

15:51:08

OCA PAD AMENDMENT - PROJECT HEADER INFORMATION

12/16/92

Active

Project #: G-33-536                      Cost share #:  
Center # : 10/11-6-06429-0A0          Center shr #:  
Contract#: 1 F31 AG05614-01            Mod #: ADMIN 12/16/92  
Prime #:  
Subprojects ? : N  
Main project #:

Rev #: 1  
OCA file #:  
Work type : INST  
Document : GRANT  
Contract entity: GTRC  
CFDA:  
PE #:

Project unit:                      CHEMISTRY            Unit code: 02.010.136  
Project director(s):  
POWERS J C                      CHEMISTRY            (404)894-4038

Sponsor/division names: DHHS/PHS/NIH                      / NATL INSTITUTES OF HEALTH  
Sponsor/division codes: 108                                      / 001

Award period:            920930            to            930930 (performance)            931230 (reports)

Sponsor amount	New this change	Total to date
Contract value	0.00	11,452.00
Funded	0.00	11,452.00
Cost sharing amount		0.00

Does subcontracting plan apply ? : N

Title: ACEYLCHOLINESTERASE INHIBITORS & DEMENTIAS

PROJECT ADMINISTRATION DATA

OCA contact: Kathleen R. Ehlinger            894-4820

Sponsor technical contact

Sponsor issuing office

DR. CARL BANNER  
(301)496-9350

JOANNE COLBERT  
(301)496-1472

NATIONAL INSTITUTE ON AGING  
NATIONAL INSTITUTES OF HEALTH  
5333 WESTBARD AVENUE  
BETHESDA, MD 20816

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BETHESDA, MD 20816

Security class (U,C,S,TS) : U  
Defense priority rating : N/A  
Equipment title vests with: Sponsor  
NONE PROPOSED.

ONR resident rep. is ACO (Y/N): N  
NIH supplemental sheet  
GIT X

Administrative comments -

ISSUED TO INCORPORATE BUDGET REVISION PER TELEPHONE CONVERSATION WITH THE  
CHEMISTRY DEPARTMENT SHIFTING FUNDS BETWEEN BUDGET CATEGORIES.

GEORGIA INSTITUTE OF TECHNOLOGY  
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Closeout Notice Date 01/11/94

Project No. G-33-536 \_\_\_\_\_

Center No. 10/11-6-06429-0A0\_

Project Director POWERS J C \_\_\_\_\_

School/Lab CHEMISTRY \_\_\_\_\_

Sponsor DHHS/PHS/NIH/NATL INSTITUTES OF HEALTH \_\_\_\_\_

Contract/Grant No. 1 F31 AG05614-01 \_\_\_\_\_

Contract Entity GTRC

Prime Contract No. \_\_\_\_\_

Title ACEYLCHOLINESTERASE INHIBITORS & DEMENTIAS \_\_\_\_\_

Effective Completion Date 930930 (Performance) 931230 (Reports)

Closeout Actions Required:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	N	_____
Final Report of Inventions and/or Subcontracts	N	_____
Government Property Inventory & Related Certificate	N	_____
Classified Material Certificate	N	_____
Release and Assignment	N	_____
Other _____	N	_____

Comments CONTINUED BY G-33-550. \_\_\_\_\_

Subproject Under Main Project No. \_\_\_\_\_

Continues Project No. \_\_\_\_\_

Distribution Required:

Project Director	Y
Administrative Network Representative	Y
GTRI Accounting/Grants and Contracts	Y
Procurement/Supply Services	Y
Research Property Management	Y
Research Security Services	N
Reports Coordinator (OCA)	Y
GTRC	Y
Project File	Y
Other CARL BAXTER-FMD _____	Y
_____	N

**USE THIS LABEL TO RETURN APPLICATION**  
INDIVIDUAL NATIONAL RESEARCH SERVICE AWARD CONTINUATION APPLICATION

<b>5 F31 AG05614-02</b> <b>NATIONAL INSTITUTE ON AGING</b> <b>GRANTS &amp; CONTRACTS</b> <b>GATEWAY BUILDING</b> <b>7201 WISC. AVE. SUITE 2N-212</b> <b>BETHESDA, MARYLAND 20892</b>	REVIEW GROUP <b>SRC -7</b>	TYPE <b>5</b>	ACTIVITY <b>F31</b>	FELLOWSHIP NUMBER <b>AG05614-02</b>
	TOTAL AWARD PERIOD			
	From: <b>10/01/92</b>		Through: <b>09/30/96</b>	
REQUESTED BUDGET PERIOD				
From: <b>10/01/93</b>		Through: <b>09/30/94</b>		

To be verified by applicant. Check information in Items 1 through 6. If incorrect, furnish correct information in Item 11.

