Brief Articles

Photochemical Synthesis of *N*-Arylbenzophenanthridine Selective Estrogen Receptor Modulators (SERMs)

Timothy A. Grese,* M. Dee Adrian, D. Lynn Phillips, Pamela K. Shetler, Lorri L. Short, Andrew L. Glasebrook, and Henry U. Bryant

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

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Selective estrogen receptor modulators are an emerging class of pharmaceutically important molecules. Many compounds in this class contain an aminoethoxyaryl moiety attached to a polycyclic framework at an asymmetric carbon atom. To assess whether this carbon atom can be replaced by nitrogen, we have employed a Ninomiya enamide photocyclization for the rapid synthesis of a novel *N*-arylbenzophenanthridine framework, **4**. Further elaboration of **4** into a new structural class of achiral, nonsteroidal estrogen receptor modulators is described.

Introduction

Nonsteroidal compounds that interact with the estrogen receptor (ER) have long been investigated as contraceptives and for the treatment of breast cancer, uterine dysfunction, and other disorders of the female reproductive system.[1] More recently, the recognition that some of these compounds can exert their effects in a tissue specific manner has led to the development of selective estrogen receptor modulators (SERMs). SERMs, which fully antagonize the effects of estrogen on uterine and mammary tissue while mimicking the effects of estrogen on bone and the cardiovascular system, have been investigated as a possible alternative to hormone replacement therapy in postmenopausal women.[2]

We have recently described a novel series of highly potent SERMs based upon tetracyclic naphtho-, benzothieno-, or benzofuranobenzopyran scaffolds **1**−**3**.[3] In each case, the required aminoalkoxyaryl side chain is attached to the scaffold via a tertiary, asymmetric carbon atom and the compounds were tested as racemic mixtures. The nonplanar orientation of this side chain is believed to be important for maintaining the observed profile of tissue-specificity.[4] We hypothesized that nitrogen for carbon replacement, as in *N*-arylbenzophenanthridines **4a**−**d**, could potentially provide a similar side chain orientation without the introduction of chirality. Although many methods for the preparation of *N*-alkylbenzophenanthridines are known,[5] only a single example of *N*-arylbenzophenanthridine synthesis, as an undesired side product of an intermolecular benzyne cycloaddition, has been described.[6] Herein, we describe the rapid synthesis of this novel framework, **4**, via a Ninomiya enamide photocyclization,[7] and its further elaboration to a new structural class of achiral, nonsteroidal SERMs.

* Phone: (317)276-1356. Fax: (317)276-2441. E-mail: grese@lilly.com.

Chemistry

Retrosynthetic analysis of targets **4a**−**d** led to the recognition of the *N*-aryldihydrobenzophenanthridone **8** as a key intermediate for the preparation of multiple analogues at different oxidation states of the benzophenathridine ring system (Figure 1). The key disconnection of the aryl substituent at the β-position of the enamide functionality led to considerable simplification and allowed for the convergent assembly of a variety of precursor molecules **7a**−**e**. Thus, O-protection of the imine derived from 6-methoxy-1-tetralone and 4-hydroxyaniline, followed by acylation with benzoyl chlorides **6a**,**c**,**e**, led to a variety of enamides, which could be optionally halogenated at the β-position (Scheme 1). Although a variety of radical- and metal-mediated cyclization protocols were unable to effect the transformation of **7a**−**d** to **8**, photocyclization of **7e** under nonoxidative conditions[8] provided **8** in 21−26% yield, along with varying amounts of rearranged product **9**.[9] Solvent degassing reduced the formation of **9** substantially; however, additional efforts to optimize the yield by changing reaction conditions and solvents were unsuccessful. The photocyclization was found to be somewhat concentration dependent, with optimum yields obtained at concentrations below 0.1 M.

Conversion of **8** to target molecule **4a** was effected by sequential desilylation, Mitsunobu alkylation with hydroxyethylpiperidine to give **10a**, and phenolic demethylation. Alternatively, dehydrogenation of **8** with DDQ followed by a similar reaction sequence provided the *N*-arylbenzophenanthridone **4b**. Reduction of **4a** with lithium aluminum hydride provided unstable **4c** in low yield. On the other hand, reduction of **10a**,**b** gave the corresponding benzophenanthridine analogues **10c**,**d** in good yields. Demethylation of **10d** then led to target molecule **4d**, which was substantially more stable than its dihydro analogue.

