# SYNTHESIS AND ANDROGEN RECEPTOR BINDING OF NOVEL DERIVATIVES OF DIHYDROTESTOSTERONE

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## ABSTRACT

SYNTHESIS AND BINDING TO ANDROGEN RECEPTOR OF NOVEL DERIVATIVES OF DIHYDROTESTOSTERONE

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This work represents the synthesis, purification and physical characterization of derivatives of dihydrotestosterone. These novel compounds were evaluated with respect to their binding to rat prostate androgen receptor and possible utilization as affinity ligands. Literature binding studies indicate importance of the D ring of the steroid nucleus in the binding of androgens to the androgen receptor. Derivatives were restricted to this portion of the molecule. Derivatives were prepared to yield steroids with carboxylic acid side chains suitable for amide linkage to an aminoagarose. Compounds were screened for binding to the androgen receptor after conversion to their corresponding n-butyl amides, a model compound that is similar to the actual structure of the steroid after reaction with the aminoresin. Novel compounds were of three classes; 16 and 17-linked derivatives, 17-O linked dicarboxylates, 17-ether and isosteres.

Relative Binding Affinity (RBA) studies using tritiated methyltrienolone demonstrated model compounds with RBA's ranging to 0.04 relative to dihydrotestosterone. Although RBA's are low they are of the magnitude of affinity ligands currently in use. Affinity resins were prepared from select ligands and compared in a single step purification of androgen receptor from rat prostate cytosol. The site of attachment to dihydrotestosterone which retains the highest binding to androgen receptor is a 17-acyl linkage. The highest fold purification was seen with dihydrotestosterone-17-succinylaminoalkyl agarose. There is satisfactory correlation between RBA of model n-butyl amides and the fold purification of the corresponding affinity resin.

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