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Triarylethylene Bisphenols with a Novel Cycle are Ligands for the Estrogen Receptor

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Abstract—We have prepared a series of triarylethylene and triarylethane systems, analogues of the selective antiestrogen tamoxifen, in which the alkyl substituent is tethered to the distal, rather than the proximal aryl ring by a 5-, 6-, or 7-membered carbocycle. This unusual cyclic structure rigidifies the ligand and adds bulk in a manner that is different from the more typical cyclization to the proximal aryl ring, as in the antiestrogen nafoxidine. These new systems were prepared efficiently by the addition of a benzylic sodium reagent, generated from the corresponding chloride by treatment with sodium naphthalenide, to a doubly protected 4,4′-dihydroxybenzophenone, followed by dehydration and deprotection. In all cases, formation of the exocyclic alkene was preferred. Two of the corresponding alkanes could be obtained by catalytic hydrogenation. All of these compounds have relatively high binding affinity for the estrogen receptor, and some of them demonstrate a significant level of affinity selectivity for the estrogen receptor alpha subtype. Accommodation of these newly rigidified cyclic triarylethylene systems into the ligand-binding pocket of the estrogen receptor can be visualized by molecular modeling.

Introduction

Estrogens have long been known to play a major role in regulating the development and function of the principal tissues of the female reproductive systems: uterus, ovaries, and breast. More recently, there has been a greater appreciation of the fact that estrogens also have important effects on many other organ systems: bone, liver, cardiovascular system, brain, etc.[1] Estrogen pharmaceuticals have been developed for hormone replacement in menopausal women, the most promising of these being the recently described selective estrogen receptor modulators (SERMs), such as raloxifene.[2] Estrogen antagonists, such as the mixed antiestrogens tamoxifen and raloxifene, and the pure antiestrogen ICI 182,780, are used for the treatment and the prevention of breast cancer, in some cases in experimental clinical protocols.[3–5]

Estrogens, whether agonists or antagonists, act through the estrogen receptor (ER). This protein is a member of the nuclear hormone receptor gene superfamily, and it functions as a ligand-modulated transcription factor.[6] ER binds many ligands with high affinity and great stereo- and structural specificity, but its preference of ligand shape and size can be rather eclectic: sometimes closely related analogues bind with very different affinities, whereas compounds with greatly differing structures may both bind very well.[7] In fact, the structural scope of non-steroidal estrogens having high affinity for ER is remarkable, being unified largely by the basic requirement for at least one *p*-monosubstituted or *m,p*-disubstituted phenol. The recent solution of the structure of the ER ligand binding domain by X-ray crystallography provides a new approach for understanding ER structure–binding affinity relationships.[8,9]

As part of our interest in the development of ER ligands of novel structure, we were struck by a curious fact. Among the structural class of triphenylethylene ligands, of which tamoxifen is a member, there are many examples of ligands in which rigidity and in some cases bulk, has been introduced by formation of an additional cycle. This cycle, however, has always linked carbon atoms of the ethyl group back to the *proximal* phenyl ring (Fig. 1), which in tamoxifen would prevent *cis–trans* isomerism, a process that affects the antagonist character of this antiestrogen.[10] The additional ring takes varied forms:[11] It has been homocyclic, as in the diphenylindenes,[12] the diphenyl-dihydronaphthalene nafoxidine,[13,14] and other tetrahydro analogues,[15] and tamoxifen analogues of larger ring sizes,[16] and it has

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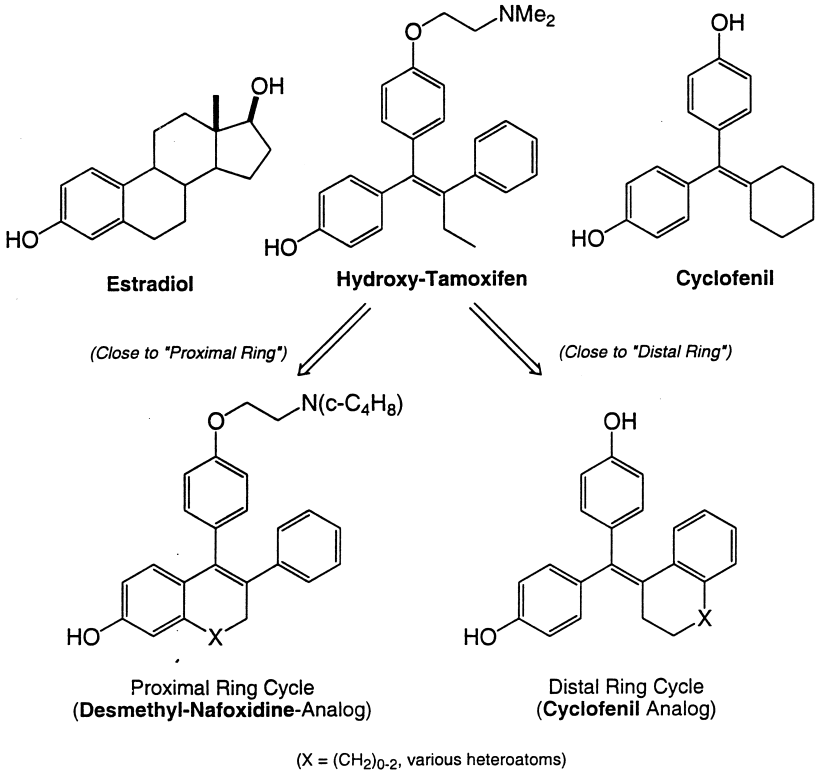


