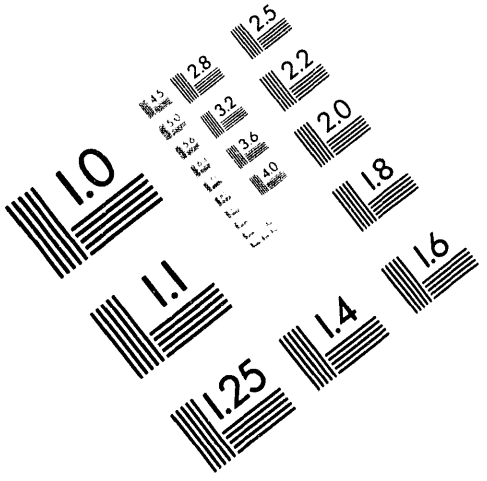

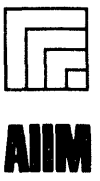

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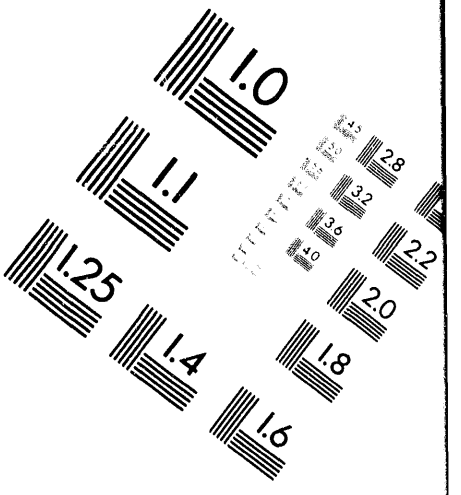

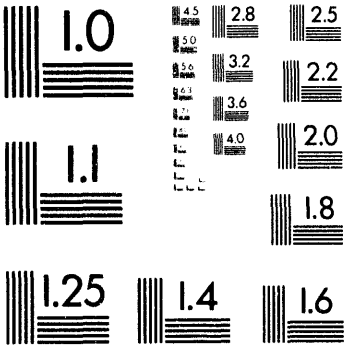

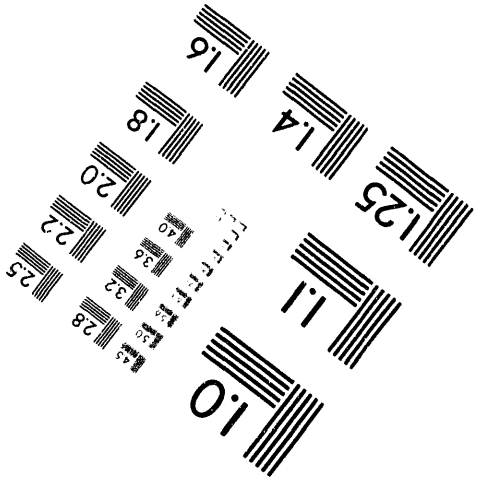

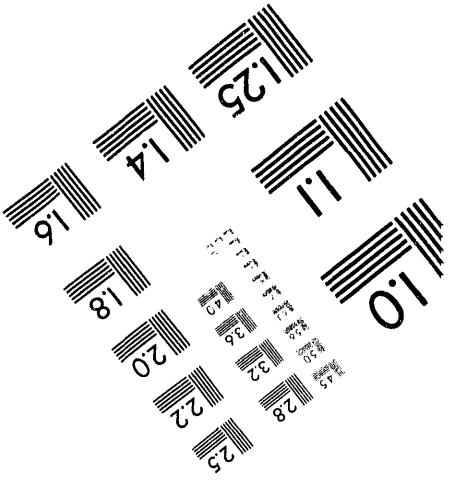

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NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING March 31, 1994

F. F. Knapp, Jr.

K. R. Ambrose
A. L. Beets
C. R. Lambert
D. W. McPherson
S. Mirzadeh
H. Luo

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NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING MARCH 31, 1994

