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Structure–activity relationship for inhibition of 5α-reductase by triterpenoids isolated from *Ganoderma lucidum*

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Abstract—In humans, 5α-reductase is involved in the development of benign prostatic hyperplasia. Triterpenoids isolated from ethanol extracts of *Ganoderma lucidum* (Fr.) Krast (Ganodermataceae) inhibited 5α-reductase activity. The presence of the C-3 carbonyl group and of the C-26-α,β-unsaturated carbonyl group was characteristic of almost all inhibitors isolated from *G. lucidum*.

1. Introduction

The microsomal enzyme steroid 5α-reductase catalyzes the NADPH-dependent reduction of the $\Delta^{4,5}$ double bonds of a variety of 3-oxo-Δ^4 steroids.[1] It is well documented that androgen-responsive tissues such as prostate, seminal vesicle, epididymis, and skin metabolize the conversion of testosterone to 5α-dihydrotestosterone (DHT).[2,3] This process amplifies the androgenic response, perhaps because of the higher affinity of the androgen receptor for DHT than for testosterone.[4] Both 5α-reductase and DHT perform critical roles physiologically and pathologically in humans. For example, DHT is necessary for adult prostate enlargement,[5] for the development of the male genitalia, and for normal beard growth,[6] while administration of DHT can enlarge the undetectable prostate[7] in males born with a genetic 5α-reductase deficiency.[8] Elevated DHT plasma levels have been reported in patients with either benign prostatic hyperplasia (BPH) or prostatic cancer.[9] Therefore, inhibition of androgen action by 5α-reductase inhibitors is a logical treatment for 5α-reductase activity disorders. Furthermore, with the assistance of modern methods of molecular biology, two types of 5α-reductases, identified as types 1[10] and 2,[11,12] have been isolated from human and rat prostatic cDNA libraries, and the structures of both genes have been elucidated. The type 1 isozyme has a broad basic pH optimum and low affinity for testosterone ($K_m > 1$ μM), while the type 2 isozyme has an acidic pH optimum and high affinity for testosterone ($K_m < 10$ nM).[13] The average sequence identity between isozymes within a given species is about 47%, while the sequence identity between the same isozyme across species is 60% for 5α-reductase type 1 and 77% for 5α-reductase type 2.[14] Early reports found that the type 1 isozyme predominates in tissues such as liver, kidney, brain, lung, and skin, whereas the type 2 isozyme is more abundant in genital tissues such as the prostate. However, some recent evidence shows that, in the human prostate, type 1 is expressed mainly in the epithelial cells, whereas type 2 is localized mainly in the stromal compartment.[13,15] Consequently in advanced prostate cancer, which is characterized by the abnormal proliferation of epithelial cells, type 1 might become the predominant isozyme probably responsible for androgen metabolism. Moreover, it has been shown that 5α-reductase type 1 activity is three to four times greater in malignant hyperplasia than in BPH, but 5α-reductase type 2 activity is similar in both diseases. Therefore, we focused on 5α-reductase type 1 activity.

The inhibition of 5α-reductase with organic molecules has been studied for more than two decades. Numerous nonsteroidal and steroidal compounds have been designed and synthesized as competitive, noncompetitive or uncompetitive inhibitors of 5α-reductase. Among them, benzonolinones[16,17] and 4-azasteroids[18,19] have high inhibitory potencies to type 1 and/or type 2 enzyme(s) in vitro and/or in vivo. Finasteride, a synthetic 5α-reductase inhibitor, is currently used to treat

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