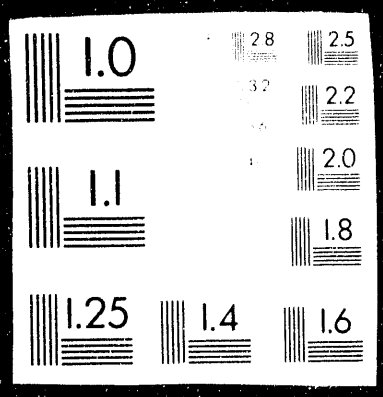

TECHNICAL PROGRESS REPORT AND INTERIM FUNDING REQUEST

DE-FG02-86ER60401

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(Total Period: February 1, 1992 - January 31, 1995)

(Reporting Period: February 1, 1992 - January 31, 1993)

John A. Katzenellenbogen, Principal Investigator

August 8, 1992

John A. Katzenellenbogen
Principal Investigator
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Date

DISCLAIMER

SUMMARY OF RESEARCH PROPOSED

Name and Official Title of Principal Investigator

John A. Katzenellenbogen, Professor of Chemistry

Name and Address of Applicant Organization

Board of Trustees of the University of Illinois
506 S. Wright Street
Urbana, IL 61801

Title of Project

Radiolabeled Androgens and Progestins as Imaging Agents for Tumors of the Prostate and Breast

Abstract

Many tumors of the breast and prostate contain receptors for progestins and androgens, respectively, and the presence and levels of these receptors can usually be correlated with the endocrine responsiveness of the cancer. These receptors also provide a potential mechanism whereby suitably radiolabeled progestins or androgens could be selectively concentrated in a manner that would permit imaging of the tumor, thus providing an assessment of the stage of the cancer and its potential for endocrine responsiveness, diagnostic and prognostic information of importance in the selection of the most favorable treatment regimen.. These receptors should be particularly useful targets for imaging in patients who are on endocrine therapy.

In this project, we are proposing to prepare progestins and androgens, labeled with the single photon emitters technetium-99m and rhenium-186 and the positron-emitting radionuclide fluorine-18. In both cases, ligands will be selected to have very high affinity for the respective receptor, low affinity for blood and non-specific binders and to be reasonably resistant to metabolism: The progestins will be derivatives of the potent progestins ORG2058, norgestrel, RU486, and an unusual retroprogestin and the androgens will be derivatives of the high affinity analogs of natural and synthetic androgens. Radiometal labeling will involve carefully designed steroid conjugates with N_2S_2 or related chelates, or novel metal linkages, and metal complexes that themselves mimic a steroid. Fluorine substitution will be made at positions where bulk and polarity are tolerated and metabolic defluorination is minimal. In vitro competitive binding studies will be performed on the unlabeled analogs to determine their binding characteristics towards a series of steroid receptors and blood binding proteins, and Log P values will be estimated from HPLC. Tissue distribution studies with the radiolabeled progestins will be done in estrogen-primed rats using the uterus as a target, and with the radioandrogens in estrogen-treated rats using the prostate as a target. Ultimately, in collaborative studies, these radiopharmaceuticals are to be used with SPECT or PET to image the receptor-positive tumors.

pgs. 3-6 - Budget info. Removed.

I. Technical Progress Report

A. Objectives

The objectives of this project are to prepare androgens and progestins labeled with fluorine-18 or technetium-99m as imaging agents for tumors of the prostate and breast. These novel diagnostic agents may enable an accurate estimation of tumor dissemination (metastasis of prostate cancer and lymph node involvement of breast cancer) and an in vivo determination of the endocrine responsiveness of these tumors. Thus, they will provide essential information for the selection of alternative therapies (the extent of surgical ablation, radiation and chemotherapy vs hormonal therapy, etc.), thereby improving the management of prostate and breast cancer patients.

B. Specific Aims (From the most recent renewal application, August, 1991)

Specific Aim 1: Develop Technetium-99m and Rhenium-186 Labeled Progestin Conjugates as Breast Tumor Imaging Agents and Agents of Therapy.

