ornl

OAK RIDGE NATIONAL LABORATORY

MARTIN MARIETTA

ORNL/TM-13053

RECEIVED
NOV 20 1995
OSTI

Nuclear Medicine Program Progress Report for Quarter Ending June 30, 1995

F. F. Knapp, Jr.
K. R. Ambrose
A. L. Beets
H. Luo
D. W. McPherson
S. Mirzadeh

MASTER

MANAGED BY
MARTIN MARIETTA ENERGY SYSTEMS, INC.
FOR THE UNITED STATES
DEPARTMENT OF ENERGY

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

This report has been reproduced directly from the best available copy.

Available to DOE and DOE contractors from the Office of Scientific and Technical Information, P.O. Box 62, Oak Ridge, TN 37831; prices available from (615) 576-8401, FTS 626-8401.

Available to the public from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161.

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.

ORNL/TM-13053

Contract No. DE-AC05-84OR21400

Health Sciences Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING June 30, 1995

F. F. Knapp, Jr.

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

Work sponsored by
DOE Office of Health and
Environmental Research

Date Published-September, 1995

OAK RIDGE NATIONAL LABORATORY
Oak Ridge, Tennessee 37831-6285
managed by
LOCKHEED MARTIN ENERGY SYSTEMS
for the
U.S. DEPARTMENT OF ENERGY

MASTER

Previous reports in this series:

ORNL/TM-5809
ORNL/TM-5936
ORNL/TM-6044
ORNL/TM-6181
ORNL/TM-6371
ORNL/TM-6410
ORNL/TM-6638
ORNL/TM-6639
ORNL/TM-6771
ORNL/TM-6916
ORNL/TM-6958
ORNL/TM-7072
ORNL/TM-7223
ORNL/TM-7411
ORNL/TM-7482
ORNL/TM-7605
ORNL/TM-7685
ORNL/TM-7775
ORNL/TM-7918
ORNL/TM-8123
ORNL/TM-8186
ORNL/TM-8363
ORNL/TM-8428
ORNL/TM-8533
ORNL/TM-8619
ORNL/TM-8746
ORNL/TM-8827
ORNL/TM-8966
ORNL/TM-9037
ORNL/TM-9124
ORNL/TM-9343
ORNL/TM-9394
ORNL/TM-9480
ORNL/TM-9609
ORNL/TM-9707
ORNL/TM-9784
ORNL/TM-9937
ORNL/TM-10082
ORNL/TM-10238
ORNL/TM-10294
ORNL/TM-10377
ORNL/TM-10441
ORNL/TM-10618
ORNL/TM-10711
ORNL/TM-10839
ORNL/TM-11014
ORNL/TM-11043
ORNL/TM-11145
ORNL/TM-11224
ORNL/TM-11304
ORNL/TM-11377
ORNL/TM-11427
ORNL/TM-11550
ORNL/TM-11570
ORNL/TM-11721
ORNL/TM-11755
ORNL/TM-11830
ORNL/TM-11881
ORNL/TM-11992
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
ORNL/TM-12909
ORNL/TM-12965

CONTENTS

Summary 5

Synthesis of (-)(-) and (-)(+) Isomers of FQNPe - A Potential Ligand for Imaging of Muscarinic Cholinergic Receptors by Positron Emission Tomography (PET) 6

HFIR Production of Molybdenum-99 13

Literature Cited 16

Other Nuclear Medicine Group Activities 16

- Recent Publications 16
- Presentations 16
- Medical Cooperative Shipments 17
- Visitors and Guest Assignments 18

SUMMARY

In this report we describe the first synthesis of the (-)(-) and (-)(+) isomers of 1-azabicyclo[2.2.2]oct-3-yl α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate ("FQNPe"). Earlier studies with the racemic FQNPe mixture had demonstrated high *in vitro* binding affinity for the muscarinic-cholinergic receptor and showed that pre-treatment of rats with this new agent significantly blocked receptor localization of subsequently injected [I-131]-Z-(-,-)-IQNP. Because of the potential important use of fluorine-18-labeled analogues for clinical evaluation of changes in muscarinic-cholinergic receptors by positron emission tomography (PET), we have now synthesized the diastereomeric isomers of FQNPe. Multi-gram quantities of ethyl-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetate were prepared and then saponified into the racemic α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid mixture. The racemic acid was resolved into (-)- and (+)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid enantiomers by isolation of the (-) salt of (S)-(-)-α-methylbenzylamine and the (+) salt of (R)-(+)-α-methylbenzylamine. The resolved (-)- ($[\alpha]_D$ =-12.1°, c = 5.8, chloroform) and (+)-acetic acids ($[\alpha]_D$ = +11.6°, c = 6.0, chloroform) were fully characterized and then converted to the enantiomeric ethyl-α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetates by a four-step reaction sequence. The (-)- and (+)-ethyl-α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetates were then each transesterified with (-)-quinuclidinol to form the (-)(-) FQNPe and (-)(+) FQNPe diastereomers. These diastereomeric esters will now be evaluated in *in vitro* studies. The availability of the substrates for preparation of the fluorine-18-labeled enantiomers will now allow evaluation of the radiolabeled compounds in animals.

During this period several radioisotopes and generators were also provided to collaborators for several on-going Medical Cooperative Programs, including rhenium-186, provided to RhoMed, Inc., as part of a CRADA. In addition, tungsten-188/rhenium-188 generators were provided to Hospital de Clinica, in Montevideo, Uruguay, and the Radiopharmaceutical Research Group at the Paul Scherrer Institute in Villigen, Switzerland. Two samples of tin-117m were provided to the Medical Department at Brookhaven National Laboratory, for preparation of tin-117m for Phase II patient studies for bone palliation in conjunction with a CRADA between BNL and Diatech, Inc.

