ornl

ORNL/TM-11014

OAK RIDGE
NATIONAL
LABORATORY

MARTIN MARIETTA

Nuclear Medicine Program Progress Report for Quarter Ending June 30, 1988

F. F. Knapp, Jr.

K. R. Ambrose
A. P. Callahan
J. F. Allred
S. L. Blystone
E. C. Lisic
D. W. McPherson
P. C. Srivastava
D. E. Rice
C. J. Rogers
G. Umbricht

OAK RIDGE NATIONAL LABORATORY
CENTRAL RESEARCH LIBRARY
CIRCULATION SECTION
4500N ROOM 175
LIBRARY LOAN COPY
DO NOT TRANSFER TO ANOTHER PERSON
If you wish someone else to see this report, send in name with report and the library will arrange a loan.

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

Printed in the United States of America. Available from
National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road, Springfield, Virginia 22161
NTIS price codes—Printed Copy: A02 Microfiche A01

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-11014

Contract No. DE-AC05-84OR21400

Health and Safety Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING JUNE 30, 1988

F. F. Knapp, Jr., Group Leader

K. R. Ambrose
A. P. Callahan
D. W. McPherson
P. C. Srivastava

J. F. Allred
S. L. Blystone
E. C. Lisic
D. E. Rice
C. J. Rogers
G. Umbricht

Work sponsored by
DOE Office of Health and
Environmental Research

Date Published - February 1989

NOTICE This document contains information of a preliminary nature. It is subject to revision or correction and therefore does not represent a final report.

OAK RIDGE NATIONAL LABORATORY
Oak Ridge, Tennessee 37831
operated by
MARTIN MARIETTA ENERGY SYSTEMS, INC.
for the
U.S. DEPARTMENT OF ENERGY

MARTIN MARIETTA ENERGY SYSTEMS LIBRARIES

3 4456 0284642 8

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

CONTENTS

Page

Summary 1

Synthesis of Bifunctional Chelating Agents for Copper and Rhenium Labeling of Monoclonal Antibodies 2

Metabolism of Radioiodinated Iodophenyl-Substituted Fatty Acids in Isolated Rat Hearts 6

Agents for Medical Cooperative Programs 8

Agents Prepared for Cost-Recovery Through the ORNL Isotopes Distribution Office 8

Other Nuclear Medicine Group Activities 8

SUMMARY

This report describes our initial studies on developing techniques of attaching radioisotopes of copper (Cu-64 and Cu-67) and rhenium (Re-186 and Re-188) to proteins. Our work has focussed on the synthesis of para-carboxyalkylphenylglyoxal-bis-(N^4-methylthiosemi-carbazone) ligands (TSC). Because of the strong binding of Cu(II) to the bis-TSC ligand, the development of bifunctional chelates for attachment of radioisotopes of copper to antibodies is of interest. We have developed an improved synthesis of the requisite α-ketoaldehyde and 1,2-diketone substrates used for derivatization to the bis-TSC ligand chelates. This approach uses the "Kornbloom" method which provides a simple alternative to the usual method for fabrication of the 1,2-bis-thiosemicarbazone compounds and avoids the use of selenium dioxide for oxidation of substituted acetophenones. Acylation of the -phenyl carboxylic acid with bromoacetyl chloride or 2-bromopropionyl chloride followed by treatment with silver nitrate readily provides the nitrate esters. Oxidative elimination with sodium acetate in DMSO then provides the α-ketoaldehyde or 1,2-diketo products. The overall yields are in the 40-60% range.

Also in this report are the results of studies with the Langendorff-perfused rat heart system. Comparison of the incorporation of [I-131]IPPA and [I-125]BMIPP in dual-labeled studies under normoxia and hypoxia (pO_2 > 120 mm) clearly showed the expected preferential incorporation into triglyceride (TG) storage products. Basic hydrolysis of the TG fraction purified by chromatography showed release of the radioactivity into products chromatographing in the free fatty acid fraction.