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Work sponsored by
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CONTENTS

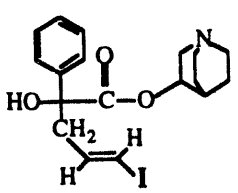
Summary

Our new radioiodinated "IQNP" agent, an analogue of "4-IQNB", has a high affinity for the muscarinic-cholinergic receptor (m-AChR). Iodine is stabilized in "IQNP" by attachment as a vinyl iodide. Various isomers of IQNP show high affinity for m-AChR subtypes and are good candidates for cerebral single photon emission computed tomography (SPECT). To evaluate the potential usefulness of a [Br-76]-labeled analogue as a candidate for positron emission tomography (PET), we have synthesized the *trans*-3-bromopropenyl analogue (BrQNP) and evaluated its ability *in vivo* to block uptake of [I-125]-Z-(R,R)-IQNP (high affinity for M_1 and M_2). Reaction of bromine with the *trans*-tributylstannyl substrate prepared from ethyl -α-hydroxy -α-phenyl-α-(1-propyn-3-yl)acetate, followed by column purification and transesterification with (R,S)-3-quinuclidinol gave BrQNP, which was characterized by ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR) and high performance liquid chromatography (HPLC). Female rats (n=5) were pre-treated with the oxalate salt of BrQNP (3 mg/kg) one hour prior to I.V. injection of [I-125]-IQNP (1.2 μCi). A control group received only [I-125]-IQNP. Rats were sacrificed after 3 hours and tissues analyzed. While the brain and heart uptake in BrQNP pre-treated animals was significantly decreased (brain = 0.31± 0.07; heart = 0.30 ± 0.08), the control animals showed the expected high uptake of IQNP in these tissues (brain = 1.07 ± 0.09; heart = 2.25 ± 0.30). These results demonstrate the receptor uptake of IQNP is significantly blocked by BrQNP in both the heart and brain, regions of high m-AChR. Studies are in progress to study the affinity and selectivity of BrQNP for m-AChR. The ease of preparation and ability to block m-AChR suggest that [Br-76]-labeled BrQNP is a potential candidate for PET studies.

In this report, we also summarize our current on-going collaborative studies assessing the usefulness of various rhenium-188-labeled therapeutic agents. Collaborative studies in conjunction with clinical colleagues are currently assessing the feasibility of treatment of colorectal cancer with antibodies labeled with carrier-free rhenium-188 from the ORNL generator. In addition, collaborative programs have been established to evaluate rhenium-188-labeled particles for treatment of arthritis (synovectomy), treatment of bone pain resulting from cancer metastheses with rhenium-188-phosphonates (palliation), and other applications.

Development of a Brominated Analogue for IQNP

We have shown in earlier studies that IQNP, an analogue of 3-quinuclidinyl benzilate (**3**), demonstrates high affinity for the muscarinic receptor. In addition to high affinity, IQNP is selective and specific for the muscarinic receptor. More recent studies have shown that the stereoisomers of IQNP demonstrate a moderate selectivity for the various muscarinic receptor subtypes (ORNL/TM-12661). Bromine-75 and bromine-76 are two cyclotron-produced positron-emitting radioisotopes of interest for positron emission tomography (PET). Bromine-75 ($t_{1/2}$=1.62 h) is produced by the $^{75}As(^{3}He,3n)^{75}Br$ reaction and bromine-76 ($t_{1/2}$=16.0 h) is produced via the $^{76}Se(p,n)^{76}Br$ route. These radioisotopes are of interest for the *in vivo* detection of neurotransmission by PET. A major advantage of PET is the higher resolution and shorter acquisition times as compared to single photon emission computer tomography (SPECT). Bromine chemistry is similar to iodine and the same radiolabeling reactions can be performed. In addition, the bromine-carbon bond (67.5 kcal/mol) is stronger than the iodine-carbon bond (50.5 kcal/mol), and would be expected to result in lower *in vivo* dehalogenation. For these reasons, we have investigated an analogue of IQNP (**1**) in which the iodine atom is replaced with bromine (BrQNP, **2**).