Synthesis of (-)(-) and (-)(+) Isomers of FQNPe - A Potential Ligand for Imaging of Muscarinic Cholinergic Receptors by Positron Emission Tomography (PET)

We recently reported the synthesis of the "FQNE" and "FQNPe" fluoroalkyl analogues of QNB (1 in Figure 1) (ORNL/TM-12909). This project, being pursued by Dr. H. Luo, a Distinguished Alexander Hollaender Postdoctoral Fellow working in the Nuclear Medicine Group, is based on our earlier development of "IQNP", in which the iodophenyl ring of IQNB (2) had been replaced with the iodopropenyl moiety (ORNL/TM-12110,-11811, and -11992). The FQNE (5) and FQNPe (6) analogues are based on a similar concept involving the replacement of a phenyl ring with a linear substituent in which fluorine is attached as a terminal fluoroalkyl group (Figure 1). Our initial studies of these new fluoroalkyl analogues in rats involved pre-blocking with racemic FQNE and FQNPe prior to administration of [I-131]-Z-(-,-)-IQNP. The results showed that pretreatment with the racemic fluorinated analogues blocked uptake of the radioiodinated ligand, and also indicated that FQNPe was a better blocking agent than FQNE. In addition, *in vitro* binding studies in conjunction with collaborators at the George Washington University Medical Center (Drs. B. Zeeberg and R. Reba, et al.) demonstrated higher binding affinity of FQNPe compared with FQNE for the cholinergic receptor subtypes. In addition to the more promising *in vivo* blocking and *in vitro* binding studies, results using FQNPe in comparison with FQNE, it was envisioned that fluorine-18 could be more readily incorporated into the five carbon chain-length FQNPe analogue. For these reasons FQNPe was chosen as the target compound for further study. Because of the potential importance of the new FQNPe ligand for imaging of muscarinic ligands by PET, we have now completed the synthesis and characterization of the two major diastereomeric FQNPe esters which are expected to be the major active isomers found in the racemic mixture.

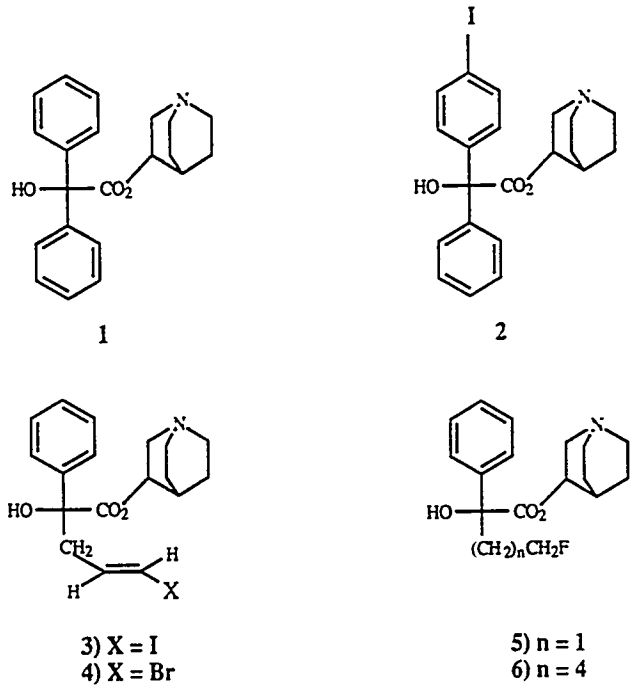

Figure 1. Structures of QNB Analogues

The synthesis of the FQNPe enantiomers is based on our earlier synthesis of the racemic FQNPe mixture (ORNL/TM-12909). Ethyl-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetate was synthesized by reaction of ethylbenozylformate with phenylmagnesium bromide. The yield of the Gringard product was low (10-15 %), and attempts to prepare this key intermediate by Reformatsky conditions or other alternative routes have been unsuccessful. The products of several Grignard reactions were therefore pooled and purified by column chromatography to yield 13 grams of the purified racemic ethyl-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetate which was converted to the racemic acid by basic hydrolysis. Resolution into the corresponding (-) and (+) acid isomers was accomplished by treatment of the racemic α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid mixture with (S)-(-)-α-methylbenzylamine as had been initially used in our successful resolution of the isomers of IQNP (ORNL/TM-12411). The initial crystals were re-

crystallized from $H_2O:C_2H_5OH$ (7.5:2.5) to provide (-)-(-) diastereomer salt (Table 1). The free acid obtained from the mother liquor by treatment with dilute HCl was then reacted with (R)-(+)-methylbenzylamine to provide the (+)(+) diastereomeric salt which was re-crystallized from $H_2O:C_2H_5OH$ (7.5:2.5)(Table 1). As expected the (-)(-) and (+)(+) diastereomeric salts had similarl rotations of opposite sign (Table 1). The final enantiomers were fully characterized.

