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SYNTHESIS AND 5α-REDUCTASE INHIBITORY ACTIVITY OF 8-SUBSTITUTED BENZO[*f*]QUINOLINONES DERIVED FROM PALLADIUM MEDIATED COUPLING REACTIONS

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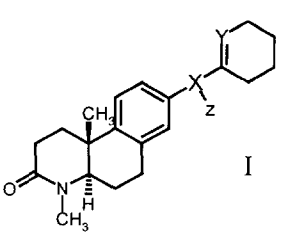
Abstract: Benzoquinolinones have been shown to be potent, selective inhibitors of the Type I 5α-reductase enzyme, which is responsible for the production of dihydrotestosterone from testosterone localized in the scalp. In an effort to identify compounds that demonstrate inhibition of both 5α-reductase isozymes, we have employed 8-bromobenzoquinolinone as an advanced intermediate for participation in a variety of palladium mediated carbon–carbon bond forming reactions. By varying the 8-substituent it is possible to alter the selectivity profile of the series.

Elevated dihydrotestosterone (DHT), resulting from the action of steroid 5α-reductase on testosterone, is believed to be the causative agent in a variety of conditions including benign prostatic hyperplasia (BPH), acne, hirsutism and androgenic alopecia. The identification of two different 5α-reductase enzymes,[1] has aided in the clarification of differential effects of the previously reported inhibitors of 5α-reductase. In a prior report,[2] we described a series of benzoquinolinones related to **I** that are potent, selective inhibitors of the Type I 5α-reductase enzyme, which is responsible for the production of DHT from testosterone localized in the scalp. The presence of both isozymes in the prostate, coupled with the incomplete effectiveness of selective steroidal Type II antagonists such as finasteride in BPH suggests that mixed inhibitors may hold promise for the treatment of BPH.[3] Recently, the SmithKline Beecham group has reported on other non-steroidal inhibitors which show varying selectivity for Type I verses Type II.[4]

Earlier structure–activity findings in our benzoquinolinone series showed that *N*–methylation led to a substantial increase in potency compared with the unsubstituted analogues, while compounds with *trans* ring fusion demonstrated greater activity than their *cis* counterparts.[2] Unexpectedly, the 10α angular methyl substituent actually led to a modest decrease in potency in benzoquinolinones unlike that observed with the natural steroids. Since certain 8-substituents had a pronounced and selective effect on the Type I enzyme, it was postulated that other 8-substituents might be found which retained good Type II activity by virtue of their hydrophobic domains. Consequently, we have employed 1 as an advanced intermediate for participation in a



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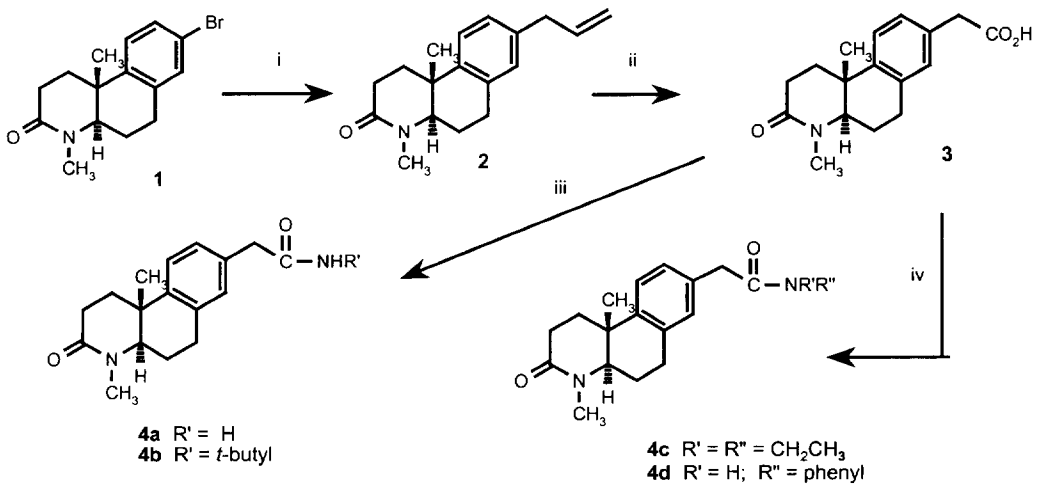
variety of palladium mediated carbon–carbon bond forming reactions in a effort to identify compounds that demonstrate good inhibition of both isozymes. This strategy allowed for the preparation of a variety of diversely substituted benzoquinolinones which ably probe the steroid D ring region of the natural substrate.

