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*Title:* NON-CARRIER-ADDED 186,188Re LABELED 17a-ETHYNYLESTRADIOL: A POTENTIAL BREAST CANCER IMAGING AND THERAPY AGENT

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# NON-CARRIER-ADDED $^{186,188}$Re LABELED 17α-ETHYNYLESTRADIOL: A POTENTIAL BREAST CANCER IMAGING AND THERAPY AGENT

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## Introduction

Receptor-targeted radiopharmaceuticals constitute potential agents for the diagnosis and therapy of cancer. Breast cancer is the most prevalent form of diagnosed cancer in women in the United States, and it accounts for the second highest number of cases of cancer fatalities (1). In Approximately two-thirds of the breast tumors, estrogen and progesterone steroid hormone receptors can be found. Such tumors can often be treated successfully with anti-estrogen hormone therapy (2). Hence, the ability to determine the estrogen receptor (ER) contend of the breast tumor is essential for making the most appropriate choice of treatment for the patient. Along with this diagnostic aspect, steroid-based radiopharmaceuticals with high specific activity offer an encouraging prospect for therapeutic applications: $^{186,188}$Re labeled steroids binding to receptors expressed by cancer cells appear to be potential agents for the irradiation of small to medium-sized tumors.

$^{186}$Re has been regarded as an ideal radionuclide for radiotherapy due to its appropriate half-live of 90 h and β-energy of 1.07 MeV. Moreover, the γ-emission of 137 keV that allows *in vivo* imaging while in therapy is an additional bonus. $^{188}$Re is obtained from a $^{188}$W/$^{188}$Re radionuclide generator system, representing an advantage for availability at radiopharmacy laboratory by daily elution. In addition, $^{188}$Re emits high energy beta particles with an average energy of 769 keV, and the emission of the 155 keV allows simultaneous imaging for biodistribution evaluation *in vivo*.

In order to avoid competitive saturation of the binding sites of the ligand receptor, Re labeled steroids with high specific activity are required, and the removal of all excess unlabeled ligands is mandatory. $^{188}$Re is eluted from a $^{188}$W/$^{188}$Re generator produced and provided by Oak Ridge National Laboratory (3).

This paper outlines the solid phase-supported preparation of an n.c.a. [$^{188}$Re]Re-imido estradiol compound. The characteristic feature of the presented route is the simultaneous formation of the steroid-radioisotope linkage and release of the labeled steroid product into solution (4,5). The unlabeled ligand can then be separated by simple filtration.

## Experimental

In order to obtain the polymer-bound estradiol conjugate,ethynylestradiol **1** is coupled to 4-iodophenyl hydrazine **2** according to Sonogashira (6) in the presence of a palladium-catalyst (7,8). The free hydrazine **3** is then attached to Tentagel carboxy resin using (1-benzotriazolyl)oxy tris(pyrrolidino) phosphonium hexafluorophosphate (PyBOP) and diisopropylethylamine in dichloromethane to give the corresponding solid-supported acetyl hydrazine derivative **4**, which is separated from the reaction mixture. In the labeling step, the coated resin **4** is treated with trichlorooxobis-(triphenylphosphane) [$^{188}$Re]rhenium (V), whereby the hydrazine is cleaved (9,10) to give a nitrido-complex: the labeled substrate **5** is released (Figure 1).