1. TITLE OF RESEARCH TRAINING PROPOSAL

**ACETYLCHOLINESTERASE INHIBITORS AND DEMENTIAS**

2a. APPLICANT (Name and address, street, city, state, zip code)

**STARKS, KENNETH M**  
**GEORGIA INST OF TECHNOLOGY**  
**SCH OF CHEMISTRY & BIOCHEM**  
**ATLANTA, GA 30332-0400**

4. SPONSORING INSTITUTION (Name and address, street, city, state, zip code)

**GEORGIA TECH RES CORP**  
**GEORGIA INST OF TECH**  
**ATLANTA, GA 30332**

5. ENTITY IDENTIFICATION NUMBER

**1580603146A1**

2b. SOCIAL SECURITY NUMBER

**3**

2c. HIGHEST DEGREE(S)

**BA**

2d. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT

**SCHOOL OF CHEMISTRY & BIOCHEM**

2e. MAJOR SUBDIVISION

**COLLEGE OF SCIENCES**

3. NAME OF SPONSOR

**POWERS, JAMES C**

Complete the following (See instructions)

7. HUMAN SUBJECTS

7a.  NO  YES {  Exemption # \_\_\_\_\_  
OR  IRB Approval Date \_\_\_\_\_

7b. Assurance of Compliance # \_\_\_\_\_

8. VERTEBRATE ANIMALS

8a.  NO  Yes... IACUC Approval Date \_\_\_\_\_

8b. Animal Welfare Assurance # \_\_\_\_\_

9. TRAINING SITE(S) (Organizations and Addresses)

6. TITLE AND ADDRESS OF OFFICIAL SIGNING FOR SPONSORING INSTITUTION

~~XXXXXXXX~~ **IN BUSINESS OFFICE**  
**Janis Goddard**  
**CONTRACTING OFFICE**  
**GEORGIA TECH RES CORP**  
**GEORGIA INST OF TECHNOLOGY**  
**ATLANTA, GA 30332-0420**

BITNET/INTERNET ADDRESS

10a. PERMANENT MAILING ADDRESS (Street, city, state, zip code)

**3546 Heritage Valley Rd.**  
**Atlanta, Georgia 30331**

10b. APPLICANT'S TELEPHONE INFORMATION

	Area Code	Phone number & extension
OFFICE	404	894-3286
FAX	404	894-7452
HOME	404	350-8244
PERMANENT ADDRESS	404	346-1862

11. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBER(S) WHERE ANSWERS APPLY.

12. APPLICANT CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, accurate, and complete to the best of my knowledge, and I agree to comply with Public Health Service terms and conditions if an award is issued as a result of this application. I certify that I have read the National Research Service Award Service Assurance, that I will abide by the Assurance if an award is made, and that the award will not support residency training. Willful provision of false information is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject me to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR Part 79).

SIGNATURE

DATE **07-15-93**

**INDIVIDUAL NATIONAL RESEARCH SERVICE AWARD  
CONTINUATION APPLICATION**

FELLOWSHIP NUMBER

AG05614-02

## 13. APPLICANT SUMMARY OF ACTIVITIES (Do not exceed 3 pages.)

## A. CHANGES

Since submission of the last application, have any significant changes occurred in the training program, particularly the research project, academic status, or time distribution of activities (*i.e.*, percentage of time devoted to research project, course work, teaching, etc.)? If so, explain.

## B. PROGRESS REPORT

Describe concisely the research performed and research training obtained during the past year. List all courses and publications.

## C. RESEARCH TRAINING PLANS

Describe concisely the research and research training planned for the requested budget period, including any course work.

## 13. APPLICANT SUMMARY OF ACTIVITIES

## A. CHANGES

There have not been any alterations in the focus of the research or the training plan of the student since the original proposal.

## B. PROGRESS REPORT

During the past academic year at Georgia Tech I have been working diligently to complete both the synthesis of specific low molecular weight inhibitors of acetylcholinesterase as well as the curriculum of required courses set forth by Georgia Tech. I have satisfied the course requirements for matriculation by successfully completing courses in Advanced Physical Organic Chemistry, Macromolecular Structure, and Immunochemistry and I am a student in good standing.

