Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 15 (2005) 4520–4525

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

An T. Vu,[a,*] Stephen T. Cohn,[a] Eric S. Manas,[a] Heather A. Harris[b] and Richard E. Mewshaw[a]

[a]*Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA*
[b]*Women's Health Research Institute, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA*

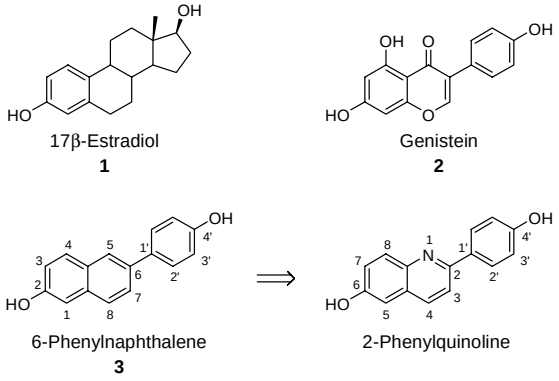
Received 3 June 2005; revised 30 June 2005; accepted 5 July 2005
Available online 10 August 2005

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.

Keywords: Estrogen receptor ligands; 2-Phenylquinoline.
* Corresponding author. Tel.: +1 484 865 8432; fax: +1 484 865 9399; e-mail: vua@wyeth.com

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.07.008

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-

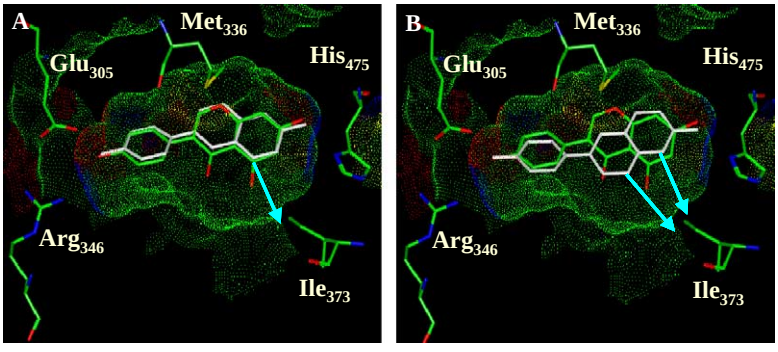
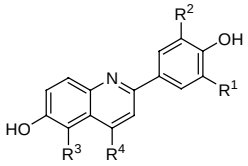


Figure 1. Two possible binding orientations of 6-phenylnaphthalene **3** (white) when docked into the binding site of ERβ–genistein complex. Genistein (green) and key residues are shown colored by atom type. Arrows depict potential substitution sites for enhancement of ERβ selectivity. Reprinted with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

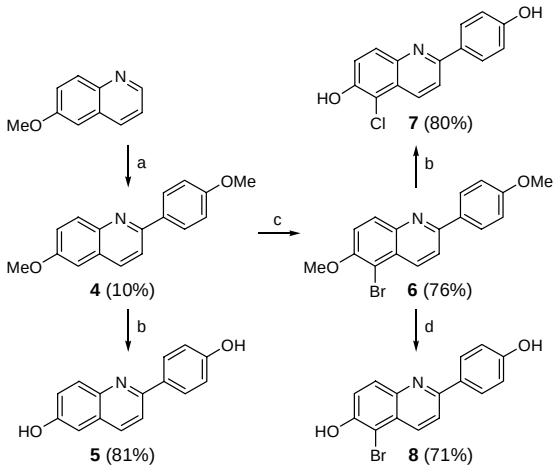
Table 1. Binding affinity for human ERα and ERβ ligand binding domain



