, Washington, DC: National Academy Press, 1995. As a course requirement, we also completed several online bioethics training modules provided on the website of the Vice Provost for Research at the University of Pennsylvania. Topics included keeping a laboratory notebook (ownership of data and intellectual property), authorship, collaborative science, misconduct in science (including Penn’s procedures regarding misconduct), conflicts of interest, and peer review materials. These modules involved presentations/lectures and quizzes. They were also discussed in class.

If this is found to be unacceptable for NIH staff, then further electronic training in the Responsible Conduct of Research will be pursued. The University of Pennsylvania maintains an online website where training can be received in these areas:

- Data acquisition, management, sharing, and ownership
- Materials, their ownership, and material transfer agreements
- Intellectual property, copyrights, patents, licenses, and technology transfer
- Authorship and publication practices
- Peer review
- Mentor/trainee responsibilities, and collaborative science
- Human subjects
- Research involving animals
- Environmental safety: radiation, chemicals, and microbial agents
- Research misconduct
- Conflict of interest
- Preparing grant proposals
- Research administration: financial and personnel management

“Each rubric includes Penn policies, lectures, guidelines, interactive quizzes, Federal policies, and hyperlinks to a few selected websites at other institutions. In the aggregate, these materials provide a systematic introduction to the fundamental issues underlying the Responsible Conduct of Research. Many Penn programs supplement these materials with small group discussions of the subjects listed above. Finally, each School or Department maintains a database that can be used to track all trainees and insure that each of them has completed an appropriate discipline-specific Responsible Conduct of Research instruction and certification program.”
Goals for Fellowship Training and Career

Beyond graduate school I plan to take a postdoctoral position at another university before pursuing a career in academia. One reason why I’m aspiring to work in academia is that I see it as an opportunity to encourage diversity and broaden the opportunities of persons with disabilities in science by serving as a role model for others that may be facing challenges and I would be in a position to teach them. Over the past few years of undergraduate and graduate school I have been a tutor for organic chemistry and calculus II, a teaching assistant for an undergraduate organic chemistry laboratory for two years, as well as a mentor for an REU student (research experience for undergraduates) from Puerto Rico. I enjoy working with and helping students learn. As an academic, not only would I have the opportunity to teach students from a classroom environment but also from a research standpoint, like the position I was in with the REU student. Due to the synthetic nature and possible health implications of the proposed research training, this will enable hands-on experience with a variety of chemical transformations and a broader background that would not necessarily be attained with methods-based or mechanistic research. I think a broader background is important for a career in academia as it enables you to personally relate your experiences and guide students with interests in different areas of chemistry, its interface with biology, and their role in improving public wellbeing.
Activities Planned Under This Award

All course work and teaching requirements of the chemistry PhD program at the University of Pennsylvania have been fulfilled during my first year of graduate study. Also, all cumulative examinations have been successfully completed. Therefore under this award, time will be allocated as follows:

Year one: 100% research
Year two: 100% research
Year three: 100% research
Research Experience

My research experience has covered a variety of disciplines in chemistry from crystal engineering and metal directed self-assembly as an undergraduate to organic synthesis as a graduate student at the University of Pennsylvania. These research experiences are included below in chronological order.

University of Virginia, Undergraduate Research 2006. In the summer of 2006 I participated in a Chemistry REU program (Research Experience for Undergraduates) at the University of Virginia. During my ten week tenure, I worked for Dr. Michal Sabat in his molecular structures laboratory where I investigated the crystal engineering of propargylic alcohols. Our goal was to form higher order supramolecular systems in the solid-state that are able to entrap gas or solvent molecules; specifically we were interested in trapping and storing hydrogen gas because more effective hydrogen gas storage would improve the practicality of using environmentally friendly hydrogen gas fueled vehicles; an outcome that would broadly benefit society. The chiral propargylic alcohol 1 has been shown to form cyclic $RSRSRS$ hexameric assemblies in the solid-state (Figure 1a). These assemblies are stabilized by a network of hydrogen bonds and $\pi-\pi$ stacking interactions and contain pores and channels that trap solvent molecules.\(^1\) My role in the project was to use crystallization and co-crystallization techniques to form novel highly ordered systems that could be tested for gas adsorption. All crystallization experiments were run independently, resulting in a few crystal structures. Collaboration with other researchers was necessary to obtain crystal structures and synthesize compounds.

Another aspect of my project focused on propargylic alcohols containing long alkyl side chains, such as 2 (Figure 1b). These derivatives may be used as gelators and may have applications in chiral discrimination, controlled flow of drugs, etc. For these compounds, I tried to grow single crystals for X-ray diffraction analysis and also used diffusion ordered NMR spectroscopy (DOSY-NMR) to measure diffusion rates for the study of aggregation in solution. Also, various properties, such as distance external to the surface ($d_e$; Figure 1c), shape index, and curvedness were plotted on a Hirshfeld surface.\(^2\) I learned to identify characteristic features of these plots and the two-dimensional fingerprint plots which are derived from the Hirshfeld surface.\(^2,3\)

Gettysburg College, Undergraduate Research 2006-2007. During my senior year at Gettysburg College I utilized a face-directed approach to metal-directed self-assembly of metalloccage coordination complexes. Specifically, I was interested in the formation of coordination complexes possessing a cubic architecture by using “naked” square-planar metals and carbazole based dipyridine ligands. Carbazole offers several advantages for use as a constructional subunit, as its photochemical behavior might confer unique properties onto the complex that could be studied and it serves as a platform for generating bidentate “corner” elements where any substituents attached to C3/C6 are oriented at a 90° angle. Ideally when the appropriate metal ion and ligand, possessing a rigid predefined geometry, are combined stoichiometrically the desired architecture will form. This requires metal-ligand bonds that are labile enough to allow for self-correction of “mistakes” as enthalpy and entropy drive the reaction forward. Ligands 6a and 6b were each synthesized via Suzuki coupling reactions (Scheme 1) and combined stoichiometrically with “naked” palladium(II) to form discrete coordination complexes in solution. These are likely cubic cages with metal ions occupying the faces and right-angle ligands spanning the edges of the cube (7).

