

NIH F31 Fellowship Application Process and Review

Is Tramadol a Natural Product?

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Zakarian Group

UC Santa Barbara

October 2nd, 2014

Outline

- Overview of NIH Awards
- Getting Started
- Nuts and Bolts - Application Process
- Review Process
- Personal Example
- Additional Resources

The Different Award Types

- Research Announcements (R01)
 - Individual Investigators
- Research Training Announcements (T32)
 - Institutional Awards
- Career Development Announcements (K01)
 - New Independent Investigators
- Fellowship Announcements (F31, F32)
 - Individual Pre/Postdoctoral Awards

What is the F31?

- Ruth L. Kirschstein National Research Service Award for Individual Predoctoral Fellows
- US citizen or permanent resident
- Up to 5 yrs of funding
 - Stipend: \$22,476, FY 2014
 - Tuition: 60% (Maximum \$16,000)
 - F32 Stipend: \$42,000 (0 yrs experience)

The Actual Webpage

Fellowship (F) Announcements

Activity Code(s)	Title	Announcement Number	Issuing Organization	Release Date	Opening Date (SF424 Only) ?	Expiration Date
F30,	Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral MD/PhD or Other Dual-Doctoral Degree Fellowship (Parent F30)	PA-14-150	NIH	03/07/2014	03/08/2014	01/08/2017
F31,	Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship to Promote Diversity in Health-Related Research (Parent F31 - Diversity)	PA-14-148	NIH	03/07/2014	03/08/2014	01/08/2017
F31,	Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship (Parent F31)	PA-14-147	NIH	03/07/2014	03/08/2014	01/08/2017
F32,	Ruth L. Kirschstein National Research Service Award (NRSA) Individual Postdoctoral Fellowship (Parent F32)	PA-14-149	NIH	03/07/2014	03/08/2014	01/08/2017
F33,	Ruth L. Kirschstein National Research Service Awards (NRSA) for Individual Senior Fellowship (Parent F33)	PA-14-151	NIH	03/07/2014	03/08/2014	01/08/2017

http://grants.nih.gov/grants/guide/parent_announcements.htm

Choose Institute Wisely

Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	<p>National Cancer Institute (NCI) National Eye Institute (NEI) National Heart, Lung, and Blood Institute (NHLBI) National Human Genome Research Institute (NHGRI) National Institute on Aging (NIA) National Institute on Alcohol Abuse and Alcoholism (NIAAA) National Institute of Allergy and Infectious Diseases (NIAID) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) National Institute of Biomedical Imaging and Bioengineering (NIBIB) <i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development (NICHD) National Institute on Deafness and Other Communication Disorders (NIDCD) National Institute of Dental and Craniofacial Research (NIDCR) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) National Institute on Drug Abuse (NIDA) National Institute of Environmental Health Sciences (NIEHS) National Institute of General Medical Sciences (NIGMS) National Institute of Mental Health (NIMH) National Institute of Neurological Disorders and Stroke (NINDS) National Institute of Nursing Research (NINR) National Institute on Minority Health and Health Disparities (NIMHD) National Library of Medicine (NLM) National Center for Complementary and Alternative Medicine (NCCAM) Division of Program Coordination, Planning and Strategic Initiatives, Office of Research Infrastructure Programs (ORIP)</p> <p>Special Note: Because of the differences in individual Institute and Center (IC) program requirements for this FOA, prospective applicants are strongly encouraged to consult the Table of IC-Specific Information, Requirements and Staff Contacts, to make sure that their application is responsive to the requirements of one of the participating NIH ICs.</p>
Funding Opportunity Title	Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship (Parent F31)
Activity Code	F31 Predoctoral Individual National Research Service Grant Award

Exploring the Announcement

Announcement Type	Reissue of PA-11-111
Related Notices	<ul style="list-style-type: none"> • September 25, 2014 - See Notice NOT-OD-14-134. Notice to Emphasize the Requirement for Additional Educational Information under PA-14-147 "Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship (Parent F31)" • August 29, 2014- See Notice NOT-OD-14-129. eRA Commons Username Required for Sponsor in Individual Fellowship Grant Applications to NIH and AHRQ. • June 4, 2014 - Notice NOT-14-074 supersedes instructions in Section III.3 regarding applications that are essentially the same. • May 21, 2014 - Notice of Clarification Regarding the Additional Educational Information Required for PA-14-147. See Notice NOT-OD-14-094.
Funding Opportunity Announcement (FOA) Number	PA-14-147
Companion Funding Opportunity	None
Number of Applications	See Section III. 3. Additional Information on Eligibility .
Catalog of Federal Domestic Assistance (CFDA) Number(s)	93.351; 93.846; 93.866; 93.213; 93.307; 93.172; 93.273; 93.233; 93.839; 93.838; 93.837; 93.361; 93.859; 93.879; 93.867; 93.847; 93.121; 93.856; 93.855; 93.398; 93.286; 93.173; 93.865; 93.242; 93.113; 93.853; 93.279
Funding Opportunity Purpose	The purpose of the Kirschstein-NRSA predoctoral fellowship (F31) award is to enable promising predoctoral students to obtain individualized, mentored research training from outstanding faculty sponsors while conducting dissertation research in scientific health-related fields relevant to the missions of the participating NIH Institutes and Centers. The proposed mentored research training must reflect the applicant's dissertation research project and is expected to clearly enhance the individual's potential to develop into a productive, independent research scientist.

Key Dates

Posted Date	March 7, 2014
Open Date (Earliest Submission Date)	March 8, 2014
Letter of Intent Due Date(s)	Not Applicable
Application Due Date(s)	<p>Standard dates apply</p> <p>Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.</p>

<http://grants.nih.gov/grants/guide/pa-files/PA-14-147.html>

Due Dates Can Change!

R01 <i>new</i>	Research Grants	SF424 (R&R)	February 5	June 5	October 5
U01 <i>new</i>	Research Grants - Cooperative Agreements	SF424 (R&R)	February 5	June 5	October 5
K series <i>new</i>	Research Career Development	SF424 (R&R)	February 12	June 12	October 12
R03, R21, R33, R21/R33, R34, R36 <i>new</i>	Other Research Grants	SF424 (R&R)	February 16	June 16	October 16
R15 <i>All - new, renewal, resubmission, revision</i>	Academic Research Enhancement Award (AREA)	SF424 (R&R)	February 25	June 25	October 25
R01 <i>renewal, resubmission, revision</i>	Research Grants	SF424 (R&R)	March 5	July 5	November 5
U01 <i>renewal, resubmission, revision</i>	Research Grants - Cooperative Agreements	SF424 (R&R)	March 5	July 5	November 5
K series <i>renewal, resubmission, revision</i>	Research Career Development	SF424 (R&R)	March 12	July 12	November 12
R03, R21, R33, R21/R33, R34, R36 <i>renewal, resubmission, revision</i>	Other Research Grants	SF424 (R&R)	March 16	July 16	November 16
R41, R42 R43, R44, U43, U44, <i>All - new, renewal, resubmission, revision</i>	Small Business Technology Transfer (STTR) Small Business Innovation Research (SBIR)	SF424 (R&R)	April 5	August 5	December 5
F Series Fellowships <i>new, renewal, resubmission</i>	Individual National Research Service Awards (Standard) (see NRSA Training Page)	SF424 (R&R)	April 8	August 8	December 8
R13, U13 <i>All - new, renewal, resubmission, revision</i>	Conference Grants and Conference Cooperative Agreements	SF424 (R&R)	April 12	August 12	December 12
F31 Diversity Fellowships <i>new, renewal, resubmission</i>	Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research (see NRSA Training Page)	SF424 (R&R)	April 13	August 13	December 13

<http://grants.nih.gov/grants/funding/submissionschedule.htm>

READ EVERYTHING!

