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NUCLEAR MEDICINE PROGRAM PROGRESS  
REPORT FOR QUARTER ENDING  
June 30, 1994

**MARTIN MARIETTA**

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Health Sciences Research Division

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## Summary

In this report we describe the first successful synthesis and *in vivo* evaluation of a fluorinated analogue of the IQNP muscarinic-cholinergic receptor ligand. Unanticipated synthetic hurdles lead to several unsuccessful approaches before the synthesis of a model compound was achieved. The successful route involved introduction of the fluoroethyl moiety at an early stage of the synthesis by alkylation of ethyl 1,3-dithiane-2-carboxylate with 1-fluoro-2-bromoethane. Subsequent unmasking of the carbonyl, followed by introduction of the phenyl group with phenylmagnesium bromide and subsequent transesterification with racemic quinuclidinol afforded the target compound, 1-azabicyclo[2.2.2]oct-3-yl  $\alpha$ -(1-fluoroethan-2-yl)- $\alpha$ -hydroxy- $\alpha$ -phenylacetate (QNF). Pretreatment of Fisher rats with QNF one hour prior to the intravenous administration of the [I-131]-Z-(R,R) IQNP isomer demonstrated that the new fluoro analogue blocked uptake of iodine-131 in those regions of the brain rich in muscarinic-cholinergic receptors measured three hours after injection. As an example, the control values for one group of nontreated animals were (5 animals; mean  $\pm$  SD): cortex,  $1.20 \pm 0.27$ ; striatum,  $0.73 \pm 0.19$ ; pons,  $0.70 \pm 0.20$ ; cerebellum,  $0.43 \pm 0.114$ . Brains from animals pretreated with the fluoro analogue had the following values (mean  $\pm$  SD; % decrease): cortex,  $0.67 \pm 0.15$  (65%); striatum,  $0.35 \pm 0.114$  (52%); pons,  $0.40 \pm 0.08$  (43%); cerebellum,  $0.16 \pm 0.09$  (63%).

Also during this period, several tungsten-188/rhenium-188 generators and tin-117m samples were provided for collaborative studies.

**Preparation and Initial *In Vivo* Evaluation of 1-Azabicyclo[2.2.2]oct-3-yl  $\alpha$ -(1-Fluoroethan-2-yl)- $\alpha$ -hydroxy- $\alpha$ -phenylacetate ("FQNE"). A Potential PET Muscarinic Ligand for the Study of Muscarinic Receptors.**

We have previously shown that the radioiodinated E-(R,R)- and Z-(R,R)-isomers of "IQNP" (Figure 1) exhibit rapid and significant localization in muscarinic-cholinergic rich areas (m-AChR) of rat brain (ORNL/TM-12661, 12411, 12312, and 12110). Due to the simple preparation and high radiolabeling yields, the iodine-123-labeled analogue is an attractive candidate for use for the evaluation of m-AChR in human studies. More recently, we have synthesized and performed initial *in vivo* evaluation of a brominated IQNP analogue, BrQNP (2) (ORNL/TM-12707), in order to develop a specific and selective muscarinic ligand for labeling with bromine-76 for positron emission tomography (PET). Because fluorine-18 is widely available from medical cyclotrons, it is a more attractive radioisotope for PET applications. The development of a fluorinated analogue of IQNP (3) was therefore initiated for the potential use of a fluorine-18-labeled m-AChR ligand for the study of muscarinic receptors density by PET.

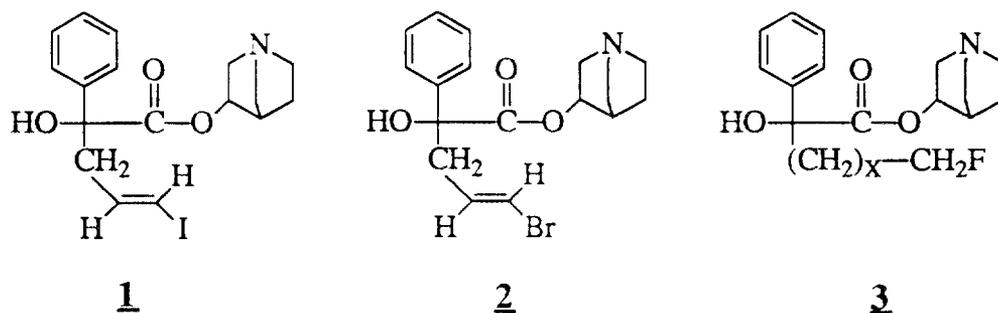
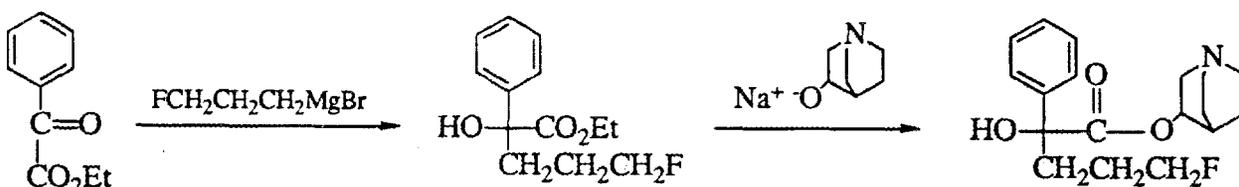