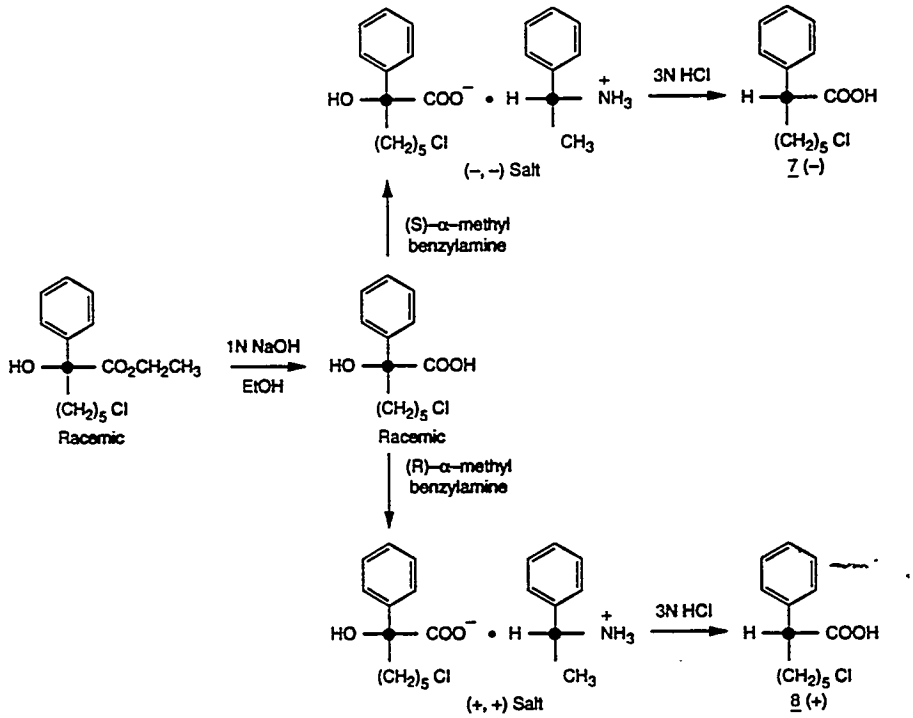

Figure 2. Synthesis of enantiomers of α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid

Analysis of the proton NMR spectra of the (-)(-) and (+)(+) diastereomeric salts provided additional information which could be used to differentiate the configuration of the acetate moiety of the two diastereomeric salts (Figure 3). While the chemical shift of the *ortho* aromatic proton in the ^1H spectrum of the (+)(-) salt exhibited a resonance at 7.51 ppm, this two proton pattern was observed at 7.41 ppm in the spectrum of the (+)(+) salt. This assignment was confirmed by freeing the (+) acid from the (+)(+) salt and forming the (+)(-) salt with the (S)-(-)-α-methylbenzylamine. Similarly, while the chemical shift of the *ortho* aromatic proton in the ^1H spectrum of the (-)(+) salt exhibited a resonance at 7.51 ppm, these two protons

were moved to 7.42 ppm in the spectrum of the (-)(-) salt. This assignment was also confirmed by freeing the (-) acid from the (-)(-) salt and forming the (-)(+) salt with the (R)-(+)-α-methylbenzylamine. The specific rotation values and melting point of these four diastereomeric salts are summerized in Table 1. The configuration at the acetate center as well as an indication of the diastereomeric purity can thus be assessed by examination of the chemical shift of the *ortho* aromatic protons from the benzene ring of the acetic acid moiety in the proton NMR spectra.

Table 1. Specific Rotation* ($[\alpha]_D$) and Melting Point of Four Diastereomeric Salts

Diastereomeric Salts	$[\alpha]_D$ (°)	c gm/ml	MP (°)
(-)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid (S)-(-)-α-methylbenzylamine salt	-7.27	1.10	155-156
(+)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid (R)-(+)-α-methylbenzylamine salt	+6.06	1.15	155
(-)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid (R)-(+)-α-methylbenzylamine salt	-11.15	1.44	112-113
(+)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid (S)-(-)-α-methylbenzylamine salt	+11.30	1.51	116-117