Required Application Instructions

It is critical that applicants follow the instructions in the [Individual Fellowship SF424 \(R&R\) Application Guide](#) except where instructed to do otherwise (in this FOA or in a Notice from the [NIH Guide for Grants and Contracts](#)). Conformance to all requirements (both in the Application Guide and the FOA) is required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in [Section IV](#). When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions. **Applications that do not comply with these instructions may be delayed or not accepted for review.**

Apply for Grant Electronically

A compatible version of [Adobe Reader](#) is required for download. For Assistance downloading this or any Grants.gov application package, please contact Grants.gov Customer Support at <http://www07.grants.gov/contactus/contactus.jsp>.

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Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

The overall goal of the NIH Ruth L. Kirschstein National Research Service Award (NRSA) program is to help ensure that a diverse pool of highly trained scientists is available in appropriate scientific disciplines to address the Nation's biomedical, behavioral, and clinical research needs. In order to accomplish this goal, NRSA training programs are designed to train individuals to conduct research and to prepare for research careers. More information about NRSA programs may be found at the [Ruth L. Kirschstein National Research Service Award \(NRSA\)](#) website.

<http://grants.nih.gov/grants/guide/pa-files/PA-14-147.html>

Starting the Process

- Start early! (~1.5 months)
- Discuss plan with your Sponsor
 - You are “PI”
- Contact department “Grants Analyst”
- UCSB - Libby McCollum
 - What Award?
 - FOA #?
 - Institute/Center?
 - Human/Animal Subjects?
- Create eRA Commons/Cayuse Accounts



Contract & Grant Analyst

READ Application Guide

- Seriously
 - Read this carefully
 - It's only ~100 pgs



U.S. Department of Health and Human Services
Public Health Service

SF424 (R&R) Individual Fellowship Application Guide for NIH and AHRQ

A guide developed and maintained by NIH for preparing
and submitting individual fellowship applications via
Grants.gov to NIH and AHRQ using the SF424 (R&R)

Forms Version C application packages

Updated December 20, 2013

Look at Previous Applications

Predocctoral F31 Sample Applications

Predocctoral F31 fellowships are designed to enhance research and career development for advanced Ph.D. students who have identified a research sponsor and a dissertation project that includes a novel approach to the problem and has strong training potential. Several investigators have agreed to let us share their successful applications. We are grateful to the fellows, their research sponsors and the institutions listed below who have enabled us to deliver this resource to the training community. For more information on F31 fellowships, see the [F31 program announcement](#) and the [FAQs](#), or contact fellowship coordinator Ms. Peggy Schnoor.

Please Note: The text of the applications is copyrighted. You may use it only for nonprofit educational purposes provided the documents remain unchanged and the investigator and grantee organization are credited. Some parts of the applications are redacted to protect personal and other private information, such as commercial interests and pending publications or funding, as well as the confidentiality of recommendations.

Accessibility: NIGMS is committed to providing resources that are accessible to people of all abilities. Because some of these applications were generated in paper format that was then scanned, persons using assistive technology may not be able to fully access all of the contents of each document posted on this page. Users who need assistance with noncompliant files may request help from [fellowship coordinator Ms. Peggy Schnoor](#) during regular business hours. She can assist users by reading, describing or summarizing the document content.

PI and Grantee Institution	Application
Christian Anthony Ibarra, University of California, Berkeley "The regulation of gene imprinting by genome-wide DNA methylation in Arabidopsis" Research Sponsors: Robert Fischer, Ph.D., and Daniel Zilberman, Ph.D.	Full application [PDF, 7.29 MB]
Angela C. Olson, University of California, Irvine "Catalytic asymmetric synthesis of vinyl chromans using palladium (II) catalysts" Research Sponsor: Larry E. Overman, Ph.D.	Full application [PDF, 1.38 MB]
Erin Eileen Podlesny, University of Pennsylvania "Synthesis of bisanthraquinone natural product and BINOL-type chiral ligands" Research Sponsor: Marisa C. Kozlowski, Ph.D.	Full application [PDF, 3.5 MB]
Emigdio D. Reyes Rodriguez, New Mexico State University "Biochemical characteristics of the RecN Protein in DNA repair mechanisms" Research Sponsors: Shelley L. Lusetti, Ph.D., and Jeffrey B. Arterburn, Ph.D.	Full application [PDF, 1.71 MB]

<http://www.nigms.nih.gov/training/indivpredoc/pages/predocctoral-f31-sample-applications.aspx>

Get Your LOR Lined Up

- Ask ~1 month in advance
- Provide due date (April 2nd), FOA #, your eRA Commons ID, CV, summary of research, etc. Anything to help them
 - Remind them!
- LORs are submitted electronically through grants.nih.gov. See section 5.4 of guide
 - Must be submitted *BEFORE* application receipt date
- 3-5 LORs – NOT your sponsor

Components of Application

- | | |
|-----------------------|-------------------------------|
| 1. Cover Letter | 11. Repective Contributions |
| 2. Project Summary | 12. Selection of Sponsor |
| 3. Project Narrative | 13. Responsible COR |
| 4. Bibliography | 14. Training and Career Goals |
| 5. Facilities | |
| 6. Equipment | 15. Activities Planned |
| 7. BioSketch | 16. Research Experience |
| 8. Specific Aims | 17. Sponsor Information |
| 9. Research Strategy | 18. Additional Education |
| 10. *Resource Sharing | |

