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Bioorganic & Medicinal Chemistry Letters 15 (2005) 145–148
Bioorganic & Medicinal Chemistry Letters

Synthesis and activity of 8-substituted benzo[*c*]quinolizin-3-ones as dual inhibitors of human 5α-reductases 1 and 2

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Received 29 July 2004; revised 5 October 2004; accepted 7 October 2004
Available online 28 October 2004

Abstract—Some potent dual inhibitors of 5α-reductases 1 and 2, based on the benzo[*c*]quinolizin-3-one structure and with IC_{50} values ranging between 93 and 166 nM for both isozymes, were found. The presence of the F atom on the ester moiety at the position 8 was crucial. This result can help in the design of other potent, dual inhibitors to be developed as drugs in the treatment of 5α-reductase related diseases.

Dihydrotestosterone (DHT) is produced by the NADPH-dependent reduction of testosterone (T) under catalysis of the enzyme steroid 5α-reductase (5αR) (EC 1.3.99.5).[1,2] The DHT production is in many cases related to the maintenance of some pathological human diseases and endocrine disorders,[3–8] so that the use of 5αR inhibitors for the possible control or suppression of DHT formation, without significant changes in the circulating testosterone, is a therapeutic target for the treatment of benign prostate hyperplasia (BPH), androgenic alopecia, and acne in men, and hirsutism in women.[9,10] Two different DNA-encoded isoenzymes of 5α-reductase, named type 1 and type 2 (5αR-1 and 5αR-2), transform T into DHT with different efficacy, which are not equally distributed in the human tissues, 5αR-1 being present mainly in scalp, skin, and liver, and 5αR-2 in the prostate. The synthesis and use of selective 5αR-2 inhibitors was initially envisioned for the specific treatment of a prostate disease such as BPH, culminating with the introduction on the market by Merck of finasteride (Fig. 1).[11] However, after the observation that finasteride was not equally efficacious in all treated patients, and that only in 30–40% of the treated cases the circulating level of DHT decreases up to 20% of the basal level,[12] the synthesis and use of dual 5αR-1 and 5αR-2 inhibitors became a therapeutic model to completely reducing the circulating DHT. This new approach has brought to development by Glaxo of azasteroid dutasteride (Fig. 1), a dual inhibitor which was approved by FDA on 2002 for the treatment of BPH.[13]

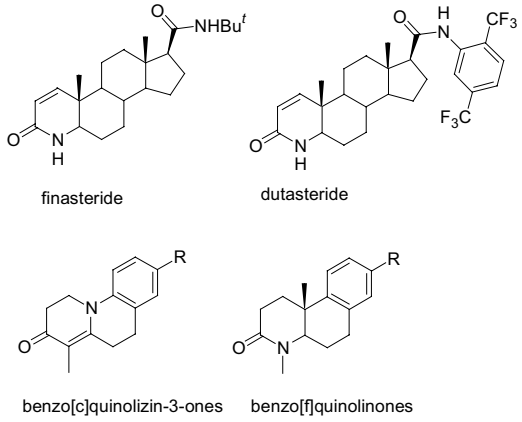

Figure 1.

As part of our studies on 5α-reductase inhibitors,[14] we recently reported on the synthesis and inhibitory activity of benzo[*c*]quinolizin-3-ones (Fig. 1) as potent and selective nonsteroidal inhibitors of 5α-reductase type 1

Keywords: 5α-Reductase; Inhibition; Benzo[*c*]quinolizinones; Dihydrotestosterone; Fluorine.
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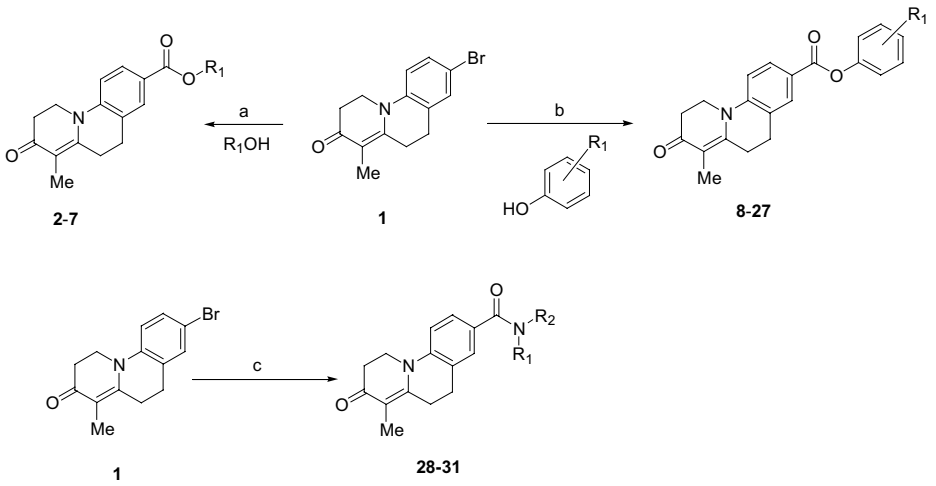
doi:10.1016/j.bmcl.2004.10.017