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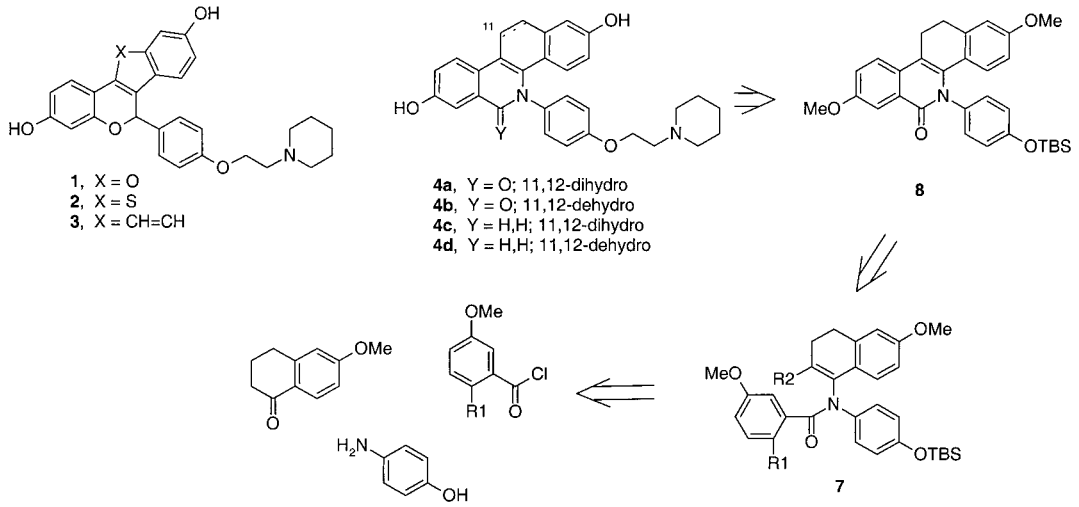
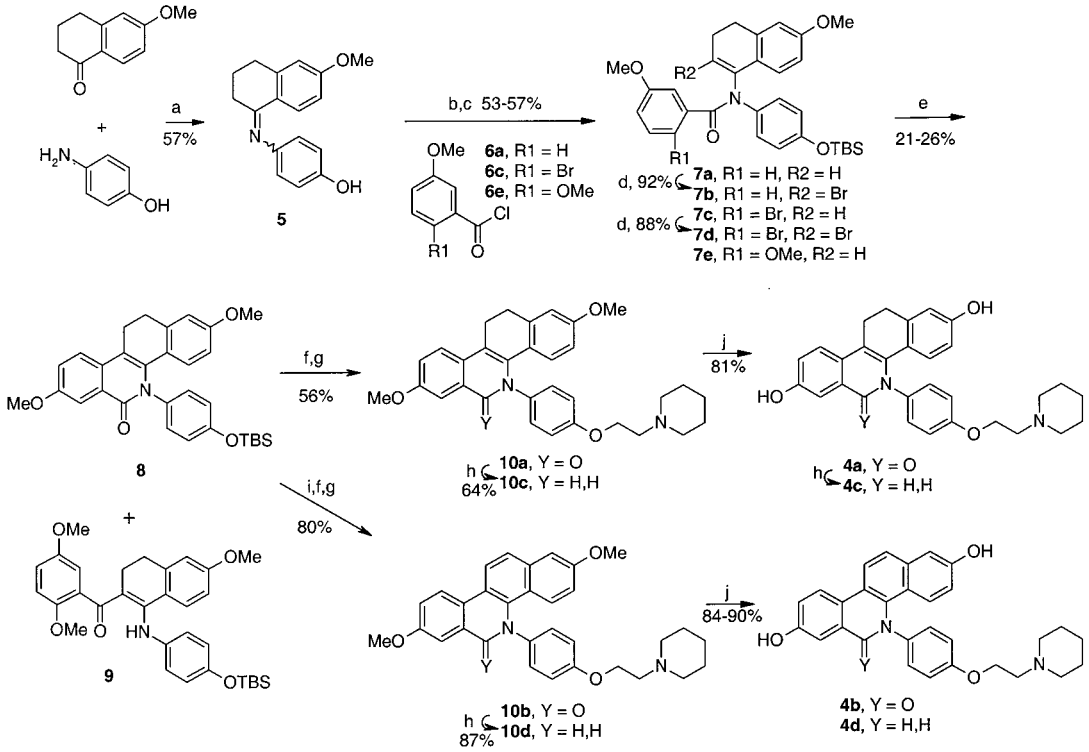


Figure 1. Retrosynthetic analysis of *N*-arylbenzophenanthridine SERMs.

