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

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Contract No. DE-AC05-84OR21400

Health Sciences Research Division

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FOR QUARTER ENDING DECEMBER 31, 1994

F. F. Knapp, Jr.

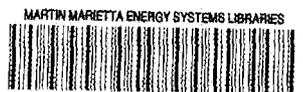
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Work sponsored by
DOE Office of Health and
Environmental Research

Date Published
February 1995

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ORNL/TM-12054
ORNL/TM-12110
ORNL/TM-12159
ORNL/TM-12222
ORNL/TM-12312
ORNL/TM-12343
ORNL/TM-12411
ORNL/TM-12485
ORNL/TM-12661
ORNL/TM-12707
ORNL/TM-12789
ORNL/TM-12875

CONTENTS

Summary	5
Synthesis of FQNPe - A New Fluorinated Analogue of QNB for Potential F-18 Labeling for Evaluation of Muscarinic-Cholinergic Receptor Density by PET	6
HFIR - Produced Tin-117m for Bone Pain Palliation	10
Literature Cited	14
Other Nuclear Medicine Group Activities	17
Recent Publications	17
Recent Meetings	18
Visitors	18
Medical Cooperative Shipments	19

Summary

1-Azabicyclo[2.2.2]oct-3-yl α -(1-fluoropentan-5-yl)- α -hydroxy- α -phenylacetate (FQNPe) has been prepared and evaluated as a new candidate for the determination of muscarinic cholinergic receptor density by positron emission tomography (PET). The results of *in vitro* binding assays demonstrated that FQNPe has high affinity for m_1 and m_2 muscarinic receptor subtypes, (nM, m_1 ; K_d , 0.45, m_2 ; K_d , 3.53). Pretreatment of female Fisher rats with unlabeled FQNPe one hour prior to the intravenous administration of radioiodinated Z-(R,R)-IQNP, a high affinity muscarinic ligand, demonstrated FQNPe significantly blocked the uptake of radioactivity in the brain and heart measured three hours post-injection of the radiolabeled ligand. These results demonstrate that this new fluoro analogue of QNB has high affinity for the muscarinic receptor and is able to effectively pass the blood-brain-barrier and localize in tissues rich in muscarinic receptors. The fluorine-18-labeled analogue thus represents an important target ligands for evaluation as potential receptor imaging agents in conjunction with PET.

During this period several radioisotopes were provided to collaborators. Tungsten-188/rhenium-188 generators were provided as part of a CRADA project (RhoMed, Inc.), a project funded by NIH (University of Massachusetts), and in conjunction with a collaborative project at the Paul Scherrer Institut in Villigen, Switzerland. Tungsten-188 solution was also provided to the Institute for Nuclear Energy Research in Lung-Tan, Taiwan, for fabrication of generators for on-going collaborative research projects.

"FQNPe" - A New Fluorinated Analogue of QNB for Fluorine-18-Labeling for Evaluation of Muscarinic-Cholinergic Receptor Density by Positron Emission Tomography (PET)

Changes in the density of muscarinic acetylcholinergic receptor (m-AChR) subtypes have been implicated in aging, memory, and dementias, and have stimulated interest in the development of m-AChR specific radiolabeled ligands for nuclear medicine imaging. A variety of ligands have been synthesized and evaluated as agents for imaging m-AChR by both Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT). Most of the reported ligands developed for imaging of m-AChR by PET have been radiolabeled with carbon-11 ($t_{1/2}$ 20 min), but because of the relatively short half-life of this radioisotope, these ligands are not ideal for studies that require a long duration. Because fluorine-18 has a longer half-life ($t_{1/2}$ 110 min) and is readily available from medical cyclotrons, it is a more attractive candidate for radiolabeling ligands for PET studies of m-AChR. There have been only a few reported examples of m-AChR-specific ligands radiolabeled with fluorine-18, however, and no studies describing successful imaging of m-AChR with these ligands have yet been reported.