Figure 1. Modes of ring closure from a tamoxifen-like triarylethylene antiestrogen. The common cyclization of the ethyl group to the proximal aryl ring creates systems that resemble nafoxidine and its analogues and congeners, whereas the less common cyclization to the distal aryl ring creates systems that resemble benzocyclofenil.

been heterocyclic, as in the benzofurans,[11] benzothiophenes,[2] benzopyrans,[17] and the indoles.[18] In all cases, the fused bicyclic system that is formed by this additional ring is thought to constitute a structural mimic of the A and B rings of estradiol. This was shown in the recent crystal structure of the ER·raloxifene complex, in which the benzothiophene of raloxifene was shown to be bound in a fashion very similar to that of the A and B rings of estradiol.[8]

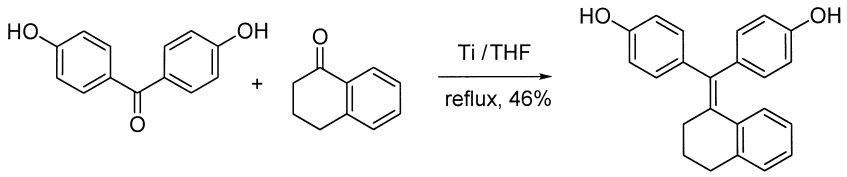
We were curious whether alternative cycles might be introduced into triarylethylene estrogens that would provide high affinity ligands having somewhat different shape, which in turn could reshape the ER, producing differing agonist/antagonist character and tissue selectivity. In particular, we wondered whether triarylethylene ER ligands in which carbon atoms of the ethyl group are linked forward to the *distal* phenyl ring would retain high ER binding affinity. Although cyclic linkage to the distal phenyl ring would not prevent olefin isomerization, in the more symmetrical systems we have examined here, this isomerism is of no consequence.

The novel tetracyclic system formed by this alternative ring closure can be considered to be an analogue of cyclofenil, a non-steroidal bisphenol with high affinity for ER that has partial antagonist activity.[19] ER is known to be tolerant of substituents on the cyclohexylidine ring of cyclofenil, and one of the analogues that we have prepared (see below) is a benzocyclofenil derivative.[20] In addition, this new structural modification would introduce bulk and shape variation in a region of the ligand that is close to the D-ring of estradiol. It has become clear from recent crystal structures of ER–ligand complexes that this region of the ligand-binding pocket is rather flexible, so that it can readily be reshaped by ligands of different size and shape, the SERMs in particular.[8,9,21] This reshaping of the ER complex might result in different degrees of agonist and antagonist character, and the generation of useful tissue selectivity.[1] It is also possible that such ligands might show preferential binding affinity and/or potency towards one of the two ER subtypes, ERα or ERβ.[22] In this report, we describe the synthesis of a series of triarylethylene and triarylethane bisphenols having this novel cyclic topology. We investigate their binding affinity for the ER, and model their fit into the binding pocket of ERα.

Results and Discussion

Synthesis of the cyclic bisphenols

An obvious approach to the synthesis of the new cyclic triarylethylene target systems involves conjoining a protected *p,p′*-hydoxybenzophenone with a benzo-cyclic ketone by a reductive process, such as the McMurray coupling with low valent titanium, exemplified in Scheme 1. Such an approach has been used successfully in the acyclic series for the synthesis of tamoxifen itself[23] and with one of the cyclic systems we have investigated.[20] In our hands, however, McMurray coupling between *p,p′*-dimethoxybenzophenone and the cyclic

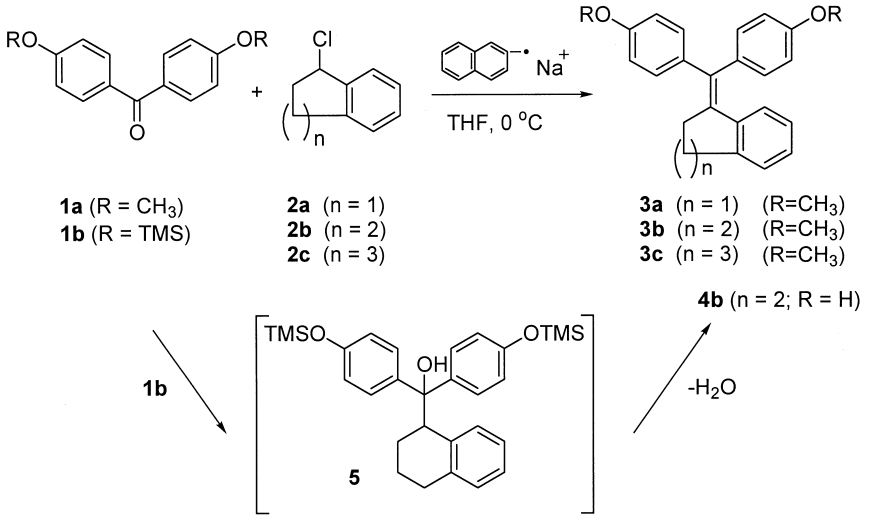


Scheme 1.