0. Project Title

- 81 characters
 - Including spaces and punctuation

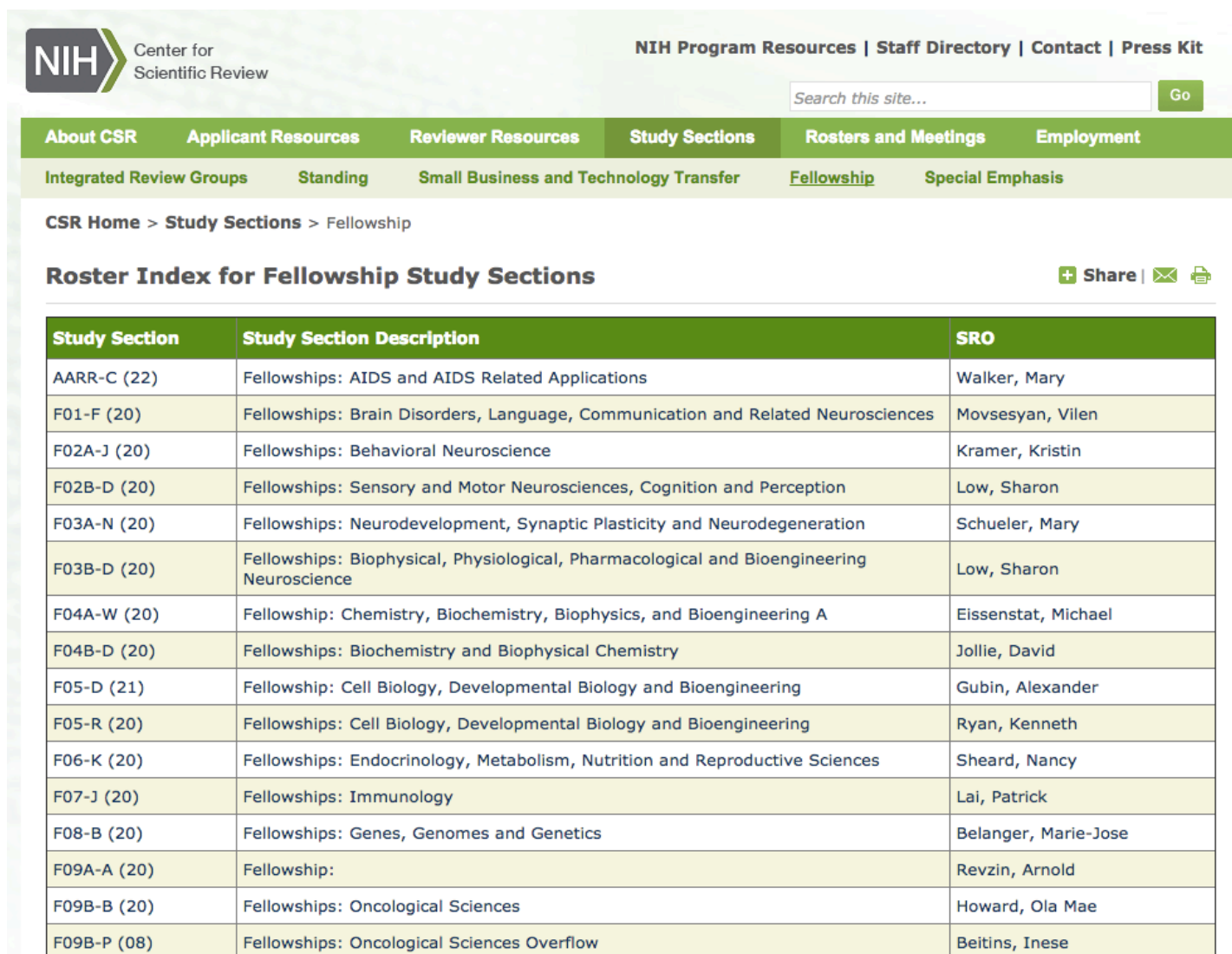
- Example

Chiral Lithium Amides: New Asymmetric Alkylation Chemistry and Application in the Enantioselective Total Synthesis of Bioactive Marine Alkaloid Dragmacidin D

1. Cover Letter

- Section 4.2 #21
- 1 page
- Application Title
- Funding Opportunity
- Institution/Center and Scientific Review Group assignment (these are based on research proposal)
- Individuals who should not review
- List of Referees
 - Name, Title, Affiliation, Contact info

Scientific Review Groups



NIH Center for Scientific Review

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CSR Home > Study Sections > Fellowship

Roster Index for Fellowship Study Sections

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Study Section	Study Section Description	SRO
AARR-C (22)	Fellowships: AIDS and AIDS Related Applications	Walker, Mary
F01-F (20)	Fellowships: Brain Disorders, Language, Communication and Related Neurosciences	Movsesyan, Vilen
F02A-J (20)	Fellowships: Behavioral Neuroscience	Kramer, Kristin
F02B-D (20)	Fellowships: Sensory and Motor Neurosciences, Cognition and Perception	Low, Sharon
F03A-N (20)	Fellowships: Neurodevelopment, Synaptic Plasticity and Neurodegeneration	Schueler, Mary
F03B-D (20)	Fellowships: Biophysical, Physiological, Pharmacological and Bioengineering Neuroscience	Low, Sharon
F04A-W (20)	Fellowship: Chemistry, Biochemistry, Biophysics, and Bioengineering A	Eissenstat, Michael
F04B-D (20)	Fellowships: Biochemistry and Biophysical Chemistry	Jollie, David
F05-D (21)	Fellowship: Cell Biology, Developmental Biology and Bioengineering	Gubin, Alexander
F05-R (20)	Fellowships: Cell Biology, Developmental Biology and Bioengineering	Ryan, Kenneth
F06-K (20)	Fellowships: Endocrinology, Metabolism, Nutrition and Reproductive Sciences	Sheard, Nancy
F07-J (20)	Fellowships: Immunology	Lai, Patrick
F08-B (20)	Fellowships: Genes, Genomes and Genetics	Belanger, Marie-Jose
F09A-A (20)	Fellowship:	Revzin, Arnold
F09B-B (20)	Fellowships: Oncological Sciences	Howard, Ola Mae
F09B-P (08)	Fellowships: Oncological Sciences Overflow	Beitins, Inese

<http://public.csr.nih.gov/StudySections/Fellowship/Pages/default.aspx>

2. Project Summary/Abstract

- Section 4.4 #7
- <30 lines of text
- Succinct and accurate description of objective and methods
- Suitable for dissemination to public
 - Make it understandable to non-chemistry scientists

3. Project Narrative

- Section 4.4 #8
- 2-3 sentences
- Describe *relevance* of this research to *public health*
- Be succinct and use language understood by a **general** audience

4. Bibliography

- Section 4.4 #9
 - No page limit
 - ACS Formatting
 - Must include names of ALL AUTHORS and ARTICLE TITLE

 - Example
5. Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs over the Last 25 Years. *J. Nat. Prod.* **2007**, *70*, 461-477.