Shipments of radioactive agents during this period to Medical Cooperative investigators included [I-125]-N-phenylmaleimide to the University of Michigan and [I-125]-(p-iodophenyl)pentadecanoic acid to the University of Bonn, West Germany.

SYNTHESIS OF BIFUNCTIONAL CHELATING AGENTS FOR COPPER AND RHENIUM LABELING OF MONOCLONAL ANTIBODIES

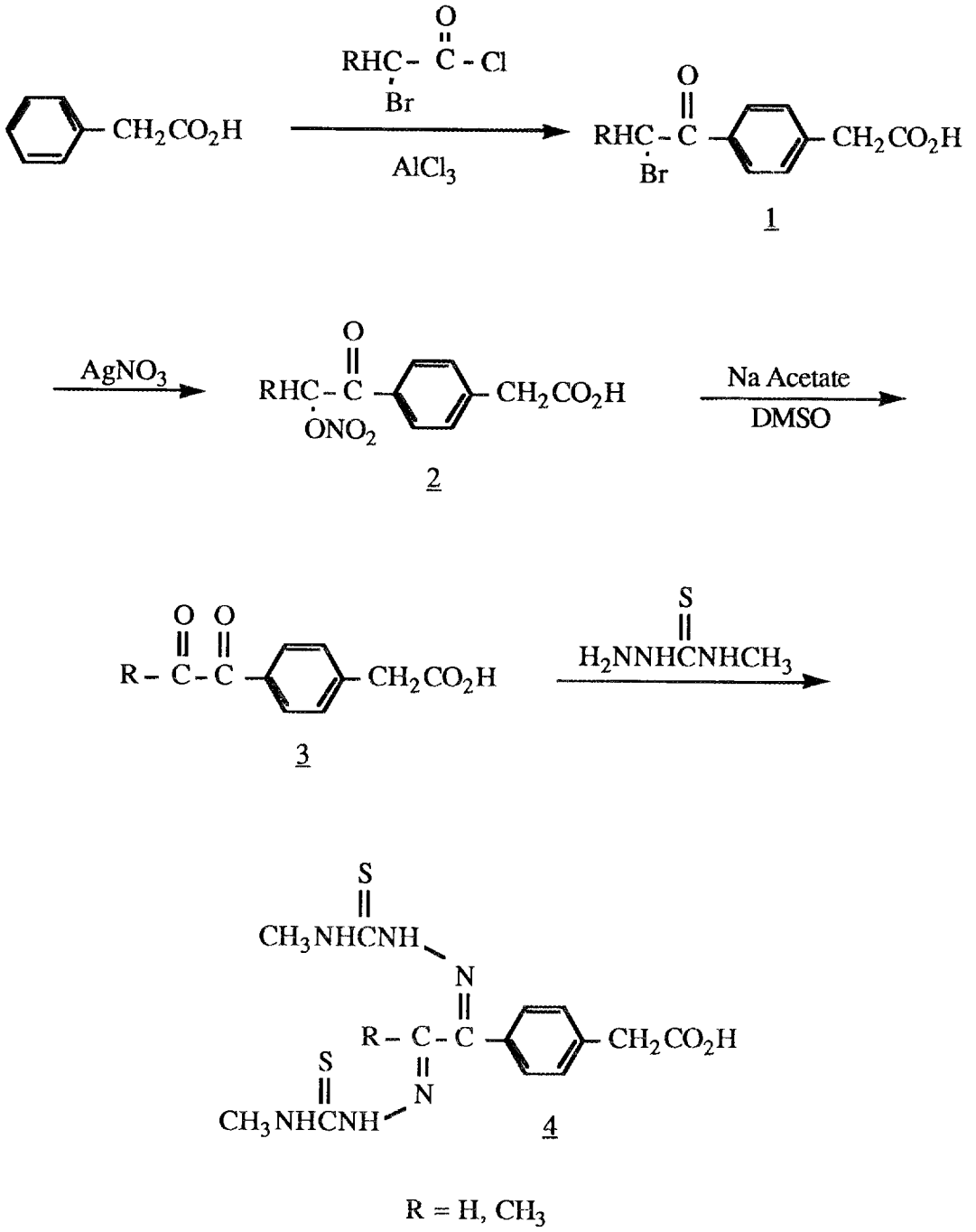
Monoclonal antibodies labeled with isotopes for both therapy and imaging purposes are important tools for cancer research and treatment. With a limited number of radionuclides such as radioiodine and technetium-99m, direct radiolabeling of antibodies is possible. Using this method, iodine-131 or iodine-125 is often incorporated onto tyrosine residues of antibodies. One major disadvantage of this technique is that the radionuclide can become detached from the antibody on exposure to physiological conditions. In addition, the direct-labeling approach cannot be used for the attachment of many other radionuclides of interest. For the metallic radioisotopes, the antibody is coupled with a chelating agent that can bind metallic radionuclides. This type of chelating agent is referred to as a "bifunctional ligand," and with this method one is able to design an agent in which the radionuclide attachment is stable to physiological conditions. This method also allows a large number of different radioisotopes to be attached to the antibody (e.g., Tc-99m, Re-188, Cu-67, Cu-64 or In-111).