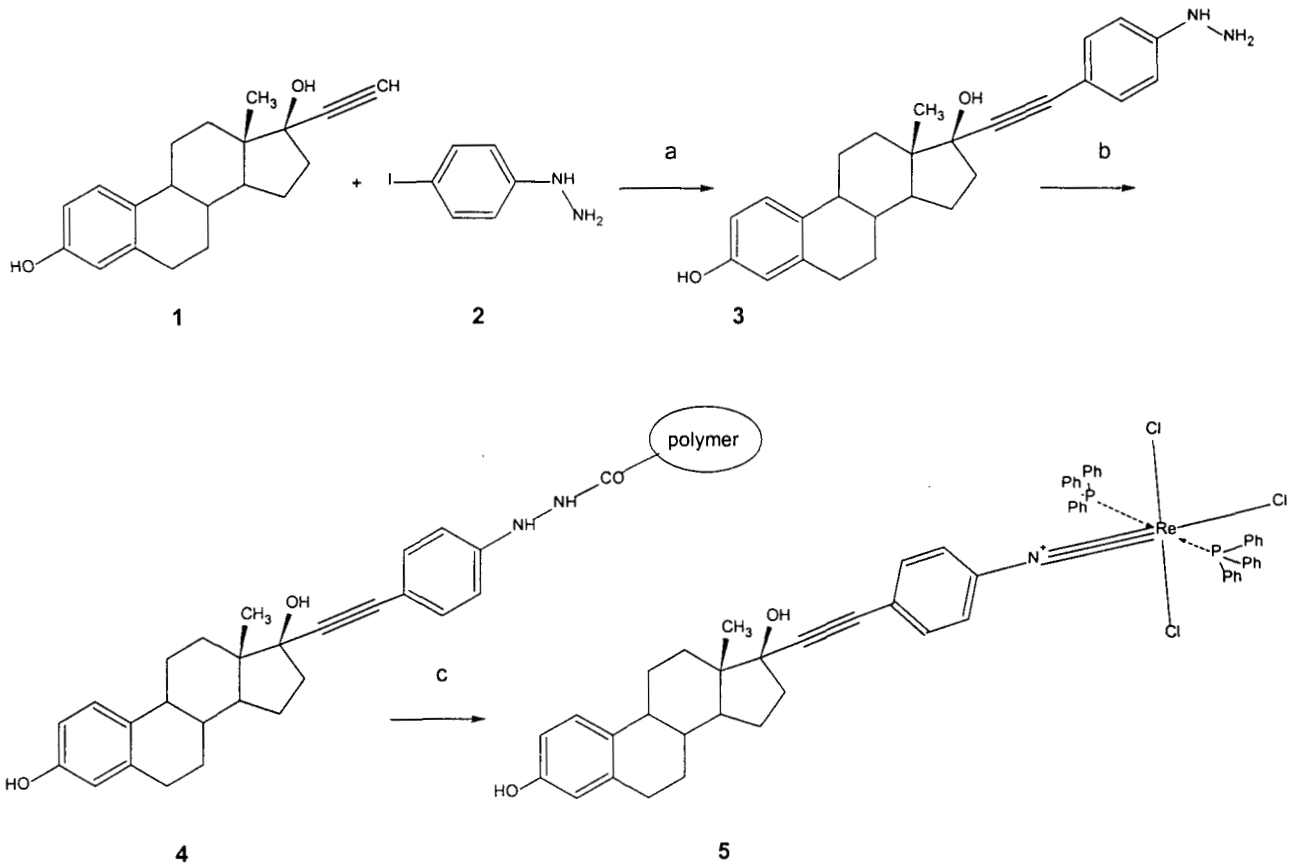


**Figure 1:** a) 5 mol % Pd(OAc), 10 mol % CuI, $PPh_3$, $NHEt_2$, 25°C, 3 h, 87 %; b) Tentagel carboxy resin, PyBOP, Net*i*$Pr_2$, $CH_2Cl_2$, 25°C, 20h, 100% (based on loading capacity=0.26 mmol$g^{-1}$); c) [$^{188}$Re][$ReOCl_3(PPh_3)_2$], $PPh_3$, $CH_2Cl_2$, 40°C, 3h.

The prepared Re-labeled steroid is subsequently purified and quality controlled using normal-phase solid-phase extraction (Silica 60, 1. $CH_2Cl_2$/hexane=60:40 (v/v); 2. $CH_2Cl_2$/methanol=90:10 )) and semi-preparative reverse-phase (C-8 on silica column, methanol/water=60:40 (v/v) eluent) HPLC.

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