3-Quinuclidinyl benzilate (QNB, **1**) is a high affinity muscarinic antagonist and has been labeled with radioiodine (4-IQNB, **2**).¹⁻³ Iodine-123-labeled IQNB has been used in SPECT studies of healthy individuals and patients with dementias to image m-AChR.⁴⁻⁹ A fluorine-18-labeled analogue of IQNB would thus appear to be a good candidate as a potential ligand for the evaluation of m-AChR by PET. The preparation of fluorinated derivatives of QNB have been described, however, *in vivo* studies of the uptake and binding to m-AChR have not been.^{2, 10-14} Analogues in which one phenyl ring of QNB has been replaced with a methyl or butyl group retain their affinity for m-AChR, and in addition, this type of modification has been shown to influence the m-AChR subtype selectivity of the ligand. We have demonstrated that our new analogues in which a phenyl group has been replaced with a vinyl iodide moiety have high affinity for m-AChR and readily pass the blood-brain barrier (BBB) and display high selectivity and specificity for m-AChR *in vivo*¹⁵ (ORNL/TM-12110, 11811 and 11992). Evaluation of the various stereoisomers of IQNP (**3**) have shown that the affinity and m-AChR subtype selectivity of the ligand is influenced by the absolute configuration at the two chiral centers¹⁶⁻¹⁷ (ORNL/TM-12411). More recently we have demonstrated the high affinity of a brominated IQNP analogue (BrQNP, **4**) which was developed as a high affinity m-AChR ligand for PET studies³⁰.

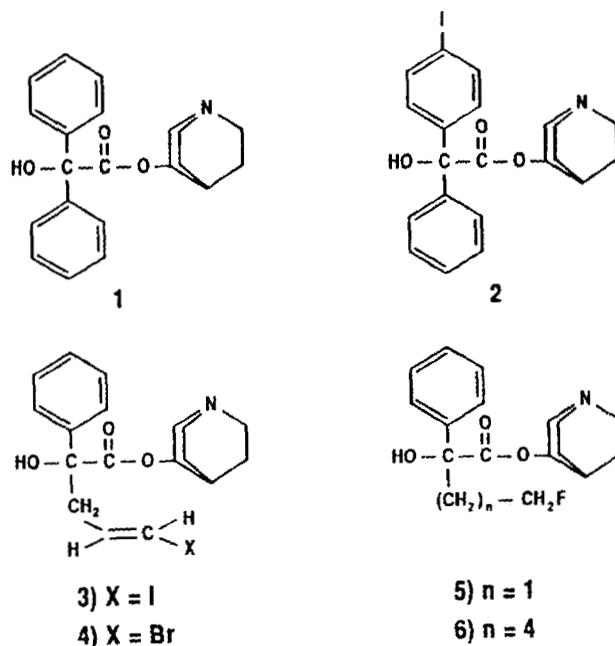
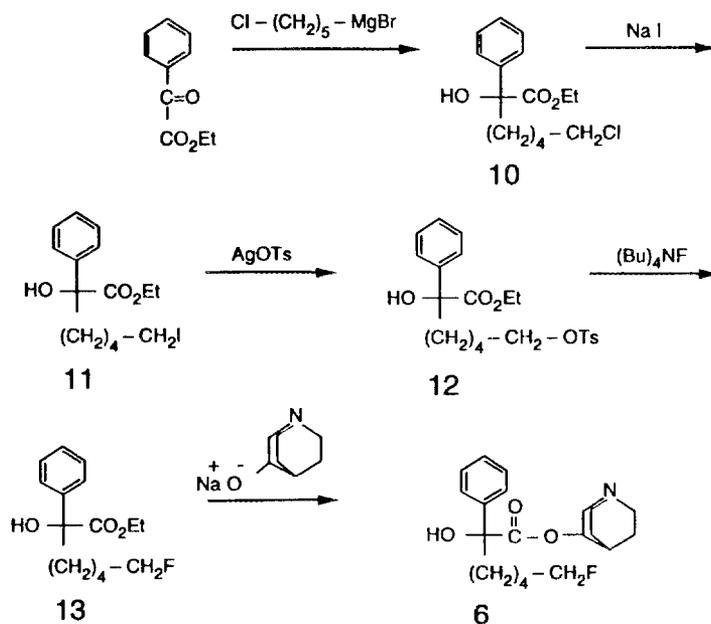


Figure 1. Structures of QNB analogues

Earlier, we had described the synthesis and biological properties of a new fluorinated analogue, FQNE (Figure 1), in which fluorine was attached as a fluoroethyl group (ORNL/TM-12789). Because fluorine-18 as the fluoride anion would be difficult to introduce into the FQNE analogue, in this report we described the synthesis, *in vitro* binding affinity and initial *in vivo* evaluation of a new fluorinated analogue of QNB in which a phenyl group has been replaced with a fluoropentyl group. This new agent (FQNPe) is a potential ligand for radiolabeling with fluorine-18 for PET studies of changes in m-AChR in various diseases. The new fluoropentyl analogues FQNPe was prepared as shown in Scheme I. Ethyl benzoylformate was reacted with 1-chloropent-5-ylmagnesium bromide to afford ethyl α -(5-chloropent-1-yl)- α -hydroxy- α -phenylacetate (**10**). Stepwise treatment with sodium iodide, silver *p*-toluenesulfonate and tetrabutylammonium fluoride afforded the desired fluorinated ethyl acetate. Transesterification with the sodium salt of 3-quinuclidinol afforded 1-azabicyclo[2.2.2]oct-3-yl α -(1-fluoropentan-5-yl)- α -hydroxy- α -phenylacetate (FQNPe).



