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Synthesis of 3-alkyl naphthalenes as novel estrogen receptor ligands

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ABSTRACT

A series of estrogen receptor ligands based on a 3-alkyl naphthalene scaffold was synthesized using an intramolecular enolate-alkyne cycloaromatization as the key step. Several of these compounds bearing a C6-OH group were shown to be high affinity ligands. All compounds had similar ERα and ERβ binding affinity ranging from micromolar to low nanomolar.

Estrogen receptors (ER) are members of the superfamily of ligand-modulated nuclear receptors that mediate the actions of steroid hormones, vitamin D, retinoids, and thyroid hormones.[1] Naturally occurring estrogens such as 17β-estradiol have been used in hormone replacement therapy (HRT) by postmenopausal women for the treatment of osteoporosis and hot flush. Although HRT is effective, it has been associated with increased risk of cardiovascular disease and breast cancer.[2] Selective estrogen receptor modulators (SERMs) are a class of therapeutic agents that provide the benefit of estrogen while limiting some associated liabilities. Their tissue selectivity allows them to function as estrogen agonists in certain tissues, while acting as estrogen antagonists in other tissues. The clinical utility of SERMs has been exemplified with tamoxifen[3] for the prevention and treatment of breast cancer and raloxifene[4] for the prevention of osteoporosis and breast cancer in postmenopausal women.[5]

A series of estrogen receptor ligands derived from a naphthalene scaffold was previously reported by researchers at Eli Lilly.[6] However, the reported scope of this series was limited by a lack of substitution at the C3 position of the naphthalene skeleton (R^3 = H, Fig. 1).

Our interest in exploring substitution at the C3 position was motivated by an X-ray crystal structure of one of our naphthalene analogues GW2368 bound to ERα, which revealed an unfilled hydrophobic region of the ligand binding pocket adjacent to the C3 position (shown in yellow in Fig. 2). We hypothesized that incorporation of lipophilic substituents at the C3 position might provide analogues with increased ER binding affinity. We herein report the synthesis of a series of C3-substituted naphthalenes and their binding affinity against ERα and ERβ.

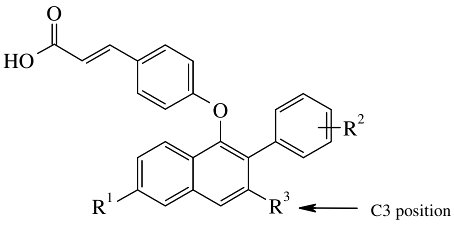

Figure 1. Generic structure of naphthalene SERMs.

We have previously explored several routes to prepare functionalized naphthalene-based ER ligands.[7] These earlier efforts included a squarate-based ring expansion chemistry approach as well as an attempt to adopt the route originally developed by researchers at Lilly. Unfortunately, while both of these approaches afforded some of our target compounds, they proved to be long, tedious, and subject to highly variable yields. Accordingly, rapid development of SAR at the C3 position demanded a more efficient synthetic route.

We focused our attention on two reports in the literature,[8,9] describing an intramolecular cycloaromatization strategy to construct 3-alkyl-1-naphthols. We envisioned that a substrate like **1** would probably undergo a similar benzannulation reaction to yield 3-alkyl-2-aryl-1-naphthol core, which could be used as a suitable intermediate for the generation of new ER ligands.

Phenylethanone **1** was prepared by three-step process (Scheme 1). Sonogashira coupling of methyl 2-iodobenzoate with 1-hexyne

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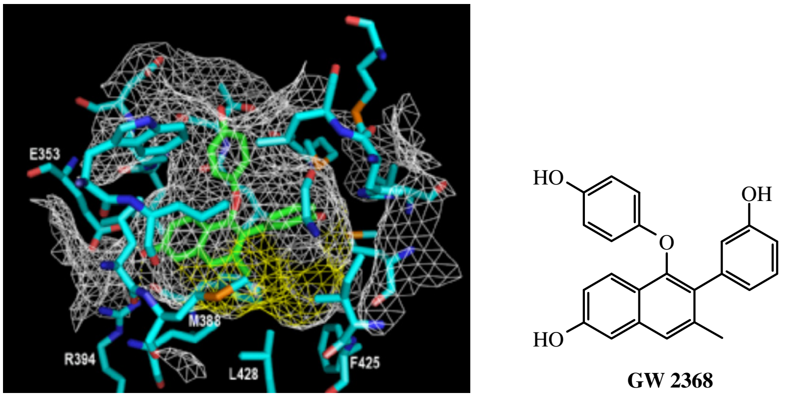
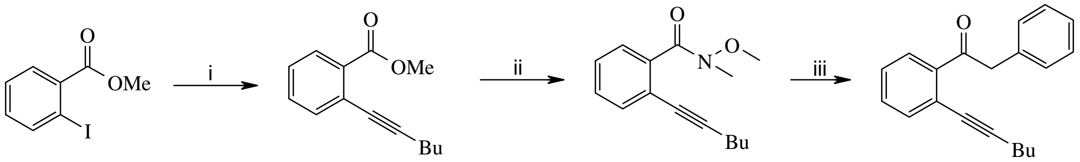