Scheme 1[a]



[a] Reagents: (a) 180 °C; (b) TBDMSCl, Et_3N, CH_2Cl_2:THF; (c) Et_3N, CH_2Cl_2, Δ; (d) NBS, CCl_4; (e) *hν*, benzene; (f) HF·pyridine, CH_3CN: CH_2Cl_2; (g) 1-(2-hydroxyethyl)piperidine, PPh_3, DEAD, THF; (h) LAH, THF, Δ; (i) DDQ, DCE, Δ; (j) $AlCl_3$, EtSH, CH_2Cl_2.

Biological Testing

ER binding affinities were determined by displacement of bound ^{3}H-17β-estradiol from MCF-7 cell lysate and are reported in Table 1.[10] Antagonism of estrogen action in a mammary tumor cell line was assayed via inhibition of MCF-7 cell proliferation stimulated by 10^{-11} M 17β-estradiol, and IC_{50} values are also included in Table 1.[11] Compound **4d** was further evaluated in the immature rat model of estrogen antagonist activity in the uterus and in the ovariectomized rat model of tissue-specific estrogen agonist effects on serum cholesterol and uterine stimulation.[3]

Results and Discussion

As expected, the benzophenanthridine analogues in which the phenolic moieties were blocked by methoxy (**10b**−**d**) showed relatively weak affinity for ER(MCF-7 lysate). Interestingly, the phenolic lactam analogues **4a** and **4b** also demonstrated low affinity. In both series, antagonist potency in the MCF-7 cell line roughly paralleled binding affinity, and similar maximal efficacy (80−90% inhibition) was observed for all active compounds. The comparison of the dihydrobenzophenanthridine skeleton to the benzophenanthridine skeleton was frustrated by the instability of **4c**. However, for the dimethoxy analogues, a substantial improvement in

Table 1. ER Binding and Inhibition of MCF-7 Cell Proliferation by SERMs

no.	ER RBA[a,b]	MCF-7 inhib. IC_{50} (nM)[c]
estradiol	1.00	NA[d]
4-OH-tamoxifen[e]	0.36	0.5
raloxifene	0.34	0.2
3	0.22	0.4
10b	NA	NA
10c	0.01	287
10d	0.01	19
4a	0.01	128
4b	0.01	NA
4d	0.24	1

[a] RBA = relative binding affinity by competition with ^{3}H-17β-estradiol in MCF-7 cell lysate. [b] Average of at least two determinations. Values are ±10%. [c] Dose required for 50% inhibition of a maximally effective (10^{-11}) dose of 17β-estradiol. Average of at least three determinations. Values are ±10%. [d] NA = not active at the doses tested. [e] 4-Hydroxytamoxifen.

antagonist potency was seen in going from **10c** to **10d**. In both the phenolic and methoxy series, reduction of the lactam was critical for antagonist potency. Only compound **4d** (k_i = 0.28 nM) bound ER(MCF-7 lysate) with affinity comparable to the reference compounds and potently inhibited MCF-7 proliferation. Preliminary in vivo data from the immature rat model indicate that this compound functions as a partial estrogen antagonist in the uterus at doses of 1 and 10 mg/kg, p.o. In the ovariectomized rat model, **4d** lowered serum cholesterol at doses of 0.1−10 mg/kg, p.o., with minimal stimulation of the uterus.

The importance of phenolic moieties for ER binding is well documented.[12] The poor affinity of the lactam analogues in this series most likely relates to the known preference of ER for molecules with a highly hydrophobic core structure.[12] The addition of an electronegative oxygen to the core benzophanthridine structure greatly inhibits its ability to bind. Compound **4d**, like tamoxifen, demonstrates partial antagonist activity on uterine tissue in contrast to compound **2** which appears to be a full antagonist in this tissue and induces no uterine stimulation in ovariectomized animals.[3] We have previously postulated that the orthogonal orientation of the side chains in raloxifene and **2** is responsible for their tissue selectivity relative to tamoxifen, in which the side chain is constrained to lie within the plane of the stilbene moiety.[4] Apparently, subtle changes in the conformational properties of these molecules can induce substantial differences in their biological properties. Alternatively, biological oxidation of **4d** could yield an *N*-arylbenzophanthridinium species in which the side chain would adopt a coplanar orientation. Further studies to discriminate these possibilities are ongoing.