* All samples were dissolved in chloroform

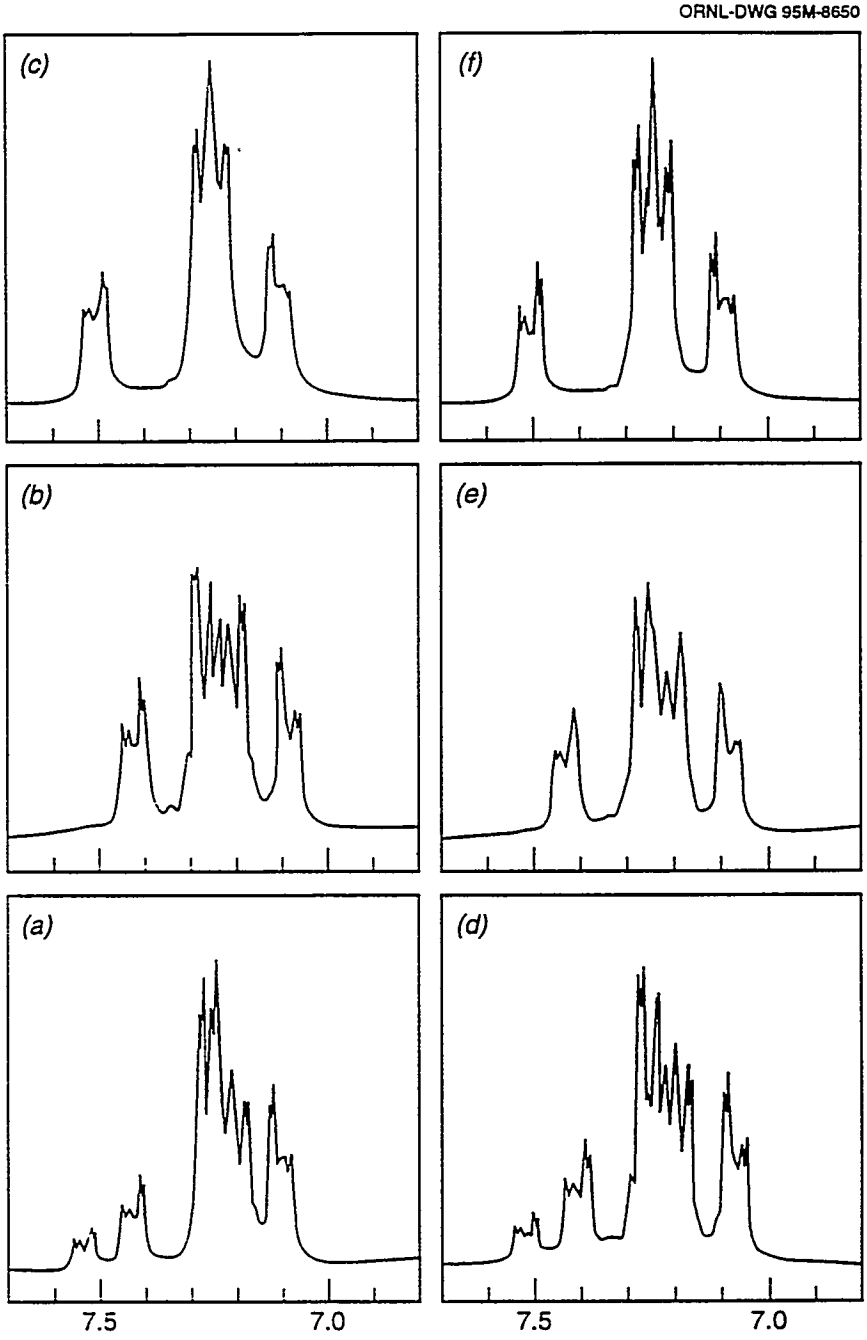

Figure 3. Selected downfield regions of the proton NMR spectra of initial impure (-)(-)- salt (a), purified (-)(-) salt (b), (+)(-) salt (c), initial impure (+)(+) salt (d), purified (+)(+) salt (e), and (-)(+) salt (f).

The two enantiomeric acetic acid moieties were then released from the diastereomeric salts to provide the (+)- and (-)- α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid isomers, which were each converted to the corresponding ethyl α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetate enantiomers (9 & 10 in Figure 4) by esterification in ethanol. The stepwise treatment of 9 and 10 with sodium iodide, silver p-toluenesulfonate, and tetrabutylammonium fluoride afforded the desired fluorinated ethyl α-hydroxyester enantiomers (11 & 12). The proposed structures of each intermediate were confirmed by NMR (see Table 2). The final step in the preparation of the (-)(-)- and (-)(+)-1-azabicyclo[2.2.2]oct-3-yl α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate isomers [(-)(-)- and (-)(+)-"FQNPe"] involved transesterification with (-)-quidnuclidinol. The racemic quinuclidinol was resolved into (+) and (-)-3-quinuclidinol isomers as described earlier by treatment with tartaric acid (ORNL/TM-12909). Synthesis of the diastereomeric quinuclidinol esters was then accomplished as shown in Figure 4. Both diastereomeric quidnuclidinol esters have been fully characterized, and all data are consistent with the proposed structures.

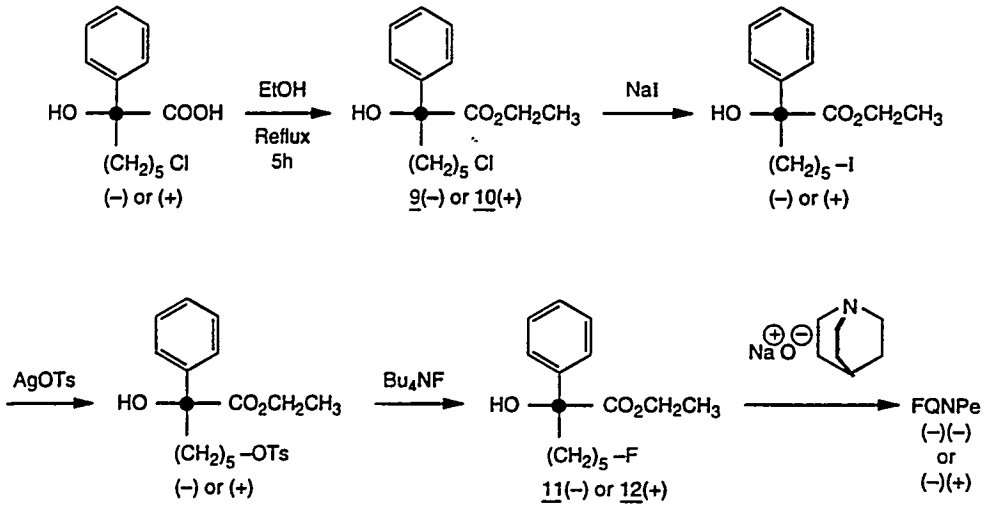

Figure 4.Synthesis of (-)(-)- and (-)(+)-diastereomers of 1-azabicyclo[2.2.2]oct-3-yl α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate [(-)(-)- and (-)(+)-("FQNPe"]