Because copper-64 is one of the few long-lived positron emitters (12.7 h) our interest has focussed on the possible use of Cu-64 for labeling tumor-specific antibodies for imaging by positron emission tomography (PET). The attractive feature for use of Cu-64 is it's compatibility with the usual prolonged period between administration and imaging (24-48 h) required to allow vascular clearance and tumor specific uptake. Another copper radioisotope of interest is Cu-67 for the treatment of cancer. A new bifunctional chelating agent, p-carboxy-ethylphenylglyoxal-di(N-methylthiosemicarbazone) has been reported for the labeling of proteins with technetium-99m.[1,2] The chelation of copper to thiosemicarbazones has been known for a long time and has been shown to form a stable complex. The goals of our study are to explore the binding of copper to this ligand for the purpose of radiolabeling monoclonal antibodies.

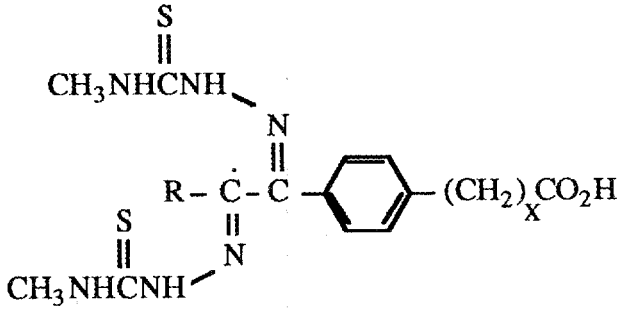
We have developed an improved synthesis of this type of bifunctional chelate which can be readily used for the synthesis of a variety of analogues (Scheme I). The first step involves the Friedel-Crafts acylation of the carboxylic acid substrate with either bromo acetyl chloride (R=H) or 2-bromo propionyl chloride (R=CH_3). In this manner, either the α-bromo methyl or α-bromo ethyl ketone (1), respectively, are formed. Traditionally, the methyl ketones (1) are oxidized to the α-ketoaldehydes (3) using selenium dioxide (SeO_2).[1] In our hands, yields of the resulting products (3) by direct oxidation of (1) were variable. In order to obtain the α-ketoaldehydes in reproducibly high yields and to avoid use of the extremely toxic SeO_2, we have pursued an alternative route