The research plan that I proposed called for the synthesis of derivatives which would improve the specificity, potency and hydrophobicity of compound 1 which has been previously synthesized by the Powers group. I have made significant progress towards completing the goals that I have set and I expect to finalize the synthesis of several compounds for testing before the end of the summer quarter 1993. Compound 2 has been synthesized and shown to inhibit acetylcholinesterase *in vitro*.

The first step in the synthesis of these analogs requires a 3-hydroxypicolinaldehyde (4) which can be synthesized by a variety of methods. I have made this compound several times by using a large excess of MnO<sub>2</sub> and acetone at room temperature. The yields for this reaction are typically low with the highest yield being approximately 51%. This reaction has however proven to be unreliable at times because of the sensitivity to inactivation of the MnO<sub>2</sub> catalyst. I am interested in carrying out other literature procedures to synthesize this aldehyde that do not require MnO<sub>2</sub> but proceed by rearrangement and hydrolysis of 3-hydroxypicolinaldehyde triacetate (3). This alternative should provide a better yield as well as improve the repeatability of the experiment.

Phenyl semicarbazide derivatives (6) have been synthesized by reacting the appropriately substituted phenyl isocyanate (5) with a 10 fold excess of hydrazine monohydrate in methylene chloride at zero degrees. The products are easily isolated by suction filtration. This method has produced several substituted phenylsemicarbazides which include: 2,6-dichloro, 4-chloro, 2,6-dimethyl, 2,6-difluoro, 4-methoxy, 4-nitro, and 3-nitro. The yields for these reactions are typically in the low eighties with the highest yield being 88% obtained from the 2,6 dimethyl derivative.

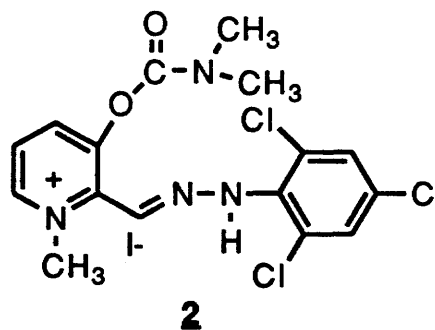
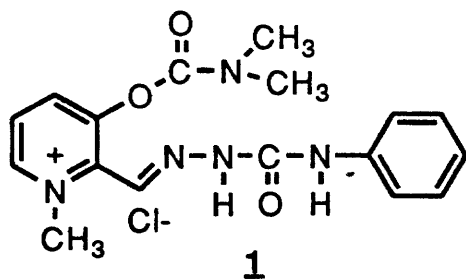
INDIVIDUAL NRSA APPLICATION  
CONTINUATION PAGE

Starks, Kenneth M.