A tetrakis(triphenylphosphine)palladium(0) mediated coupling of tri-*n*-butyl-2-propenyl-stannane with 8-bromobenzoquinolinone (**1**) afforded the 8-allyl compound **2** in greater than 90% yield as shown in Scheme I. The oxidative cleavage of **2** gave the phenylacetic acid derivative **3** and a small amount of over oxidation to the benzoic acid derivative. Separation of the homologous acids was possible by preparative HPLC. The amides **(4a–d)** were prepared either from the acid chloride generated in situ or via the activation of **3** with carbonyldiimidazole.

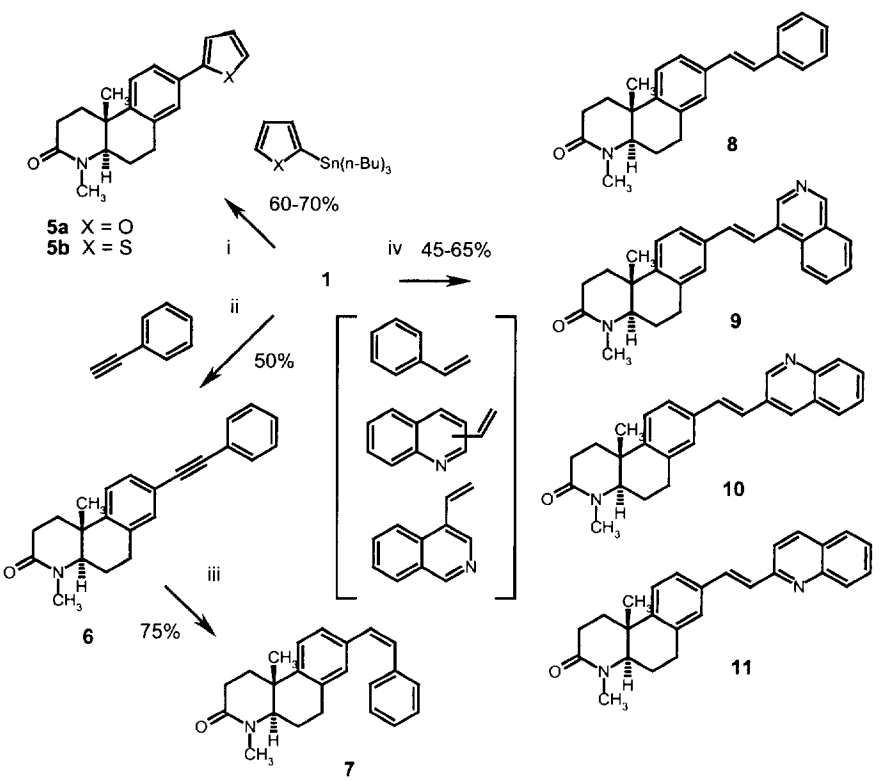


Scheme I. (i) $Pd(PPh_3)_4$, $(n\text{-}Bu)_3SnCH_2CH{=}CH_2$; (ii) $NaIO_4$, $RuCl_3$; (iii) 1. ClCOCOCl 2. NH_4OH or t-$BUNH_2$; (iv) 1. CDI 2. Dimethylamine or aniline

The 8-substituted 2-furanyl **5a** and 2-thiophenyl **5b** derivatives were prepared from the tin reagents of furan and thiophene,[5] respectively, using bis(triphenylphosphine)palladium(II) chloride as catalyst as summarized in Scheme II. The same catalyst was utilized in the preparation of the 8-phenylacetylene derivative. The cis olefin **7** was obtained selectively by a $BaSO_4$ poisoned catalytic hydrogenation of the phenylacetylene **6**.