developed by Kornbloom and co-workers based on reductive-elimination of an intermediary nitrate ester (2). Using this approach, α-keto aldehyde (3, R=H) was prepared in reproducibly high yields (> 80%). Compound (1) is treated with silver nitrate to give the nitrate ester (2) followed by a sodium acetate catalyzed oxidation in dimethyl sulfoxide to yield compound (3), which is subsequently reacted with N-methylthiosemicarbazide to give the desired product (4) in moderate yield. In addition to the smooth formation of the α-ketoaldehydes by this procedure, we have also explored preparation of a variety of methyl-1,2-diketones. We expected the diketones to be more stable and have higher melting points, which would allow for a straight-forward purification technique to be used. We have observed that the Kornbloom approach also works very well for the synthesis of the methyl-1,2-diketones (3). By this route, we have prepared a series of analogues of both the α-ketoaldehydes and methyl-1,2-diketones shown in Figure 1. The effect of the alkyl chain length on binding of the copper-64 and copper-67 labeled chelates to proteins is now being pursued.

We are currently utilizing these bifunctional chelates to label a model protein with both copper-67 and copper-64 in order to determine which chelate will be the best candidate for use in the monoclonal antibody labeling studies.


RHC - C - Cl
O
Br
CH2CO2H
AlCl3
RHC - C
O
Br
CH2CO2H
1
AgNO3
RHC - C
O
ONO2
CH2CO2H
2
Na Acetate
DMSO
R - C - C
O O
CH2CO2H
3
S
H2NNHCNHCH3
S
CH3NHCNH
N
R - C - C
CH2CO2H
S
N
CH3NHCNH
4
R = H, CH3

Scheme I.



X	R
1	H, CH_3
2	H, CH_3
3	H, CH_3
4	H, CH_3
5	H, CH_3
8	H
9	CH_3

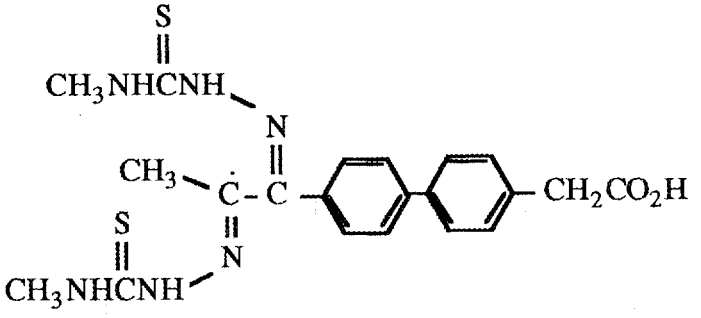


Figure 1. Bifunctional chelates prepared for protein labeling studies.

METABOLISM OF RADIOIODINATED IODOPHENYL-SUBSTITUTED FATTY ACIDS IN ISOLATED RAT HEARTS

The Langerdorff-perfused rat heart system described previously (ORNL/TM-10441, -10531) provides an opportunity to assess the effects of hypoxia on myocardial metabolism of methyl-branched fatty acids. Under conditions of ischemia or reduction of blood flow, myocardial tissue becomes hypoxic. The experimental condition of hypoxia in the isolated rat system is thus relevant to ischemic heart disease in humans. Our goal has been to determine the effect of hypoxia on the global release of radioactivity and the tissue lipid distribution in isolated rat hearts injected with a mixture of [I-125] BMIPP (methyl-branched fatty acid) and [I-131] IPPA (unbranched analogue). In Figure 2 the release of [I-125] and [I-131] products from the hypoxic hearts is illustrated. The clearance curve for IPPA is similar to that observed under normoxic conditions (ORNL/TM-10441) although the levels of radioactivity released are much less under hypoxic conditions. On the other hand, the clearance curve for BMIPP from hypoxic hearts shows a major difference from that observed in normoxic hearts in that the peak of activity typically observed between 5 and 8 minutes is not present (ORNL/TM-10441). Nonetheless, the [I-125] component extracted from the later perfusates of the hypoxic hearts appears to be the same polar component isolated from the outflow of normoxic hearts injected with BMIPP (ORNL/TM-10441, -10531).