Figure 1. Structures of New QNB Analogues.

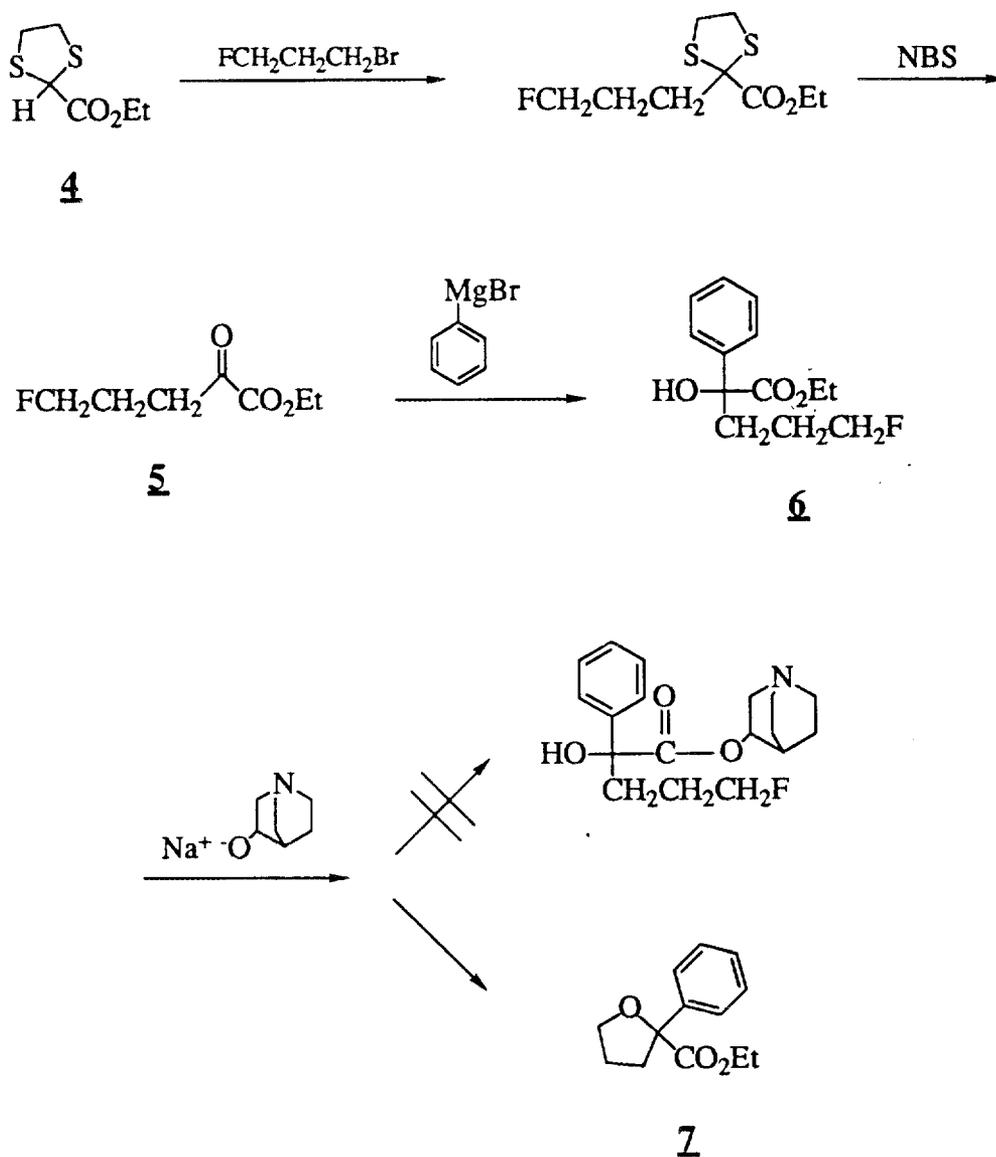
Although the synthesis of the proposed analogue appeared straightforward, a number of unexpected synthetic problems were encountered and delayed the preparation of a model compound for testing. The synthesis of a fluorinated analogue of IQNP is being pursued in conjunction with Huimin Luo, Ph.D., who is working in the Nuclear Medicine Program as a Alexander Hollaender Distinguished Postdoctoral Fellow. Introduction of the fluoride early in the synthetic scheme was chosen due to the ease of the chemistry and would allow for the testing of this type of molecule on its ability to block the uptake of a radioiodinated muscarinic ligand in m-AChR rich areas. The initial synthetic route envisioned the use of a Grignard reagent prepared from 1-bromo-3-fluoropropane and magnesium metal (Scheme I). A search of the literature, however, indicated that Grignard reagents of this type could not be prepared and the synthesis thus required development of a new route.



