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ERβ ligands. Part 4: Synthesis and structure–activity relationships of a series of 2-phenylquinoline derivatives

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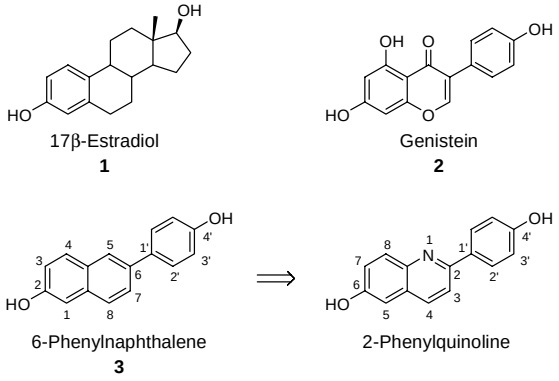
Abstract—A new class of estrogen receptor β (ERβ) ligands based on the 2-phenylquinoline scaffold was prepared. Several analogues with C4 substitution displayed high affinity (3–5 nM) and significant selectivity (up to 83-fold) for ERβ. The best compound, **13b**, was profiled as a selective partial agonist for ERβ at 1 μM in a cell-based transcriptional assay. Uterine weight bioassay of **13b** indicated no activation of ERα in vivo.

The estrogen receptor (ER) is a ligand-activated transcription factor, which plays a crucial role in the development, maintenance, and function of the mammalian reproductive system, as well as other non-sexual tissues such as the skeletal, cardiovascular, and central nervous systems.[1] The discovery in 1996 of a second subtype of estrogen receptor, estrogen receptor β (ERβ),[2] with its unique tissue distribution patterns and transcriptional properties from those of ERα,[3] has raised optimism about ERβ as a viable new drug target[4] and offered new opportunity for developing novel, tissue and cell-selective estrogens.[5] Recently, a report demonstrated a potential therapeutic utility of ERβ-selective agonists in treating inflammation.[6]

Although the ligand binding domains (LBD) of ERα and ERβ share only modest homology (58% identity), their ligand binding cavities are nearly identical, differing by only two amino acid residues (ERα Leu_{384} is replaced by ERβ Met_{336}, and ERα Met_{421} is replaced by ERβ Ile_{373}).[7] This slight variation in the binding cavities presents a great challenge in developing ER subtype-selective ligands. Phytoestrogens including the natural product genistein (**2**),[8] as well as constrained phytoestrogens[9] displayed approximately 10- to 40-fold ERβ selectivity. Similar modest selectivity has been observed in a number of other scaffolds.[10] Diarylpropionitriles (DPN)[11] and biphenyls[12] exhibited up to 70-fold selectivity. Current medicinal chemistry efforts have yielded several structural motifs with impressive ERβ selectivity. Indazoles[13] and benzofurans[14] showed selectivities up to 100-fold, whereas benzoxazoles[15] displayed as high as 200-fold selectivity for ERβ.

We recently reported a series of 6-phenylnaphthalenes which was developed as a simplified structure to mimic the genistein framework (Scheme 1).[16] Docking studies suggested that the 6-phenylnaphthalene scaffold could



Scheme 1. Scaffold evolution.

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exploit several binding orientations to achieve selectivity. The appropriate substituents placed at positions 1, 4, and 8 were shown to be essential to gain ERβ selectivity by interacting favorably with ERβ Ile_{373} and/or repulsively with ERα Met_{421} using two different binding orientations (Fig. 1).[16] In particular, several derivatives with C8 substitution displayed superior ERβ selectivity and affinity versus genistein. However, the synthetic inaccessibility of certain functional groups at this position prompted us to investigate the 2-phenylquinoline scaffold (Scheme 1), which has a similar structural motif as the 6-phenylnaphthalene. The facile assembly of this heterocyclic ring core allows us to further explore the effects of substitution at positions 4 and 5 of the 2-phenylquinoline scaffold, which correspond to positions 1 and 8 of the 6-phenylnaphthalene framework, respectively (Fig. 1B).

For the new 2-phenylquinoline template, we decided to retain the hydroxyl groups at the 6 and 4′ positions to mimic the two terminal hydroxyl groups of genistein, which is known to be essential for its binding to ER.[8] Moreover, similar geometrical arrangement of the two hydroxyl groups of the 6-phenylnaphthalene scaffold has been shown to be optimal for both ERβ affinity and selectivity.[16] In this report, we describe the synthesis and structural–activity relationships (SARs) of a series of 2-phenylquinolines. A number of these derivatives, particularly those with C4 substitution, exhibited high binding affinity and significant selectivity towards ERβ.