The hypoxic hearts were homogenized at the conclusion of the perfusion, the lipids extracted, and the [I-125] and [I-131] radioactive components analyzed by thin-layer chromatography (TLC). The results presented in Table 1 indicate that the majority of myocardial radioactivity chromatographed in the triglyceride region. Other radioactive components are observed in the diglyceride and the free fatty acid (BMIPP or IPPA) regions. Comparison of these distribution patterns with those reported previously for normoxic hearts (ORNL/TM-10839) indicates increased storage in triglycerides under hypoxic conditions. This is to be expected since there would be less opportunity to catabolize the extracted fatty acid under hypoxic conditions, and more fatty acid would thus be shunted into storage.

In a parallel study, the radioactive extracts of hypoxic and normoxic hearts chromatographing with the triglyceride standard were isolated and subjected to basic hydrolysis to determine whether these are truly triglycerides. Basic hydrolysis resulted in the release of the free [I-125]BMIPP and [I-131]IPPA fatty acids, which was confirmed by TLC analysis. This study confirmed the incorporation of these iodophenyl fatty acids into triglycerides in the myocardium.

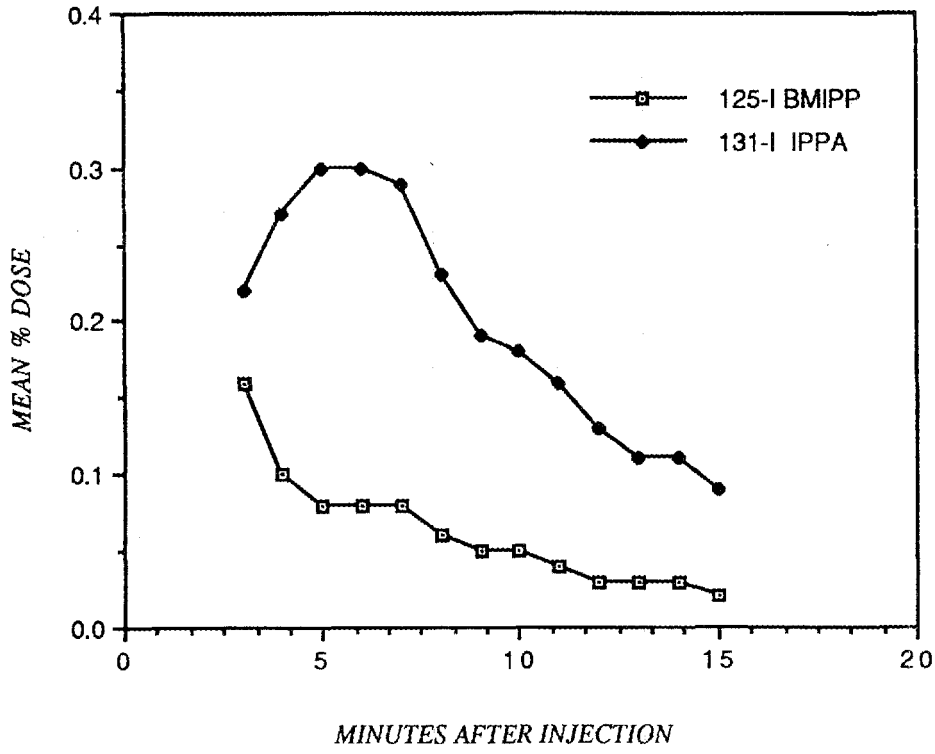


Figure 2. Release of radioactive components following administration of a [I-131]IPPA/[I-125]BMIPP mixture to Langendorff-perfused rat hearts.

Table 1. Radioactive lipids in homogenates of isolated rat hearts following administration of a [I-131]IPPA/[I-125]BMIPP mixture.

	Percent of total radioactivity		
Agent	Triglyceride	Diglyceride	Free fatty acid
BMIPP	55.00 ± 1.74	9.80 ± 1.42	13.02 ± 1.52
IPPA	43.56 ± 7.41	8.55 ± 3.47	4.76 ± 2.49

LITERATURE CITED

1. Arano, Y., Yokoyama, A., Furukawa, T., et al, "Technetium-99m-Labeled Monoclonal Antibody with Preserved Immunoreactivity and High In Vivo Stability," J. Nucl. Med., 28:1027-1033 (1987).