5. Facilities & Other Resources

- Section 4.4 #10
- No page limit (1 page)
- Describe the facilities to be used (laboratory, computer access, office space, machine/electronic shops, etc)

6. Equipment

- Section 4.4 #11
- No page limit (1 page)
- List major items of equipment available for the project
- Identify location and capabilities
- HPLC, NMR, MS, etc

7. Biographical Sketch

- Section 4.5
- 4 pages
- Specific form available from NIH website
 - Personal Statement
 - Positions and Honors
 - Publications
 - Scholastic Performance (include GRE scores)
- You will also need Sponsor BioSketch

<http://grants.nih.gov/grants/funding/424/applicant-fellowbiosketch.docx>

<http://grants.nih.gov/grants/funding/424/applicant-fellowbiosketchsample.docx>

8. Specific Aims

- Section 5.5 #2
- 1 page
- 2-3 concisely stated (list) goals of proposed research
 - Summarize outcomes including impact
 - They should not be dependent on each other
 - If 1 fails the other(s) should still be achievable

9. Research Strategy

- Section 5.5 #3
- 6 pages
- Discuss Significance/Innovation/Approach for each specific aim
- Preliminary results are VERY helpful
- Discuss potential problems/solutions
- Label all structures and keep formatting *clear and organized!*
- Many online resources for writing research proposals

*10. Resource Sharing Plan

- Section 5.3 B.14
- 1 brief paragraph
- Separate document not required if requesting <\$500,000
 - Address briefly in Research Strategy
- How will work be disseminated with scientific community?

11. Respective Contributions

- Section 5.3 B.15
- 1 page
- Describe the collaborative process between you and sponsor involving the training plan
- Discuss roles in accomplishing research

12. Selection of Sponsor and Institution

- Section 5.3 B.16
- 1 page
- Describe rationale/justification for selection of sponsor and institution.
- Explain why sponsor is qualified to help accomplish research training goals.

13. Responsible Conduct of Research

- Section 5.3 B.17 (for more info see ref. site)
- 1 page
- Detailed requirements but straightforward
 1. Format
 - F2F lecture, coursework, discussion groups
 - Online-only lecture not sufficient
 2. Subject Matter
 - Conflict of interest, misconduct, ethics, etc.

<http://grants.nih.gov/grants/funding/424/>

SupplementalInstructions.pdf#1_16_policy_on_instruction_in_the

13. Responsible Conduct of Research (cont)

3. Faculty Participation

- Mentor (sponsor) involvement is important

4. Duration of Instruction

- Total number of contact hours of instruction

5. Frequency

- Must occur at least once every 4 years
- Describe applicant's plans to obtain instruction
- Describe institution's plans to provide instruction
- Don't let them dock you on this!

14. Training and Career Goals

- Section 5.3 C.7
- 1 page
- Describe overall career goals
 - How will proposed research enable these goals?
 - Identify individual skills, theories, concepts, etc.

15. Activities Planned Under Award

- Section 5.3 C.8
- 1 page
- Describe by year activities you will be involved in during award duration
 - Research, coursework, professional development
 - Do not put 100% research!
 - Relate activities to proposal

15. Activities Planned Under Award

Activities Planned Under This Award

The majority of activities planned under this award will be devoted to synthetic organic chemistry related lab research. During the second and third years of this award, I plan to attend various conferences and symposia so that I may share my findings with the scientific community, in addition to writing scientific papers for publication in high impact chemistry journals. I also plan to devote 5% of my time per year to my development through attending other scientist's seminars and presentations, including research ethics seminars. Throughout my graduate career, I have made an effort to mentor and train younger coworkers and scientists. I will contribute 5% of my time per year to this mentorship training.

Year	Research	Data Sharing	Development	Mentoring
First	90%	-	5%	5%
Second	85%	5%	5%	5%
Third	85%	5%	5%	5%

16. Dissertation and Research Experience

- Section 5.3 C.9
- 2 pages
- Summarize research in chronological order
- If advanced to candidacy, must include narrative of dissertation
- Keep structures and formatting *clear and organized!*

17. Sponsor Information

- Section 5.3 D
- 6 pages
- Completed by/with Sponsor/Co-Sponsor
- Create heading: Section II--Sponsor and Co-Sponsor Information.
- Complete following items as comprehensively as possible
 1. Research Support Available
 - List all current and pending research support

17. Sponsor Information

2. Previous Fellows/Trainees

- Total all and list 5 previously sponsored individuals and current positions

3. Training Plan, Environment, and Research Facilities

- Describe research training plan developed specifically for applicant

4. Number of Fellows/Trainees to be Supervised During the Fellowship

- Indicate pre- or postdoctoral

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

- Describe how suited applicant is for this research training opportunity (sponsor LOR)

18. Additional Education Info

- Special Requirement for F31 as of Sept. 25, 2014
- Section IV.2 – SF424 (R&R) Other Project Information Component
- Describe Graduate Program applicant is enrolled
 - Structure, milestones and timings, average time to degree, etc

<http://grants.nih.gov/grants/guide/pa-files/PA-14-147.html>

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-134.html>

Misc Advice

- Prepare to submit your application 2 weeks in advance of hard deadline (March 25th for Cycle I, April 8th)
 - Must go through University “approval process”
 - Check for required documents, etc
 - You may continue editing and re-uploading pdfs as they check it.
- You will get one last look before University submits application (~April 2nd)
- Make sure your LORs are submitted!
- Check for spelling/grammar errors!

Scoring System and Process

- Assigned 3 reviewers from assigned SRG
- Provide scores (1-9) for each of 5 criteria
- Criterion scores influence impact scores (1-9)
- Impact scores are averaged and multiplied by 10 to give overall score (10-90)
- Assigned percentile (lower = better)

Overall Impact or Criterion Strength	Score	Descriptor
High	1	Exceptional
	2	Outstanding
	3	Excellent
Medium	4	Very Good
	5	Good
	6	Satisfactory
Low	7	Fair
	8	Marginal
	9	Poor

Review Criteria

- Fellowship Applicant
 - Academic and research record
 - Development potential
- Sponsors, Collaborators, and Consultants
 - Track record
 - Matching research interests?
 - Adequate research funds?

Review Criteria

- Research Training Plan
 - High scientific quality
 - Time-frame feasible
 - Is project sufficiently distinct
- Training Potential
 - Potential to provide mentored developmental experiences
 - Will it facilitate the applicants transition to next career stage

Review Criteria

- Institutional Environment & Commitment to Training
 - Are resources adequate and appropriate



Personal Example

PROGRAM CONTACT: **SUMMARY STATEMENT** **Release Date: 07/15/2014**
Oleg Barski
301-435-9291
oleg.barski@nih.gov
(Privileged Communication)

Application Number: 1 F31 GM113302-01
Jackson, Jeffrey James
The Regents of the University of California, Santa
MC9510
Santa Barbara, CA 93106-2050

Review Group: ZRG1 F04A-W (20)
Center for Scientific Review Special Emphasis Panel
Fellowships: Synthetic and Biological Chemistry
Meeting Date: 07/08/2014
Council: OCT 2014 **PCC: T132OB**
Requested Start:

Project Title: Chiral Lithium Amides: New Asymmetric Alkylation Chemistry and Application in the Enantioselective Total Synthesis of Bioactive Marine Alkaloid Dragmacidin D
Requested: 3 years
Sponsor: Zakarian, Armen S
Department: Chemistry and Biochemistry
Organization: UNIVERSITY OF CALIFORNIA SANTA BARBARA
City, State: SANTA BARBARA CALIFORNIA
SRG Action: Impact Score: 45 Percentile: 36
Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm
Human Subjects: 10-No human subjects involved
Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Personal Example

Training in the Responsible Conduct of Research **UNACCEPTABLE**

RESUME AND SUMMARY OF DISCUSSION: The applicant proposes using chiral lithium amides for the asymmetric total synthesis of the marine natural product dragmacidin D. This excellent applicant shows an upward trend in his grades, but his GRE scores are modest. He has won teaching awards and already has a first-author publication from his graduate work. The well-funded sponsor has a good publication record, but a limited mentoring history. The choice of collaborator is a plus. The research plan has significant preliminary data and the synthetic methodology is important. Weaknesses are that the synthesis of the target has been reported previously and there was insufficient justification provided for the proposed synthesis. While the combination of synthetic methodology and total synthesis will provide the applicant with good training, he does not describe in much detail how he will take advantage of opportunities for professional development. The various weaknesses led to a substantial reduction in enthusiasm for this good application.