Compound	R^1	R^2	R^3	R^4	ERβ IC_{50} (nM)[a]	ERα IC_{50} (nM)[a]	Selectivity (α/β)[b]
1	17β-Estradiol				3.6 ± 1.6	3.2 ± 1.0	1
2	Genistein				10 ± 4	395 ± 181	41
3	6-Phenylnaphthalene				16 ± 7	211 ± 74	13
5	H	H	H	H	171 ± 60	1775 ± 417	10
7	H	H	Cl	H	30 ± 11	632 ± 294	21
8	H	H	Br	H	88 ± 2	1140 ± 71	13
11a	H	H	H	Cl	4.6 ± 2.1	213 ± 38	46
11b	F	H	H	Cl	5.3 ± 3.2	246 ± 93	46
13a	H	H	H	Br	4.3 ± 2.3	212 ± 87	50
13b	F	H	H	Br	3.4 ± 1.5	283 ± 113	83
13c	F	F	H	Br	36 ± 6	783 ± 273	22
16a	H	H	H	$CH{=}CH_2$	60	504	8
16b	F	H	H	$CH{=}CH_2$	44 ± 11	385 ± 104	9
17a	H	H	H	Et	52 ± 13	634 ± 287	12
17b	F	H	H	Et	79 ± 55	1750 ± 1018	22
18a	H	H	H	C≡CH	75 ± 15	1500 ± 113	20
18b	F	H	H	C≡CH	27 ± 12	1309 ± 451	48
18c	F	F	H	C≡CH	750	4820	6
15a	H	H	H	CN	28 ± 7	455 ± 107	16
15b	F	H	H	CN	23 ± 10	1047 ± 429	46
20a	H	H	H	COMe	221 ± 13	3138 ± 285	14
20b	F	H	H	COMe	93 ± 28	3370 ± 85	36
19	F	H	H	Ph	211 ± 118	1815 ± 615	19
14	H	H	H	OMe	1190	6630	6
21	F	H	H	CH(OH)Me	>5000	>5000	ND

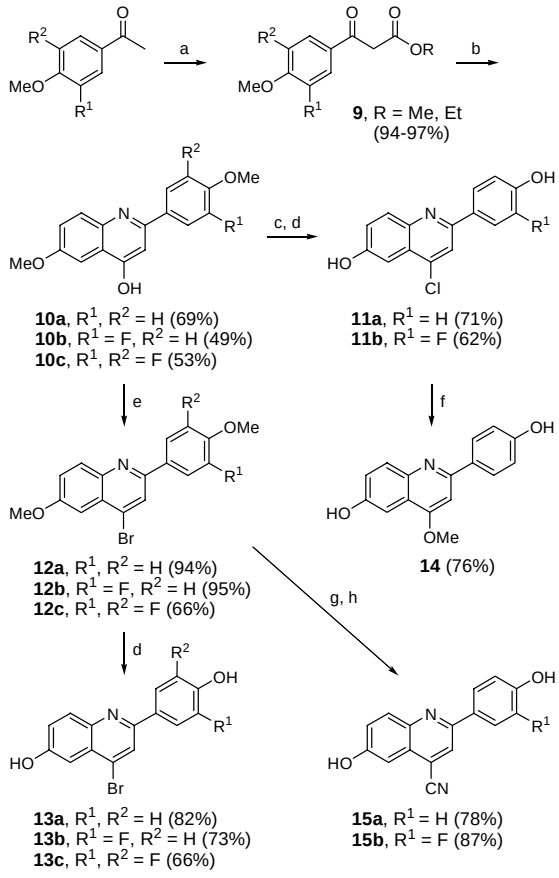
[a] IC_{50} values are the means of at least two experiments ± STD, determined from eight concentrations (performed in triplicate). Values without STDs are for a single determination only.
[b] ERβ selectivity is expressed as ERα IC_{50}/ERβ IC_{50} ratio.

ing pocket.[24] Moreover, the weaker affinities of **5** for both ER subtypes compared to those of the corresponding unsubstituted 6-phenylnaphthalene **3** may be attributed to a greater desolvation penalty upon binding for the quinoline moiety relative to naphthalene.[25] Based on the SAR and docking studies of the 6-phenylnaphthalene series,[16] substitution at positions 4 and 5 of the 2-phenylquinoline scaffold may provide the greatest opportunity for further enhancing ERβ selectivity by interacting with the ERβ Ile_{373}/ERα Met_{421} residues. As anticipated, derivative **7** with a chloro substituent at the C5 position exhibited a 2-fold increase in ERβ selectivity, with a concomitant 5.7-fold improvement in ERβ binding affinity (**7** vs **5**). However, the larger bromine group of **8** lowered both ERβ affinity and selectivity (compared to **7**), presumably due to steric repulsion with the distal His_{475} residue.