Scheme I

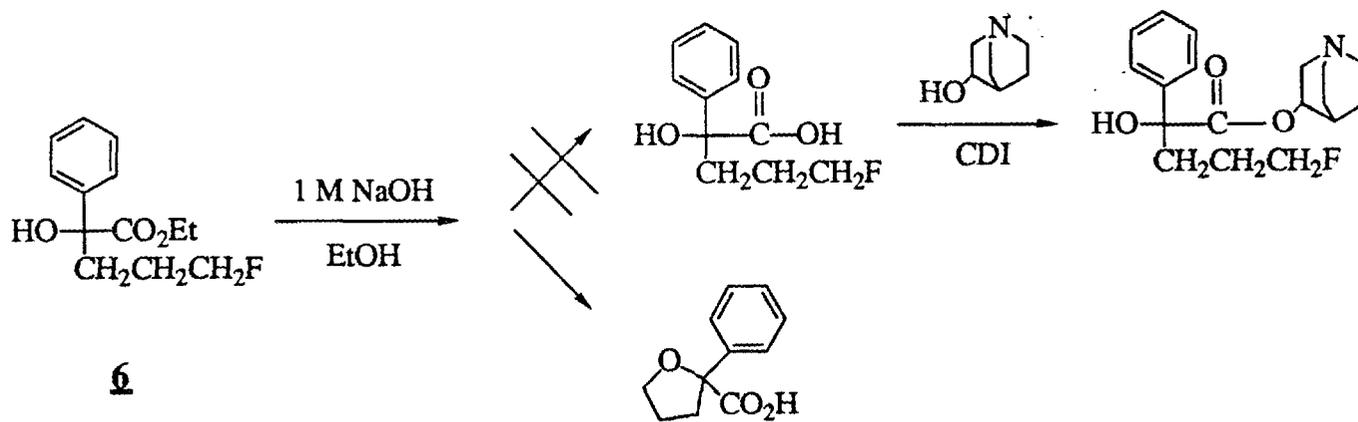
An alternative route involved protection of an  $\alpha$ -keto ester as a 1,3-dithiane, as shown in Scheme II. This route involved alkylation of ethyl 1,3-dithiane-2-carboxylate (4) with 1-fluoro-3-bromopropane followed by removal of the dithiane moiety with N-bromosuccinimide to provide the desired fluorinated  $\alpha$ -ketoester (5). Compound (5) was then treated with phenyl magnesium bromide to afford ethyl- $\alpha$ -(1-fluoro-3-propyl)- $\alpha$ -hydroxy- $\alpha$ -phenylacetate (6). We were surprised to observe that compound (6) readily

cyclized to the substituted furan derivative (7) under the reaction conditions which are routinely used for transesterification with 3-quinuclidinol. Not unexpectedly, when the reaction sequence was performed using 1-bromo-4-chloro butane, the corresponding pyran analogue was obtained.