Fellowship Applicant

CRITIQUE 1:

Fellowship Applicant: 3

Sponsors, Collaborators, and Consultants: 3

Research Training Plan: 5

Training Potential: 2

1. Fellowship Applicant:

Strengths

Mostly A/B's (22/14) as an undergraduate but nearly all A's in graduate school. (moderate)

Two publications so far in graduate school – one as first author in JOC. (moderate)

PI has made a number of presentations at ACS meetings. (moderate)

Letters of recommendation are generally strong with about equal numbers of 1's and 2's – placing the applicant in the upper 20%. (minor)

Weaknesses

GRE scores are in the middle of the pack range (Q = 710/61%ile; V = 520/62%ile; Chem = 770/68%ile). (moderate)

Couple of C's, including a chemistry class. (minor)

Research Training Plan

CRITIQUE 1:

Fellowship Applicant: 3

Sponsors, Collaborators, and Consultants: 3

Research Training Plan: 5

Training Potential: 2

3. Research Training Plan:

Strengths

The applicant will be exposed to both methodology development and complex molecule synthesis; this will provide excellent training in synthetic organic chemistry. (major)

Reasonable and convergent strategy outlined for development of an asymmetric synthesis of dragmacidin D using a reagent controlled asymmetric alkylation. (moderate)

Key preliminary results in hand, including asymmetric alkylation (80% ee) and Larock indolization. (major)

Weaknesses

While the proposed synthesis is reasonable and provides a platform for showcasing the sponsor's chemistry, the target has been prepared previously, albeit in racemic form. (moderate)

The PI appears to be unaware that Movassaghi and coworkers have reported very similar chemistry for the construction of 2-aminoimidazoles from thioesters – *JOC* 2013, 78, 11970. (moderate)

The model for explaining the erosion of the enantioselectivity for 2-phenylbutanoic acid seems confusing – the figure shows monosubstituted enolates, when the substrate is disubstituted. There does not appear to be a change in the conformation of a piperidine ring and the numbers in the text are confusing. (minor)

Details are lacking on the preparation of the chiral "diamines". (minor)

Training Potential

CRITIQUE 3:

Fellowship Applicant: 3

Sponsors, Collaborators, and Consultants: 4

Research Training Plan: 6

Training Potential: 4

Institutional Environment & Commitment to Training: 4

4. Training Potential:

Strengths

The applicant has described useful training in terms of coursework, presentations, mentoring, and other components that will be buttressed within his department and research group. (moderate)

The proposed research will train the candidate in reaction development and multi-step synthesis at the forefront of modern synthetic prowess, rendering him capable of addressing in the future any area of study where the synthesis of small molecules can be empowering. (moderate)

Weaknesses

Discussion of possible outreach and other educational activities outside of standard scientific presentations would have given a stronger impression of the impact that an F31 award could have on the applicant. Funding to allow the student to be a full-time research assistant instead of being supported in part as a teaching fellow is a non-convincing argument for support, though clearly it will help in the progression of the chemistry described. (moderate)

Institutional Environment & Commitment to Training

CRITIQUE 2:

Fellowship Applicant: 3

Sponsors, Collaborators, and Consultants: 4

Research Training Plan: 3

Training Potential: 3

Institutional Environment & Commitment to Training: 5

5. Institutional Environment & Commitment to Training:

Strengths

UCSB Chemistry is a good department for synthetic organic chemistry. (Minor)

The NMR and mass spectral facilities are outstanding for the support of these projects. (Moderate)

There are six organic groups at UCSB, and an interactive atmosphere. (Moderate)

Weaknesses

None noted.

Additional Resources

- How to Win an NIH/Kirschstein/F30-F31 Predoctoral Fellowship – James M. Slauch
 - <http://www.grad.illinois.edu/sites/default/files/pdfs/slauchjim-nih-nrsaworkshop2012.pdf>
- NIH Ruth L. Kirschstein NRSA for Individual Predoctoral Fellows Cheat Sheet – mailman.columbia.edu
 - <http://www.mailman.columbia.edu/sites/default/files/NIH%20NRSA%20F31%20Cheat%20Sheet.pdf>

Additional Resources

- **Tips on Writing NRSA Predoctoral Fellowship Proposals From Real NRSA Reviewers – Greg J. Siegle**
 - http://www.pitt.edu/~gsiegle/Siegle-f31hints-BehaviorTherapist10_fordistrib.pdf
- **NIH Funding for Doctoral Students – Mary Rogers Gillmore**
 - <http://sirc.asu.edu/research/retc/research-application-tips-2>

Some Funding Rates

Office of Extramural Research (OER) /Office of Planning, Analysis and Communications (OPAC)/ Division of Statistical Analysis & Reporting (DSAR)

OERStats@mail.nih.gov / www.report.nih.gov

Table #203
NIH FELLOWSHIPS (F)¹
 Competing Applications, Awards, Success Rates and Total Funding
 by Activity Code and NIH Institutes/Centers

2013	F31	NCI	372	118	31.7%	\$4,268,106
2013	F31	NEI	14	2	14.3%	\$85,138
2013	F31	NHLBI	42	16	38.1%	\$562,188
2013	F31	NIA	141	28	19.9%	\$1,050,811
2013	F31	NIAAA	58	23	39.7%	\$812,908
2013	F31	NIAID	56	18	32.1%	\$653,425
2013	F31	NIAMS	15	7	46.7%	\$255,170
2013	F31	NIBIB	13	0	0.0%	\$0
2013	F31	NICHD	40	7	17.5%	\$259,921
2013	F31	NIDA	133	40	30.1%	\$1,418,160
2013	F31	NIDCD	67	24	35.8%	\$832,723
2013	F31	NIDCR	44	24	54.5%	\$872,710
2013	F31	NIDDK	29	9	31.0%	\$312,742
2013	F31	NIEHS	12	2	16.7%	\$75,210
2013	F31	NIGMS	97	26	26.8%	\$913,427
2013	F31	NIGMS	97	26	26.8%	\$913,427
2013	F31	NIMH	250	57	22.8%	\$2,027,007
2013	F31	NINDS	355	105	29.6%	\$3,719,318
2013	F31	NINR	65	29	44.6%	\$1,073,064
2013	F31	Total	1,807	536	29.7%	\$19,235,260