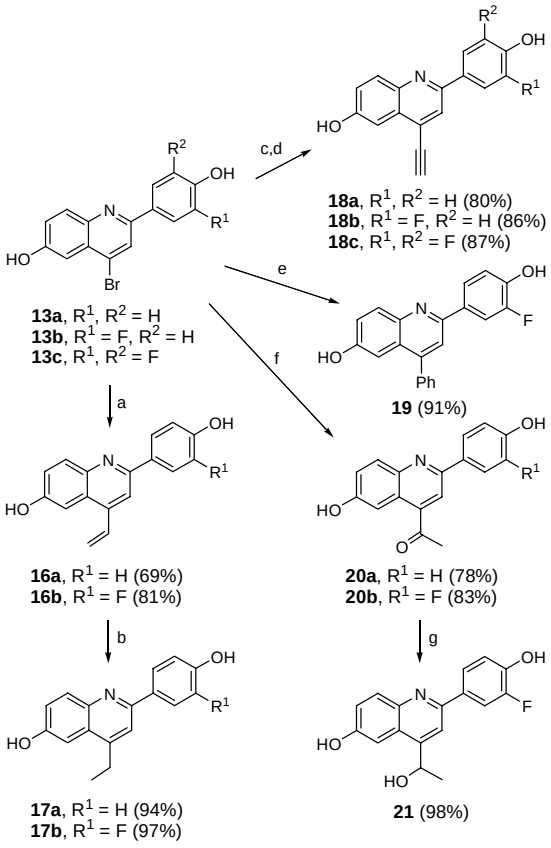


Scheme 2. Reagents and conditions: (a) 4-MeO-Ph-Li, Et_2O, 0 °C; (b) Pyr·HCl, 200 °C; (c) NBS, DMF, 40 °C; (d) BBr_3, $ClCH_2CH_2Cl$, 40 °C.

Next, we focused on the C4 substitution and examined a variety of functional groups including electronegative, electron-rich, aliphatic, aromatic, and polar substituents. Introduction of a halogen group led to approximately 40-fold increase in ERβ affinity as shown by **11a** and **13a** (vs **5**), both of which exhibited ERβ IC_{50} values less than 5 nM. Moreover, since these analogues had only a minor increase in ERα affinity, they displayed approximately 50-fold selectivity for ERβ. This affinity enhancement for both ER isoforms can be attributed to a favorable overall hydrophobic effect (due to the substituent itself as well as to reduced polarity of the quinoline core induced by the electronegative



Scheme 3. Reagents and conditions: (a) NaH, $CO(OMe)_2$ or $CO(OEt)_2$, 1,4-dioxane, reflux; (b) *p*-anisidine, cat. *p*-TsOH, toluene, 80 °C, then Ph_2O, 250 °C; (c) $POCl_3$, reflux; (d) BBr_3, $ClCH_2CH_2Cl$, 40 °C; (e) $POBr_3$, DMF, 70 °C; (f) NaOMe, MeOH, 150 °C; (g) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 80 °C; (h) Pyr·HBr, 200 °C.