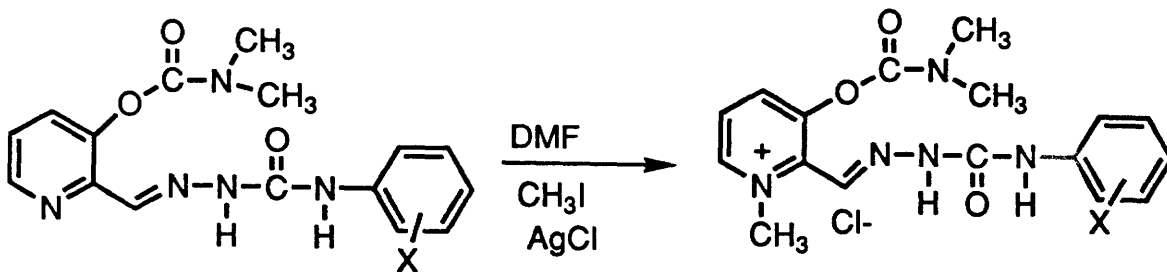
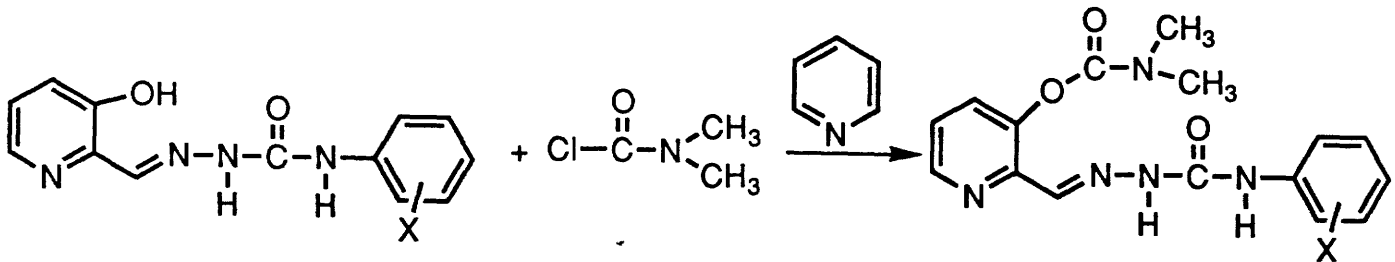
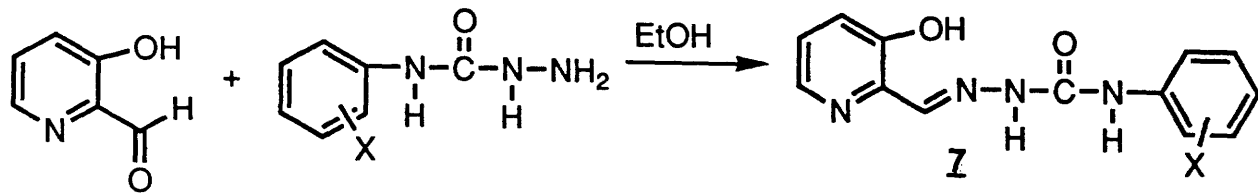
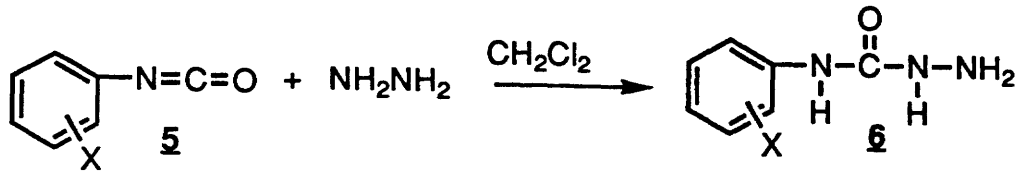
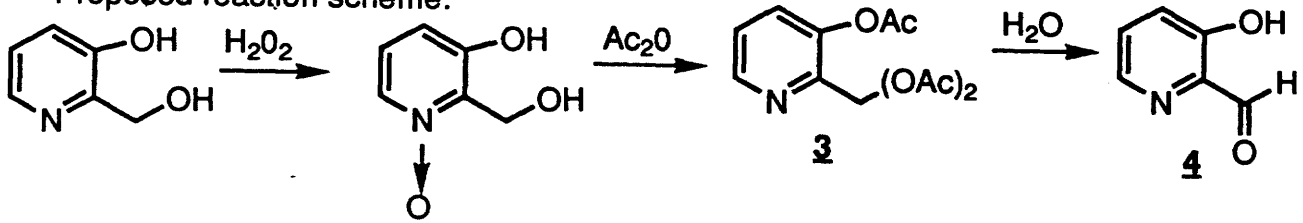
The synthesis of pyridine semicarbazones (7) and hydrazides (compound 2 is an example of a hydrazide) have been carried out by reacting the appropriate phenylsemicarbazide or phenylhydrazide with the pyridine aldehyde in ethanol at reflux temperature for one hour. The clean products are isolated by suction filtration. Yields for this reaction are generally 70-75%. The Schiff base analogs are then carbamylated by using pyridine and dimethylcarbamyl chloride at room temperature for 14 hours with subsequent methylation of the pyridinal nitrogen by methyl iodide then ion exchange by silver chloride. The carbamylation reaction yields up to 85% of its products while the yield for the salt ion exchange has not been determined.

### C. RESEARCH TRAINING PLAN

During the upcoming budget period I will be synthesizing more derivatives of compound 1 as potential acetylcholinesterase inhibitors. I will also be testing my compounds for their effectiveness by *in vitro* assays that have been worked out by the Power's group. All of the compounds that are deemed successful will be tested in animal models by a team of behavioral pharmacologists at The Medical College of Georgia. In the future we plan to submit the results of our joint investigations for publication.



Proposed reaction scheme:



DO NOT TYPE IN THIS SPACE—BINDING INFORMATION

**INDIVIDUAL NATIONAL RESEARCH SERVICE AWARD  
CONTINUATION APPLICATION**

*(To be completed by sponsor—follow instructions)*

FELLOWSHIP NUMBER

AG05614-02

14. SUPPLEMENTATION OF FELLOW:  NO  YES — If "yes," specify the amount(s) and dates on which supplementation occurred, and the source of the funds.

15. COMMENTS OF SPONSOR *(Use additional page, if necessary)*

- A. Evaluate the quality of the training (including academic work) and research progress made by the fellow during the past year. Include performance on cumulative and qualifying examinations, if applicable.
- B. Human subjects and vertebrate animals *(see instructions)*.

