Synthesis and Biological Evaluation of 11β-F-DHT and 11β-F-19-nor-DHT as PET Imaging Agents for Prostate Cancer

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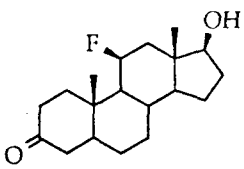
We have synthesized and evaluated 11β-fluoro-5α-dihydrotestosterone (11β-F-DHT, **1**) and 11β-fluoro-19-nor-5α-dihydrotestosterone (11β-F-19-nor-DHT, **2**) as potential androgen receptor (AR)-based imaging agents for prostate cancer. *In vitro* properties of these new androgens were investigated in terms of their lipophilicity (log $P_{O/W}$) and relative binding affinities (RBA, relative to R1881 = 100). RBA of 11β-F-DHT and 11β-F-19-nor-DHT to AR are 53.1 and 75.3, respectively, the latter being the highest reported among fluorine-substituted androgens. Introduction of a fluorine-18 label into the 11β-position of DHT and 19-nor-DHT was adapted from the fluorination reaction employed for the synthesis of androgens **1** and **2**. The reaction involved addition of halogen fluoride across the 9(11)-double bond, followed by reductive dehalogenation at the 9α-position. The resulting two fluorine-18 labeled androgens [^{18}F]-**1** and [^{18}F]-**2** were evaluated *in vivo*, in tissue distribution studies using diethylstilbestrol-pretreated mature male rats. The *in vivo* properties of 11β-F-DHT in rats show high prostate uptake and selective prostate to blood and prostate to muscle uptake ratios. Moreover, this ligand has low uptake in bone, displaying the lowest *in vivo* defluorination among all fluorine-18 labeled androgens tested. On the other hand, 11β-F-19-nor-DHT shows low prostate uptake with low selectivity and high uptake in liver, kidney, and bladder, indicating that this ligand is rapidly metabolized *in vivo*. The *in vivo* data thus suggest that 11β-F-DHT holds promise as an imaging agent for receptor-positive prostate cancer.



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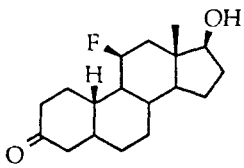

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