2. Arano, Y., Yokoyama, A., Magata, Y., et al, "Synthesis and Evaluation of a New Bifunctional Chelating Agent for Tc-99m Labeling Proteins: p-Carboxyethylphenylglyoxal di(N-methylthiosemicarbazone)," Int. J. Nucl. Med. Biol., 12:425-430 (1986).

3. Kornbloom, N., and Frazier, H. W. "A New and Convenient Synthesis of Glyoxals, Glyoxalate Esters, and α-Diketones," J. Amer. Chem. Soc., 88:865-866 (1966).

AGENTS FOR MEDICAL COOPERATIVES

Two shipments of N-(p-[I-125]iodophenyl)maleimide were supplied to The University of Michigan, Ann Arbor, Michigan (Dr. Buchsbaum) for collaborative protein radiolabeling studies.

AGENTS PREPARED FOR COST-RECOVERY THROUGH THE ORNL ISOTOPES DISTRIBUTION OFFICE

One shipment of Pt-195m labeled cis-dichlorodiammineplatinum(II) was made to Rambam Medical Center, Haifa, Israel (Prof. D. Front), Beth Israel Hospital, Boston, Massachusetts (Dr. Reich), and one to New York University Medical Center, New York, New York (Dr. T. Reich).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

In conjunction with members of the ORNL Office of Technology Applications, F. F. Knapp, Jr. visited a major U.S. radiopharmaceutical manufacturer to describe the development and applications of the osmium-191/iridium-191m generator system. This manufacturer is interested in the possibility of licensing this system, for which a patent waiver has recently been granted to Martin Marietta Energy Systems, Inc. by DOE for technology transfer.

A patent describing the development of a new protein radiolabeling technique entitled "Radioiodinated Maleimides and Use as Agents for Radiolabeling Antibodies," has been granted to P. C. Srivastava and was described in the April 5, 1988 issue of Patent Abstracts (No. 4,735,792).

Personnel. Gisela Umbricht, an organic chemistry graduate student from the Technical University in Zurich, Switzerland, joined the Nuclear Medicine Group for a six month

period as a guest scientist working on the synthesis of substrates for radiopharmaceutical labeling.

Eleven papers were presented or co-authored by members of the Nuclear Medicine Group at the 35th Annual Meeting of the Society of Nuclear Medicine held in San Francisco, California on June 13-17:

C. Brihaye, M. Guillaume, F.F. Knapp, Jr., S. Dewez, D. E. Rice, and A. P. Callahan "Efficient Removal of Ir-192 from Reactor-Produced Os-191 by Distillation or Solvent Extraction of OsO_4."

M. M. Goodman, G. W. Kabalka, R. Marks, F. F. Knapp, Jr., and S. Truelove "Radioiodinated 5-Iodo-2-Thienylamphetamines Synthesis and Evaluation of a New Class of Brain Imaging Agents."

M. Guillaume, C. Brihaye, R. Redote, M. Zicot and F. F. Knapp, Jr. "Ir-191m: A New Tracer for Arterioscintigraphy."

A. Hoetze, A. Bockish, M. Ruther, R. Knopp, F. F. Knapp, Jr., H. J. Biersack "Retention of Inflammatory Diseases Using a Tc-99m Labeled Anti-Granulocyte - Antibody (AGAB).

G. Kirsch and F. F. Knapp, Jr. "Synthesis of -Hydroxy Fatty Acids for Metabolic Studies via Acylation of a "Masked" Malonic Ester."

G. Kirsch and F. F. Knapp, Jr., "Synthesis of Para-Substituted Phenyl Glyoxals Via Bromoacetylation - Alternative Preparation of 1,2-Bis-(N_4-Alkylsemithicarbazones) for Cu(II) Binding."

