**BORON IN NUCLEAR MEDICINE: NEW SYNTHETIC APPROACHES TO
PET AND SPECT**

Progress Report

May 1, 1993 - April 30, 1994

George W. Kabalka

Department of Chemistry
The University of Tennessee
Knoxville, Tennessee 37996-1600

FEBRUARY 1994

PREPARED FOR THE U.S. DEPARTMENT OF ENERGY
UNDER GRANT NUMBER DE-FG05-86ER60434

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

MASTER

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

TABLE OF CONTENTS

I.	OBJECTIVE	2
II.	RESEARCH ACCOMPLISHMENTS	3
A.	New Isotope Incorporation Reactions	3
1.	Iodination	3
2.	Oxygen-15	4
3.	Nitrogen-13	5
4.	Carbon-11	5
5.	Fluorine-18	7
B.	Preclinical Evaluation of New Agents	8
III.	BIBLIOGRAPHY OF DOE PUBLICATIONS SINCE PREVIOUS REPORT . . .	10
A.	Journal Articles	10
B.	Research Presentations	11
IV.	GRADUATE AND POSTDOCTORAL STUDENTS	13
A.	Postdoctoral Students	13
B.	Graduate Students	13
V.	BUDGET	14
A.	Current (Analysis of Budget as of July 31, 1992)	14
B.	Projected Budgets	14

I. OBJECTIVE

The primary objective of the D.O.E. Nuclear Medicine Program at The University of Tennessee is the creation of new methods for introducing short-lived isotopes into agents for use in PET and SPECT. The new methodology is based on reactive organometallic precursors containing organic functional groups that are generally responsible for physiologic responses. The uniqueness of the U.T. program is its focus on the design of new chemistry (molecular architecture) and technology as opposed to the application of known reactions to the synthesis of specific radiopharmaceuticals. The new technology which is often based on organoborane chemistry is then utilized in nuclear medicine research at the U.T. Biomedical Imaging Center and in collaboration with colleagues at other D.O.E. facilities such as Brookhaven National Laboratory and Oak Ridge National Laboratory. New radiopharmaceuticals are evaluated preclinically by colleagues at U.T. and other PET centers (e.g., Emory University and The University of Pennsylvania) as well as by contract laboratories such as Nova Screen.

An important goal of the D.O.E. Nuclear Medicine Program at U.T. is to provide training for students (predoctoral and postdoctoral) in the scientific aspects of nuclear medicine. The University of Tennessee is one of the very few institutions in the world where students have "hands-on" access to all modern nuclear medicine modalities: PET, SPECT and MRI. The academic nature of the program facilitates collaborative interactions with other D.O.E. nuclear medicine programs and helps to insure the continued availability of skilled scientists dedicated to the advancement of nuclear medicine.

II. RESEARCH ACCOMPLISHMENTS

I am pleased to report that this has been a productive year for the D.O.E. Program at Tennessee. Ten journal articles have appeared in print since our last progress report. Fourteen research abstracts of oral presentations have also been published. In addition, I was invited to chair scientific sessions at two international meetings and to present lectures at a number of universities and at national scientific meetings.

A. New Isotope Incorporation Reactions

1. IODINATION: We have continued to develop new routes for radioiodinating physiologically active agents. The most versatile route involves the direct reaction of no-carrier-added sodium [^{123}I]-iodine with organometallic reagents. Utilizing this new methodology, we have synthesized a variety of radioiodinated agents for use in nuclear medicine. Since our last progress report, we have reported an improved iodination reaction involving vinyl boronic acids such as I.

We also prepared a number of physiologically active iodinated agents which were evaluated in mice. The new agents included the 3-*N*-5-iodo-2-thienylbutyrophenones (III) and the iodinated nortropane (IV).

[Section IIIa, articles 3 and 5; Section IIIb, abstracts 1, 11, and 12]

2. OXYGEN-15: We have developed a new oxygen-15 ($t_{1/2} = 2$ min) incorporation route involving the direct reaction of organoboranes with $[^{15}\text{O}]\text{O}_2$. We synthesized polystyrene reagents with butylborane groups attached and then utilized them to incorporate oxygen-15 into physiologically active agents.