Some Funding Rates

Office of Extramural Research (OER) / Office of Planning, Analysis and Communications (OPAC) / Division of Statistical Analysis & Reporting (DSAR)

OERStats@mail.nih.gov / www.report.nih.gov

Table #203
NIH FELLOWSHIPS (F)¹
 Competing Applications, Awards, Success Rates and Total Funding
 by Activity Code and NIH Institutes/Centers
 Made with Direct Budget Authority Funds

2013	F32	NCI	265	50	18.9%	\$2,516,840
2013	F32	NEI	93	19	20.4%	\$996,156
2013	F32	NHGRI	4	1	25.0%	\$49,214
2013	F32	NHLBI	209	59	28.2%	\$3,206,739
2013	F32	NIA	58	10	17.2%	\$517,996
2013	F32	NIAAA	27	13	48.1%	\$655,037
2013	F32	NIAID	246	50	20.3%	\$2,587,224
2013	F32	NIAMS	71	19	26.8%	\$1,043,875
2013	F32	NIBIB	45	4	8.9%	\$210,552
2013	F32	NICHD	128	22	17.2%	\$1,073,520
2013	F32	NIDA	57	21	36.8%	\$1,100,494
2013	F32	NIDCD	46	22	47.8%	\$1,130,474
2013	F32	NIDCR	18	8	44.4%	\$440,292
2013	F32	NIDDK	176	49	27.8%	\$2,627,518
2013	F32	NIEHS	28	6	21.4%	\$354,330
2013	F32	NIGMS	473	117	24.7%	\$5,875,926
2013	F32	NIMH	138	24	17.4%	\$1,243,804
2013	F32	NINDS	205	56	27.3%	\$2,885,673
2013	F32	NINR	3	3	100.0%	\$153,342
2013	F32	†OD Other	0	0	NA	\$37,968
2013	F32	Total	2,297	555	24.2%	\$28,842,034

Writing Tips

- Utilize opportunity to learn and grow
- Get feedback from peers/sponsor/anyone
- Use clear language
 - Avoid jargon
- Create interest and build enthusiasm
- Wrap up in nice “package”
 - Use headings and sub-headings

Final Thoughts

- Keep trying!
 - Majority of applications are funded after resubmission
- For the love of god and all that is holy!
 - CHECK YOUR SPELLING/GRAMMAR
 - CHECK YOUR STRUCTURES
 - CHECK DOCUMENT MARGINS AND PAGE LIMITS
- Make your application as easy to read for the reviewer as possible

Comparing Scores

CRITIQUE 1:

Fellowship Applicant: 3

Sponsors, Collaborators, and Consultants: 3

Research Training Plan: 5

Training Potential: 2

Institutional Environment & Commitment to Training: 2

CRITIQUE 2:

Fellowship Applicant: 3

Sponsors, Collaborators, and Consultants: 4

Research Training Plan: 3

Training Potential: 3

Institutional Environment & Commitment to Training: 5

CRITIQUE 3:

Fellowship Applicant: 3

Sponsors, Collaborators, and Consultants: 4

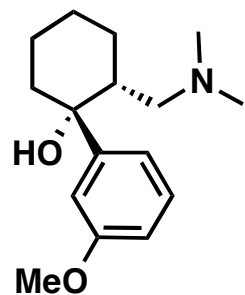
Research Training Plan: 6

Training Potential: 4

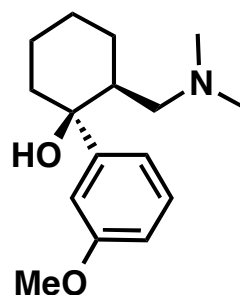
Institutional Environment & Commitment to Training: 4

Tramadol (Ultram)

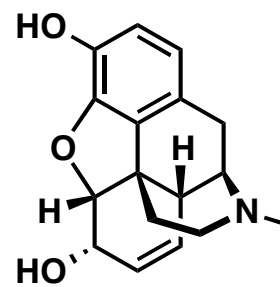
- Schedule IV controlled substance (US)
- Worldwide use to treat moderate to severe pain
 - Weakly binds to μ -opioid receptors (morphine)
 - Serotonin and norepinephrine reuptake inhibitor (SNRI)



(1*R*,2*R*)-tramadol



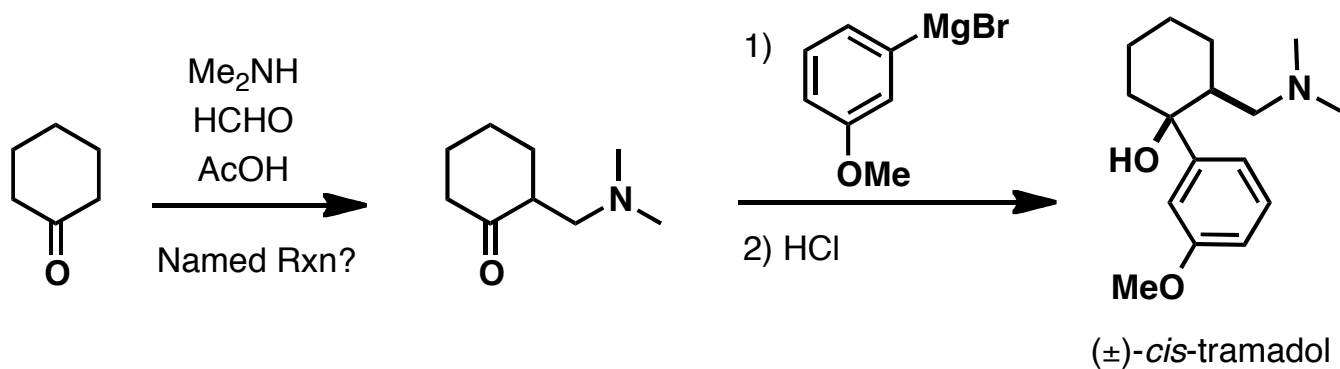
(1*S*,2*S*)-tramadol



Morphine

Synthesis?

- 175 kg scale



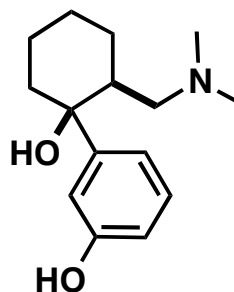
Schickaneder, H.; Nikolopolus, A. Tamadol, salts thereof and process for their preparation. U.S. Patent 6,469,213 B1, Oct. 22, 2002.

Discovery

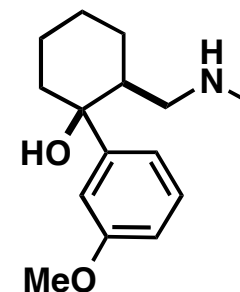
- Manufacture by Grünenthal GmbH (Germany)
 - Clinical usage – 1970's
 - Widespread use – 1990's
- 1/10th potency of morphine
 - Equally potent compared to codeine
- Minor side-effects
 - Dizziness, nausea, headache, etc
- Evidence of adverse effects from abuse
 - Seizures, organ dysfunction, death

Metabolites more active!