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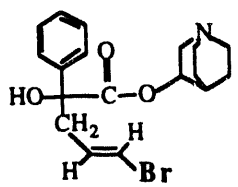

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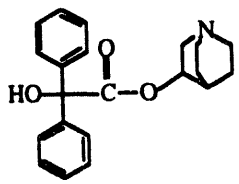

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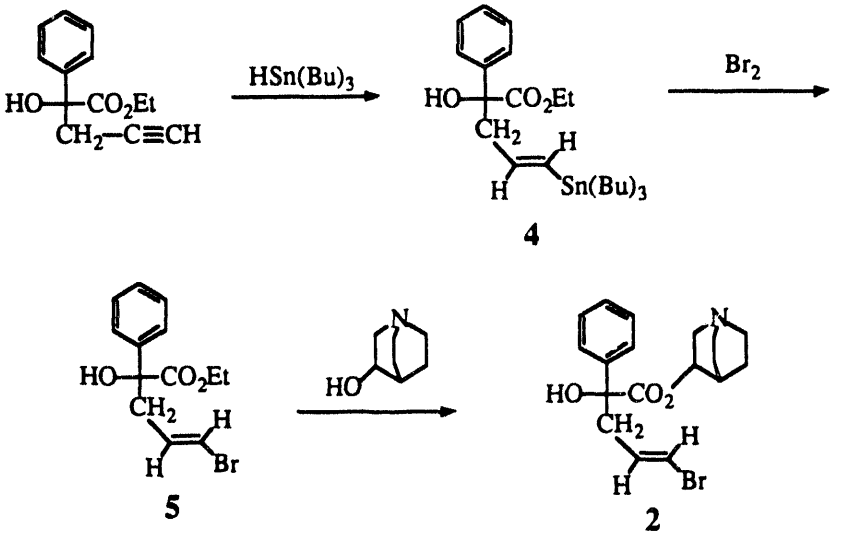
We have prepared racemic BrQNP in an analogous manner developed for IQNP as shown in Scheme 1. This project is being pursued in conjunction with Dr. H. Luo, a Alexander Holleander post doctoral fellow. Dr. Luo joined the ORNL Nuclear Medicine Program after she completed her Ph.D. in Chemistry at the University of Tennessee in October 1993. The synthetic route involves bromination of the tributylstannyl derivative **4** using bromine in chloroform to afford the vinyl bromo compound **5**. Compound **5** was then transesterified with the sodium salt of 3-quinuclidinol to afford BrQNP (**2**). Since

the labeling chemistry will be analogous to IQNP, the various IQNP steroisomers which were prepared earlier to evaluate the effects of structure on receptor affinity (ORNL/TM-12661) will also be employed for preparation of the various radiobrominated BrQNP analogues.



Scheme 1. Preparation of BrQNP

An initial *in vivo* competitive study was performed in which unlabeled BrQNP was preinjected into female rats followed by the injection of iodine-125-labeled Z-(R,R)-IQNP one hour later. The rats were then sacrificed after three hours, and the accumulation of activity in whole brain, heart, and blood were compared to data from a control set of rats (n=5) in which iodine-125 labeled Z-(R,R)-IQNP was injected followed by sacrifice after three hours. The results of this study are shown in Figure 1, and demonstrate that BrQNP blocks the uptake of Z-(R,R)-IQNP by greater than 60% in the brain and heart, tissues with high muscarinic receptor density, while there was no effect on blood levels of activity. These results demonstrate that BrQNP exhibits affinity for the muscarinic receptor and is a promising candidate for further studies. *In vitro* binding assays are currently in progress with collaborators at the George Washington University (B. Zeeberg, Ph.D., and colleagues) and the University of Chicago (R. Reba, M.D.) to determine the affinity of BrQNP for the muscarinic subtypes. Future studies will involve radiolabeling of BrQNP stereoisomers with readily available reactor-produced bromine-82 for more detailed *in vivo* evaluation to determine the cerebral uptake distribution, selectivity and selectivity of this new ligand.