In conclusion, the ability to rapidly assemble substrate molecules such as **7e** allowed for an efficient synthesis of the target *N*-arylbenzophenanthridine scaffold **8** via the Ninomya photocyclization, even though the yield of the photocyclization was modest. The convergent nature of the assembly of **7e** bodes well for additional analogue synthesis. A number of the compounds bound ER(MCF-7 lysate) and inhibited MCF-7 cell proliferation. In particular, compound **4d** demonstrated a selective estrogen receptor modulator profile of biological activity similar to that which has previously been described for tamoxifen.[13]

Experimental Section

General experimental procedures have been recently published.[13] The abbreviations THF, DMF, DCE, DMSO, DDQ, TBAF, and DEAD refer to tetrahydrofuran, dimethylformamide, 1,2-dichloroethane, dimethyl sulfoxide, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, tetra-*N*-butylammonium fluoride, and diethyl azodicarboxylate, respectively. All spectra were recorded in acetone-d_6 unless otherwise indicated. Elemental analyses were carried out by the Physical Chemistry Department of Lilly Research Laboratories.

6-Methoxy-1-[(4-hydroxy)phenyl]imino-1,2,3,4-tetrahydronaphthalene (5). A mixture of 6-methoxytetralone (25 g, 142 mmol) and 4-hydroxyaniline (16.3 g, 149 mmol) was heated to 180 °C under a nitrogen stream for 2 h. After cooling to ambient temperature, the solid mass was recrystallized from toluene/methanol to provide 21.6 g (57%) of the title compound: ^{1}H NMR (300 MHz) δ 8.15 (d, J = 9.7 Hz, 1H), 6.5−7.9 (m, 6H), 3.80 (s, 3H), 2.84 (t, J = 7.3 Hz, 2H), 2.51 (t, J = 6.8 Hz, 2H), 1.85 (m, 2H).

6-Methoxy-1-[*N*-[[4-(*tert*-butyldimethylsilyl)oxy]phenyl]-*N*-(2,5-dimethoxybenzoyl)]amino-3,4-dihydronaphthalene (7e): (a) Imine **5** (46 g, 172 mmol) was slurried in 1:1 CH_2Cl_2:THF (400 mL) and treated with triethylamine (52 g, 72 mL, 513 mmol) and *tert*-butyldimethylsilyl chloride (51.5 g, 342 mmol). The mixture was stirred overnight then diluted with ether (1 L), filtered, and concentrated. The residue was purified by chromatography (10:1 hexane:ethyl acetate) to give 46.3 g (71%) of the O-protected imine as a yellow foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 9.7 Hz, 1H), 6.86 (m, 3H), 6.73 (m, 3H), 3.92 (t, J = 5.8 Hz, 2H), 2.57 (t, J = 6.8 Hz, 2H), 1.96 (m, 2H), 1.05 (s, 9H), 0.26 (s, 6H).

(b) The imine (46.3 g, 121 mmol) was dissolved in CH_2Cl_2 (400 mL), cooled to 0 °C, and treated with triethylamine (23.3 g, 32 mL, 230 mmol) followed by a solution of 2,5-dimethoxybenzoyl chloride (42.5 g, 212 mmol) in CH_2Cl_2 (100 mL), dropwise. The mixture was warmed to reflux for 60 h, then concentrated in vacuo. The residue was dissolved in ether (1 L), washed with brine (1 L), dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography (9:1−4:1 hexane:ethyl acetate) provided 48.7 g of the title compound as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.4−7.6 (br m, 11H), 5.83 (br s, 1H), 3.4−3.8 (br m, 9H), 1.9−3.0 (br m, 4H), 0.95 (2 br s, 9H), 0.14 (2 br s, 6H); IR ($CHCl_3$) 1651, 1607, 1507 cm^{-1}; MS (FD) *m/e* 545 (M^+); Anal. $C_{32}H_{39}NO_5Si$: C, H, N.