Scheme II

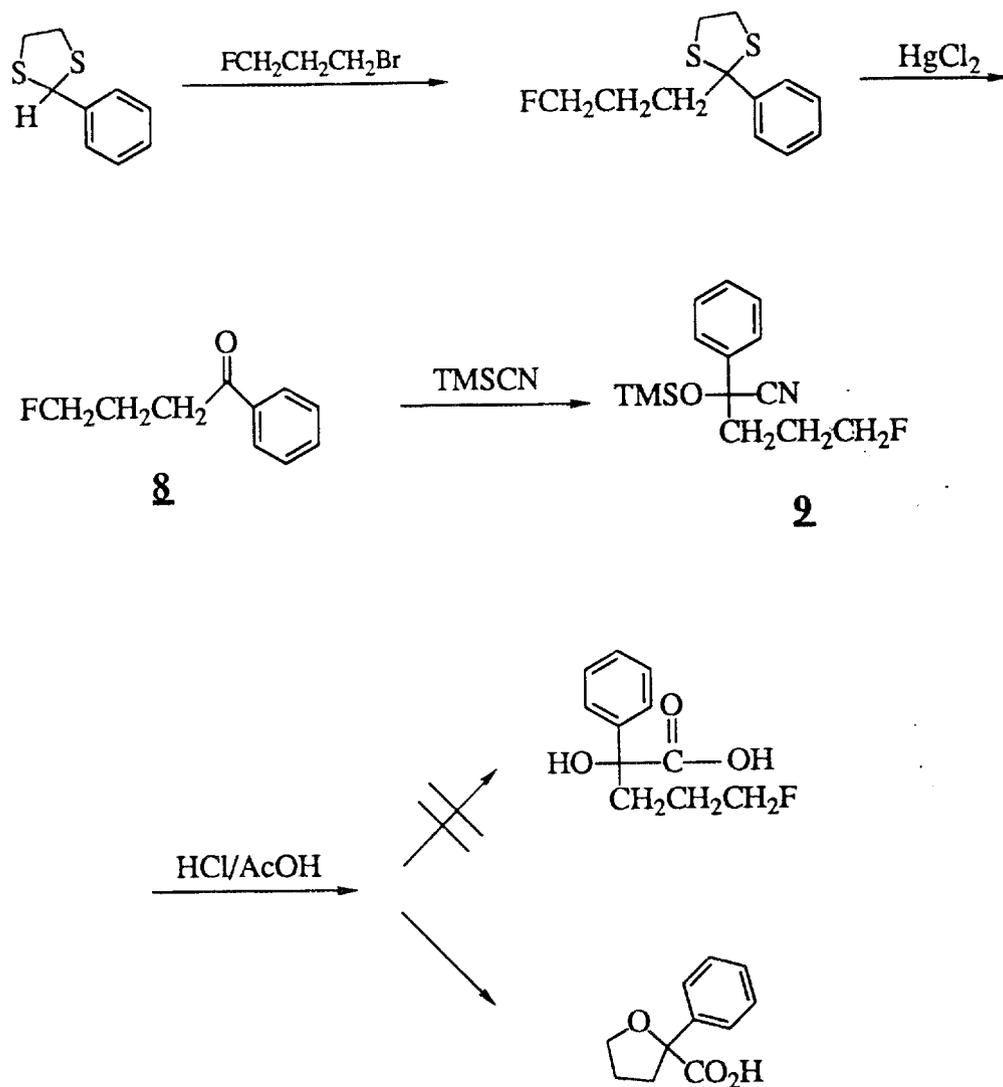
Esterification of (6) was then investigated using an activated ester approach, as shown in Scheme III. This route involved saponification of the ethyl ester to the free acid. When treated with an ethanolic 1 M NaOH solution, however, compound (6) readily converted to the furan derivative (7) described earlier. Preparation of the acid directly was then investigated using the dithiane approach (Scheme IV). This route involved reaction of phenyl-1,3-dithiane with 1-fluoro-3-bromopropane followed by removal of the dithiane with mercury(II)chloride to afford (1-fluoro-3-propyl)phenylketone. Treatment with trimethylsilyl cyanide produced  $\alpha$ -cyano- $\alpha$ (1-fluoro-3-propyl)- $\alpha$ (trimethylsilyl ether)- $\alpha$ -phenylmethane (9) in good yield. Attempts to hydrolyze the nitrile group with acid, however, again resulted in formation of the furan analogue observed previously.