GW 2368

Figure 2. X-ray structure of GW2368 bound to ERα (RCSB Protein Data Bank ID: 3DT3).



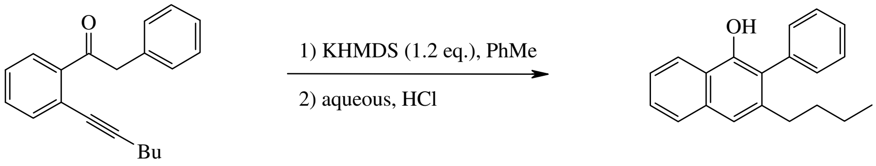
2 3 1

Scheme 1. Reagents and conditions: (i) 1-hexyne, Pd$(PPh_3)_2Cl_2$, CuI, DIPEA, DMF; (ii) *N*,*O*-dimethylhydroxylamine HCl salt, *n*BuLi, −20 °C; (iii) benzylmagnesium chloride, THF, 0 °C.

provided *o*-hexynylbenzoate **2**,[10] which was then reacted with the lithium salt of *N*,*O*-dimethylhydroxylamine to give Weinreb amide **3**.[11] Treatment of **3** with benzylmagnesium chloride in THF afforded **1** in 78% yield.[12]

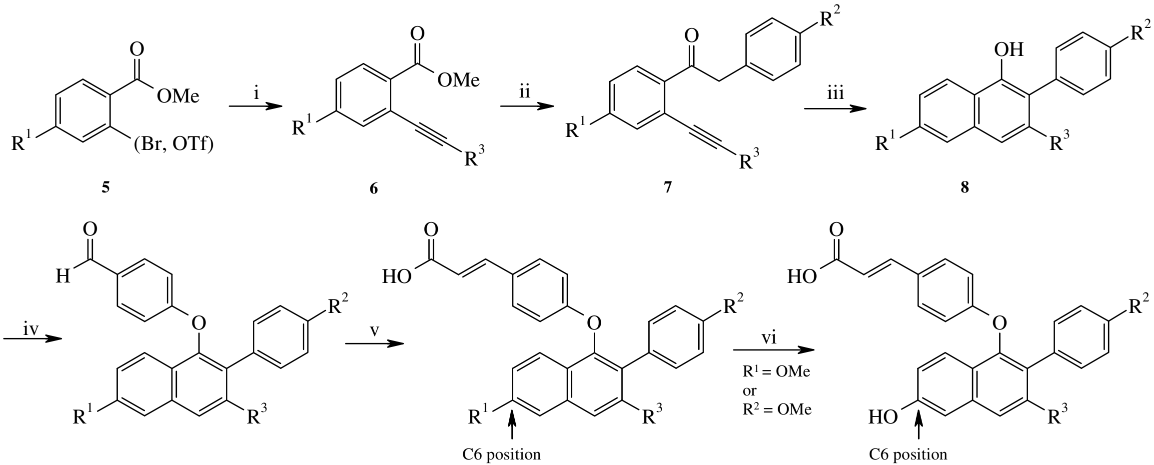
A variety of cycloaromatization conditions were applied to phenylethanone **1**. Deprotonation of this ketone with KHMDS (1.2 equiv) in toluene at −78 °C followed by heating at 80 °C for an hour gave the desired naphthol **4** in 68% yield (Scheme 2).[13]

Similar to what was reported previously,[9] a potassium counterion appears to be required. KOtBu and KH in THF provided **4** in comparable yields, but NaOMe, NaH and NaOtBu in THF afforded either none or a very low yield of the desired product along with



1 4

Scheme 2.