The styryl **8** and heteroaryl substituted benzoquinolinones **9–11** were prepared via a Heck[6] coupling reaction of the appropriate olefin with **1** as summarized in Scheme II. The vinyl substituted quinolines used were obtained by coupling the requisite bromoquinoline or bromoisoquinoline with ethenylstannanes using tetrakis(triphenylphosphine)palladium(0) as catalyst.

The phenylacetic acid derivative **3** only weakly inhibited the Type II enzyme (IC_{50} = 0.87 ± 0.16 μM.) The amides **4a–c** failed to significantly inhibit (IC_{50} >10 μM) either isoform of the enzyme. This is possibly a result of subtle conformational effects on the disposition of the amide imposed by the planar aromatic C-ring not found in the natural steroids.

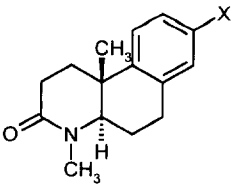


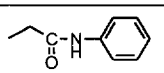
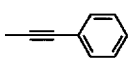
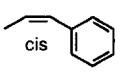
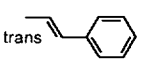
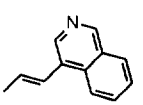
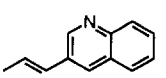
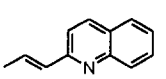
Scheme II. (i & ii) $PdCl_2(PPh_3)_2$, Et_3N, 80–110 °C; (iii) H_2, $Pd/BaSO_4$; (iv) $Pd(OAc)_2$, $(o\text{-}CH_3\text{ø})_3P$, Et_3N, 80–110 °C

The 2-thiophenyl analogue **5b** was only weakly active as a 5α-reductase inhibitor, while the 2-furanyl derivative **5a** showed improved inhibition. However, when simple heterocycles were replaced with styryl carbocycles or quinolines **(6–11)**, very potent inhibitors of the enzyme resulted. Indeed the *trans*-3-quinolinyl compound **10** proved to be the most potent inhibitor of the Type I enzyme, possessing selectivity of nearly a hundredfold over that of the Type II enzyme. Of the more active analogues, the acetylene **6** exhibits the least selectivity between the two isozymes and may hold promise for the design of other potent, nonselective inhibitors.

Enzyme Assay: Generation of human scalp and prostatic enzyme preparations used modifications of a previously published protocol.[7] The 5α-reductase enzymatic assay was based on the conversion of [^{3}H]-T to [^{3}H]-DHT in nuclear membrane preparations from human scalp (Type I) or prostate (Type II). Scalp 5α-reductase activity was assayed in a total volume of 200 μL containing 2.6 μCi [^{3}H]-T (50 nM), 500 μM NADPH and 100 mM Tris-HCl, (pH 7.5). Prostatic 5α-reductase activity was determined in 1.0 mL buffer containing 2.6 μCi [^{3}H]-T (50 nM), 500 μM NADPH and 400 mM disodium citrate, (pH 5.5). Compounds were added over a concentration range of 1 to 1000 nM in 5μL of MeOH for Type I or in 10 μL of DMSO for Type II. Enzymatic reactions were initiated by the addition of tissue homogenates containing 0.015-0.025 scalp or 0.080-0.100 mg prostatic protein. Scalp reaction mixtures were incubated at 37 °C, while prostatic tissues were incubated at 25 °C. Enzymatic reactions were terminated after 30 minutes by the addition of ice-cold stopping solution. Stopping solution contained 40 μM each of nonradioactive testosterone, dihydrotestosterone, androstenedione, androstanedione, androsterone, androstan-3B, 17 B-diol and androstan-3α, 17B-diol.

TABLE 1. 5α-REDUCTASE ENZYME INHIBITION



Cpd	X	Type 1 Human Scalp IC_{50} μM	Type 2 Human Prostate IC_{50} μM
4d		> 10	0.52
5a		0.059 ± 0.004	> 10
5b		> 10	> 10
6		0.021 ± 0.004	0.052 ± 0.063
7		0.0060 ± 0.001	1.40 ± 0.18
8		0.023 ± 0.003	0.18 ± 0.117
9		0.063 ± 0.052	1.34 ± 0.166
10		0.0034 ± 0.0015	0.32 ± 0.163
11		0.032 ± 0.002	0.55 ± 0.183

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