Scheme III

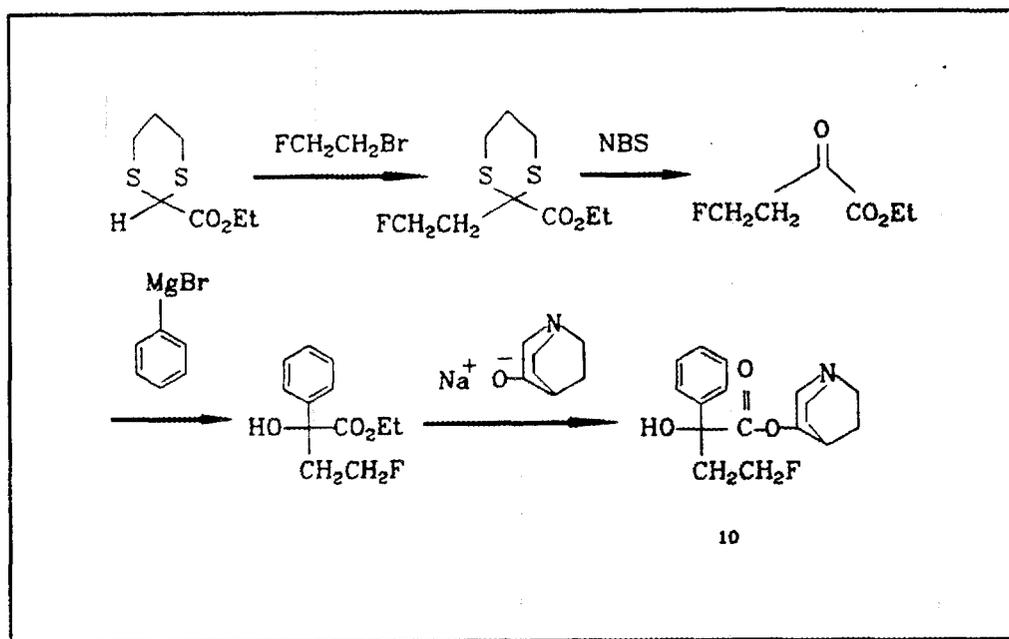
These results indicated that displacement of fluoride with the oxygen of the hydroxy moiety to form the furan or pyran ring systems was the favored reaction pathway in either acidic or basic media. Use of a 1-fluoro- $\omega$ -alkane which would not be susceptible to ring closure was then investigated. We envisioned that use of 1-fluoro-2-bromoethane with the two carbon spacer, would be successful since possible formation of a four carbon furan analogue would not be favorable. Preparation of the desired compound, 1-azabicyclo[2.2.2]oct-3-yl- $\alpha$ -(1-fluoro-2-ethyl)- $\alpha$ -hydroxy- $\alpha$ -phenylacetate (FQNE, 10)

succeeded by the route in Scheme V. Pertinent regions of the 200 MHz proton and carbon nmr spectra of FQNE are shown in Figure 2, and confirm the synthesis of the first fluorinated IQNP analogue.



Scheme IV

To determine if the new fluoro analogue (10) demonstrates affinity for m-AChR, competitive studies were pursued by pretreatment of animals with compound (10) at a dose of 3 mg/kg one hour prior to the intravenous administration of iodine-131-Z-(R,R)-IQNP. In addition, one group of animals received iodine-131-Z-(R,R)-IQNP as a control. The rats were killed 3 hours post-injection of radioiodinated ligand. The results of this study are shown in Table 1 and demonstrate that the fluorinated compound (10) blocked uptake of activity in brain regions rich in m-AChR. From these promising results methods are now being developed for the introduction of fluorine-18 into the FQNE analogue (10) for evaluation of the *in vivo* brain uptake, selectivity and specificity of this new ligand.