5 6 7 8

9 10 a-e 11 a-e

Scheme 3. Reagents and conditions: (i) HC≡C-R^3, Pd$(PPh_3)_2Cl_2$, CuI, DIPEA, DMF; (ii) a—*N*,*O*-dimethylhydroxylamine HCl salt, *n*BuLi, −20 °C; b—ArCH_2MgCl, THF, 0 °C; (iii) KHMDS, toluene, 80 °C; (iv) 4-F benzaldehyde, base, heat; (v) a—*n*BuLi, $(EtO)_2POCH_2CO_2Et$; b—NaOH, heat; or malonic acid, piperidine, Py., heat; (vi) BBr_3, CH_2Cl_2.

Table 1
ERα and ERβ binding data

Compound	R^1	R^2	R^3	ERα binding K_i (nM)	ERβ binding K_i (nM)
Estradiol	—	—	—	2	2
Raloxifene	—	—	—	2	23
10a	H	H	CH_3OCH_2	692	501
10b	H	H	Bu	977	170
10c	H	F	Bu	724	110
10d	H	OCH_3	Bu	158	162
10e	H	OH	Bu	52	48
11a	OH	H	*cyclo*-Pr	60	16
11b	OH	H	Bu	4	4
11c	OH	H	*i*-Bu	28	22
11d	OH	H	Pentyl	2	3
11e	OH	H	Octyl	55	30

multiple by-products. Refluxing **1** with 1 equiv of camphorsulfonic acid in $CHCl_3$ only resulted in a trace amount of **4**.

Using this cycloaromatization reaction, we synthesized various 3-alkyl-2-aryl-1-naphthols **8** starting from an appropriate aryl bromide or aryl triflate **5** for the Sonogashira coupling[14] (Scheme 3). 1-Naphthol **8** was then heated with 4-F benzaldehyde in the presence of a base (NaH or Cs_2CO_3)[15] to give aryloxy benzaldehyde **9**. Formyl group of **9** was converted to acrylic acid side chain of **10a–e** using Horner-Emmons olefination[16] followed by saponification or Knoevenagel condensation[17]with malonic acid in pyridine. When R^1 = OMe, demethylation with BBr_3 in CH_2Cl_2 yielded C6-OH naphthalene analogues **11a–e**.

Compounds **10a–e** and **11a–e** were tested for their ability to compete with ^{3}H-estradiol for binding to full length biotinylated human ERα and ERβ linked to an SPA bead (Table 1).[7] Consistent with the observed binding mode of GW2368 to ERα, the C6-H (des hydroxyl) analogues **10a–e** are significantly less potent than the corresponding C6-OH analogues **11a–e** due to the inability of **10a–e** to form hydrogen bonds with Glu 353 and Arg 394 in ERα and Glu 305 and Arg 346 in ERβ.[18] Enhanced potency in the R^1 = H series was observed with the R^2 phenol analogue **10e**, which is well positioned to form a hydrogen bond with His-524 (ERα) or His-475 (ERβ).[18] In general, small unbranched alkyl groups are well tolerated at C3 position of the naphthalenes as predicted in Figure 2. The octyl analogue (**11e**) appears to approach the steric limit for accommodating unbranched alkyl chains in this region of the binding pocket resulting in a loss of binding affinity.

In summary, we have modified a previously described cycloaromatization procedure to prepare a series of 3-alkyl substituted naphthalenes with good affinity for ERα and ERβ. This route provides a more efficient approach to the naphthalene scaffold than those previously reported for structurally related ER ligands, and provides a method to directly examine the impact of substitution at the C3-position on binding to estrogen receptors.

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13. *General procedure for cycloaromatization:* A solution of acetophenone **1** (0.88 g, 3.18 mmol) in toluene (8 mL) was added to a solution of KHMDS in toluene (0.5 M, 1.2 equiv) at −78 °C under N_2. After completion of addition, the cold bath was removed, and the reaction mixture was allowed to warm up to room temperature, then heated at 80 °C for 1 h. The reaction mixture was then cooled in an ice bath, quenched with 2 N HCl, diluted with 50 mL of water, and extracted with EtOAc. The organic extracts were combined and washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel (5% EtOAc in hexanes) to afford naphthol **4** as a light yellow solid (0.60 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, J = 7.3 Hz, 3H), 1.15–1.30 (m, 2H), 1.45–1.55 (m, 2H), 2.49 (t, J = 7.8 Hz, 2H), 5.20 (s, 1H), 7.33 (s, 1H), 7.36 (d, J = 7.0 Hz, 2H), 7.39–7.50 (m, 3H), 7.50–7.57 (m, 2H), 7.75 (d, J = 7.9 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H).
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