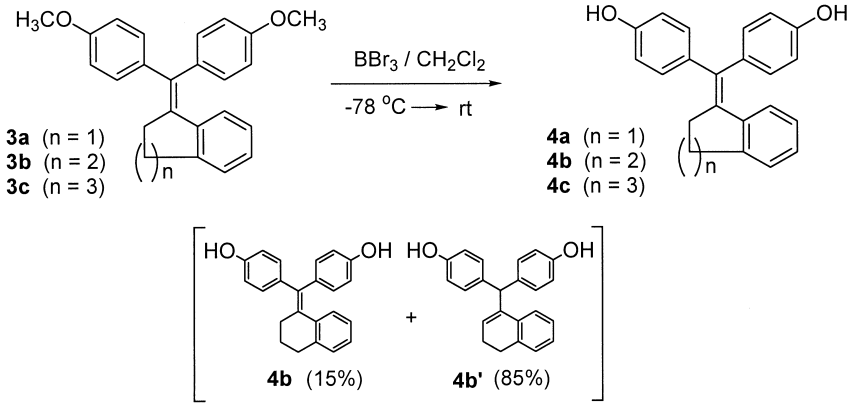
ketones proved to be sluggish and proceeded in relatively poor yield.

By contrast, an alternate though related approach, that involves the addition of an organosodium reagent derived by the corresponding benzo-cyclic chlorides (**2a**–**c**) to *p*,*p*′-dimethoxybenzophenone (**1a**), worked very well (Scheme 2). The requisite chlorides (**2a**–**c**) were obtained from the cyclic ketones by borohydride reduction, followed by treatment with thionyl chloride.[24,25] Treatment of the ketones directly with lithium metal resulted predominantly in Wurtz coupling. However, we found that treatment with sodium naphthalenide readily furnished the benzylic organosodium reagents.[26] Subsequent treatment with 4,4′-dimethoxybenzophenone gave after workup the desired olefins (**3a**–**c**) directly in good yields, the reaction presumably proceeding through the labile benzhydrol intermediate **5**. Only the isomers with exocyclic double bonds (**3a**–**c**) were obtained at this stage. Subsequent deprotection to the bisphenols (**4a**–**c**) with boron tribromide proceeded smoothly with the 5- and 7-membered ring systems (Scheme 3). The six-membered ring system, however, gave the bisphenol as a mixture of *exo*- and *endo*-cyclic double bond isomers, **4b** and **4b′**, respectively, in which the undesired endo-cyclic isomer(**4b′**) predominated.

It proved to be impractical to separate these regioisomers by crystallization or chromatography. Fortunately, by replacing the methyl ether phenol protecting group in ketone **1a** with the more labile trimethylsilyl group (**1b**), we were able to effect the addition of the organosodium



Scheme 2.



Scheme 3.

reagent and the dehydration–deprotection conversions under milder conditions that gave exclusively the *exo*-cyclic double bond isomer **4b** in high yield (Scheme 3).

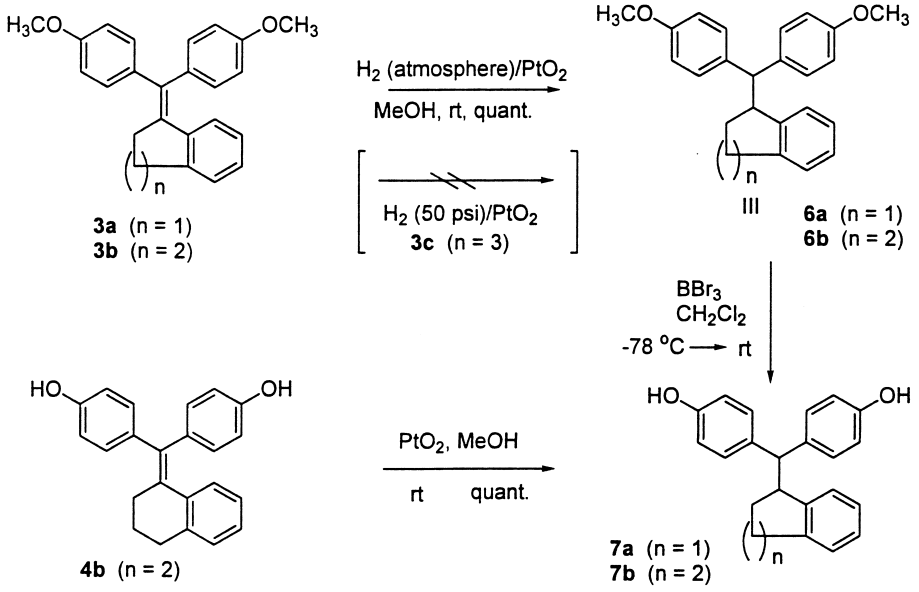
The 5- and 6-membered ring triarylethylene systems (**3a** and **3b**) were readily hydrogenated over a platinum oxide catalyst to give the corresponding saturated cyclic triarylethane systems **6a** and **6b** (Scheme 4). The 7-membered ring ketone (**3c**), curiously, was resistant to hydrogenation under these and even more vigorous conditions (up to 50 psi hydrogen over a platinum oxide catalyst). Deprotection as before gave the two saturated bisphenols, **7a** and **7b**. The unsaturated bisphenol **4b** could also be hydrogenated directly to the saturated analogue **7b**.