Table 2. Specific Rotation Values for intermediators and FQNPe Diastereomers*

Compound		$[\alpha]_D$ (°)	c 10mg/ml
(-)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetic acid	(-)	-12.1	5.80
	(+)	+11.6	6.05
ethyl-(-)-α-(1-chloropent-5-yl)-α-hydroxy-α-phenylacetate	(-)	-17.4	8.06
	(+)	+19.3	9.31
ethyl-(-)-α-(1-iodopent-5-yl)-α-hydroxy-α-phenylacetate	(-)	-14.1	11.30
	(+)	+15.5	9.66
ethyl-(-)-α-(1-tosyloxypent-5-yl)-α-hydroxy-α-phenylacetate	(-)	-12.0	8.30
	(+)	+12.2	6.56
ethyl-(-)-α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate	(-)	-23.7	1.31
	(+)	+23.7	1.14
(-)(-)-1-azabicyclo[2.2.2]oct-3-yl α-(1-fluoropent-5-yl)-α-hydroxy-α-phenylacetate, (-)(-)-FQNPe	(-)	-11.72	1.28
(-) (+)-FQNPe	(+)	+24.14	1.16

* All samples were dissolved in chloroform

HFIR Production of Molybdenum-99

Because the fission route produces high levels of radioactive waste, there are distinct long-term advantages for the routine production of ^{99}Mo via neutron capture by an enriched ^{98}Mo target. For fabrication of $^{99}Mo/^{99m}Tc$ generators, the principal issue which differentiates fission-produced ^{99}Mo from the direct neutron capture route is specific activity. The specific activity of ^{99}Mo attainable at HFIR via neutron capture reaction are summarized in Table 2. These data indicate that specific activities of 50-100 mCi/mg of ^{98}Mo can be reached within 3 days of irradiation in the hydraulic tube of the HFIR.

Although molybdenum-99 used in the United States is produced in Canada from fission of uranium, there are distinct long-term advantages for routine production of molybdenum-99 by neutron activation of enriched molybdenum-98 targets. For fabrication of molybdenum-99/technetium-99m generators, the principal issue which differentiates fission-produced Mo-99 from neutron-activated production of molybdenum-99 is specific activity. Since the fission route produces high levels of radioactive waste, the preferred route for molybdenum-99 production would be expected to be neutron-activation, <u>if sufficient specific activity could be attained.</u> With its very high neutron flux, the HFIR offers an opportunity for routine production of molybdenum-99 by neutron activation with high enough specific activity for generator fabrication. Experimental production yields are summarized in Table 3. A comparison of the experimental and theoretical data is shown in Figure 5. Theoretical calculations were performed for position 5 of the HT with thermal neutron flux of 2.0×10^{15} $n.s^{-1}.cm^{-2}$ and thermal-to-epithermal ratio of 25. Contributions from burn-up of ^{99}Mo and depletion of ^{98}Mo were included in the computation. For sake of comparison, the experimental yields were adjusted to represent the yields expected for position 5 of the HT.

