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ANDROGEN RECEPTOR-BASED IMAGING AGENTS FOR THE PROSTATE: SYNTHESIS AND TISSUE DISTRIBUTION STUDIES WITH TRITIUM AND FLUORINE-18 LABELED ANDROGENS.

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The growth and development of the prostate depends on androgens, and prostatic tissue and most prostate tumors contain receptors for androgens. These receptors offer a means for the selective localization of a suitable radiolabeled androgen that could act as an imaging agent for prostatic tumors. If such imaging agents could provide definitive determination of the extent of tumor invasion and metastasis, which is difficult to achieve with diagnostic methods in current use, it would be very helpful in guiding the selection of alternative therapies for the management of prostatic cancers.

In order to develop suitable androgen-receptor based imaging agents, we first investigated the uptake of five androgens, available commercially in high specific activity tritium-labeled form, in the prostate of one-day castrated rats (250 g) (1). Testosterone (**T**; Relative Binding Affinity (RBA) = 5.9), 5α-dihydrotestosterone (**DHT**; RBA = 60), 19-nortestosterone (**nor-T**; RBA = 31), mibolerone (**Mib**; RBA = 120) and methyltrienolone (**R1881**; RBA = 100) all showed selective uptake by the ventral prostate that was 61-90% displaceable by co-injection of an excess of unlabeled steroid. The greatest uptake was with **R1881** (0.69% ID/g at 1 h), and **Mib** (0.56% ID/g); the other three showed lower uptake (ca. 0.4% ID/g). The target tissue activity remained high for all compounds up to 4 h after injection, and at 2-4 h the prostate to blood ratio for **Mib** and **R1881** exceeded 10 and 20, respectively. The uptake efficiency and selectivity of these five androgens appear to be related to their affinity for the androgen receptor and their resistance to metabolism. **Mib** and **R1881** have substantial affinity for other steroid receptors, but competition studies with triamcinolone acetonide and **DHT** show that prostate uptake depends upon binding to the androgen receptor. The prostate uptake of **Mib** and **R1881** in intact animals was significantly lower than in castrated animals, but treatment of the intact animals with diethylstilbestrol restored uptake nearly to the level seen in castrated animals.

Based on these uptake studies, we have synthesized 20-fluoromibolerone (2). The synthesis begins with 7α-methyltestosterone and proceeds to the 17β,20-spiro cyclic sulfate, which undergoes fluoride substitution at C-20 in good yield. This compound has high affinity for the androgen receptor (RBA = 56), and it was prepared in fluorine-18 labeled form in reasonable yield and in high effective specific activity. Tissue distributions in diethylstilbestrol-treated (1 mg s.c. at -24 and -3 h) rats (175 g) (2) indicated selective uptake and prolonged retention by the target tissue: The % ID/g prostate and the prostate/muscle ratio were 0.9 and 4, respectively, at 0.5 h, and 0.58 and 12, respectively, at 4 h. Co-administration of a high dose (36 μg) of testosterone reduced prostate uptake to the level of non-target tissues.

Thus, high affinity androgens – particularly derivatives of mibolerone (**Mib**) or methyltrienolone (**R1881**) – appear to be promising candidates for receptor-based imaging of androgen target tissues and tumors, even when patients are already receiving hormonal therapy.