Estrogen receptor binding affinity of the cyclic bisphenols

The binding affinity of the triarylethylenes (**4a**–**c**) and the triarylethanes (**7a**–**b**) for the estrogen receptor (ER) was determined in a competitive radiometric binding assay, using tritium-labeled estradiol as tracer.[27,28] ER preparations used in these experiments were lamb uterine cytosol[28] or commercially obtained purified human ERα or ERβ, expressed in a baculovirus system.[27]

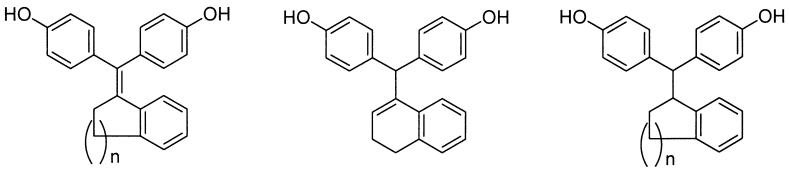
The binding affinity of these new compounds is recorded in Table 1, together with the affinity of a few related non-steroidal estrogens. Cyclization of the ethyl group to the *distal* phenyl substituent produces ligands that bind to the estrogen receptor with an affinity comparable to that of either the acyclic triarylethylene systems (exemplified by hydroxy-tamoxifen), as well as to those in which the cycle is made with the proximal phenol (exemplified by desmethyl-nafoxidine), or to the "parent system" cyclofenil (see Fig. 1). There is some variation in affinity among the compounds in this series: In both the ethylene and ethane case, the analogues with the six-membered cycle (**4b** and **7b**) have the highest affinity (except for **4c** with ERα); a moderate, but variable degree of ER subtype affinity selectivity is apparent in the ethylene series, with the six membered analogue **4b** favoring ERβ, but the seven-membered analogue **4c** favoring ERα.

Perhaps most remarkable is the fact that the affinities measured with the pure human ERα preparations are uniformly much higher than those measured in lamb uterine ER preparations, which, based on results from other species, are presumed to contain mostly ERα.[22] It is unlikely that this is the result of a species difference in ER ligand binding preference, because such effects are rather rare among the estrogens.[21] Rather, it is more likely a consequence of the high lipophilicity of these compounds. This high lipophilicity is evident from comparisons of the calculated octanol–water partition coefficients (log *P* values), which are also given in Table 1. Compared to estradiol, which is both the tracer and the standard used in the competitive binding affinity assay, all of the non-steroidal compounds are predicted to be very lipophilic, some up to 100-fold more lipophilic. As a result, when the assay is done in uterine cytosol, the non-steroidal ligands would be more highly bound to non-receptor proteins (i.e. proteins that constitute the "non-specific" binding fraction) than would estradiol. This would reduce their free concentration and result in a lower measured competitive binding affinity. Such effects of reduced apparent affinities of lipophilic compounds in competitive binding assays have been noted before.[29] The purified ERα and ERβ preparations should contain none of these "non-specific" proteins, so that the RBA values obtained here would represent their inherent affinities for these ERs. The log *P* value for hydroxy-tamoxifen is also high, but the uterine cytosol and pure ERα affinity values are not discordant. This compound, however, is an amine, which at physiological pH will be protonated, so it may



Scheme 4.

Table 1. Estrogen receptor binding affinities



4a-c **4b'** **7a-b**

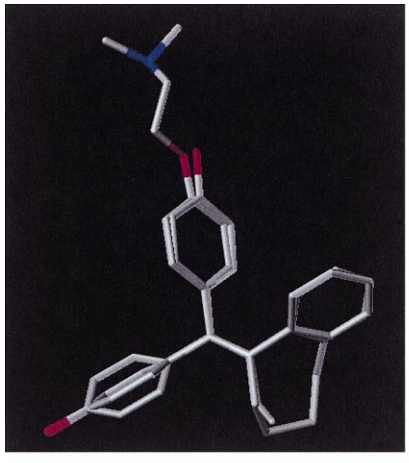
Compound	*n*	log *P*[b]	RBA[a] (%) 0 °C	25 °C	ERα	ERβ
Estradiol		3.37(3.51)[c]	(100)	(100)	(100)	(100)
4a	1	4.99	7.1	3.98	41.7	42.7
4b	2	5.41	11.2	5.88	132	240
4c	3	5.82	17.8	3.16	166	63.1
(4b′ + 4b)[d]	3	4.72	1.41	1.78	N/A[e]	N/A
7a	1	4.93	4.5	1.15	31.6	35.5
7b	2	5.38	3.3	1.41	50.1	47.9
Cyclofenil[f]		4.57(4.81)[c]	16	N/A	152	243
Desmethylnafoxidine[f]		5.57	105	N/A	N/A	N/A
Hydroxytamoxifen[f]		5.68	166	N/A	131	62

[a]Binding affinities are expressed relative to that of estradiol = 100% (RBA = relative binding affinity) and are the average of duplicate determinations. The first two determinations (0 and 25 °C) are in lamb uterine cytosol; the last two determinations are in pure human ERα and ERβ.
[b]These log *P* values are calculated using the ChemDraw Ultra program.
[c]The log *P* value in parentheses was measured by HPLC.
[d]**4b′**: **4b** = 85:15.
[e]N/A = not available.
[f]For structures, see Figure 1.