Specific Aim 2: Develop Novel, Less Bulky Systems for the Attachment of Technetium and Rhenium to Steroid Ligands.

Specific Aim 3: Investigate Technetium and Rhenium Metal Complexes Which are Structural Mimics of Steroids.

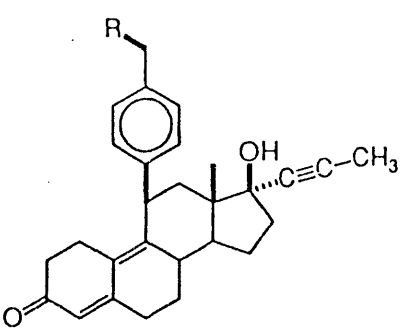
Specific Aim 4: Prepare Novel Fluorine-18 Labeled Ligands for the Progesterone Receptor.

Specific Aim 5: Complete our Analysis of Fluorine-18 Labeled Androgens as Imaging Agents for Prostatic Cancer.

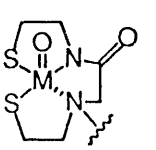
C. Research Accomplished During the Past Budget Period (Feb 1, 1992 - Jan 31, 1993)

During the past budget period, we have made substantive progress on Aims 1, 2, and 4.

1. Progestin Conjugates with Technetium and Rhenium (Aim 1) — We have prepared the new progestin rhenium and technetium conjugates shown below. These incorporate an amine-amide-bisthiol metal chelating system that is less lipophilic than the bisamine-bisthiol system that we prepared initially. The octanol-water partition coefficients of these systems is noted.



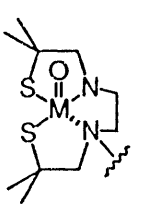
New: amine-amide-bisthiol



log P = 4.5

(M = Tc or Re)

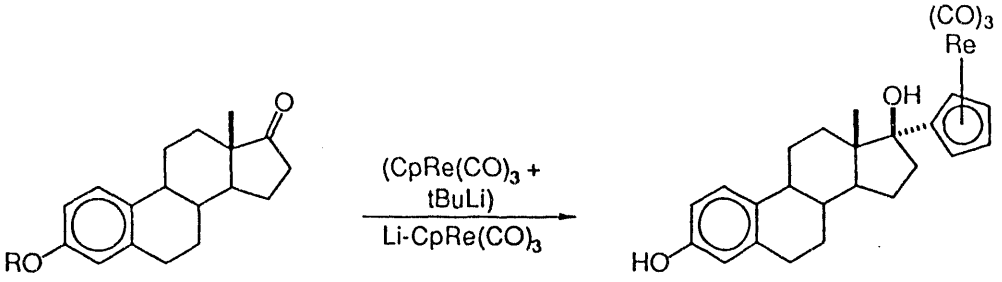
Old: bisamine-bisthiol



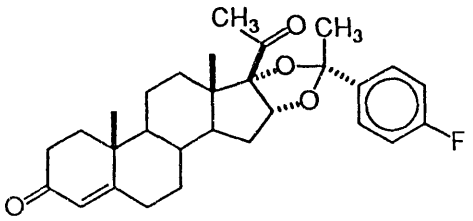
log P = 6.3

We are in the process of preparing these conjugates labeled with technetium-99m for in vivo tissue distribution studies.

2. Less Bulky Systems for the Attachment of Rhenium and Technetium (Aim 2) — We have prepared the first cyclopentadienyl tricarbonylrhenium derivative of a steroid. For chemical simplicity sake, the first system we have prepared is an estrogen, but this approach can be extended to androgens and progestins. We are currently preparing other analogs, and we will determine their binding affinity for the steroid receptors to determine the tolerance of receptor to this strategy for metal incorporation.