- Hepatic metabolism via cytochrome P450
 - CYP2B6, CYP2D6, CYP3A4
- *O*-desmethyltramadol
 - <200x binding affinity to μ -opioid receptors
 - High-affinity for δ - and κ -opioid receptors
 - Agonists of δ - known to induce seizures
- *N*-desmethyltramadol



O-desmethyltramadol



N-desmethyltramadol

Cytochrome P450 Enzymes

- Superfamily of proteins which perform enzymatic reactions on a variety of substrates
 - Drug metabolism and MUCH MORE
 - Very important in drug discovery/ pharmacokinetics
- CYP2D6 deficient in 6-10% Caucasians and 1-2% Asians
 - 30% tramadol dose increase required

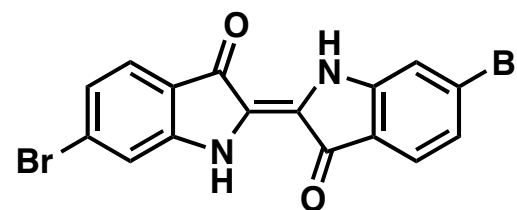
Tramadol in African Medicinal Plant

- Isolated from methanolic extract of root bark of *N. latifolia* in North Cameroon (2013, M.D. Waard)
- Later revealed anthropogenic contamination with synthetic material (2014, M. Spiteller, ACIE VIP)



Not the First Time!

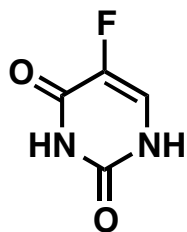
- Tyrian Purple
 - Ancient dye isolated from sea mollusks
 - Main component: dibromoindigo



dibromoindigo

Not the Second Time!

- Fluorouracil
 - Synthesized in 1957
 - Used to treat cancer
- Isolated from marine sponge *Phakellia fusca* (2003)

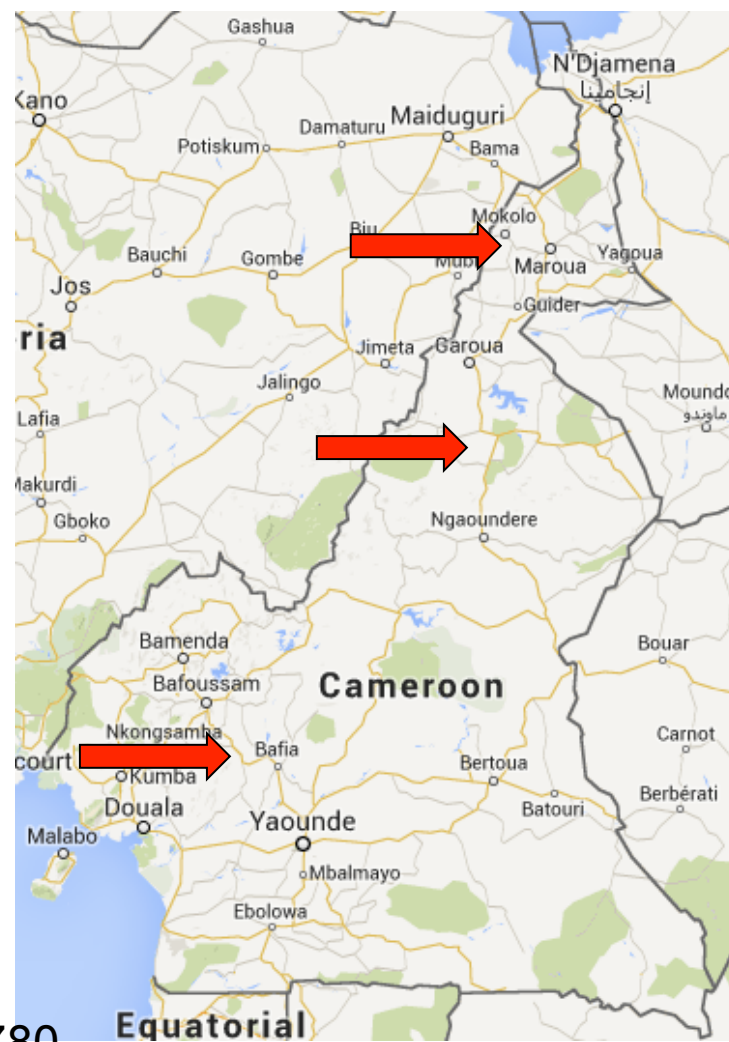


fluorouracil



Cameroonian Vacation

- Waard (2013)
 - National Park of Benoué (North)
- Spitteller (2014)
 - NW Maroua (North)
 - Bafia (South)

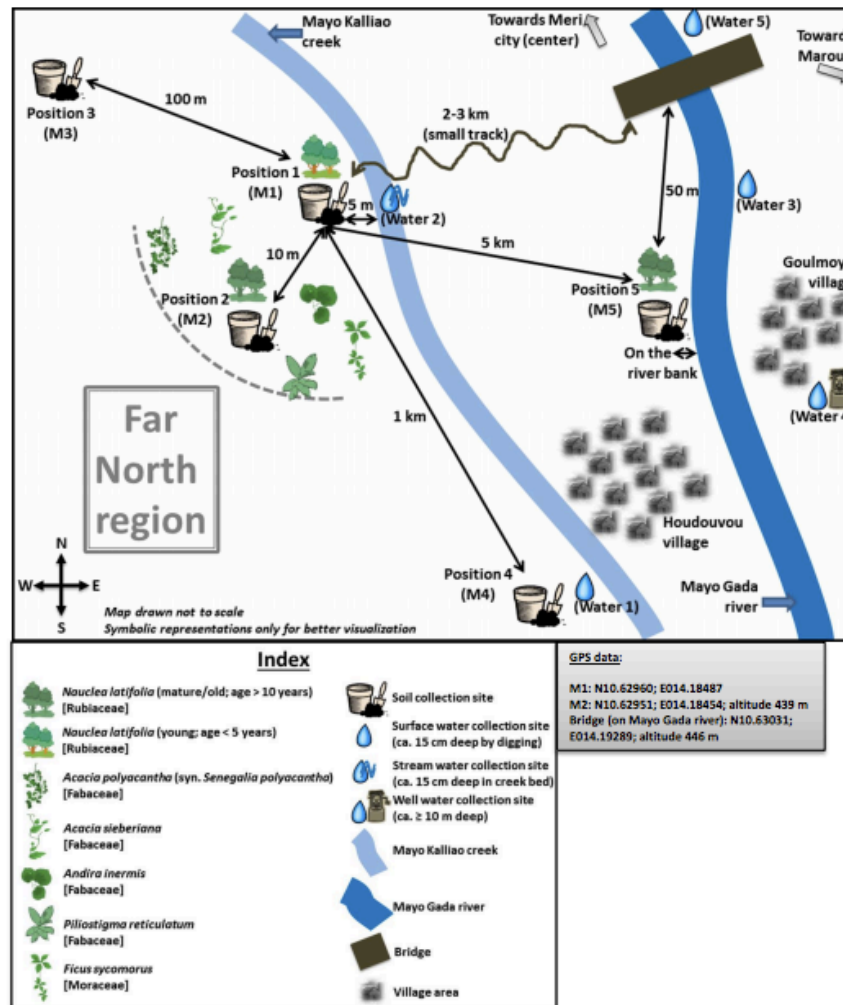


Waard, M.D. *Angew. Chem. Int. Ed.* **2013**, 52, 11780.