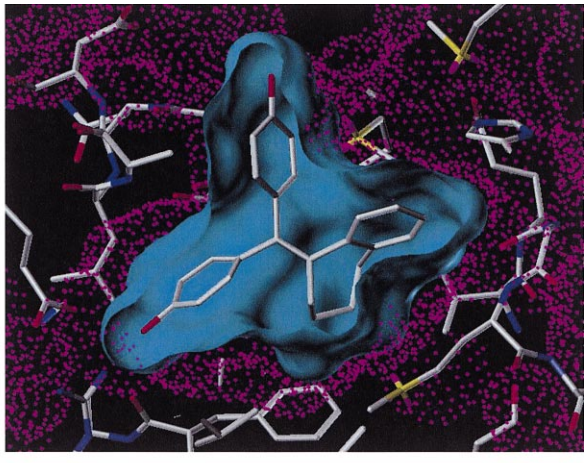
have less protein binding than do the neutral analogues **4** and **7**.

The estrogen receptor is known to accommodate various non-steroidal ligands of different shape and size, especially when these variations are at some distance from the portion of the ligand that mimics the A-ring of estradiol. Thus, the good affinity of these ligands is not surprising. A picture of how one of these ligands, the 7-membered analogue **4c**, might be accommodated in the binding pocket of the estrogen receptor is illustrated in Figure 2. This figure was created by first docking the ligand onto the structure of hydroxytamoxifen (Fig. 2A) in a recent ER·tamoxifen X-ray crystal structure.[9] Use of the Flexidock routine within the molecular modeling program SYBYL (Tripos) then enables this ligand to be accommodated without van der Waals overlap (Fig. 2B), by making small, energetically allowable adjustments to the side chains of the residues that line the ligand binding pocket. Although it is not reasonable to assign binding energies to a structure created in this manner, the neatness of the final fit is quite appealing. Similar structures can be generated, as well, for the 5- and 6-membered analogues (not shown).

Panel A



BF99158 Figure 2A



BF99158 Figure 2B

Panel B

Figure 2. Overlay of distal cyclic analogue **4c** and hydroxytamoxifen (Panel A) and accommodation of analogue **4c** into the ligand-binding pocket of estrogen receptor α (Panel B). The overlay (Panel A) was done using a minimized conformation of compound **4c** and the structure of hydroxytamoxifen from its crystal structure with the estrogen receptor,[9] and the ligand pocket fit (Panel B) was done using Flexidock routine within the modeling program SYBYL (Tripos).

Conclusions

To probe the tolerance of the estrogen receptor (ER) binding to defined structural changes in certain non-steroidal ligands, we have developed an efficient and generally useful synthesis of triarylethylene ligands for the estrogen receptor that have a novel ring topology, created by forming an additional cycle between the ethyl group and the *distal* aryl ring. This additional conformational constraint alters the shape of these ligands in a region that corresponds to the D ring of estradiol, a region where steric changes are known to be well tolerated by ER. The compounds could cause a change in the shape of the ER, which might result in increased selectivity, or the generation of differential agonist/antagonist character or ERα versus ERβ subtype affinity and/or potency selectivity. The sensitive benzylic organosodium reagents that are required by our approach can be formed conveniently from the corresponding benzylic chlorides using sodium naphthalenide, and protecting group strategies were developed so that only the exocyclic double bond isomers are obtained. Saturated analogues of two of these cyclic alkenes were also produced by hydrogenation.

The binding affinities of these new triarylethylene ligands for lamb uterine cytosol ER or human ERα and ERβ are comparable to those of related acyclic and cyclic triarylethylene or cyclofenil parental ligands, and some moderate affinity selectivity between the two human ER subtypes is apparent. Much higher affinities are obtained in assays done with purified receptor preparations than with a uterine cytosol preparation. These findings indicate that the estrogen receptor is remarkably shape and size tolerant in the region remote from the A-ring binding subpocket, a feature that can be visualized by molecular modeling.

Experimental

General methods

Melting points (uncorrected) were recorded on Thomas-Hoover Electrothermal apparatus. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel F-254 glass-baked plates, with visualization by short-wave (254 nm) UV light. Flash column chromatography was performed according to Still[30] using Woelm 32–63 μm silica gel.

^{1}H and ^{13}C NMR were recorded on Varian U400 and Varian U500 spectrometers. Chemical shifts (δ) were recorded in ppm downfield from TMS and were referenced to either TMS internal standard or the residual proton peak in $CDCl_3$, acetone-d_6, or methanol-d_4 solvent peak. Coupling constants are reported in Hz. Electron ionization (EI) mass spectra were obtained using Finnigan-MAT-CH5 spectrometer at 70 eV. Fast atom bombardment (FAB) mass spectra were recorded on a VG ZAB-SE spectrometer, whereas a VG VSE-B instrument provided chemical ionization (CI) mass spectra. Elemental analysis was performed by the Microanalytical Service Laboratory at the University of Illinois.

All reactions using water- and air-sensitive reagents were conducted under a nitrogen atmosphere with dry solvent. Solvents were distilled as follows: CH_2Cl_2 from CaH_2 and tetrahydrofuran (THF) from sodium benzophenone ketyl. 1-Chlorobenzocycloalkanes were prepared according to known procedures.[24,25] All other reagents were purchased from commercial suppliers and were used without further purification.