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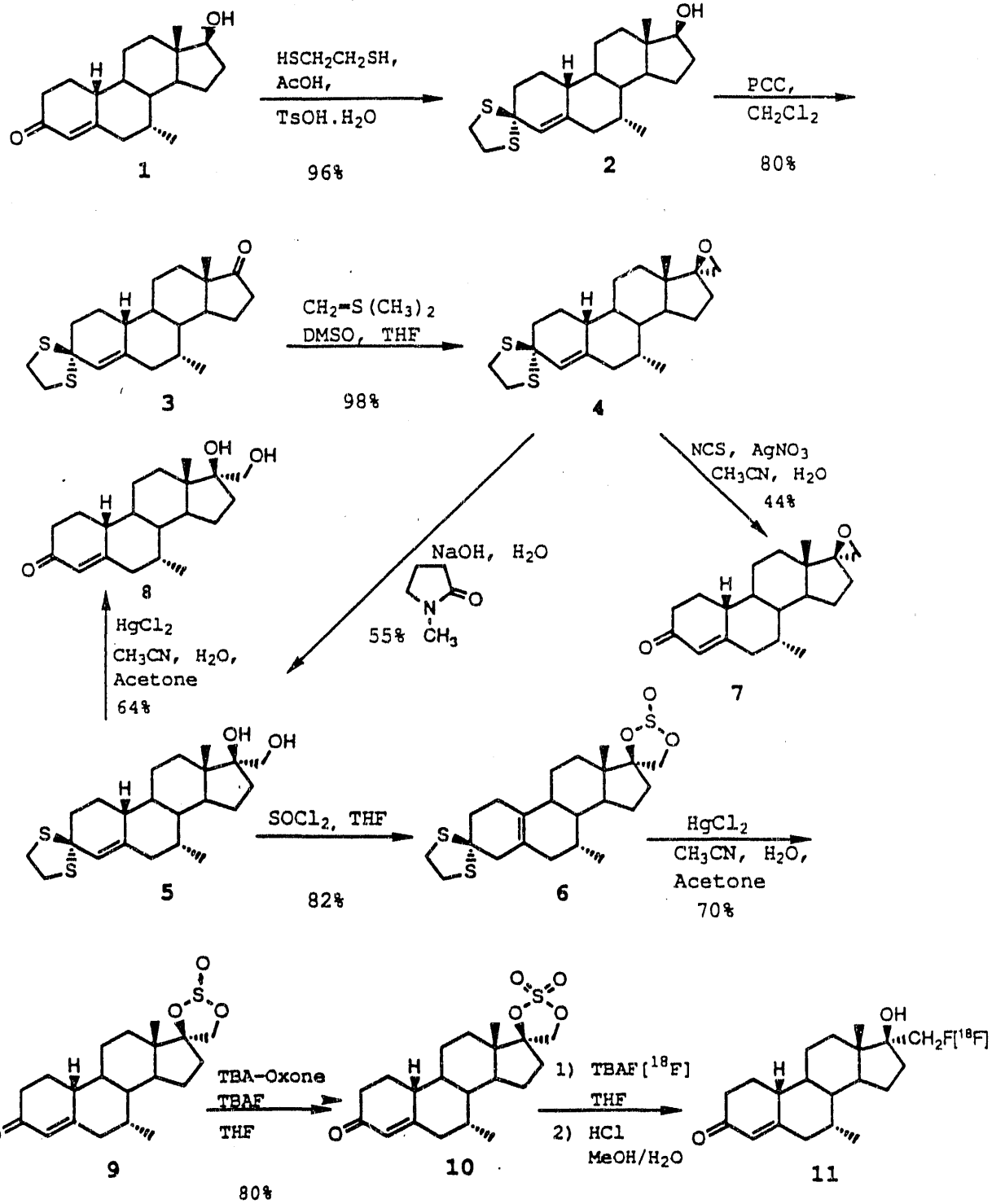
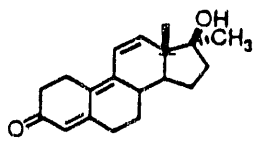
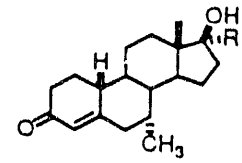
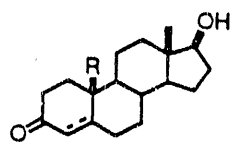
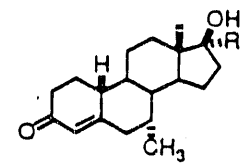
1. K. E. Carlson and J.A. Katzenellenbogen, *Nuclear Med. Biol.*, submitted.
2. A. Liu, J. A. Katzenellenbogen, H. VanBrocklin, C. J. Mathias, and M. J. Welch, *J. Nucl. Med.*, submitted.