Scheme V

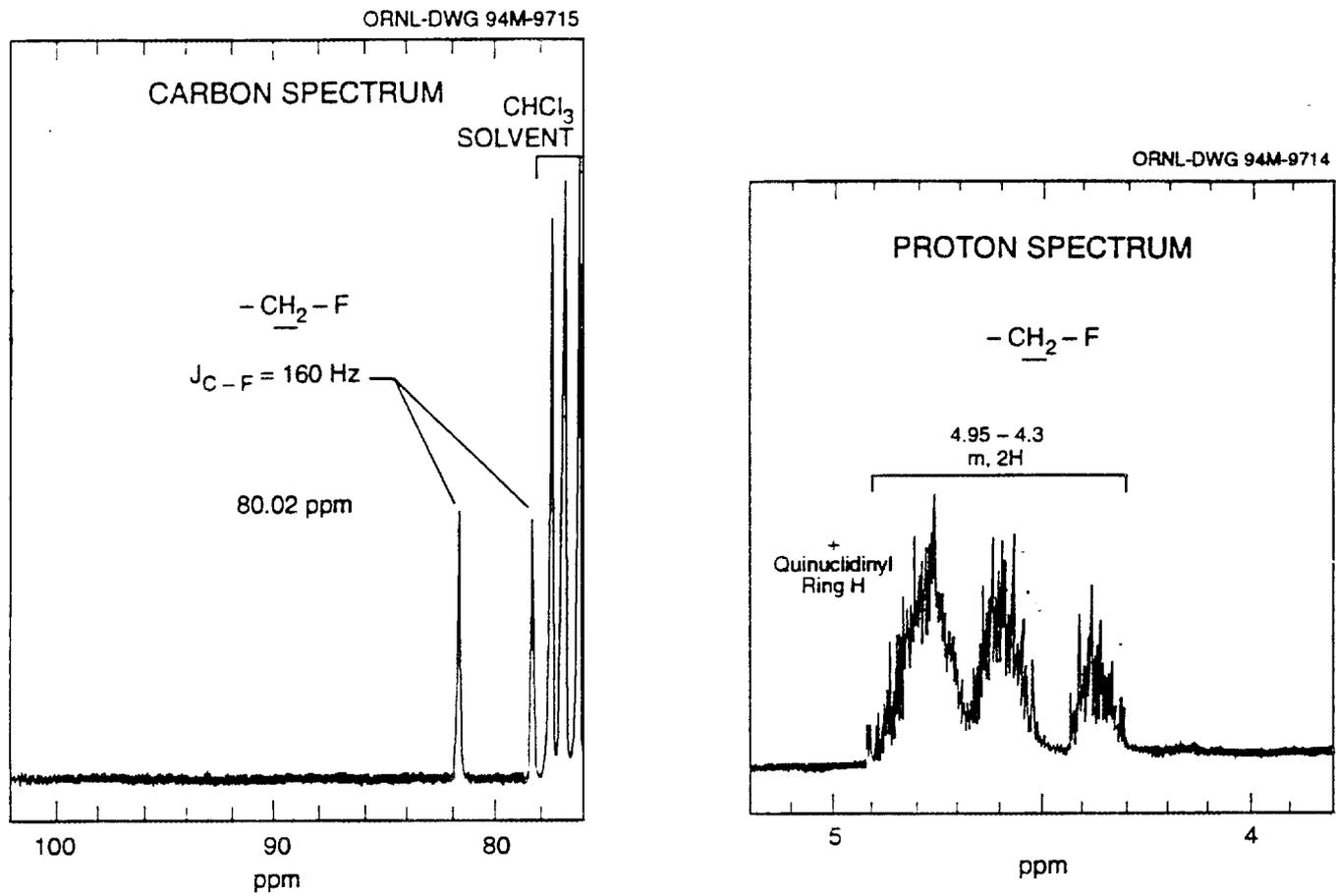


Figure 2. Selected regions of the  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra of FQNP.

Table 1. Regional Cerebral Levels of Radioactivity Three Hours Following Intravenous Administration of [ $^{131}\text{I}$ ]-Z-(R,R)-IQNP in Control Rats and Rats Pretreated One Hour Earlier With Unlabeled FQNE (3 mg/kg).\*

Pretreatment Agent	Cortex	Striatum	Hippocampus	Pons	Cerebellum	Heart	Blood
Control	1.20±0.27	0.73±0.19	0.67±0.08	0.70±0.20	0.43±0.14	1.98±0.4	0.18±0.05
"FQNP"	0.67±0.15	0.35±0.14	0.22±0.19	0.40±0.08	0.16±0.09	0.78±0.3	0.16±0.02

\* Five female Fischer rats per group.

## OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

### Recent Publications

De Geeter, F., Franken, P. R., Knapp, F. F., Jr. and Bossuyt, A. "Relationship Between Blood Flow and Fatty Acid Metabolism in Subacute Myocardial Infarction: A Study by Means of  $^{99m}\text{Tc}$ -Sestamibi and  $^{123}\text{I}$ - $\beta$ -methyl iodiphenylpentadecanoic Acid," *European Journal of Nuclear Medicine*, **21**, 283-291 (1994).