Biological methods

Binding affinity measurements. Competitive radiometric binding assays were performed with lamb uterine cytosol preparations or purified ERα and ERβ (PanVera), as reported previously.[27] The receptor preparation was diluted to approximately 1.5 nM of receptor and was incubated with several concentrations of unlabeled competitor, together with 10 nM [^{3}H]estradiol, for 18–24 h. Unlabeled competitors were dissolved and diluted in 1:1 DMF buffer to ensure solubility; the final DMF concentration was 7%. The receptor–ligand complexes were separated from free tracer by adsorption of the free ligand onto charcoal-dextran when using lamb uterine cytosol preparations, or by adsorption of the bound complex onto hydroxylapatite when using purified ERα and ERβ preparations.

Octanol–water partition coefficient measurements. Octanol–water partition coefficients, a measure of lipophilicity, were estimated from the long k'_w values determined by reversed phase HPLC methods, as previously reported.[31,32]

Chemical synthesis

1-[Bis(4-methoxyphenyl)methylidenyl]indane (3a). Sodium naphthalenide complex was prepared by adding sodium (138 mg, 6.0 mmol) to a solution containing naphthalene (1.2 g, 10 mmol) in dry THF (40 mL) and stirring until dissolution of sodium was complete. A mixture of 4,4′-dimethoxybenzophenone (**1a**, 605 mg, 2.5 mmol) and 1-chloroindane (**2a**, 458 mg, 3.0 mmol) in THF (25 mL) was added dropwise to this deep-green solution at 0–5 °C under nitrogen atmosphere, over a 1-h period. After the reaction was complete, the excess of sodium naphthalenide was destroyed by the addition of few drops of methanol. Water (50 mL) and ether (100 mL) were added to the reaction mixture, and the pH of the water was adjusted to 7 with 3 N HCl solution. The organic layer was separated and was washed with brine, water (100 mL×1) , and dried over $MgSO_4$. Removal of the solvent, followed by silica gel flash column chromatography of the residue with hexane (300 mL) removed the non-polar naphthalene derivatives. Subsequent elution with CH_2Cl_2 (150 mL) gave a title compound (**3a**) as a colorless solid (555 mg, 65%). Sample for microanalysis was prepared by recrystalization from ether; mp 139–140 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.93 (s, 4H), 3.81 (s, 3H), 3.84 (s, 3H), 6.49 (d, J = 7.5 Hz, 1H), 6.83–6.88 (m, 5H), 7.06 (t, J = 7.5 Hz, 1H), 7.13–7.23

(m, 5H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 30.71, 34.47, 55.22, 113.23, 114.06, 116.53, 124.88, 125.02, 125.57, 127.07, 130.44, 131.12, 134.22, 135.39, 139.45, 141.68, 147.58, 158.15, 158.64; EI–MS *m*/*z* (%) 342 (M^+, 100), 221 (9), 121 (9). Anal. calcd for $C_{24}H_{22}O_2$: C, 84.18; H 6.48. Found C, 84.30; H, 6.54.

1-[Bis(4-methoxyphenyl)methylidenyl]-1,2,3,4-tetrahydronaphthalene (3b). The reaction of 1-chloro-1,2,3,4-tetrahydronaphthalene (**2b**, 500 mg, 3.0 mmol) according to the procedure described for the preparation of compound **3a**, followed by chromatography as described previously, gave a mixture of 1-[bis(4-methoxyphenyl)-hydroxymethyl]-1,2,3,4-tetrahydronaphthalene and **3b**. However, after evaporation of the CH_2Cl_2, only compound (**3b**) was detected, as a colorless solid (657 mg, 74%). **5**: mp 103–104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40–1.52 (m, 1H), 1.71–1.83 (m, 2H), 1.91–2.02 (m, 1H), 2.03 (s, 1H, OH), 2.60–2.78 (m, 2H), 3.77 (s, 6H, 2×OCH3), 4.09 (t, *J* = 6.4 Hz, 1H), 6.54–7.48 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 21.51, 26.33, 30.10, 46.03, 55.18, 55.21, 81.16, 113.34, 113.37, 125.04, 126.38, 127.11, 127.23, 129.18, 130.43, 135.11, 138.71, 140.53, 141.27, 157.86, 158.07; EI–MS *m*/*z* (%) 373 ($M^+ - 1$, 2), 357 ($M^+ - OH$, 59), 356 (39), 267 (49), 243 (100), 153 (21.7). Anal. calcd for $C_{25}H_{26}O_3$: C, 80.18; H 7.00. Found C, 80.28; H, 7.01. **3b**: Mp 135–136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84 (quintet, 2H, *J* = 6.4 Hz), 2.52 (t, 2H, *J* = 6.4 Hz), 2.80 (t, 2H, *J* = 6.4 Hz), 3.75 (s, 3H), 3.83 (s, 3H), 6.66–7.26 (m, 12H): ^{13}C NMR ($CDCl_3$, 125 Hz) δ 24.11, 29.56, 30.60, 55.10, 55.22, 113.28, 124.58, 126.23, 127.97, 130.56, 131.61, 132.28, 134.35, 136.58, 136.61, 136.99, 137.90, 139.27, 158.08, 158.31. Anal. calcd for $C_{25}H_{24}O_2$: C, 84.24; H 6.79. Found C, 84.28; H, 6.85.