Preliminary experiments demonstrate that butanol (a PET blood flow agent) can be produced by simply passing oxygen gas over the surface. Current research efforts are also focused on the development of a flow through module ("kit") containing butylborane on alumina which can be directly attached to The University of Tennessee, 11 MeV, clinical cyclotron to

generate oxygen=¹⁵ labeled butanol "on-line." Microprocessor controlled systems are also being examined in a effort to reduce radiation exposure to personnel. [Section IIIb, abstracts 2 and 12.]

3. **NITROGEN-13:** We continue to develop new routes for incorporating nitrogen into organic molecules.

We reported the initial use of polymeric reagents for the synthesis of nitrogen-13 labeled amines. The procedure has the advantage that no soluble byproducts contaminate the desired product.

Microprocessor controlled units are also currently under development.

[Section IIIa, article 6; Section IIIb, abstract 7.]

4. **CARBON-11:** We continue to investigate the potential use of surfaces for use in carbon-11 syntheses of agents for possible use in clinical PET. The concept involves the attachment of reactive agents to surfaces such as activated alumina. The overall objective is presented on the next page.

During the past year we have examined a series of carbon-carbon bond reactions carried out in the presence of Lewis acids such as alumina surfaces and lithium perchlorate in the absence of solvents. We discovered that a moderate diastereoselectivity is obtained when cyclopentadiene is reacted with dimethylfumarate in the presence of lithium perchlorate.

We then investigated a series of Diels-Alder reactions on dehydrated alumina. It was found that the diastereoselectivity of the reaction between methyl acrylate and cyclopentadiene and cyclopentadiene. The endo to exo ratio increased from 5:8 to 52:1 as the temperature of the alumina activation was increased from 25°C to 800°C.

[Section IIIa, articles 8 and 9; Section IIIb, abstract 6.]

5. **FLUORINE-18:** We have been investigating the use of organoboranes for incorporation of fluorine-18. To date, we have relied on traditional fluoride displacement reactions to achieve fluorination. A number of exciting molecules have been prepared and evaluated. The molecules were a fluorinated nortropane analog V, the 4-fluoro-deoxyglucose, VI, and the thienylspiropiperidol, VII. However, fluorine-18 targets are now commercially

available and one is being installed on our cyclotron. We plan to investigate the direct fluorine-18 fluorination of boronic acids as a means to prepare a variety of physiologically active compounds.

The reaction would be based on our earlier studies which demonstrated that boron reagents react readily with halogen molecules but not with halide ions.

[Section IIIa: article 4; Section IIIb: abstracts 8, 14 and 15]

B. Preclinical Evaluation of New Agents

We have actively pursued preclinical evaluation of promising new agents via routes that are funded by the other government agencies; these include collaboration with other PET centers and commercial screening controls. [This DOE project does not support biological testing.]

Nova-Screen Corporation has provided binding assay data for seven of our new butyrothiophenones of the general structural type:

The preliminary data presented below demonstrates that all of the new reagents are receptor site active.

Nova-Screen Binding Assay Data

Compound		**% Inhibition at [10 ⁻⁵ M]		
X	Y	*D2(dopamine)	S1(serotonin)	S2(serotonin)
-H	-H	100.2		104.6
-H	-CH ₃	100.5		104.2
-H	-CH ₂ CH ₃	99.5		102.3
-H	-(CH ₂) ₂ CH ₃	100.5		103.6
-I	-H	100.9		92.7
-I	-CH ₂ CH ₃	100.0	42.5	93.9
-I	-(CH ₂) ₃ CH ₃	100.8		95.8

*The parentheses denote the reference compounds. **A % inhibition greater than 90.0 means that saturation occurred.

We are now negotiating with Nova-Screen to test the compounds at more dilute ($10^{-9}M$) concentrations. We are also collaborating with Dr. Hank Kung at The University of Pennsylvania in Philadelphia who is helping to evaluate the new neuroreceptor agents in both mice and baboons. Dr. Kung carried out a complete receptor-site radiographic analysis on our two new cocaine analogs, VIII and IX.

Baboon studies reveal that both reagents are active but the *Syn* [IMMG 142(Z)] isomer, IX, demonstrated unexpected affinity for the D2 receptor sites. Further evaluation of these agents and related fluorine-18 labeled agents is currently underway.