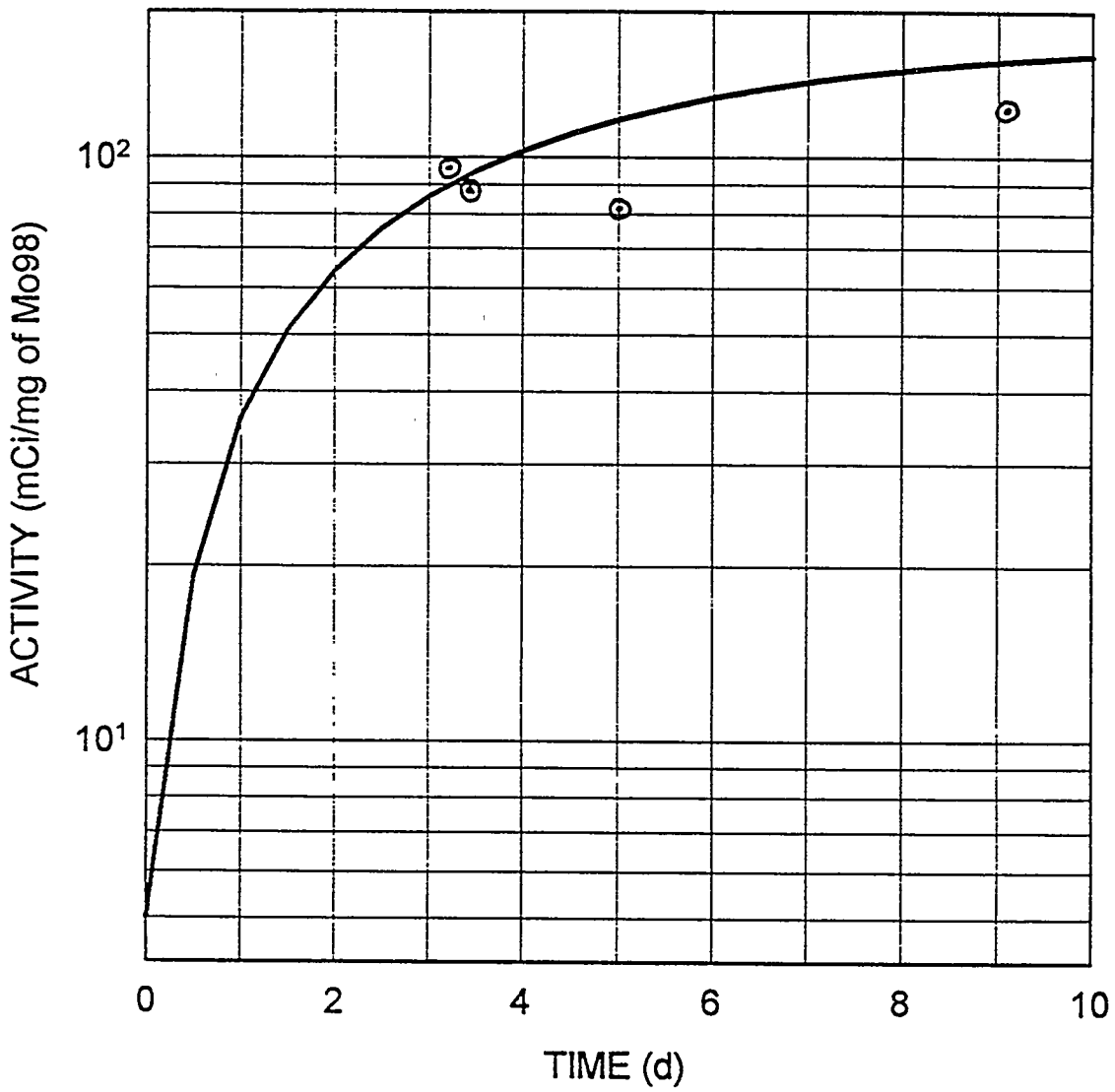

Figure 5. Comparison of experimental values (data points) and the theorectical curve for HFIR production of molybdenum-99 from irradiation of molybdenum-98. Experimental values are extrapolated to position number 5.

Table 3. Summary of HFIR Production of ^{99}Mo [a]

	^{98}Mo Target as MoO_3				Yield at EOB ($mCi.mg^{-1}$)	
Expt. No.	Mass (mg)	Enrich. (at. %)	HT Level	T_{irr}	Exp.	Exp./Theo.
1	11.5	98.5	(2)	9.1d	6.58×10^{1}	0.90
2	11.5	97.6	(8)	5.0 d	5.30×10^{1}	0.71
3	9.6	97.3	(8)	3.2 d	6.23×10^{1}	1.10
4	7.3	97.3	(4)	3.3 d	7.88×10^{1}	0.97

[a] Reactor power level = 98 MWt

Literature Cited

1. Luo, H., et al, Nucl. Med. Biol, *in press.*

Other Nuclear Medicine Group Activities

Publications

Knapp, F. F. Jr. and Kropp, J. "Iodine-123-Labeled Fatty Acids for Myocardial Single-Photon Emission Tomography: Current Status and Future Perspectives, "*Invited Review*, Eur. J., Nucl. Med., 22, 361-381 (1995).

Knapp, F. F. Jr., "Mycardial Metabolish of BMIPP," *Invited Editorial*, J. Nucl. Med., 36, 1051-1054 (1995).

Knapp, F. F. Jr., Franken, P. and Kropp, J., Cardiac SPECT with Iodine-123-Labeled Fatty Acids - Evaluation of Myocardial Viability with BMIPP," *Clinical Commentary*, J. Nucl. Med., 36, 1022-1030 (1995).

Presentations

Dr. F. F. Knapp, Jr., Group Leader of the ORNL Nuclear Medicine Program, presented *Invited Lecture* at the special symposium on "Basic and Clinical Findings with Iodine-123-BMIPP", hosted by Nihon Medi-Physics, Inc. in conjunction with the Second International Symposium of Nuclear Cardiology, held in Cannes, France on April 22-28, 1995. On May 7-12, 1995, he presented a lecture on reactor-produced medical radioisotopes for therapeutic applications at the "International Conference on Isotopes," held in Beijing, China, and also served as co-chairman for the Radiopharmaceutical Session. In addition, during this period he presented invited lectures at the clinic for Nuclear Medicine at the medical university in Shanghai, and at the Institute for Nuclear Research, presented an Invited Lecture on the ORNL development and

evaluation of new radiopharmaceuticals for evaluating muscarinic-cholinergic receptors, at the Fifth Meditteranean Symposium on Nuclear Medicine and Radiopharmaceuticals, held in Athens, Greece, on May 22-28, 1995.

Dr. D. W. McPherson, a staff member of the ORNL Nuclear Medicine Program who worked as a Guest Scientist at the Clinic for Nuclear Medicine in Ulm, Germany during the June 1994- June 1995 period, presented a lecture on the development of new radiohalogenated legands for imaging muscarinic-cholinergic receptors on March 29, 1995, at the Department of Imaging Research in Pharmacology and Physiology, at the Hospital Frederic Joliot, of the French Atomic Energy Agency in Orsay, France.

Medical Cooperative Shipments

During this period several HFIR-produced radioisotopes and radioisotopes generator systems were provided to collaborators. Samples of tin-117m were provided to the Medical Department at the Brookhaven National Laboratory on April 18 (600 mCi) and May 9 (400 mCi) for preparation and patient use of Sn-117m-DTPA for palliative treatment of bone pain. On April 27, 100 mCi of rhenium-186 perrhenate solution was provided to RhoMed, Inc., for peptide radiolabeling through a DOE-supported Cooperative Research and Development Agreement (CRADA). Tungsten-188/rhenium-188 generators were provided for collaborative research projects to the Paul Scherrer Institute in Villigen, Switzerland (A. Schubiger, Ph.D.) to provide carrier-free rhenium-188 for labeling new ligands with Re(I) and to the University Hospital in Montevideo, Uruguay (Gaudiano, M.D.) for optimization of phosphonate radiolabeling in anticipation of initiation of clinical trials for bone palliation.