5-[Bis(4-methoxyphenyl)methylidenyl]-benzocycloheptene (3c). The reaction of 5-chloro-5*H*-benzocycloheptene (**2c**, 542 mg, 3.0 mmol) according to the procedure described for the preparation of compound **3a**, followed by chromatography as described previously, gave **3c** as a colorless solid from hexane; mp 103–104 °C; yield 82%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55–1.86 (m, 6H), 2.86–2.97 (m, 2H), 3.68 (s, 3H), 3.82 (s, 3H), 6.49–7.23 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 27.44, 30.40, 33.51, 36.27, 54.98, 55.21, 112.67, 113.67, 126.02, 126.16, 128.59, 129.60, 130.84, 131.01, 135.58, 135.65, 137.72, 140.72, 141.12, 144.45, 157.45, 158.11; EI–MS *m*/*z* (%) 370 (M^+, 100), 227 (55), 121 (14). Anal. calcd for $C_{26}H_{26}O_2$: C, 84.29; H 7.07. Found C, 84.08; H, 6.98.

1-[Bis(4-hydroxyphenyl)methylidenyl]indan (4a). To the solution of **3a** (227 mg, 0.66 mmol) in dichloromethane (5 mL) was added dropwise boron tribromide (2.5 mL, 1 M CH_2Cl_2 solution) by syringe at −78 °C under a nitrogen atmosphere. When the addition was complete, the reaction mixture was allowed to warm to room temperature overnight with stirring, and then was hydrolyzed with few drops of water. Chloroform (15 mL) and water (5 mL) were added, and the organic phase was collected, washed with aqueous 5% $NaHCO_3$, brine, and water, dried over $MgSO_4$, and collected by filtration. Evaporation under reduced pressure gave compound **4a** as a colorless solid (170 mg, 82%). Further purification for microanalysis and binding affinity assay was carried out by recrystallization from methanol: mp 235–236 °C; ^{1}H NMR (methanol-d_4, 400 MHz) δ 2.70 (t, *J* = 7.2 Hz, 2H), 2.90 (t, *J* = 7.2 Hz, 2H), 6.50–7.10 (m, 12H); ^{13}C NMR (methanol-d_4, 100 Hz) δ 28.02, 30.50, 113.74, 114.32, 125.35, 125.47, 125.82, 126.31, 128.98, 130.96, 131.74, 134.08, 134.15, 135.40, 136.14, 137.32, 154.94, 155.43; FABMS *m*/*z* (%) 314 (M^+, 78), 199 (17), 155 (56), 135 (44), 119 (100). Anal. calcd for $C_{22}H_{18}O_2$: C, 84.05; H 5.77. Found C, 83.82; H, 5.82.

1-[Bis(4-hydroxyphenyl)methylidenyl]-1,2,3,4-tetrahydronaphthalene (4b). A. The reaction of 4,4′-bis(trimethylsilyloxy)benzophenone (1b) with 1-chloro-1,2,3,4-tetrahydronaphthalene (2b). 4,4′-Di(trimethylsilyloxy)benzophenone (**1b**, 890 mg, 2.94 mmol) was prepared by the reaction of 4,4′-dihydroxybenzophenone (642 mg, 3.0 mmol) with trimethylsilyl chloride (658 mg, 6.5 mmol) in THF (30 mL). This material was allowed to react with 1-chloro-1,2,3,4-tetrahydronaphthalene (**2b**, 599 mg, 3.6 mmol) and sodium naphthalenide, as described in the preparation of **3a**. Purification, as described, gave compound **4b** as a colorless solid (675 mg, 70%). **4b**: Mp 216–217 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77 (quintet, *J* = 6.4 Hz, 2H), 2.46 (t, *J* = 6.4 Hz, 2H), 2.78 (t, *J* = 6.4 Hz, 2H), 2.82 (brs, 2H, 2×OH), 6.52–7.24 (m, 12H); ^{13}C NMR (methanol-d_4, 100 Hz) δ 23.95, 29.38, 30.39, 114.43, 114.48, 124.26, 125.81, 127.69, 130.36, 131.51, 132.18, 133.50, 135.65, 135.69, 137.22, 137.92, 138.97, 154.79, 155.08; FABMS *m*/*z* (%) 328 (M^+, 86), 307 (34), 154 (100), 136 (72). Anal. calcd for $C_{23}H_{20}O_2$: C, 84.12; H 6.14. Found C, 83.73; H, 6.09.

B. The treatment of 3b with boron tribromide. The reaction of **3b** (182 mg, 0.5 mmol) with boron tribromide (1.5 mL, 1 M CH_2Cl_2 solution) as described in the preparation of compound **4a** gave a reaction mixture (175 mg) composed of 4-[bis(4-hydroxyphenyl)methyl]-1,2-dihydronaphthalene (**4b′**) and **4b** in the ratio of 85:15, as determined by ^{1}H NMR analysis. Separation of this mixture of regioisomers by routine methods, using flash column chromatography and fractional crystallization, failed. **4b′**: Mp 107–110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (m, 2H, $\underline{CH_2}$-vinyl), 2.77 (t, *J* = 7.6 Hz 2H), 4.81(brs , 2H, 2×$\overline{OH}$), 5.30 (s, 1H, -$\underline{CH}(Ph)_2$), 6.72 (d, 4H), 7.00–7.24 (m, 8H); FABMS *m*/*z* ($\overline{\%}$) 328 (M^+, 80), 307 (37), 154 (100), 136 (70).