All compounds in Table 1 were synthesized as shown in Schemes 2–4. The synthesis began with the addition of *p*-anisyllithium to 6-methoxyquinoline to give the 2-phenylquinoline core **4** (Scheme 2).[18] Subsequent demethylation using pyridine hydrochloride gave the parent unsubstituted 2-phenylquinoline **5**. Bromination of **4** with NBS gave **6**, which upon initial deprotection using pyridine hydrochloride at high temperature, the bromo group was displaced by chloride exclusively to furnish quinoline derivative **7**. Thus, the brominated analogue **8** was obtained by an alternative demethylation method using BBr_3.

The 2-phenylquinoline core can also be prepared using a modification of the general Conrad–Limpach–Korr synthesis (Scheme 3).[19] Thus, alkoxycarbonylation of 4-methoxyacetophenones gave benzoylacetates **9**, which upon reaction with *p*-anisidine, followed by cyclization furnished hydroxyquinolines **10a**–**c**. Intermediates **10a**,**b** were treated with $POCl_3$, followed by demethylation to afford the 4-chloroquinolines **11a**,**b**. Compounds **10a**–**c** were also treated with $POBr_3$ to give **12a**–**c**, which upon removal of the methyl protecting group afforded the 4-bromo derivatives **13a–c**. The chloro group of **11a** was displaced by methoxide to furnish 4-methoxyquinoline **14**. The cyano analogues **15a**,**b** were prepared by palladium-mediated coupling reaction of **12a**,**b** with $Zn(CN)_2$,[20] followed by demethylation.

The bromo derivatives **13a**–**c** were also the common intermediates from which a number of 4-substituted 2-phenylquinolines could be prepared using various transition metal-mediated cross-coupling reactions (Scheme 4). Thus, Stille coupling of **13a**,**b** with tributyl(vinyl)tin afforded the vinyl analogues **16a**,**b**, which upon reduction furnished the ethyl targets **17a**,**b**. Similarly, the alkynyl derivatives **18a–c** were prepared by reaction of **13a**–**c** with (trimethylsilylethynyl)tributyltin[21] followed by desilylation. Suzuki reaction of **13b** with phenylboronic acid provided target **19**. Coupling of **13a**,**b** with (1-ethoxyvinyl)tributyltin gave the acetyl analogues **20a**,**b** after acid hydrolysis. Subsequent reduction of the acetyl group of **20b** yielded the hydroxyethyl derivative **21**.

The 2-phenylquinoline analogues were evaluated in a competitive radioligand binding assay measuring the relative binding affinity (IC_{50}) of the compounds for the human ERα and ERβ LBD.[22] Results are presented in Table 1. As expected, endogenous ligand 17β-estradiol bound equally well to both ER isoforms in this assay.

The unsubstituted quinoline **5** displayed some selectivity (10-fold) for ERβ, although binding affinity was modest. The observed ERβ selectivity of the 2-phenylquinoline core (**5**) is consistent with the general observation that the smaller overall binding pocket of ERβ[7] relative to ERα would favor small and planar molecular structures,[23] as well as the specific observation that aromatic moieties appear capable of making a more favorable interaction with ERβ Met_{336} than ERα Leu_{384}, given the way these two side chains are presented to the bind-

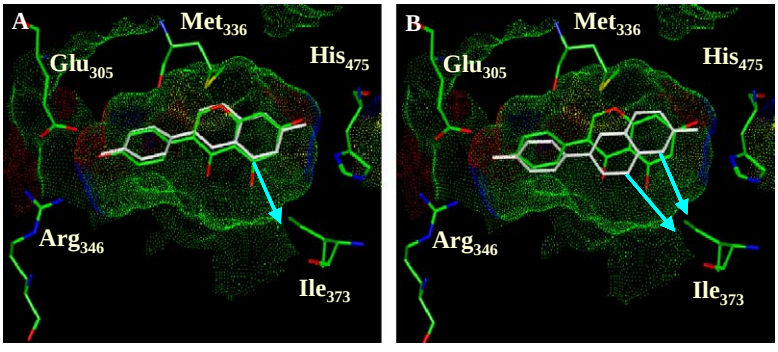

Figure 1. Two possible binding orientations of 6-phenylnaphthalene **3** (white) when docked into the binding site of ERβ–genistein complex. Genistein (green) and key residues are shown colored by atom type. Arrows depict potential substitution sites for enhancement of ERβ selectivity. Reprinted with permission from Ref. 16. Copyright (2005) American Chemical Society.