DEVELOPMENT OF RADIOIODINATED NONSTEROIDAL ANDROGEN RECEPTOR LIGANDS FOR SPECT IMAGING OF PROSTATE CANCER

M. E. Van Dort, Y-W Jung, P. S. Sherman, K. K. Kuszpit

Division of Nuclear Medicine
Department of Radiology
University of Michigan Medical School
Ann Arbor, MI 48109-0552

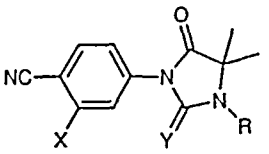
Key Words: androgen receptor, antiandrogen, iodine-125, nonsteroidal, prostate cancer, SPECT

The appropriate treatment strategy for prostate cancer is critically dependent on its accurate staging (1). Current screening techniques (CT, MRI, Ultrasound) fail to reliably distinguish clinically-localized disease from metastatic disease. A reliable noninvasive method for detection of prostate cancer metastases would thus be of immense clinical benefit for a) disease staging b) implementing the appropriate treatment strategy c) monitoring the effects of therapy. To address this need, many research groups have focused on the development of radiolabeled androgen receptor (AR) ligands for prostate cancer imaging, based on the observation that most prostate tumors and metastases express AR (2,3). The majority of these studies to date have focused on steroid-based ligands (2,4,5).

The antiandrogens RU 59063 and RU 58841 (Table 1), are prototypes of a new series of nonsteroidal androgen receptor ligands that display high AR affinity and selectivity (6,7). The ease of synthesis and structural modification of these compounds as compared to steroid-based AR ligands, prompted us to select them as leads for development of a SPECT AR radioligand. We have previously shown that substitution of the trifluoromethyl group of RU 59063 with iodine leads to an improvement in AR binding affinity (8). Accordingly, a series of iodinated analogs of RU 59063 and RU 58841 was synthesized for investigation as *in vivo* AR radioligands (Table 1).

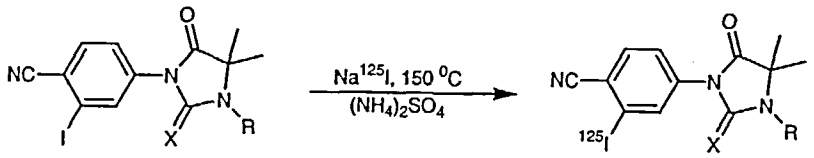
Compounds 1-4 were synthesized from 4-cyano-3-iodoaniline using previously reported methods (8). Radioiodination of compounds 1–4 with iodine-125 were achieved in 50-65% radiochemical yield by an ammonium sulfate catalyzed solid phase exchange procedure (Scheme 1). Radiolabeled products were purified either by elution through an anion exchange resin or

Table 1. Inhibition Constants (Ki) for Ligands at the Rat AR



Compd	X	Y	R	Ki ± SEM (nM)
RU 59063	CF_3	S	$(CH_2)_4OH$	2.23 ± 0.50
RU 58841	CF_3	O	$(CH_2)_4OH$	26 ± 5
1	I	S	$(CH_2)_4OH$	0.71 ± 0.22
2	I	O	$(CH_2)_4OH$	2 ± 1
3	I	S	CH_3	2.5 ± 0.7
4	I	O	CH_3	11 ± 5

Scheme 1



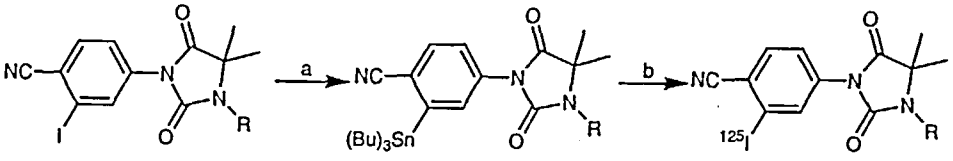
X = O, S

R = CH_3, $(CH_2)_4OH$

X = O, S

R = CH_3, $(CH_2)_4OH$

Scheme 2 [a]



R = CH_3, $(CH_2)_4OH$

R = CH_3, $(CH_2)_4OH$

[a] Reagents: (a) $Sn_2(Bu)_6$, $(Ph_3P)_4Pd$, toluene, reflux; (b) 3% aq. H_2O_2, $Na^{125}I$.

a silica gel Sep Pak. The chemical purity and specific activity of the radioiodinated ligands were >95% and >155 Ci/mmole, respectively. In addition, the hydantoin derivatives [^{125}I]2 and [^{125}I]4 were obtained in 76-85% radiochemical yield by a no-carrier-added radioiododestannylation procedure from their corresponding tri-n-butylstannyl derivatives (Scheme 2).

In conclusion, a series of [^{125}I]-labeled nonsteroidal AR radioligands has been synthesized using either carrier-added or no-carrier-added methods. Biological studies are underway to evaluate their utility as *in vivo* radioligands for AR imaging.

References

1. Carter H. and Partin A.W. In *Recent Advances in Prostate Cancer and BPH*, Schroder F.H., Ed., The Parthenon Publishing Group, New York, 1997.
2. Katzenellenbogen J.A.- *J. Nucl. Med.* 36(Suppl): 8S (1995).
3. Hobisch A., Culig Z., Radmayr C., Bartsch G., Klocker H., Hittmair A. -*The Prostate* 28: 129 (1996).
4. Bonasera T.A., O'Neil J.P., Xu M., Dobkin J.A., Cutler P.D., Lich L.L., Choe Y.S., Katzenellenbogen J.A., Welch M.J.- *J. Nucl. Med.* 37: 1009 (1996).
5. Liu A.J., Katzenellenbogen J.A., Van Brocklin H.F., Mathias C.J., Welch M.J.-*J. Nucl. Med.* 32: 81 (1991).
6. Teutsch G., Goubet F., Battmann T., Bonfils A., Bouchoux F., Cerede E., Gofflo D., Gaillard-Kelly M., Philibert D.- *J. Steroid Biochem. Molec. Biol.* 48: 111 (1994).
7. Battmann T., Bonfils A., Branche C., Humbert J., Goubet F., Teutsch G., Philibert D.- *J. Steroid Biochem. Molec. Biol.* 48: 55 (1994).
8. Van Dort M.E., Robins D.M., Wayburn B.- *J. Med. Chem.* 43: 3344 (2000).

Acknowledgement
This work was supported by grants from the National Institutes of Health (CA 77287) and the SPORE in Prostate Cancer (P50 CA 69568).