Scheme 4. Reagents and conditions: (a) $Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$, tol., reflux; (b) H_2, Pd/C, EtOAc; (c) $Bu_3SnC{\equiv}C$-TMS, $Pd(PPh_3)_4$, tol., reflux; (d) K_2CO_3, MeOH; (e) Ph-$B(OH)_2$, $Pd(PPh_3)_4$, DME, aq Na_2CO_3, reflux; (f) $Bu_3Sn(OEt)C{=}CH_2$, $Pd(PPh_3)_4$, tol., reflux, then 1 N HCl; (g) $NaBH_4$, EtOH.

halogen[26]), and to additional van der Waals interactions between the halogen and surrounding residues. Furthermore, the significantly smaller increase in ERα affinity is presumably due to a less favorable interaction between the halogen atom and the ERα Met_{421} side chain. Although the relative contribution of dispersion, electrostatics, and exchange repulsion is unclear, it is possible that the electronegativity of the halogens and the methionine sulfur makes an unfavorable electrostatic contribution to the total interaction.[17] Small aliphatic groups such as ethyl (**17a**), vinyl (**16a**), alkynyl (**18a**), and small electron-withdrawing cyano (**15a**) group all showed some ERβ affinity enhancement (relative to **5**), but with minimal or no effect on selectivity, whereas the larger acetyl (**20a**) and phenyl (**19**) groups provided only slight selectivity improvement. Interestingly, the methoxy group (**14**) caused a great loss of activity, presumably due to the unfavorable basicity of the quinoline core induced by the electron-rich methoxy group. Introduction of the polar hydroxyethyl group (**21**) resulted in a complete loss of affinity.

With respect to phenyl ring substitution, introduction of a 3′-fluoro group generally led to a subtle increase in ERβ selectivity as shown by derivatives **13b**, **15b**, **17**–**18b**, and **20b** (relative to **13a**, **15a**, **17**–**18a**, and **20a**, respectively). Similar selectivity enhancement induced by the 3′-fluoro substituent has been observed with other scaffolds as well.[14–16] A structure-based explanation for this effect has been proposed elsewhere.[17] Surprisingly, the addition of a second fluoro group at the 5′ position (**13c** and **18c** vs **13a**,**b** and **18a**,**b**, respectively) proved to be detrimental. A possible reason for this loss of activity is most likely due to the electrostatic repulsion between one of the fluoro substituents and the side chain of Glu_{305}.[15] We point out that **13b** is the most potent and selective of the 2-phenylquinolines reported, with an ERβ IC_{50} value of 3.4 nM and 83-fold selectivity. Docking of **13b** to the binding pocket of the ERβ LBD/WAY-202196 cocrystal structure (PDB accession code 1YYE[16]) places the bromo group in close proximity to the ERβ Ile_{373} → ERα Met_{421} residue substitution (analogous to the cyano group of WAY-202196, see Fig. 2 and Ref. 16), suggesting that a differential interaction with these residues may contribute to the enhanced ERβ selectivity. Modulation of the quinoline electronic structure (and thus interaction with ERβ Met_{336} → ERα Leu_{384}) may also contribute to the selectivity enhancement.[16]

Compound **13b** was further evaluated in a cell-based transcriptional assay measuring its ability to regulate human keratin19 (KRT19) mRNA. This gene is upreg-

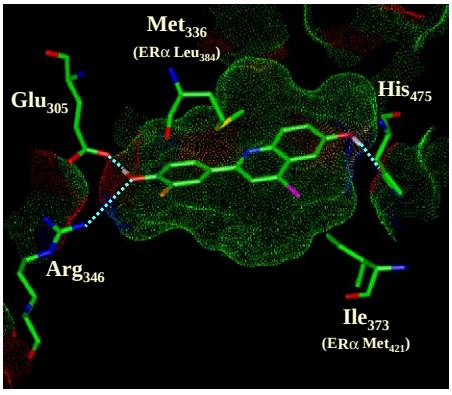


Figure 2. Compound **13b** docked to ERβ LBD/WAY-202196 complex. Docking calculations were performed as described in Ref. 12.

ulated by 17β-estradiol in human prostate cancer cells (LNCaPLN3) engineered to express either ERα or ERβ and thus can be used to determine agonist/antagonist activity of compounds.[10b] Analogue **13b** was tested at 1 μM and was compared to that of 10 nM 17β-estradiol. It was found to be inactive via ERα and was about 60% as efficacious as 17β-estradiol via ERβ. When tested in combination with 17β-estradiol, there was no marked antagonist activity. The results thus suggest that **13b** is a selective partial agonist for ERβ at 1 μM.