Scheme 1



1 2 3 4 5 6 7 8 9 10 11

Table 1. Binding Affinity for Rat Prostatic Androgen Receptor[a]

Compound	Relative Binding Affinity (RBA)	Compound	Relative Binding Affinity (RBA)
 R1881 Methyltrienolone	100		
		R = H (1)	420
		R = CH_3 (Mibolerone)	120
		R = CH_2OH (8)	1.4
		R = CH_2F (11 F-Mib)	56
			
R = CH_3 Testosterone (Δ)	5.9		
R = CH_3 5α-Dihydrotestosterone	60	R = $-CH_2-$ (7)	3.1
R = H 19-nor-testosterone (Δ)	31	R = $-S(O)-O-CH_2-$ (9, mixture A)[b]	3.2
		R = $-S(O)-O-CH_2-$ (9, mixture B)[b]	2.6

a The binding affinity was determined in our Lab by a competitive binding assay using [^{3}H]R1881 as a tracer.

b Mixture A: the ratio of epimer a and b is ca.70 to 30; mixture B: the ratio is ca.30 to 70.

Table 2. Tissue Radioactivity Distribution of 20-[^{18}F]Fluoro-mibolerone[a]

organ	0.5h	1h	2h	2h(unt)[b]	2h(blocked)[c]	4h
% ID/g ±SEM						
blood	0.234±0.003	0.159±0.014	0.091±0.006	0.064±0.002	0.081±0.011	0.050±0.001
bone	0.189±0.011	0.197±0.010	0.251±0.014	0.184±0.017*	0.220±0.007	0.226±0.006
muscle	0.232±0.006	0.177±0.008	0.092±0.005	0.069±0.003	0.067±0.011	0.050±0.009
spleen	0.237±0.011	0.170±0.013	0.092±0.006	0.064±0.002	0.070±0.011	0.045±0.001
lung	0.417±0.011	0.300±0.012	0.165±0.011	0.107±0.004	0.078±0.011	0.080±0.006
liver	2.362±0.075	1.839±0.095	0.805±0.032	0.514±0.036	0.739±0.069	0.402±0.029
fat	0.573±0.049	0.264±0.012	0.132±0.020	0.112±0.014	0.137±0.020	0.067±0.003
kidney	0.880±0.038	0.753±0.035	0.423±0.018	0.266±0.012	0.361±0.078	0.174±0.008
prostate (v)[d]	0.886±0.037	0.969±0.140	0.601±0.056	0.384±0.073	0.150±0.034*	0.611±0.034
prostate (d)	0.923±0.028	1.188±0.304	0.775±0.135	0.393±0.068	0.111±0.009	0.545±0.057*
Ratio ± SEM						
prostate/ (v)	3.825±0.189	5.532±0.935	6.541±0.543	5.615±1.113	2.773±0.389*	13.25±2.22
muscle (d)	3.985±0.138	6.913±1.919	8.563±1.775	5.709±0.924	1.761±0.306	10.82±3.14
prostate/ (v)	3.790±0.105	6.385±1.302	6.707±0.671	6.128±1.388	2.159±0.298*	12.41±0.92
blood (d)	3.953±0.103	8.021±2.502	8.818±1.953	6.200±1.204	1.428±0.184	10.95±1.46*

a In the study, mature Sprague-Dawley rats were injected with 100 µCi dose of 20-[^{18}F]fluoro-mibolerone in 10% ethanol-saline. Average animal weight at time of experiment was 173±16g. All rats were treated with 1mg of DES in 0.2mL sunflower oil per rat 24h and 3h prior to injection with activity except "c" then untreated. n=4, except *, then n=3. SEM is standard error of mean.

b Animals are untreated (see a).

c Blocked: in order to block receptor-mediated uptake, 36µg of testosterone was added to each injected dose

d "v" = ventral, "d" = dorsal.

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