SYNTHESIS OF A CARBON-11 LABELED NONSTEROIDAL ANTIANDROGEN AS A POTENTIAL RADIOLIGAND FOR PET IMAGING OF PROSTATE CANCER

M. E. Van Dort, D. M. Jewett, 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

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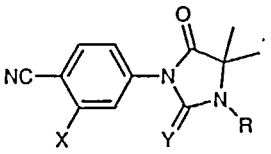
The hormone dependency of prostate cancer is well established and androgen receptor (AR) expression is frequently observed in primary prostate tumors and metastases (1). As a consequence, the development of radioligands that target the AR for prostate tumor imaging is an active area of research (2). The majority of these studies to date have focused on steroid-based ligands, including the naturally occurring androgens (testosterone, dihydrotestosterone) and synthetic steroids (mibolerone, metribolone) (3,4).

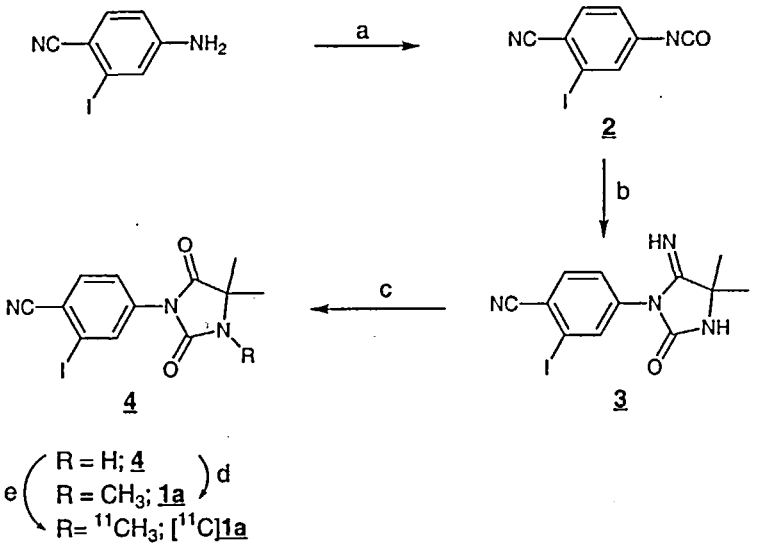
The recent emergence of AR-selective, high-affinity, nonsteroidal antiandrogens such as RU 59063, (Table 1), offers a useful alternative approach towards AR radioligand development (5). Our goal in this study was to develop a suitable carbon-11 labeled nonsteroidal AR radioligand for PET imaging of prostate cancer. We recently showed that replacement of the trifluoromethyl group of RU 59063 with iodine (DTIB, Table 1) leads to a 3-fold enhancement in AR binding affinity (6). This observation led us to synthesize the *N*-methylated hydantoin and thiohydantoin derivatives (**1a**,**1b**), which were subsequently shown to retain high affinity towards AR (Table 1). Since the synthesis of [^{11}C]**1b** by direct *N*-[^{11}C]methylation of its normethyl precursor is not feasible (due to preferential methylation on sulfur), the *N*-methyl derivative **1a** was selected for carbon-11 labeling. We report here the radiosynthesis of [^{11}C]**1a** for evaluation as a AR radioligand for PET.

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
DTIB	I	S	$(CH_2)_4OH$	0.71 ± 0.22
1a	I	O	CH_3	11 ± 5
1b	I	S	CH_3	2.5 ± 0.7

Figure 1[a]



[a] Reagents and conditions: (a) $COCl_2$, toluene, rt; (b) 2-amino-2-cyanopropane, Et_3N, 1,2-DCE, reflux; (c) 2 N HCl, CH_3OH, reflux; (d) 1. NaH 2. CH_3I; (e) 1. KF/Alumina 2. $^{11}CH_3I$.

A four step synthetic route starting from 4-cyano-3-iodoaniline provided **1a** in 37% overall yield (Figure 1). Radiosynthesis of [^{11}C]**1a** with [^{11}C]CH_3I was conducted in a microcolumn by a captive solvent method following adsorption of the normethyl precursor of **1a** on a solid phase mixture of 20% KF and 2% water in alumina. The labeled product was eluted with anhydrous ether through a column of basic alumina, concentrated, and dissolved in physiological saline:EtOH (95:5) for animal studies. The radiochemical yield and specific activity of the product were 45% (EOB) and >1300 Ci/mmole (EOS), respectively.

In conclusion, a reliable and efficient synthesis of a carbon-11 labeled nonsteroidal androgen receptor ligand is reported. Biological studies are underway to determine the applicability of [^{11}C]**1a** as a PET radioligand for AR imaging.

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