Scheme 1

Analogues of QNB have been evaluated for their ability to retain affinity for m-AChR as well as their potential use in nuclear medicine techniques. The 3-quinuclidinyl 4-iodobenzilate analogue (4-IQNB) has been used to study changes in m-AChR by SPECT in healthy individuals and patients with dementias. There are several problems associated with the preparation and use of IQNB, however, which may limit the application of this ligand for routine patient studies. These include the extended time period (> 18 hours) between administration and imaging required for maximal cerebral uptake and vascular clearance. To potentially overcome these disadvantages of IQNB, we have developed an analogue of QNB in which one of the phenyl rings is replaced with an iodovinyl moiety. This new analogue ("IQNP") demonstrates high binding affinity for m-AChR *in vitro* and high cerebral uptake, selectivity and specificity for m-AChR *in vivo*. Interest in the use of a high affinity ligand for m-AChR for use in PET studies has prompted preparation of analogues of IQNB which can be radiolabeled with positron-emitting radioisotopes. We have recently evaluated a brominated analogue of IQNP in which iodine is replaced with bromine. This analogue (BrQNP) was observed to block the uptake of radioiodinated IQNP in rat brains (ORNL/TM-12707).

Due to the limited availability of a positron emitting isotope of bromine, fluorine-18 is a more attractive radioisotope for routine PET studies. Although various fluorinated analogues of QNB have been developed, however, the *in vivo* cerebral uptake and distribution of these agents has not yet been reported. Since the replacement of a phenyl ring with an alkyl or alkenyl group has led to analogues of QNB which retain affinity for m-AChR, we have therefore investigated the potential use of an analogue which contains a fluoroalkyl group in place of one of the phenyl rings. The results of *in vitro* binding assays performed with racemic FQNPe are summarized by comparison with data for FQNE in Table 1. These data were determined by Drs. B. Zeeberg and colleagues in a collaborative program with the George Washington University School of Medicine. While both new fluoroalkyl analogues displayed nanomolar affinity for m-AChR, slightly higher affinity was observed with both analogues for the m_1 subtype compared to the m_2 m-AChR subtype. In addition, FQNPe demonstrated a higher affinity for m-AChR relative to FQNE and a similar affinity for m-AChR as QNB. It would thus be expected that FQNPe containing the resolved R-quinuclidinyl ring to demonstrate an increased affinity for m-AChR.

Table 1. *In Vitro* Binding Affinity of FQNP (5) and FQNPe (6), K_d (nM) (Mean \pm SD)

<u>QNB</u>	<u>FQNE</u>	<u>FQNPe</u>
0.32 \pm 0.05	12.5 \pm 3.9	0.45 \pm 0.06
0.20 \pm 2.8	62.8 \pm 2.8	3.53 \pm 0.02

A study was performed by pretreatment of a group of rats with FQNPe at a dose of 2-3 kg/mg one hour prior to the intravenous injection of iodine-125-Z-(R,R)-IQNP. In addition, a group of rats received only iodine-125-Z-(R,R)-IQNP as controls. At three hours post-injection of the radioactive ligand, the rats were killed and the uptake of activity in the brain and heart was evaluated. These results of these studies summarized in Table 2 illustrate that FQNPe was able to effectively block the uptake of activity in the brain and heart by greater than 80 %. From these promising results, development of methods for the introduction of fluorine-18 are currently being pursued for evaluation of the *in vivo* brain uptake, selectivity and specificity of this new fluorinated m-AChR ligand.