Spitteller, M. *Angew. Chem. Int. Ed.* **2014**, 53, ASAP.

X Marks the Spot!

Figure S1. Schematic map showing the exact bioprospecting (sampling) sites for collection of plants, soil, and water samples (see also Tables S1-S3).



Discrepancies Between Publications

- Chemical identity clearly confirmed
 - Analgesic properties*
 - HRMS, NMR, X-Ray
- Isolated racemic mixture
 - Rare but present in literature
- Isotope ratio analysis
 - $\delta^{15}\text{N}/^{14}\text{N}$ and $\delta^{13}\text{C}/^{12}\text{C}$

Identifying Analgesic Activity

- AcOH-induced abdominal constriction test
- Formalin-induced nociception (nervous system response to harmful stimuli)
- Hotplate test
- Tail-flick test
- Glutamate-induce nociception

The tail-flick test was carried out according to the method described by D'Amour and Smith ^[6]. This involved immersing the extreme 3 cm of the tail of each mouse in a water bath containing water at a temperature of $55 \pm 0.5^\circ\text{C}$. Within a few second, the mice reacted by withdrawing the tail. The reaction time was recorded with a stopwatch. The mice were treated with purified tramadol isolated

Isotope Ratio Analysis

- $\delta^{13}\text{C}/^{12}\text{C}$ negligible
- Large range of values for commercial $\delta^{15}\text{N}/^{14}\text{N}$ but not for natural
 - *Therefore; not-likely synthetic source

Table 1: Isotope ratios $^{15}\text{N}/^{14}\text{N}$ and $^{13}\text{C}/^{12}\text{C}$ in extracts of natural tramadol and in samples of commercial tramadol.

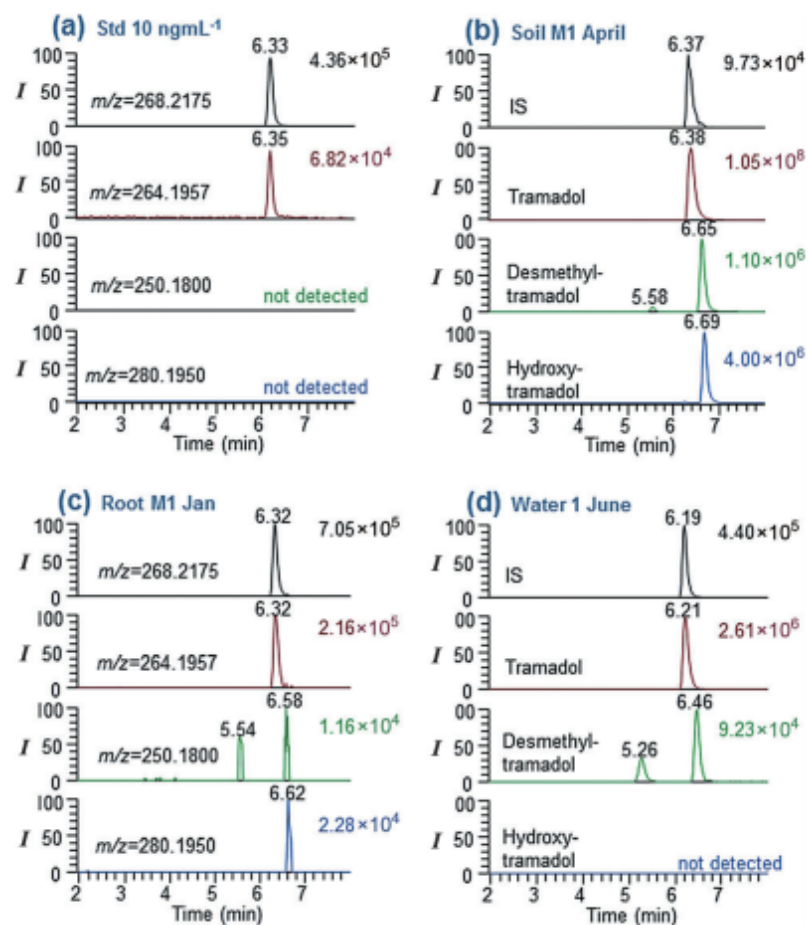
Sample	$\delta^{15}\text{N}$ [ppt]	Range	$\delta^{13}\text{C}$ [ppt]	Range
commercial 1-1	-2.61	0.05	-29.97	0.15
commercial 1-2	-9.24	0.84	-29.73	0.20
commercial 1-3	5.68	0.30	-29.61	0.12
commercial 2-1	-1.79	0.10	-31.97	0.10
natural 1	-3.22	0.45	-32.68	0.10
natural 2	-3.13	0.23	-31.98	0.04

More Inconsistencies

- Tramadol detected in much lower concentrations
 - 0.0000017% (w/w) vs 0.4% (w/w)
- Tramadol not detectable from samples collected from Bafia (South Cameroon)
- Also found in root inner core, soil, and water samples

It's in the SOIL and WATER?!

Figure 1. Selected mass traces (< 2 ppm) of the internal standard [¹³C-D₃]tramadol, tramadol, *O*-desmethyltramadol (*R*_t = 5.5 min), *N*-desmethyltramadol (*R*_t = 6.6 min), as well as 4-hydroxycyclohexyltramadol. a) Reference compound tramadol, b) extract of soil (Soil M1 April), c) extract of *N. latifolia* root (Root M1 Jan), and d) surface water sample (Water 1 June).



What about Endophytes/Fungi?

- Spitteller independently isolated and fermented in suitable media
- No detectable tramadol was extracted from endophytic bacteria or fungi

Insightful Interviews

- Extensive off-label use of synthetic tramadol in northern Cameroon
- Human and animal consumption
 - Used so draft animals don't get tired
- Administered to horses prior to races
- Tramadol use not known in southern Cameroon

Threat to Human Health?

- Synthetic tramadol contamination found in
 - Soil
 - Surface, stream, and well water
 - Other plant species
- “Immediate measures should be taken to restrict the off-label use of tramadol in Northern Cameroon.”

C&EN Report

TRAMADOL DRAMA

HUMAN-CAUSED CONTAMINATION may explain
2013 report of narcotic in a medicinal plant

CARMEN DRAHL, C&EN WASHINGTON

- Neither side 100% convincing
- Future plant feeding studies
 - Use isotope labeled compounds