5-[Bis(4-hydroxyphenyl)methylidenyl]-benzocycloheptene (4c). The reaction of **3c** (335 mg, 0.9 mmol) with boron tribromide (3 mL, 1 M CH_2Cl_2 solution), as described in the preparation of **4a**, followed by flash column chromatography on silica gel with ether as an eluent, gave **4c** (302 mg, 97%) as a colorless solid. Recrystalization from chloroform was carried out; mp 168–169.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55–1.89 (m, 6H), 2.86–2.97 (m, 2H), 4.52 (s, 1H, OH), 4.76 (s, 1H, OH), 6.49–7.23 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 27.29, 30.26, 33.13, 36.14, 114.04, 115.01, 125.82, 126.04, 128.43, 129.40, 130.87, 131.03, 135.58, 135.61, 137.36, 140.76, 140.95, 144.17, 153.16, 153.84; FABMS *m*/*z* (%) 342 (M^+, 58), 307 (30), 289 (18), 154 (100), 136

(69). Anal. calcd for $C_{24}H_{22}O_2$: C, 84.18; H 6.48. Found C, 83.84; H, 6.36.

1-[Bis(4-hydroxyphenyl)methyl]-1,2,3,4-tetrahydronaphthalene (7b). A solution of **4b** (20 mg, 0.06 mmol) and a catalytic amount of platinum oxide in methanol (10 mL) was stirred overnight under hydrogen atmosphere at room temperature. After the reaction was complete, the catalyst was removed by filtration. Evaporation of the solvent gave compound **7b** (20 mg, 99%) as a colorless solid: mp 103–105 °C; ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.54–1.66 (m, 2H), 1.78–1.94 (m, 2H), 2.69–2.77 (m, 1H), 2.83–2.90 (m, 1H), 3.53–3.58 (m, 1H), 3.96 (d, 1H, J = 10.8 Hz), 6.42 (d, 1H, J = 8.4 Hz), 6.61–6.74 (m, 2H), 6.78 (d, 2H, J = 8.4 Hz), 6.93–7.01 (m, 4H), 7.25 (d, 2H, J = 8.4 Hz), 8.06 (brs, 2H, 2×OH); ^{13}C NMR (acetone-d_6, 100 Hz) δ 17.89, 26.00, 28.19, 42.32, 55.37, 114.63, 115.14, 123.94, 125.48, 128.58, 129.32, 129.48, 130.20, 135.37, 135.96, 136.84, 139.75, 155.40, 155.54; MS(CI) m/z (%) 331 ($M^+ + 1$, 1.5), 329 (($M^+ - H_2$) + 1, 4.1), 328 (3.8), 199 ((4,4′-dihydroxyphenylmethyl)$^+$, 100), 131 (1,2,3,4-tetrahydronaphtyl$^+$, 12.1); CI-HRMS calcd/found ($C_{23}H_{23}O_2$ ($M^+ + 1$)) 331.16979/331.16981.

1-[Bis(4-Methoxyphenyl)methyl]-indane (6a). This compound was obtained in 90% yield from the reduction of **3a** by the same method described in the preparation of **7b**: mp 119.5–120.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.74–1.83 (m, 1H), 2.06–2.15 (m, 1H), 2.75–2.78 (m, 2H), 3.77 (s, 3H), 3.78 (s, 3H), 3.86 (d, J = 10.4 Hz, 1H), 3.97–4.03 (m, 1H), 6.43 (d, J = 7.6 Hz, 1H), 6.79–6.85 (m, 4H), 6.90 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.16–7.21 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 30.88, 31.73, 48.99, 55.21, 55.22, 55.26, 113.76, 113.80, 124.31, 125.37, 125.52, 126.45, 128.96, 129.30, 137.05, 137.23, 144.66, 145.98, 157.82, 157.98; FABMS m/z (%) 345 ($M^+ + 1$, 3.5), 343 (($M^+ - H_2$) + 1, 7.3), 227 ((4,4′-dimethoxyphenylmethyl)$^+$, 100), 117 (indanyl$^+$, 6.8); FAB–HRMS calcd/found ($C_{24}H_{25}O_2$ ($M^+ + 1$)) 345.18544/345.18545.

1-[Bis(4-hydroxyphenyl)methyl]indane (7a). The treatment of **6a** with boron tribromide as described in the preparation of **4a**, followed by column chromatography on silica gel with ether as an eluent afforded compond **7a** as a colorless solid: mp 170–171 °C; yield 57%; ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.68–1.76 (m, 1H), 2.01–2.08 (m, 1H), 2.66–2.84 (m, 2H), 3.77 (d, J = 10.8 Hz, 1H), 3.99–4.05 (m, 1H), 6.42 (d, J = 7.2 Hz, 1H), 6.81–6.77 (m, 4H), 6.83 (t, J = 7.2 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 7.11–7.22 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 30.81, 31.64, 49.01, 55.25, 115.05, 115.11, 116.53, 124.20, 125.39, 126.31, 128.98, 129.34, 136.38, 136.54, 144.65, 146.09, 154.57, 154.74; EI–MS m/z (%) 316 (M^+, 1.5), 314 ($M^+ - H_2$, 2.2), 199 ((4,4′-dihydroxyphenylmethyl)$^+$, 100); EI-HRMS calcd/found ($C_{22}H_{20}O_2$) 316.14633/316.14633.

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