15A. Ken received low grades in his courses in the fall quarter of 1992 and was placed on probation during the winter quarter of 1993. During the spring quarter of 1993, he received good grades in several courses and returned to normal graduate student status (good standing). He has decided to complete a Masters degree in chemistry before continuing with his graduate studies. He has now completed all of the necessary course work and must simply complete enough research work for a Masters thesis. I expect Ken to complete sufficient research for a Masters thesis sometime during the next year.

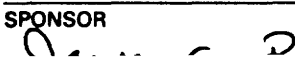
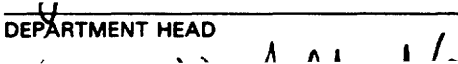
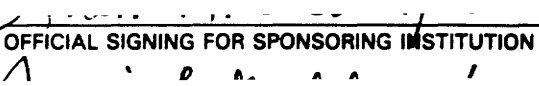
Ken's research progress to date has been satisfactory, but quite slow. He works consistently in the laboratory and is enthusiastic and interested in his research problem. He is very interested in the research field and is reading constantly in the area. However, he had taken a long time to learn synthesis skills and is still learning how to effectively perform techniques as simple as the recrystallization of reaction products. As he progresses, Ken is slowly making more of these skills part of his repertoire. He is beginning to work out the synthetic methods for the synthesis of the proposed acetylcholinesterase inhibitors (see progress report). He has now synthesized his first final inhibitor structure. Since he plans to synthesize a number of closely related derivatives to complete his thesis work, the remainder of the compounds should be more easily and quickly synthesized now that he has worked out the methods with the first derivative.

15B. No human subjects or vertebrate animals are involved in this research.

Provide the number of subjects enrolled in the study *to date* according to the following categories (see Page 6 for definitions).

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	TOTAL
Female							
Male							
Unknown							
<b>TOTAL</b>							

16. CERTIFICATION. We, the undersigned, certify that: (a) the information herein, including involvement of Human Research Subjects, Recombinant DNA Research, and Vertebrate Animals, are true, accurate, and complete to the best of our knowledge; (b) if this application results in an award, appropriate training, adequate facilities, and supervision will be provided; and (c) we will comply with the Public Health Service terms and conditions of award. A willfully false certification is a criminal offense (U.S. Code Title 18, Section 1001). We are aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject us to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR Part 79).

SIGNATURE	TYPED NAME	OFFICE TELEPHONE	DATE
	James C. Powers	894-4038	7/27/93
	Laren M. Tolbert	894-4002	7/29/93
	Janis L. Goddard	404/894-4817	7/30/93

14. The fellow was given a supplement of \$295/month from a seed grant from the Georgia Tech/Medical College of GA seed grant program. The amount is the difference between the normal stipend of \$13,000/year for chemistry graduate students and the amount provided by the NIH fellowship.



**INDIVIDUAL NRSA CONTINUATION APPLICATION  
CHECKLIST**

Applicant completes Section I. Sponsor completes Section II.

FELLOWSHIP NUMBER

AG05614-02

**Section I—Applicant**

**ASSURANCES/CERTIFICATIONS**

The following assurances/certifications are made by checking the appropriate boxes and are verified by your signature in Item 12 on the FACE PAGE of the application. Descriptions of individual assurances/certifications begin on page 2 of the application instructions.

- A. Debarment and Suspension  No  Yes (Attach explanation)  
B. Delinquent Federal Debt  No  Yes (Attach explanation)

**Section II—Sponsoring Institution**

The following assurances/certifications are made by checking the appropriate boxes and verified by the signature of the Official Signing for Sponsoring Institution in Item 16. Descriptions of sponsoring institution assurances/certifications begin on page 7 of the application instructions.

- A. Human Subjects (Complete Item 7 on the Face Page)  Full IRB Review  Expedited Review

Use of Human Subjects:  Change  No Change Since Previous Submission

- B. Vertebrate Animals (Complete Item 8 on the Face Page)

Use of Vertebrate Animals:  Change  No Change Since Previous Submission

- C. Debarment and Suspension  No  Yes (Attach explanation)

- D. Misconduct in Science (Form PHS 6315)  Filed  Not Filed  
If filed, date of Initial Assurance or latest Annual Report. 1/14/92

- E. Civil Rights (Form HHS 441)  Filed  Not Filed

- F. Handicapped Individuals (Form HHS 641)  Filed  Not Filed

- G. Sex Discrimination (Form HHS 639A)  Filed  Not Filed

- H. Age Discrimination (Form HHS 680)  Filed  Not Filed