Compound **13b** was also evaluated in a highly sensitive uterine weight estrogenic bioassay measuring the weight gain in sexually immature mouse uterus. Because rodent uterus expresses primarily ERα, this model can be used to assess the in vivo ER selectivity of compounds. Sexually immature mice were dosed subcutaneously for 4 days with 50 mg/kg of **13b** in an oil-based vehicle.[17] In contrast to 17β-estradiol, which increased organ weight 4-fold, no significant uterine weight gain was observed for **13b**, indicating no ERα activation in this in vivo model.

In summary, we have identified the 2-phenylquinolines as a new series of ERβ-selective ligands. Substitution at the C4 position, particularly with electronegative groups, was essential for ERβ selectivity. Further selectivity enhancement could be achieved by incorporating a fluoro group at the 3′ position of the phenyl ring. A number of substituted 2-phenylquinolines displayed superior ERβ affinity and selectivity to that of genistein. Quinoline **13b**, which was the best compound of this study, was found to be a selective partial agonist for ERβ in a cell-based transcriptional assay. Its uterine weight bioassay showed no significant uterine stimulation, suggesting that this compound will not activate ERα in vivo. Efforts are continuing in our laboratories to expand upon our multiple binding orientation strategy to maximize ERβ selectivity.

Acknowledgment

We thank the Wyeth Discovery Analytical Chemistry Department for the spectral data.