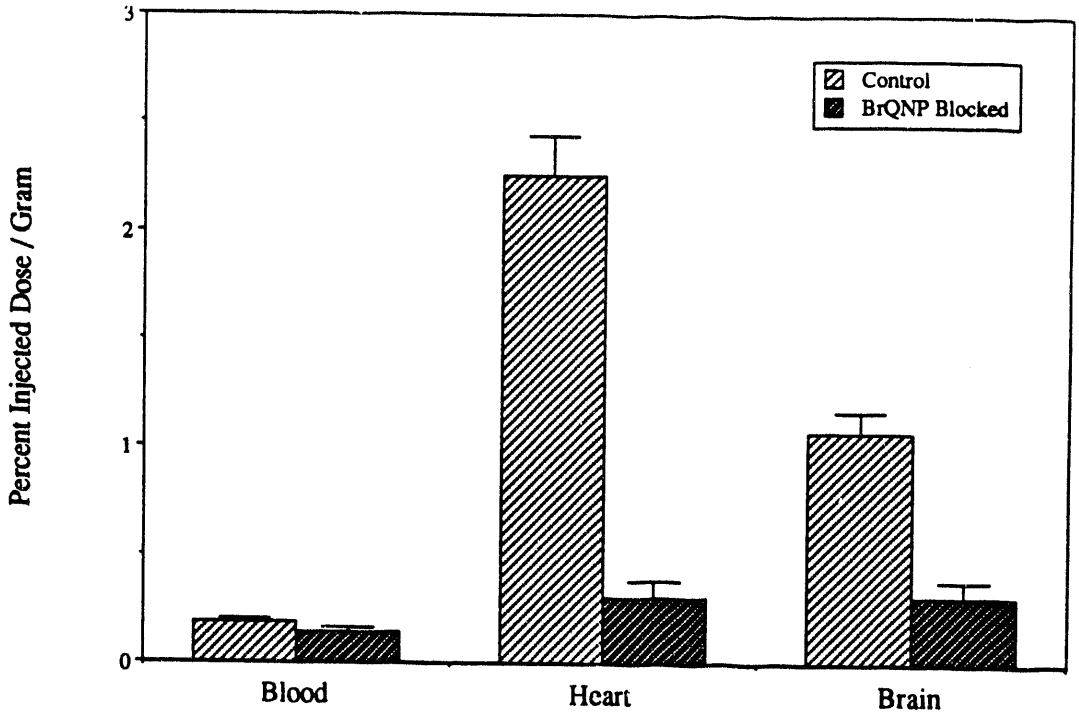


Figure 1. Results of blocking study with BrQNP on (I-125)-Z-(R,R)-IQNP tissue uptake.

Status of Collaborative Programs Evaluating Therapeutic Applications of Rhenium-188 from the ORNL Tungsten-188/Rhenium-188 Generator

An important aspect of the development of the tungsten-188/rhenium-188 generator system is collaboration with external programs with special expertise which complement our program capabilities. We are currently collaborating with several programs to assess the effectiveness of attaching rhenium-188 to antibodies and peptides by "direct labeling" technology, in order to evaluate the targeting of rhenium-188-labeled antibodies toward colorectal cancer, and to develop radiolabeling technology to explore the potential use of rhenium-188 for treatment of arthritis (radionuclide synovectomy), treatment of bone pain from cancer (palliation) and potential bone marrow ablation with rhenium-188-labeled antibodies.