III. BIBLIOGRAPHY OF DOE PUBLICATIONS SINCE PREVIOUS REPORT

A. Journal Articles

1. Kabalka, G. W.; Pace, R. D. "Allylboronic Ester Synthesis: A Mechanistic Study", *Tetrahedron Lett.* **1993**, *34*, 783.
2. Goodman, M. M.; Collier, T. L.; Kabalka, G. W.; Longford, C. P. D. "Synthesis of Carbon-11 Labeled (1R-2-exo-3-exo)-2-carbomethoxy-8-methyl-8-azabicyclo [3.2.1.]octyl-3-N-(3'-nitrophenyl) carbamate as a Potential Dopamine Receptor Imaging Agent." *J. Labelled Compd. Radiopharm.* **1993**, *32*, 286-288.
3. Goodman, M. M.; Kabalka, G. W.; Waterhouse, R. N.; Collier, T. L. "Synthesis of Iodine-123 Labeled 3-N-alkyl-5-iodo-2-thienyl-butyrophenones for SPECT Analysis of Dopamine Receptors." *J. Labelled Compd. Radiopharm.* **1993**, *32*, 237.
4. Goodman, M. M.; Kabalka, G. W.; Langford, C. P. D. "Synthesis of Fluorine-18 Labeled 4-Fluoro-4-deoxy-D-glucose as a Potential Brain, Heart and Tumor Imaging Agent." *J. Labelled Compd. Radiopharm.* **1993**, *32*, 568.
5. Kabalka, G. W.; Goodman, M. M.; Maddox, J. T. "The Synthesis of Radioiodinated Vinyl Iodides Via Organoborane Chemistry," *J. Labelled Compd. Radiopharm.* **1993**, *32*, 201.
6. Kabalka, G. W.; Goodman, M. M.; Green, J. F.; Marks, R.; Longford, D. "Synthesis of Nitrogen-13 Labeled Amines Using Organoborane Polymers." *J. Labelled Compd. Radiopharm.* **1993**, *32*, 165.
7. Kabalka, G. W.; Reddy, N. E.; Narayana, C. "Oxidative Deselenylation with Sodium Perborate and Sodium Percarbonate", *Synth. Comm.* **1993**, *23*, 543.
8. Pagni, R. M.; Kabalka, G. W.; Bains, S.; Plesco, M.; Wilson, J.; Bartmess, J. "A Chemical Spectroscopic and Theoretical Assessment of The Lewis Acidity of LiClO₄ in Diethyl Ether", *J. Org. Chem.* **1993**, *58*, 3130.
9. Pagni, R. M.; Kabalka, G. W.; Hondrogiannis, G.; Bains, S.; Anosike, P.; Kurt, R. "The Cycloaddition Reactions of Unsaturated Esters with Cyclopentadiene on γ -Alumina", *Tetrahedron* **1993**, *49*, 6743.
10. Yang, D. T. C.; Evans, T. J.; Yamazaki, F.; Narayana, C.; Kabalka, G. W. "Sodium Perborate: A Convenient Oxidative Cleavage of α -Diketones" *Synth. Commun.* **1993**, *23*, 1783.