Table 2. Regional Levels (Per Cent Injected Dose/gm \pm S.D.) of Radioactivity Three Hours Following Intravenous Administration of [I-125]-Z-(R,R)-IQNP in Control Rats and Rats Pretreated One Hour Earlier With Unlabeled FQNPe (2-3 mg/kg).*

	<u>Blood</u>	<u>Liver</u>	<u>Heart</u>	<u>Lung</u>	<u>Brain</u>
Control	0.16 ± 0.05	0.80 ± 0.25	1.34 ± 0.38	0.69 ± 0.23	1.00 ± 0.34
FQNPe	0.20 ± 0.05	0.70 ± 0.14	0.19 ± 0.05	0.69 ± 0.16	0.21 ± 0.04

* Five Female Fischer rats per time point

HFIR-Produced Tin-117m for Bone Palliation

An important growing area of nuclear medicine is the use of beta-emitting or Auger-emitting radioisotopes for the therapeutic treatment of bone pain from cancer metastases. Cancer cells released from primary tumors at other sites reach the bone through the circulation. Pain is produced by activation of the pain receptors (i.e. nociceptor) through inflammation triggered by the release of bradykinin and other inflammatory substances and pressure from edema. Although reduction of pain is generally not felt to be directly extended to eradication of the cancer cells, the reduction of pain through this palliative process can greatly increase patient quality of life. Such use of therapeutic radioisotopes is also an important alternative to the prolonged use of high levels of anti-inflammatory steroids and pain killing narcotics.

A list of radioisotopes which are under evaluation or are approved for bone palliation is given in Table 3. Strontium-89 is one key agent which had been used for a number of years in Europe before its recent approval by the FDA for use in the use. Other promising agents are rhenium-186 and samarium-153 phosphonates. The use of inexpensive rhenium-188 from the tungsten-188/rhenium-188 is expected to be assessed in the near future. Tin-117m as the tin(IV)-DTPA complex is an additional alternative and is currently in Phase II/III clinical trials for bone pain palliation. Tin-117m is also a reactor-produced "high spin" radioisotope (13/2+). The therapeutic effects of Auger emissions of tin-117m are mediated differently than the other beta-

emitting radioisotopes listed in Table 2. Our recent studies have indicated that the yield of Sn-117m similar to Sn-119m and Pt-195m at hydraulic tube of the HFIR is higher from the $[n, n'\gamma]$ reactions than from the $[n, \gamma]$ reactions. The relative gains in the specific activity were 1.4, 1.6 and 8.3 for Pt-195m, Sn-117m and Sn-119m, respectively. Our experimental data indicate a specific activity of 14.0 mCi/mg for ^{117m}Sn obtained in one cycle irradiation (21d) at 85 MWt power level. This value is extrapolated from 1 h irradiation at 10 MWt power level.

In collaboration with colleagues in the Medical Department at the Brookhaven National Laboratory (BNL), large-scale production of Sn-117m via inelastic scattering reactions are currently under evaluation in the ORNL HFIR, which has a much greater tin-117m production capacity than any other nuclear reactor in North America. During the 1994 fiscal year, eight targets ranging in mass from 4 to 100 mg and enrichment of 87% were irradiated at the position 5 of the HT facility for one reactor cycle each (21 d), and the average yield was 7.9 ± 0.8 mCi/mg of Sn (corresponding to 9.2 mCi/mg of ^{117}Sn). The average yield at saturation was 12.9 ± 1.2 mCi/mg of Sn (Table 4). The irradiated targets were sent to BNL for processing and incorporation into radiopharmaceuticals. Under phase II trials, 16 patients so far have been treated with Sn-117m radiopharmaceutical. These studies are expected to substantially increase since BNL has a Cooperative Research and Development Agreement (CRADA) with Diatech, Inc., for the commercial development, regulatory approval and distribution of this agent for routine clinical use.

Table 3. Reactor Produced Radioisotopes for Bone Palliation

Radio-nuclide	Half-Life (d)	Av. Beta Energy (keV)	Gamma Photon (keV)(%)	Tissue Penetration ^a (mm)	Chemical Form	Clinical status
^{117m} Sn ^b	14.0	160 ^c	158 (86)	0.29	SnDTPA	Phase II/III
¹⁵³ Sm	1.9	290	103 (28)	0.8	Sm-EDTMP	Phase III
¹⁸⁶ Re ^b	3.8	350	many low	1.1	Re(Sn)HEDP	Phase III
⁸⁹ Sr	50.5	580	910 (0.01)	2.4	SrCl ₂	FDA approved
³² P	14.3	700	none	3.0	Na ₂ PO ₄	FDA approved
¹⁸⁸ Re ^b	0.71	768	155 (15)	3.4	Re(Sn)HEDP Re(Sn)MDP Re(IV)DMSA	Protocols Being Formulated

^aAverage penetration in soft tissue

^bCurrently produced at the HFIR

^cConverted electrons

Table 4. Summary of Sn-117m Production

Target I. D.	Target Mass (mg)	HT Level	T _{irr} (h)	Yield (mCi/mg of Sn)	
				EOB	Saturation
NMG-90-40	4.2	5	500	7.0	10.9
BNL-90-7	10.1	6	228	4.5 ^a	13.9 ^b
NM-223	26.0	5	492.5	8.4	13.2
NM-254	67.4	5	404.0	7.1	12.6
NM-259	83.0	5	476.0	8.2	13.1
8/91-1	100.5	5	452.1	8.8	14.5
NM-266	100.5	5	468.7	8.5	13.7
NM-269	86.33	5	474.7	7.2	11.5
			Average	7.9±0.8	12.9±1.2