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

### Recent Meetings

Dr. S. Mirzadeh, a research staff member in the Nuclear Medicine Program, presented a lecture at the *International Conference on Nuclear Data for Science and Technology*, which was held in Gatlinburg, Tennessee, on May 9-13, 1994. This research describes the results of alternative methods for production of the tin-117m and platinum-195m radioisotopes via inelastic neutron scattering.

Mirzadeh, S., Knapp, Jr., F. F. and C. W. Alexander. "Evaluation of Neutron Inelastic Scattering for Radioisotope Production, *International Conference on Nuclear Data for Science and Technology*, May 9-13, 1994.

Members of the ORNL Nuclear Medicine Group participated and presented several papers at the Annual Meeting of the Society of Nuclear Medicine recently held in Orlando, Florida, on June 6-10, 1994.

Mirzadeh, S., Alexander, C. W., and Knapp, Jr., F. F. "The Advanced Neutron Source (ANS) - A Proposed National Resource for Medical Radioisotope Production", *J. Nucl. Med.*, **35**, 245P (1994).

McPherson, D. W., Lambert, C. R., Zeeburg, B., Sood, V., McRee, R. C., Reba, R., and Knapp, Jr., F. F. "Effects of Absolute Configuration of IQNP on Muscarinic Receptor Subtype Selectivity *In Vitro* and *In Vivo*," *J. Nucl. Med.*, **35**, 93P (1994).

Som, P., Wang, G. J., Oster, Z. H., Knapp, Jr., F. F., McPherson, D. W. Yousef, K., and Cabahug,, C. "Quantitative ARG Microimaging Studies of Two Muscarinic Antagonist Isomers: Blocking and the Effects of Cocaine," *J. Nucl. Med.*, **35**, 201P (1994).

### **Cooperative Research and Development Agreement (CRADA)**

A Cooperative Research and Development Agreement (CRADA) developed by F. F. (Russ) Knapp, Jr., has been funded by the Department of Energy to support collaborative research with RhoMed, Inc., to explore the radiolabeling of antibodies and small peptides for cancer therapy with the rhenium-188 radioisotope using the ORNL tungsten-188/rhenium-188 generator system. Collaborators at RhoMed, located in Albuquerque, New Mexico, are developing antibodies for cancer treatment. Availability of radioisotope generator systems and radioisotopes resulting from research in the ORNL program will provide this technology to assess antibody radiolabeling strategies and to evaluate the potential use of these new agents for development into new therapeutic tools for cancer treatment.

### **Visitors**

During the April 1-June 30, 1994 period, visitors included B. Coursey, Ph.D., a Program Director at the National Institute for Standards and Technology (NIST), who visited the Nuclear Medicine Program on April 8 to discuss continuing collaboration on several projects involving reactor-produced radioisotopes. On April 19-20, Ralph Zingaro, Ph.D., Professor of Chemistry at Texas A&M University, visited to discuss collaboration on the synthesis of several radiopharmaceutical precursors and the possibility of a Guest Assignment in the Nuclear Medicine Program in 1995. Joachim Kropp, M.D., Assistant Director of the Nuclear Medicine Department at the University of Dresden, Germany, had an extended visit on June 9-24, 1994, as part of a NATO Collaborative Program to discuss continued collaboration with several new radiopharmaceutical agents developed in the ORNL Nuclear Medicine Program and to complete several joint manuscripts and review articles. On June 17, Lisa Karam, Ph.D., visited from NIST as a follow-up to discussions initiated earlier by Dr. B. Coursey on areas on joint collaboration.

### **Awards**

Members of the Nuclear Medicine Group were awarded a Martin Marietta Energy Systems Annual "Research and Development Award for 1994," for the development of the alumina-based tungsten-188/rhenium-188 generator system which provides the important rhenium-188 radioisotope for various therapeutic applications.

### **Medical Cooperative Shipments**

One shipment of tin-117m metal was made to the Medical Department at the Brookhaven National Laboratory (BNL) for continuing studies of bone pain palliation treatment of cancer patients in conjunction with the University of New York at Stony Brook. The Nuclear Medicine Group is assisting the BNL project during the period that the Brookhaven Reactor is not in operation. The tungsten-188/rhenium-188 generator is now routinely available for sale as a radiochemical through the ORNL Isotopes Distribution Office, and the first generator was sold to Biomira, Inc. on a full-cost recovery basis, in June 1994.

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