References and notes

1. *Selective Estrogen Receptor Modulators*; Manni, A., Verderame, M. F., Eds.; Humana Press: Totowa, NJ, 2002.
2. (a) Mosselman, S.; Polman, J.; Dijkema, R. *FEBS Lett.* **1996**, *392*, 49; (b) Kuiper, G. G.; Enmark, E.; Pelto-Huikko, M.; Nilsson, S.; Gustafsson, J.-A. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 5925.
3. (a) Weihua, Z.; Andersson, S.; Cheng, G.; Simpson Evan, R.; Warner, M.; Gustafsson, J.-A. *FEBS Lett.* **2003**, *546*, 17; (b) Kian, T. M.; Rogatsky, I.; Tzagarakis-Foster, C.; Cvoro, A.; An, J.; Christy, R. J.; Yamamoto, K. R.; Leitman, D. C. *Mol. Biol. Cell* **2004**, *15*, 1262.
4. Nilsson, S.; Kuiper, G.; Gustafsson, J. A. *Trends Endocrinol. Metab.* **1998**, *9*, 387.
5. (a) Miller, C. P. *Curr. Pharm. Des.* **2002**, *8*, 2089; (b) Wallace, O. B.; Richardson, T. I.; Dodge, J. A. *Curr. Top. Med. Chem.* **2003**, *3*, 1663.
6. Harris, H. A.; Albert, L. M.; Leathurby, Y.; Malamas, M. S.; Mewshaw, R. E.; Miller, C. P.; Kharode, Y. P.; Marzolf, J.; Komm, B. S.; Winneker, R. C.; Frail, D. E.; Hederson, R. A.; Zhu, Y.; Keith, J. C., Jr. *Endocrinology* **2003**, *144*, 4241.
7. Pike, A. C. W.; Brzozowski, A. M.; Hubbard, R. E.; Bonn, T.; Thorsell, A.-G.; Engstrom, O.; Ljunggren, J.; Gustafsson, J.-A.; Carlquist, M. *EMBO J.* **1999**, *18*, 4608.
8. Kuiper, G. G.; Lemmen, J. G.; Carlsson, B.; Corton, J. C.; Safe, H.; Saag, P. T.; Burg, B.; Gustafsson, J. *Endocrinology* **1998**, *139*, 4252.
9. Miller, C. P.; Collini, M. D.; Harris, H. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2399.
10. (a) Schopfer, U.; Schoeffter, P.; Bischoff, S. F.; Nozulak, J.; Feuerbach, D.; Floersheim, P. *J. Med. Chem.* **2002**, *45*, 1399; (b) Yang, C.; Edsall, R., Jr.; Harris, H. A.; Zhang, X.; Manas, E. S.; Mewshaw, R. E. *Bioorg. Med. Chem.* **2004**, *12*, 2553; (c) Yang, W.; Wang, Y.; Ma, Z.; Golla, R.; Stouch, T.; Seethala, R.; Johnson, S.; Gungor, T.; Feyen, J. H. M.; Dickson, J. K., Jr. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2327.
11. Meyers, M. J.; Sun, J.; Carlson, K. E.; Marriner, G. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *44*, 4230.
12. Edsall, R. J.; Harris, H. A.; Manas, E. S.; Mewshaw, R. E. *Bioorg. Med. Chem.* **2003**, *11*, 3457.
13. Angelis, M. D.; Stossi, F.; Carlson, K. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2005**, *48*, 1132.
14. Collini, M. D.; Kaufman, D. H.; Manas, E. S.; Harris, H. A.; Henderson, R. A.; Xu, Z. B.; Unwalla, R. J.; Miller, C. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4925.
15. Malamas, M. S.; Manas, E. S.; McDevitt, R. E.; Gunawan, I.; Xu, Z. B.; Collini, M. D.; Miller, C. P.; Dinh, T.; Henderson, R. A.; Keith, J. C., Jr.; Harris, H. A. *J. Med. Chem.* **2004**, *47*, 5021.
16. Mewshaw, R. E.; Edsall, R., Jr.; Yang, C.; Manas, E. S.; Zhang, B. X.; Henderson, R. A.; Keith, J. C., Jr.; Harris, H. A. *J. Med. Chem.* **2005**, *48*, 3953.
17. Manas, E. S.; Unwalla, R. J.; Xu, Z. B.; Malamas, M. S.; Miller, C. P.; Harris, H. A.; Hsiao, C.; Akopian, T.; Hum, W.-T.; Malakian, K.; Wolfrom, S.; Bapat, A.; Bhat, R. A.; Stahl, M. L.; Somers, W. S.; Alvarez, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 15106.
18. Hamana, M.; Takeo, S.; Noda, H. *Chem. Pharm. Bull.* **1977**, *25*, 1256.
19. Kohno, Y.; Awano, K.; Miyashita, M.; Ishizaki, T.; Kuriyama, K.; Sakoe, Y.; Kudoh, S.; Saito, K.; Kojima, E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1519.

20. Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887.
21. Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.
22. Harris, H. A.; Bapat, A. R.; Gonder, D. S.; Frail, D. E. *Steroids* **2002**, *67*, 379.
23. Compound **5** was previously reported to exhibit some degree of ERβ selectivity: Wallace, O. B.; Lauwers, K. S.; Jones, S. A.; Dodge, J. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1907.
24. Manas, E. S.; Xu, Z. B.; Unwalla, R. J.; Somers, W. S. *Structure* **2004**, *12*, 2197.
25. Log *P* measurements (octanol–water) for naphthalene generally exceed that of quinoline by at least one log unit, indicating greater likelihood of partitioning into a hydrophobic environment. See for example: Rogers, K.; Cammarata, A. *J. Med. Chem.* **1969**, *12*, 692.
26. B3LYP/6-31G** calculations utilizing a Poisson–Boltzmann self-consistent reaction field model (Jaguar 6.0; Schrödinger, LLC, Portland, OR) indicate that a 4-chloro substituent decreases both the quinoline dipole moment and the aqueous desolvation energy.