^aNot included in the average

^bCorrected by a factor of 1.16 for flux difference

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Other Nuclear Medicine Group Activities

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Presentations

IN VIVO METABOLIC EVALUATION OF IODINE-125-LABELED E-(R,R)-IQNP, A HIGH AFFINITY MUSCARINIC LIGAND. D. W. Mcpherson, C. R. Lambert and F. F. Knapp, Jr., Nuclear Medicine Group, Oak Ridge National Laboratory (ORNL), Oak Ridge, Tennessee, USA, submitted.

OPTIMIZED PROCESSING OF REACTOR-PRODUCED TUNGSTEN-188 FOR CLINICAL-SCALE W-188/Re-188 GENERATORS. F. F. Knapp, Jr., A. L. Beets, A. P. Callahan, S. Mirzadeh and B.-T. Hsieh, Nuclear Medicine Group, Oak Ridge National Laboratory (ORNL) Oak Ridge, Tennessee, USA. submitted.

F. F. (Russ) Knapp, Jr., Group Leader of the Nuclear Medicine Program, presented a lecture entitled, "Curie-Scale Tungsten-188/Rhenium-188 Generators Can Cost Effectively Provide Carrier-Free Rhenium-188 for Routine Clinical Applications," at the *Fourth International Symposium on Technetium and Rhenium*, held in Bressenaro, Italy, on September 11-14, 1994. He also co-authored two other papers in conjunction with collaborators describing the labeling of peptides and antibodies with rhenium-188 for cancer therapy. Prior to the symposium, he participated in the European Nuclear Medicine Congress in Dueselldorf on August 21-24, and met with collaborators and presented lectures at several Nuclear Medicine Departments in Germany, including Dresden, Rossendorf,, Bonn, Mainz and Frankfurt, describing the development of new radiopharmaceuticals at ORNL.

Awards

Arnold L. Beets, a member of the ORNL Nuclear Medicine Group, received special recognition on December 15 from the Office of Technology Applications in recognition of his technical contributions for the further development of the tungsten-188/rhenium-188 generator system. His design of improved generator components and an apparatus used for processing the tungsten-188 radioisotope have permitted optimization of the fabrication of large-scale tungsten-188/rhenium-188 generators. Rhenium-188 is one of interest for cancer and arthritis therapy and the generator system has been licensed to Isotope Products Laboratory, Inc.

Visitors

On December 8, 1994, Saed Mirzadeh, a staff member in the ORNL Nuclear Medicine Program, presented an overview of medical radioisotope research and

development at ORNL to a group of representatives from the Japan Science and Technology Agency (JSTA). Apparently, JSTA is seeking to broaden the scope of cooperative R & D with DOE and the aim of this group was to identify new areas of collaborative R & D activities. These JSTA representatives have already visited LLNL and PNL. and they will visit most of the DOE multi-program laboratories. The permission for these exploratory discussions were reportedly approved by the office of Jim Decker at the Energy Research.

October 10, 1994 G. Ting, Ph.D., Institute of Nuclear Energy Research (INER),
Lung tan, Taiwan

December 5-6, 1994 Areeratt Kornduangkaeo, Bangkok, Thailand

Medical Cooperative Shipments

During this period one tungsten-188/rhenium-188 generator was provided to RhoMed, Inc., as part of a CRADA to evaluate rhenium-188 labeling of antibodies and peptides for cancer therapy. Generators were also provided to the Nuclear Medicine Department at the University of Massachusetts (D. Hnatowich, Ph.D.) for a NIH project for rhenium-188-labeled antibodies and one generator was provided to the Paul Scherrer Institute in Villigen, Switzerland (A. Schubiger, Ph.D.) for development of radiolabeling methods. A solution of tungsten-188 was provided to the Institute for Nuclear Energy Research in Lung-Tan, Taiwan (B.-T. Hsieh, Ph.D. and G. Ting, Ph.D.) for ongoing collaborative studies for fabrication of generators. Two shipments of tin-117m (700 mCi each) produced in the ORNL HFIR were provided to the Medical Department at Brookhaven National Laboratory for ongoing patient studies with tin-117m-DTPA for treatment of bone pain from cancer.

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