Visitors and Guest Assignments

Several visiting scientists and students joined the Nuclear Medicine Program during this period. Joachim Kropp, M.D., who has collaborated with the ORNL Nuclear Medicine Program since 1986, visited for one week beginning June 5, to complete several manuscripts and protocols for on-going collaborative studies. On May 1, Ekaterina Dadachova, Ph.D., a radiochemist from the Australian National Science and Technology Organization (ANSTO), joined the ORNL Nuclear Medicine Program for six months to work on joint collaborative projects. On May 29, Qun Lin, Associate Professor at Xavier University in New Orleans, Louisiana, began working for a three month period on the synthesis of radiopharmaceutical substrates. Students who joined the program for the summer included Jason McAllister (Duke University), Donald Marsh (University of Tennessee) and Pedro Rivera Matos (University of Puerto Rico). In addition, visitors included Elena S. Kalevich, Prof. Yeugeny A. Karelin, and Dr. Rostislav A. Kuznetzoo from the research reactor in Ulyanovsh, Russia.

ORNL/TM-13053

INTERNAL DISTRIBUTION

1. C. W. Alexander
2. K. R. Ambrose
3. A. L. Beets
4. B. A. Berven
5. E. D. Collins
6. K. F. Eckerman
7-11. F. F. Knapp, Jr
12. H. Luo
13. D. W. McPherson
14. S. Mirzadeh
15. B. Patton
16. G. Prosser
17. D. E. Reichle
18. P. S. Rohwer
19. R. E. Swaja
20. S. J. Wolfe
21-23. Central Research Library
24. Document Record Section
25-27. Laboratory Records Dept
28. Lab Records, ORNL - RC
29. ORNL Patent Section

EXTERNAL DISTRIBUTION

30. S. James Adelstein, M.D., Department of Radiology, Harvard Medical School, Boston, MA 02115
31. H. L. Atkins, M.D., Radiology Dept., State Univ. of New York, Stony Brook, NY 11794-8460
32 H. J. Biersack, M.D., Director, Klinik fuer Nuklear Medizin, Der Universitaet Bonn, Sigmund Freud Strasse 25, 53127, Bonn 1, Germany
33. A. Bockisch, Ph.D., M.D., Klinik und Poliklinik fuer Nuklearmedizin, Postfach 39 60, Langenbeckstrasse 1, 55101 Mainz, Germany
34. C. Brihaye, Centre de Recherches du Cyclotron, Universite de Liege, Belgium
35. A. B. Brill, M.D., Ph.D., Dept. of Nuclear Medicine, Univ. of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01655
36. T. F. Budinger, M.D., MS 55/121, Lawrence Berkeley Laboratory, 1 Cyclotron Road, Berkeley, CA 94720
37. A. P. Callahan, Route 1, Box 305, Harriman, TN 37748
38. D. Cole, Medical Applications and Biophysical Research Division, ER-73, Department of Energy, GTN, Washington, D.C. 20585-1290
39. B. Coursey, National Institute for Standards and Technology, Building 245, RM C214 Gaithersburg, MD 20899
40. J. G. Davis, M.D., Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37831
41. R. F. Dannals, Division of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, MD 21205-2179

42. S.J. DeNardo, M.D., University of California, Davis Medical Center, 4301-X Street, FOCB II-E Sacramento, CA, 95817
43. R. Dudczak, M.D., Dept. Nuclear Medicine, I. Medizinische Universitatsklinik, A-1090 Wien, Lazarettgasse 14, Vienna, Austria
44. G. Ehrhardt, Missouri University Research Reactor, University of Missouri, Research Park, Columbia, MO 65211
45. D. R. Elmaleh, Physics Research Dept., Massachusetts General Hospital, Boston, MA 02114
46. L. Feinendegen, Medical Department, Brookhaven National Laboratory, Upton, NY 11973
47. A. Fritzberg, NeoRx Corporation, 410 West Harrison, Seattle, WA 98119
48. D. M. Goldenberg, M.D., Center of Molecular Medicine and Immunology, 1 Bruce Street, Newark, NJ 07103
49. G. Goldstein, DOE-OHER, Washington, DC 20585
50. G. Griffiths, Immunomedics, Inc., 300 American Rd, Morris Plains, NJ 07950
51. J. Hiltunen, Managing Director, MAP Medical Technologies, Inc., Elementtitie 27, SF-41160 Tikkakoski, Finland
52. Bor-Tsung Hsieh, Ph.D., Institute of Nuclear Energy Research, (INER) Lung-Tan, Taiwan, Republic of China
53. K. Hubner, M.D., Department of Radiology, UT Memorial Hospital, Knoxville, TN 37920
54. J. M. R. Hutchinson,Ph.D., U. S. Dept. of Commerce, National Institute of Standards and Technology, Gaithersburg, MD 20899-0001
55. B. Johannsen, Ph.D., Forschungszentrum Rossendorf e.V.Postfach 51 01 19, D-01314 Dresden, Federal Republic of Germany.
56. A. Jones, HMS Radiology Dept., Shields Warren Radiation Laboratory, 50 Binney Street, Boston, MA 02115
57. G. W. Kabalka, Chemistry Department, University of Tennessee, Knoxville, TN 37996-1600
58. G. Kirsch, Department of Chemistry, Universite de Metz, Metz, France
59. J. Kropp, M.D., Klinik fur Nuklearmedizin, der Medizinischen Akademie, Fetscher - Str. 74, 01307 Dresden, Germany
60. D. E. Kuhl, M.D., Division of Nuclear Medicine, University of Michigan Hospitals, University Hospital BIG 412/0028, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0028
61. C. Lambert, 119 Montclair Blvd., Savannah, GA 31419
62. R. Lambrecht, Ph.D. Pet-Zentrum des Universitaetsklinikum, Eberhard-Karls-Universitaet Tuebingen, 15 Roentgenweg, Tuebingen 72076, Germany
63. S. Larson, M.D., Sloan-Kettering Inst. for Cancer Research, New York, NY 10021
64. E. C. Lisic,Ph.D., Department of Chemistry, Tennessee Technological University, Cookeville, Tennessee 38505
65. J. Lister-James, Ph.D., Director, Research Administration, Diatech, Inc., 9 Delta Drive, Londonderry, New Hampshire 03053
66. O. Lowe, Isotope Production and Distribution Program, U.S. Department of Energy, NE-46, GTN, Room B-419, Washington, D. C. 20585-1290
67. G. Limouris, Nuclear Medicine Department, Areteion University Hospital, Athens Medical School, Athens, Greece