In continuing studies in conjunction with David Goldenberg, M.D., R. Sharkey, Ph.D., and their colleagues at the Center for Mollecular Medicine and Immunology (CMMI) in Newark, New Jersey, clinical studies are in progress to assess the targeting of tumor-specific antibodies for gastrointestinal cancer. Studies are assessing the potential usefulness of Re-188 anti-CEA antibody (MN-14 IgG) for treatment of gastrointestinal cancer. "Direct" antibody labeling readily provides the labeled antibody in good yields (80-90%). Escalating doses of up to 80 mCi/m^2 have been administered in 3 patients within one week on an outpatient basis. Adsorbed doses to normal organs were similar to those obtained for [I-131]-MN-14 with exception of the liver, which was about 3 times higher with [Re-188]-MN-14. Grade

3 or 4 myelotoxicity was observed in 3 patients receiving 46, 67 and 70 mCi/m^2, respectively, however one patient received a total dose of 161 mCi without any toxicity. Human antimouse antibody response (HAMA) developed in 9 of 11 patients, but only 2-3 weeks after the initial injection, thus allowing completion of the full treatment cycle. In 3 patients for whom adsorbed doses were calculated (4 tumors), tumor doses ranging from 7.0-53cGy/mCi were found, and tumor/red marrow ratios ranged from 1.2-9.1. These preliminary data compare favorably with data obtained for [I-131]-MN-14, where tumor/red marrow dose values ranged from 1.2-10.5. Rhenium-188-labeled MN-14 may thus be useful for treatment of certain tumors with favorable dosimetry on a completely outpatient basis and with controllable toxicity. We are also working with RhoMed, Inc., an antibody technology company based in Albuquerque, New Mexico, to pursue "direct labeling" technology to attach rhenium-188 to peptides by "direct labeling" technology. We are in the process of applying for a Small Business Research and Development Contract (CRADA) to support this work.

We are also collaborating with Prof. S. N. Reske, M.D., and his colleagues in the Nuclear Medicine Department at the University of Ulm, Germany, to assess potential use of rhenium-188-labeled phosphonates for palliative treatment of bone pain from cancer. Gamma camera measurement of radioisotope distribution permits dose estimation. The advantages of using rhenium-188 include its similarity to technetium for "direct" antibody labeling and its availability in carrier-free form from the tungsten-188/rhenium-188 generator on a daily basis. The 69-day half-life of tungsten-188 minimizes the logistic problems of radionuclide availability. Since the chemical properties of the rhenium-188 perrhenate are similar to those of technetium-99m-pertechnetate, radiolabeling of various bone-seeking phosphonate complexes with rhenium-188 is possible.

AGENTS FOR MEDICAL COOPERATIVES

During this period a large-scale tungsten-188/rhenium-188 generator loaded with 751 mCi of tungsten-188 was supplied to the Center for Molecular Medicine and Immunology (CMMI) for continuing escalating targeted patient dose studies with rhenium-188-labeled antibodies for colorectal cancer (D.M. Goldenberg, M.D., R. Sharkey, Ph.D., and colleagues). As part of an international collaborative project, tungsten-188 sodium tungstate was supplied to the Institute for Nuclear Energy Research (INER), in Lung-Tan, Taiwan, for fabrication of generators for collaborative research studies in Taiwan (B.-T. Hsieh, Ph.D. and G. Ting, Ph.D).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Recent Publications

McPherson, D. W., Knapp, Jr., F. F., and Hudkins, R. L. "Synthesis and Biological Evaluation of Iodine-125-labeled-Iodocaramiphen. A Potential M_1 Imaging Agent for SPECT," J. Labl. Cmpds. Radiopharm., **XXXIV**, 239-246, (1994).

Wang, G.-J, Som, P., Oster, Z. H., Volkow, N. D., Knapp, Jr., F. F., and Sacker, D. F. "Quantitative Autoradiographic Measurement of Cocaine-Induced Regional Myocardial Changes in Hypertensive Rats," Nucl. Med. Biol., **21**, 245-250 (1994).