---

**Scheme 1.**

- 1. R-X, NaOH
- 2. I₂ / KIO₃, HOAc

**N:**
- 1. \( \text{H} \)
- 2. \( \text{CH}_3\text{CH}_2\text{O} \)
- 3. \( \text{CH}_3 \)

**R:**
- a: \( R = \text{n-Bu} \) (91%, 2 steps)
- b: \( R = (\text{CH}_3\text{CH}_2\text{O})_2\text{CH}_3 \) (73%, 2 steps)

The reaction conditions for each step are as follows:

- **4a:** Reaction temperature: \( 100^\circ C \)
- **4b:** Reaction temperature: \( 100^\circ C \)
- **5:** Reaction temperature: \( 100^\circ C \)

---

**Figure 1.**

- a) Crystal structure of 1
- b) Crystal structure of 2
- c) Plot of \( d_e \) on the Hirshfeld surface

---

**Gettysburg College, Undergraduate Research 2006-2007.** During my senior year at Gettysburg College I utilized a face-directed approach to metal-directed self-assembly of metalloccage coordination complexes. Specifically, I was interested in the formation of coordination complexes possessing a cubic architecture by using “naked” square-planar metals and carbazole based dipyridine ligands. Carbazole offers several advantages for use as a constructional subunit, as its photochemical behavior might confer unique properties onto the complex that could be studied and it serves as a platform for generating bidentate “corner” elements where any substituents attached to C3/C6 are oriented at a 90° angle. Ideally when the appropriate metal ion and ligand, possessing a rigid predefined geometry, are combined stoichiometrically the desired architecture will form. This requires metal-ligand bonds that are labile enough to allow for self-correction of “mistakes” as enthalpy and entropy drive the reaction forward. Ligands 6a and 6b were each synthesized via Suzuki coupling reactions (Scheme 1) and combined stoichiometrically with “naked” palladium(II) to form discrete coordination complexes in solution. These are likely cubic cages with metal ions occupying the faces and right-angle ligands spanning the edges of the cube (7). Complex
formation was demonstrated in solution (DMSO-d$_6$) via $^1$H NMR. Evidence for complexation included the presence of a single species with high symmetry, as would be expected for the formation of cubic cages, downfield shifting of the $\alpha$-py and $\beta$-py protons ($\Delta\delta_{\alpha-py} = 0.75$ and $\Delta\delta_{\beta-py} = 0.50$), indicative of complexation with the metal ion, and moderately broad peaks suggesting that a large supramolecular complex had formed. The self-assembly of discrete two- and three-dimensional complexes, such as cage 7, is significant to host-guest chemistry and materials science. These complexes have applications in reaction catalysis, chiral resolution, molecular recognition and guest binding/encapsulation, which is beneficial as it may, for example, inspire development of new chemical sensors, switches, or gas storage materials.

**University of Pennsylvania, Graduate Research 2008-present.** At the University of Pennsylvania, I have been synthesizing axially chiral bisnaphthoquinones, which are potentially useful BINOL derivatives (8) for asymmetric catalysis with possible redox properties. The chiral bisnaphthoquinones are also versatile intermediates for accessing the bisanthraquinone natural products, such as those shown in Figure 2 (9-13). No stereoselective syntheses have been reported and an efficient synthesis of these biaryls would be beneficial as skyrin (9), for example, has been shown to suppress growth of tumor cell lines.

Much of the research thus far has been carried out on a simpler system, without substitution on C4 (Scheme 2). This simpler system serves as both a model for the bisanthraquinones 9-13, as well as the means for generating unique BINOL analogs. Working with racemic substrates initially, compound 15a can be synthesized in only three steps. Ideally, deprotection of the methyl ether groups followed by oxidation would produce the desired bisnaphthoquinone intermediate. While oxidation to the bis-para-quinone can be achieved in moderate yield (56%), the preceding deprotection of 15a was found to be inefficient. As such, a different C8 protecting group (benzyl group) was chosen. Enantioselective oxidative coupling of this new substrate with 19 is very promising, generating (S)-15b in 97% ee. With CuCl(OH)TMEDA, coupling to form racemic 15b also proceeded well (91% yield). Methylation of the C2 phenols, removal of the benzyl groups via hydrogenation and subsequent oxidation with salcmine formed the bis-para-naphthoquinone 16. A regioselective Diels-Alder reaction with diene 17 and subsequent oxidation produces bisanthraquinone 18.

![Scheme 2](image)

<table>
<thead>
<tr>
<th>Step</th>
<th>Reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>$\text{H}_2\text{SO}_4, \text{MeOH}, 99%$</td>
<td>14</td>
</tr>
<tr>
<td>2.</td>
<td>(15a) $\text{Me}_2\text{SO}_4, \text{K}_2\text{CO}_3, 70%$; (15b) $\text{Bn}, \text{K}_2\text{CO}_3, 73%$</td>
<td>15a/15b</td>
</tr>
<tr>
<td>3.</td>
<td>CuCl(OH)TMEDA, $\text{O}_2$, (15a) 87%; (15b) 91%</td>
<td>(S)-15b</td>
</tr>
</tbody>
</table>