S. N. Reske, F. F. Knapp, Jr., J. Nitsch, S. Kohlen, and J. Kolkmeier "Preserved I-123 Phenylpentadecanoic Acid (IP) Uptake in Reperfused Myocardium."

J. Ruhlman, A. Bockisch, W. Dewee, U. Loos, A. Hotze, F. F. Knapp, Jr., H. J. Biersack "Bone Marrow Scintigraphy (BMS) Compared with Magnetic Resonance Tomography in Plastocytoma."

P. Som, Z. H. Oster, K. Kubota, M. M. Goodman, F. F. Knapp, Jr., D. F. Sacker, and D. A. Weber "The Regional Myocardial Uptake of 19-Iodo-3,3-Dimethyl-18-Nonadecenoic Acid (I* DMIVN) in Hypertensive Rats and the Effects of Verapamil."

P. C. Srivastava, F. F. Knapp, Jr., J. F. Allred, and D. J. Buchsbaum "Monoclonal Antibodies (MoAb) Radiolabeled with N-(p-[^{125}I]Iodophenyl)maleimide (IPM) Retain Tumor Uptake and Show Insignificant In Vivo Deiodination Compared with [^{125}I]ICl Radiolabeled MoAb."

P. C. Srivastava, J. A. Suggs, and J. F. Allred "Synthesis and Biodistribution of a P-[^{125}I]Iodophenyl Analogue of a Naturally Occurring Imidazole Ribonucleoside."

INTERNAL DISTRIBUTION

1. J. F. Allred
2. K. R. Ambrose
3. S. L. Blystone
4. T. A. Butler (Consultant)
5. A. P. Callahan
6. K. F. Eckerman
7. A. S. Garrett, Jr., M.D.
8. W. R. Garrett
9. M. M. Goodman (Consultant)
10. A. R. Hawthorne
11. G. W. Kabalka (Consultant)
12. S. V. Kaye
13. S. J. Kennel

14-18. F. F. Knapp, Jr.
19. E. C. Lisic
20. D. W. Ramey
21. D. E. Rice
22. C. R. Richmond
23. C. J. Rogers
24. P. C. Srivastava

25-27. Central Research Library
28. Document Record Section
29-30. Laboratory Records Dept.
31. Lab. Records, ORNL RC
32. ORNL Patent Section

EXTERNAL DISTRIBUTION

33. S. J. Adelstein, M.D., Shields Warren Radiation Lab., Boston, MA 02115.
34. H. L. Atkins, M.D., Radiology Dept., State Univ. of New York, Stony Brook, NY 11794
35. R. J. Baranczuk, Biomedical Products, 7899 Mastin, Overland Park, KS 66204
36. H. J. Biersack, M.D., Institut fur Klinische und Experimentelle Nuklear Medizin Der Universitat Bonn, Sigmund Freud Strasse 25, 5300 Bonn 1, West Germany
37. C. Brihaye, Centre de Recherches du Cyclotron, Universite de Liege, Belgium
38. A. B. Brill, M.D., Ph.D., Commonwealth of Massachusetts, Univ. of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01605
39. T. F. Budinger, M.D., Donner Lab., LBL, Berkeley, CA 94720
40. W. Burr, M.D., Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37831
41. P. Cho, OHER, U.S. DOE, MS-ER-73, Washington, D.C. 20545
42. D. W. Cole, Jr., U.S. DOE, ER-73, GTN, Washington, D.C. 20545
43. J. Crook, M.D., Ph.D., Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37831
44. R. F. Dannals, Division of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, MD 21205
45. R. Dudczak, M.D., Dept. Nuclear Medicine, I. Medizinische Universitatsklinik, A-1090 Wien, Lazarettgasse 14, Vienna, Austria
46. J. Dunn, Mallinckrodt, Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
47. D. R. Elmaleh, Physics Research Dept., Massachusetts General Hospital, Boston, MA 02114
48. L. Feinendegen, Institut fur Medizin, Postfach 1913, D-5170, Julich 1, West Germany
49. A. Fritzberg, NeoRx Corporation, 410 West Harrison, Seattle, WA 98119
50. D. M. Goldenberg, M.D., Center of Molecular Medicine and Immunology, 1 Bruce Street, Newark, NJ 07103