3. Novel Fluorine-18 Labeled Ligands for the Progesterone Receptor (Aim 4) — We have prepared two progestin ketals labeled with fluorine-18 on an aromatic position. The first of these is a simple fluorine-substituted derivative of a progestin reported in the 1960's. The second, prepared to reduce the lipophilicity and non-specific binding of the first, is more polar and has higher binding affinity for the progesterone receptor. The receptor binding affinity, octanol water partition coefficients, and selective in vivo tissue distribution data are presented.

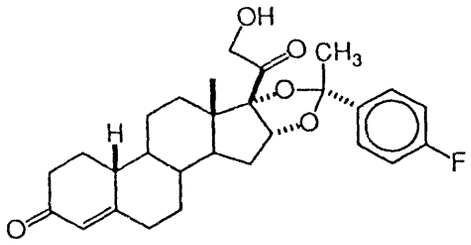


RBA = 56 (vs. R5020 = 100;
log P = 34.90 Progestin = 15)

Biodistribution data for [F-18]DPFA

% ID/g

	1 hr	1 hr low	1 hr block	3 hr
blood	0.47 ± 0.04	0.52 ± 0.08	0.43 ± 0.08	0.28 ± 0.06
liver	3.41 ± 0.26	3.62 ± 0.53	3.16 ± 0.30	1.93 ± 0.22
kidney	2.18 ± 0.12	2.27 ± 0.30	2.18 ± 0.41	1.47 ± 0.42
muscle	0.82 ± 0.15	0.82 ± 0.14	0.76 ± 0.07	0.49 ± 0.20
fat	5.76 ± 1.35	5.39 ± 1.88	3.77 ± 0.72	5.06 ± 0.99
bone	1.76 ± 0.48	1.77 ± 0.32	1.44 ± 0.40	1.69 ± 0.35
uterus	3.08 ± 0.43	3.30 ± 0.44	1.27 ± 0.22	2.13 ± 0.33
ovaries	3.93 ± 0.77	3.68 ± 1.49	2.29 ± 0.39	2.19 ± 0.42
ut/blood ratio	6.59 ± 0.68	6.34 ± 0.98	3.06 ± 0.74	7.56 ± 0.92
ut/muscle ratio	3.85 ± 0.74	4.08 ± 0.67	1.69 ± 0.92	4.61 ± 0.98



RBA = 246 (vs. R5020 = 100;
log P = 3.83 Progestin = 15)

Biodistribution data for [F-18]TNPFA 7 May 1992

% ID/g

	1 hr	1 hr low	1 hr block	3 hr
blood	0.26 ± 0.02	0.28 ± 0.04	0.23 ± 0.03	0.10 ± 0.02
liver	4.25 ± 0.39	3.93 ± 0.56	3.56 ± 0.40	1.36 ± 0.22
kidney	1.42 ± 0.08	1.57 ± 0.28	1.28 ± 0.17	0.45 ± 0.10
muscle	0.44 ± 0.04	0.46 ± 0.07	0.35 ± 0.03	0.16 ± 0.09
fat	3.53 ± 1.05	3.78 ± 0.99	2.76 ± 0.39	1.64 ± 0.21
bone	0.62 ± 0.08	0.68 ± 0.14	0.60 ± 0.09	0.64 ± 0.11
uterus	3.65 ± 1.11	4.06 ± 0.70	0.86 ± 0.26	3.86 ± 0.99
ovaries	2.80 ± 0.70	2.66 ± 0.42	1.37 ± 0.31	1.78 ± 0.36
ut/blood ratio	14.0 ± 4.2	14.5 ± 2.1	3.69 ± 1.03	38.0 ± 8.3
ut/muscle ratio	8.2 ± 2.5	8.8 ± 1.3	2.42 ± 0.62	27.9 ± 9.5

C. Plans for the Coming Budget Year

We plan to continue our search for a suitable progestin receptor and androgen receptor based imaging agents, according to the aims outlined in the renewal application.