68. D. J. Maddalena, FRACI, Department of Pharmacology, Sydney University, NSW 2006, Sydney, Australia
69. John Maddox, 4608 Flower Valley Drive, Rockville, MD 20853-1733.
70. H.-J. Machulla, Eberhard-Karls-Universität Tübingen, Radiologische Universitätsklinik, Pet-Zentrum, Röntgenweg 11, 7400 Tübingen, Germany
71. Frederick J. Manning, National Academy of Sciences, Institute of Medicine, 2101 Constitution Ave., M.W., Washington, D.C. 20418
72. M. Meyer, M.D., Biomedical Research Foundation, P.O. Box 38050, Shreveport, LA 71133-8050
73. Office of Assistant Manager for Energy Research and Development DOE-ORO, Oak Ridge, TN 37831
74. G. Notohamiprodjo, M.D., Ph.D., Institute of Nuclear Medicine, Heart Center North Rhine-Westphalia, Bad Oeynhansen, D-4970, Germany
75. C. L. Partain, M.D., Professor and Vice Chairman, Dept. Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN 37232
76. R. C. Reba, M.D., Department of Radiology, 5841 S. Maryland Ave., MC 2026, Chicago, IL 60637
77. S. N. Reske, M.D., Klinik für Nuklearmedizin, Arztlicher Direktor der Nuklearmedizin, Klinikum der Universität Ulm Oberer Eselsberg, D-7900, Ulm, Germany
78. M. P. Sandler, M.D., Chief, Nuclear Medicine Section, Vanderbilt University Medical Center, Nashville, TN 37232
79. R. E. Schenter, HO-37, Westington Hanford Co., P.O. Box 1970, Richland, WA 99352
80. A. Serafini, Nuclear Medicine Division (D-57), University of Miami School of Medicine, P. O. Box 016960, Miami, FL 33101
81. S. K. Shukla, Prof., Servizio Di Medicina Nucleare, Ospedale S. Eugenio, Pizzale Umanesimo, 10, Rome, Italy
82. S. Smith, Biomedicine & Health Program, Australian Nuclear Sci. & Tech. Org., Lucas Heights Research Laboratories, Private Mail Bag 1, Menai NSW 2234, Australia
83. J. Smith, Ph.D., Research & Development, DuPont Merck Pharmaceutical Company, 331 Treble Cove Rd., North Billerica, MA 01862
84. A. Solomon, M.D., UT MRCH, 1924 Alcoa Highway, Knoxville, TN 37920-6999
85. P. Som, DVM, Medical Department, BNL, Upton, NY 11973
86. P. C. Srivastava, DOE-OHER, Washington, DC 20585
87. S. C. Srivastava, Bldg. 801, Medical Dept., BNL, Upton, NY 11973
88. G. Strathearn, Isotope Products Laboratories, Inc., 3017 N. San Fernando Blvd., Burbank, CA, 91504.
89. H. W. Strauss, M.D., Vice President, Diagnostics, Pharmaceutical Research Institute, Bristol Meyers Squibb, Rt. 2 Provinceline Road, P.O. Box 4000, Princeton, New Jersey 08543-4000

90-91. Office of Scientific and Technical Information, DOE, Oak Ridge, TN 37831

92. E. A. van Royen, M.D., Ph.D., Head, Department of Nuclear Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam ZO, The Netherlands.

93. F. C. Visser, M.D., Cardiology Dept., Free University Hospital, De Boelelaan 117, Amsterdam, The Netherlands
94. H. N. Wagner, Jr., M.D., Div. of Nuclear Medicine, Johns Hopkins Medical Institutions, 615 N. Wolfe Street, Baltimore, MD 21205-2179
95. A.P. Wolf, Chemistry Department, Brookhaven National Laboratory, Upton, NY 11973
96. R. Wolfangel, Mallinckrodt, Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
97. J.-I. Wu, Ph.D., Senior Research Representative, Nihon Medi-Physics Co., Ltd., 2200 Powell Street, Suite 765, Emeryville, CA 94608.
98. S. Wynchank, Research Institute for Medical Biophysics (RIMB), Republic of South Africa
99. Y. Yonekura, M.D., Kyoto University Faculty of Medicine, Shogoin, Sakyo-kuy, Kyoto, 606-01, Japan