51. M. Guillaume, Chef de Travaux, Centre de Recherches du Cyclotron, Universite de Liege, Belgium
52. D. R. Hamilton, Nuclear Medicine Branch, OTA/NCDRH/FDA, Rockville, MD 20857
53. C. J. Hardy, Chief, Isotope Division, Australian Nuclear Science and Technology Organization, Private Mail Bag 1, Menai, N.S.W. 2234, Australia
54. J. Hiltunen, Technical Research Centre of Finland, Reactor Laboratory, Otakaari 3 A, SF-02150 Espoo, Finland
55. K. Hubner, Department of Radiology, UT Memorial Hospital, Knoxville, TN 37920
56. K. J. Irgolic, Chemistry Dept., Texas A&M University, College Station, TX 77840
57. A. Jones, Dept. of Radiology, Harvard Medical School, Boston, MA 02115
58. G. Kirsch, Universite de Metz, Metz, France
59. 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.
60. J. S. Laughlin, Sloan-Kettering Inst. for Cancer Research, New York, NY 10021
61. J. Logic, M.D., University of Alabama Medical Center, Birmingham, AL 35233
62. H.-J. Machulla, Institut fur Med. Strahlenphysik, Universitats-klinikum, Hufelandstrasse 55, D-4300, Essen 1, West Germany
63. J. N. Maddox, DOE-OHER, ER-73, Washington, DC 20545
64. D. Moody, Group INC-11, MS J-519, LASL, Los Alamos, NM 87545
65. Office of Assistant Manager for Energy Research and Development DOE-ORO, Oak Ridge, TN 37831
66. K. J. Panek, Mallinckrodt Diagnostica (Holland) B.V., Westerduinweg 3, P.O. Box 3, 1755 ZG Petten, Holland
67. C. L. Partain, M.D., Director, Medical Imaging Division, Vanderbilt University Medical Center, Nashville, TN 37232
68. R. C. Reba, M.D., George Washington Univ. Med. Center, Washington, DC 20037
69. S. N. Reske, M.D., Nuklear Medizin Abteilung, RWTH Aachen, Pauwelsstrasse 1, 5100 Aachen, West Germany
70. M. Robbins, Mallinckrodt, Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
71. J. S. Robertson, DOE-OHER, ER-73/GTN, Washington, DC 20545
72. M. P. Sandler, M.D., Chief, Nuclear Medicine Section, Vanderbilt University Medical Center, Nashville, TN 37232
73. F. Snyder, ORAU, Oak Ridge, TN 37831
74. P. Som, DVM, Medical Department, BNL, Upton, NY 11973
75. S. C. Srivastava, Bldg. 801, Medical Dept., BNL, Upton, NY 11973
76. A. Solomon, M.D., UT MRCH, Knoxville, TN 37920
77. H. W. Strauss, M.D., Nuclear Medicine Div., Massachusetts General Hospital, Boston, MA 02114

78-87. Office of Scientific and Technical Information, DOE, Oak Ridge, TN 37831

88. A. Vessey, Eastman Pharmaceuticals, 25 Great Valley Parkway, Great Valley, PA 19355
89. F. Visser, M.D., Cardiology Dept., Free University Hospital, De Boelelaan 117, Amsterdam, The Netherlands
90. H. N. Wagner, Jr., M.D., Div. of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, MD 21205
91. L. C. Washburn, Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37831
92. A. P. Wolf, BNL, Upton, NY 11973
93. D. V. Woo, Hahnemann University, Philadelphia, PA 19102

94. R. W. Wood, Jr., DOE-OHER, Washington, DC 20545
95. S. Wynchank, Research Institute for Medical Biophysics (RIMB), Republic of South Africa