Hasan, A., Knapp, Jr., F. F., Kilbourn, M. R., and Buchsbaum, D. J. "New Azomycin Acyclonucleosides - Synthesis and Biodistribution of Radiohalogenated Analogues in Tumor-Bearing Mice," J. Heterocyc. Chem., **30**, 1351-1355 (1993).

The "Proceedings" of the Third International Symposium on Radioiodinated Free Fatty Acids, held in Kyoto, Japan, in February, 1993, were recently published in the *Annals of Nuclear Medicine*. The symposium focused on the development and use of the iodine-123 "BMIPP" cardiac imaging agent developed in the ORNL Nuclear Medicine Program. The lead article in this special "Supplement" described the key role ORNL researchers had in the design and development of BMIPP, and four other articles describing collaborative studies between ORNL and institutions in the U.S. Europe and Asia, were co-authored by ORNL researchers.

Knapp, Jr., F. F., Kropp, J., Goodman, M. M., Ambrose, K. R., Som, P., Biersack, J. H., Sloof, G., and Visser, F. C. "The Development of Iodine-123-Methyl-Branched Fatty Acids and their Applications in Nuclear Cardiology, *Annals of Nuclear Medicine*, 7, S-II, 1-14 (1993).

Fujibayashi, U., Yonekura, Y., Tamaki, N., Yamamoto, K., Som, P., Knapp, Jr., F. F., Konishi, J., and Yokoyama, A. "Myocardial Accumulation of BMIPP in Relation to ATP Concentraion," *Annals of Nuclear Medicine*, 7, S-II, 15-18 (1993).

Som, P., Wang, G. J., Oster, Z. H., Knapp, Jr., F. F., Yonekura, Y., Fujibayashi, U., Yamamoto, K., and Kubota, K. "Myocardial Uptake of Cocaine on Myocardial Substrate Utilization and Perfusion in Hypertensive Rats," *Annals of Nuclear Medicine*,7, S-II, 19-26 (1993).

Kropp, J., Eichorn, W., Fehske, W., Likungu, J., Kirchoff, P. C., Luederitz, B., Knapp, Jr., F. F. and Biersack, H.-J. "Influence of Revascularization on Myocardial Perfusion, Metabolism and Function," *Annals of Nuclear Medicine*, 7, S-II, 69-78 (1993).

Kropp, J., Joergans, M., Glaenzer, K. P., Knapp, Jr., F. F., Luederitz, B., and Biersack, H.-J. "Evaluation of Ischemia and viability in Patients with Coronary Artery Disease (CAD) with Iodine-123-Labeled 15-(p-iodophenyl)-3-R,S)-methylpentadecanoic Acid (BMIPP)," *Annals of Nuclear Medicine, 7, S-II, 93-100 (1993).*

Meetings

D. W. McPherson presented an "Invited Lecture" entitled, "Development of Radiohalogenated Muscarinic Ligands for the *In Vivo* Imaging of M-AchR by Nuclear Medicine Techniques," at the *Symposium on Applied Nuclear Chemistry,* held in conjunction with the Bi-Annual Meeting of the Americal Chemical Society in San Diego, California, on March 14-18, 1994.

Patents

A second patent describing the medical use of carrier-free perrhenic acid from the tungsten-188/rhenium-188 generator developed in the ORNL Nuclear Medicine Program was recently issued.

> Knapp, Jr., F. F., Lisic, E. C., Mirzadeh, S., and Callahan, A. P. "Tungsten-188/Carrier-Free Rhenium-188 Perrhenic Acid Generator System," U. S. Patent 5,275,802, Issued January 4, 1994.

Appointments

F. F. (Russ) Knapp, Jr. has accepted an initial four year appointment to the Editorial Board of the *International Journal of Applied Radiation and Isotopes,* which is published by Pergamon Press, Ltd.

Saed Mirzadeh has been appointed to the "Publications Committee" of the American Chemical Society (ACS) Division of Nuclear Chemistry and Technology. The three-year appointment will involve coordination of annual reviews which will be published in the *Journal of Radioanalytical and Nuclear Chemistry.*

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