II. List of Publications

PUBLICATIONS

1. F. Dehdashti, A. H. McGuire, H. F. VanBrocklin, B. A. Siegel, D. P. Andriole, M. G. Pomper, J. A. Katzenellenbogen, M. J. Welch, Assessment of 21-[^{18}F]Fluoro-16α-Ethyl-19-Norprogesterone as a Positron-Emitting Radiopharmaceutical for the Detection of Progestin Receptors in Human Breast Carcinomas. *J. Nucl. Med.*, **1991**,*32*, 1532-1537

2. J. P. DiZio, R. Riaschi, A. Davison, A. G. Jones, J. A. Katzenellenbogen, Progestin-Rhenium Complexes; Metal-Labeled Steroids with High Receptor Binding Affinity, Potential Receptor-Directed Agents for Diagnostic Imaging or Therapy, *Bioconjugate Chem.*, **1991**, 2, 353-366.

3. A. Liu, K. E. Carlson, and J. A. Katzenellenbogen, Synthesis of High Affinity Fluorine-Substituted Ligands for the Androgen Receptor. Potential Agents for Imaging Prostatic Cancer by Positron Emission Tomography. *J. Med. Chem.* **1992**, *35*, 2113-2129.

4. J. P. DiZio, C. J. Anderson, A. Davison, G. J. Ehrhardt, K. E. Carlson, M. J. Welch, and J. A. Katzenellenbogen, Technetium and Rhenium Labeled Progestins: Synthesis, Receptor Binding and In Vivo Distribution of 11β-Substituted Progestin Labeled with Technetium-99 and Rhenium-186, *J. Nucl. Med.* **1992**, *33*, 558-569.

5. A. Liu, C. S. Dence, M. J. Welch, and J. A. Katzenellenbogen, Fluorine-18 Labeled Androgens: Radiochemical Synthesis and Tissue Distribution Studies on Six Fluorine-Substituted Androgens. Potential Imaging Agents for Prostatic Cancer, *J. Nucl. Med.* **1992**, *33*, 724-734.

6. J. P. DiZio, K. E. Carlson, C. J. Bannochie, M. J. Welch, E. von Angerer, and J. A. Katzenellenbogen, Estrogen Platinum-Diamine Complexes: Preparation of a non-Steroidal Estrogen Platinum-Diamine Complex Labeled with Platinum-191 and a Study of Its Binding to the Estrogen Receptor *In Vitro* and its Tissue Distribution *In Vivo*. *J. Steroid Biochem. Molec. Biol.* **1992**, *42*, 363-373.

7. J. A. Katzenellenbogen, Probes for Steroid Receptors - Studies at the Molecular, Cellular, and Whole Organism Levels, in *Robert A. Welch Foundation Conference on Chemical Research XXXV Chemistry at the Frontiers of Medicine,* October 28-29, **1991**. Chapter 11.

ABSTRACTS

8. J. A. Katzenellenbogen, A. Liu, S. J. Brandes, K. E. Carlson, and M. J. Welch, The Development of Fluorine-18 Labeled Androgens as PET Imaging Agents for Prostatic Cancer, 4th Internal. Congress on Hormones and Cancer, Amsterdam, The Netherlands, September 1991

9. A. Liu, C. S. Dence, M. J. Welch, and J. A. Katzenellenbogen, Fluorine-18 Labeled Androgens: Radiochemical Synthesis and Tissue Distribution Studies on Fluorine-Substituted Androgens, Potential Imaging Agents for Breast Cancer. Society for Basic Urologic Research, 1991 Annual Meeting, Rochester MN, November 1991

10. H. F. VanBrocklin, P. R. Kym, J. P. O'Neil, T. A. Bonasera, M. J. Welch, and J. A. Katzenellenbogen, A Novel Metabolically Stable Site for Fluorine-18 Labeling of Progestins, Useful in the Development of Imaging Agents for Progesterone-Positive Tumors. 9th International Symposium on Radiopharmaceutical Chemistry, Paris, April 1992.

11. P. R. Kym, K. E. Carlson, H. F. VanBrocklin, and J. A. Katzenellenbogen. Molecular Probes for the Progesterone Receptor: Design, Synthesis and Biochemical Evaluation. American Chemical Society, San Francisco, CA. April 1992.

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