Scheme 1. Reagents and conditions: (a) R_1OH, CO, $PdCl_2$, Et_3N, benzene, 115 °C, 24 h, 50 bar; (b) phenol, CO, $PdCl_2$, Et_3N, benzene, 115 °C, 24 h, 50 bar; (c) amine, CO, $PdCl_2$, Et_3N, benzene, 115 °C, 24 h, 50 bar.

isozyme. We have shown that the potency of these compounds can be modulated by the substituent at the position 8 on the aromatic ring. Similar findings have been reported on Ely Lilly benzo[*f*]quinolinone compounds (Fig. 1), which, if bearing particular groups on the aromatic ring, showed even a weak to fair activity toward 5αR-2.[15] Aimed at discovering new nonsteroidal, dual inhibitors of 5α-reductases 1 and 2, having possible therapeutic applications, we started a program based on the synthesis and the evaluation of a series of benzo[*c*]quinolizin-3-ones bearing diverse substituents at position 8.

By a modification of the aza-Robinson annulation, involving lactams as starting materials, we prepared, as recently reported,[16] a bulk quantity of 8-bromo-4-methyl-benzo[*c*]quinolizin-3-one **1** (Scheme 1), a common intermediate which can be easily, and possibly in a single step, transformed into the target compounds by Pd-catalyzed cross-coupling reactions. A random screening of various benzo[*c*]quinolizinones prepared starting from **1**, allowed us to observe for the first time a dual inhibition (although inhibition of 5α-reductase 2 was still weak) when a carbomethoxy group was inserted in place of the bromine atom (compound **2**, Table 1, entry 1). Other compounds, lacking the ester moiety, were inactive toward 5αR-2. Based on this observation we synthesized a series of esters of aliphatic alcohols **3**–**7** and phenols **8**–**27**. The synthesis of these compounds was realized by Pd-catalyzed carbonylation of **1** in the presence of the suitable alcohol or phenol as depicted in Scheme 1.[17] The introduction of F and CF_3 groups in our inhibitors was dictated by the knowledge that H–C(α)–C=O fragments in an enzyme active site provide a pronounced fluorophilic environment due to occurrence of C–F·C=O contacts that are best described in terms of multipolar interactions between the intrinsically polar C–F and C=O units. Such F-interactions could be effectively exploited for enhancing ligand affinity or selectivity in structure based design.[18] Dutasteride (Fig. 1), indeed, possesses two CF_3 groups on the phenyl ring of the 17-amide moiety. We prepared and tested also a series amides **28**–**31**.[17] The synthesis of these amides was realized as described above by using the correspondingly substituted amine as the nucleophile. All of the esters showed weak activity toward 5αR-2 (Table 1, entries 1–6), with the exception of compound **8** (entry 7), which displayed a fair activity toward this isozyme (295 nM), and the other substituted phenol esters.

All of esters **9**–**27** were tested toward 5αR-1 and 2 expressed by CHO 1827 and CHO 1829, respectively, as already reported.[14b] They maintained activity toward 5αR-1, with IC_{50} values always below 1 μM (one exception only, entry 12), some of them being potent inhibitors of this isozyme. In particular, among the most potent were those having on the phenol moiety a small lipophilic group: compound **9**, bearing a *p*-methyl group on the phenol moiety, and compounds **11** (*p*-OMe substituted), **14** (*p*-F substituted), **17** (*p*-CF_3 substituted), and **22** (*p*-COOMe) all displayed inhibition toward 5αR-1 with IC_{50} in the 93–149 nM range. An increase in steric bulk (compare entries 8 and 10 to entries 9 and 11) determined an appreciable decrease of activity. As for the position of the substituent on the phenol moiety, a group in *meta* appears to be less tolerated: among the series of F-, CF_3-, and COOMe-substituted compounds (entries 13–18 and 21–22), *para*- and *ortho*-substituted derivatives were the most potent inhibitors. In particular for *o*-CF_3 derivative **19** (entry 18) the IC_{50} value was 42 nM, that is, close to the inhibition value of the most potent 5αR-1 inhibitor belonging to the benzo[*c*]quinolizinone series, that is, 8-Cl-benzo[*c*]quinolizin-3-one (IC_{50} = 7.6 nM).[14b] Substitution with a *p*-amino group (entries 19–20) lead to a general decrease of activity compared to the *p*-F or *p*-CF_3 substituted compounds. Also, positioning a *p*-amide group on the phenol moiety (entries 23–26) did not lead to better inhibitors and in one case (entry 26) inhibition toward 5αR-2 was quite low.

As for the 5αR-2 inhibition, this seems directly dependent on the size of the *para* substituent: *p*-*t*-butyl substituted compound **10** (entry 9) showed low activity; *p*-EtO substituted compound **12** (IC_{50} 3300 nM) was less