B. Research Presentations

1. "Radioiodinated 2 β -Carboisopropoxy-3 β -(4-chlorophenyl)-8-(3/e-iodopropen-2-yl) nortropane: Synthesis and Potential Radioligand for Mapping Dopamine Reuptake Sites by SPECT", M. M. Goodman, M. P. Kung, G. W. Kabalka, H. F. Kung and M. A. Meyer, 40th Annual Meeting of the Society of Nuclear Medicine, Toronto, Canada (June 1993).
2. "The Synthesis of Oxygen-15 Butanol From Solid-Supported Tributyl Boranes: A Comparison of Inorganic and Organic Supports", J. F. Green, G. W. Kabalka, M. M. Goodman, J. T. Maddox, and S. J. Lambert, Eighth International Meeting on Boron Chemistry, Knoxville, Tennessee (July 1993).
3. "Nickel Catalyzed Hydroboration with Catecholborane", G. W. Kabalka, C. Narayana, and N. K. Reddy, Eighth International Meeting on Boron Chemistry, Knoxville, Tennessee (July 1993).
4. "Sodium Perborate: A Convenient Reagent for Benzylic Hydroperoxide Rearrangements", G. W. Kabalka, C. Narayana, and N. K. Reddy, Eighth International Meeting on Boron Chemistry, Knoxville, Tennessee (July 1993).
5. "Sodium Perborate: A Convenient Reagent for Preparation of Diaroyl Preparation of Diaroyl Peroxides", G. W. Kabalka, and J. T. Maddox, Eighth International Meeting on Boron Chemistry, Knoxville, Tennessee (July 1993).
6. "Reaction of Vinylboronic Acids with Bromine on γ -Alumina", G. W. Kabalka, R. M. Pagni, and D. A. Willis, Eighth International Meeting on Boron Chemistry, Knoxville, Tennessee (July 1993).
7. "Synthesis of Functionally Diverse Amino Alcohols Via Allylboration", G. W. Kabalka, and R. D. Pace, Eighth International Meeting on Boron Chemistry, Knoxville, Tennessee (July 1993).
8. "Synthesis of Fluorine-18 Labeled Compounds for Brain Imaging", M. M. Goodman, and G. W. Kabalka, American Chemical Society Annual Meeting, Nucl. III, Chicago, Illinois (August 1993).
9. "Sodium Perborate: New Reagent for the Hydroxylation of Polycyclic Aromatic Hydrocarbons", G. W. Kabalka, N. K. Reddy, and C. Narayana, Southeast Regional American Chemical Society Annual Meeting, John City, Tennessee (October 1993).
10. "Diastereoselective Synthesis of Amino Alcohols Via Crotylboration of α -Amino Carbonyl Compounds", G. W. Kabalka, and R. David Pace, Southeast Regional American Chemical Society Annual Meeting, John City, Tennessee (October 1993).

11. "Synthesis of Radioiodinated Vinyl Iodides", M. M. Goodman, R. S. Srivastava, K. R. Bowers, and R. C. Marks, Tenth International Symposium on Radiopharmaceutical Chemistry, Kyoto, Japan (October 1993).
12. "The Synthesis of Oxygen-15 Butanol Via the Oxidation of Tributylborane Adsorbed on Solid Surfaces", G. W. Kabalka, J. F. Green, M. M. Goodman, J. T. Maddox, and S. J. Lambert, Tenth International Symposium on Radiopharmaceutical Chemistry, Kyoto, Japan (October 1993).
13. "Microprocessor-Controlled Open Vessel System for the Production of No-Carrier-Added 1-[¹¹C]-1-Aminocyclobutane-1-Carboxylic Acid", M. M. Goodman, J. L. Devinney, G. W. Kabalka, M. Ladetsky, K. F. Hubner, M. A. Meyer, and S. J. Lambert, Tenth International Symposium on Radiopharmaceutical Chemistry, Kyoto, Japan (October 1993).
14. "Synthesis of N-3-[¹⁸F]Fluoropropyl-2 β -Carbomethoxy-3 β -(4-Chlorophenyl)Tropane: A High Affinity Neuroligand to Map Dopamine Reuptake Sites by PET", M. M. Goodman, G. W. Kabalka, M. P. Kung, H. F. Kung, and M. A. Myer, Tenth International Symposium on Radiopharmaceutical Chemistry, Kyoto, Japan (October 1993).
15. "Synthesis of [¹⁸F]-N-3-Fluoropropyl-2-Thienylspiroperidol: A New Radioligand for PET Study of the Dopamine D₂ Receptor", Tenth International Symposium on Radiopharmaceutical Chemistry, Kyoto, Japan (October 1993).

IV. GRADUATE AND POSTDOCTORAL STUDENTS

One postdoctoral student and two graduate students were supported during this period by the Department of Energy Nuclear Medicine Program.

A. Postdoctoral Students

Dr. Chatla Narayana

B. Graduate Students

Max Hair (Ph.D. candidate)

Kathy Bogas (Ph.D. candidate)

*Budget removed.
ds*

DATE

FILMED

3 / 18 / 94

END