2,8-Dimethoxy-5-[4-[(*tert*-butyldimethylsilyl)oxy]-phenyl]-11,12-dihydro-6*H*-benzo[*c*]phenanthrid-6-one (8). A solution of the product of **7e** (2.73 g, 5 mmol) in benzene (250 mL) was degassed via three freeze/pump/thaw cycles and irradiated with a 450 W internal mercury lamp in a quartz immersion well under nitrogen. After 22 h, the mixture was concentrated, and the residue was purified by chromatography (20:1 toluene:ether) to provide 675 mg (26%) of the title compound as a yellow foam. An analytical sample was obtained by crystallization from hexane/ether as light yellow crystals, mp 194−95 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, 2.8 Hz, 1H), 7.73 (d, 8.9 Hz, 1H), 7.32 (dd, J = 8.9, 2.8 Hz, 1H), 7.17 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.76 (d, J = 2.6 Hz, 1H), 6.67, (d, J = 8.8 Hz, 1H), 6.35 (dd, J = 8.8, 2.7 Hz, 1H), 3.94 (s, 3H), 3.75 (s, 3H), 2.90 (s, 4H), 0.99 (s, 9H), 0.21 (s, 6H); MS (FD+) *m/e* 513 (M^+); Anal. $C_{31}H_{35}NO_4Si$: C, H, N.

In some runs, substantial amounts of compound **9** were also isolated as a viscous, yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.02 (s, 1H), 7.17 (d, 6.1 Hz, 1H), 6.85 (m, 5H), 6.70 (m, 3H), 3.80 (s, 9H), 2.69 (t, J = 7.4 Hz, 2H), 2.33 (t, J = 7.4 Hz, 2H), 0.98 (s, 9H), 0.18 (s, 6H); MS (FD) *m/e* 545 (M^+).

2,8-Dimethoxy-5-[4-[2-(1-piperidinyl)ethoxy]phenyl]-6*H*-benzo[*c*]phenanthrid-6-one (10b): (a) A mixture of **8** (7.3 g, 14.2 mmol) and DDQ (2.9 g, 12.9 mmol) in DCE (10 mL) was heated at reflux for 2 h, inducing the formation of a precipitate. The mixture was cooled to room temperature, filtered, and concentrated. The remnant was recrystallized from hexane:ethyl acetate to provide 6.9 g (95%) of the silylated benzophenanrthridone as a white solid, mp 211−213 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 9.0 Hz, 1H), 8.16 (d, J

= 8.9 Hz, 1H), 7.95 (d, J = 2.8 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.37 (dd, J = 9.0, 2.8 Hz, 1H), 7.25 (d, J = 9.7 Hz, 1H), 7.21 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 2.7 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 6.66 (dd, J = 9.7, 2.8 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 1.02 (s, 9H), 0.25 (s, 6H); MS (FD) *m/e* 511 (M^+).

(b) The product (6.8 g, 13.3 mmol) of part a, above, was dissolved in 1:1 acetonitrile:CH_2Cl_2 (200 mL) and treated with hydrogen fluoride−pyridine (80 mL) for 1 h. The mixture was diluted with brine (500 mL) and extracted with THF (3 × 300 mL). The combined organic layers were neutralized with saturated $NaHCO_3$, and the resulting aqueous layer was washed with THF (2 × 500 mL). All aqueous layers were then combined and washed with THF (500 mL), the combined organic layers were dried (Na_2SO_4) and concentrated, and the solid residue was washed with acetone to provide 5.27 g (100%) of the phenol as an off-white powder, mp 310 °C: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.79 (bs, 1H), 8.52 (d, J = 9.0 Hz, 1H), 8.42 (d, J = 9.0 Hz, 1H), 7.72 (m, 2H), 7.47 (dd, J = 8.7, 2.3 Hz, 1H), 7.31 (d, 2.1 Hz, 1H), 7.21 (d, J = 9.6 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 6.68 (dd, J = 9.3, 2.6 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H); MS (FD) *m/e* 397 (M^+).

(c) A mixture of the crude product obtained above (4.8 g, 12.1 mmol), triphenylphosphine (6.3 g, 24.2 mmol), and 1-(2-hydroxyethyl)piperidine in THF (100 mL) was treated with DEAD (4.2 g, 24.2 mmol), and the mixture was stirred at ambient temperature for 72 h. After concentation in vacuo, chromatography (1:1 hexane:ethyl acetate, 5−20% methanol, 0.1% NH_4OH) and recrystallization from ethyl acetate provided 5.14 g (84%) of the title compound as a white solid, mp 176 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 9.1 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 2.8 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.40 (dd, J = 9.0, 2.8 Hz, 1H), 7.31 (d, J = 9.7 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 2.7 Hz, 1H), 6.99 (d, J = 8.9 Hz, 2H), 6.70 (dd, J = 9.6, 2.7 Hz, 1H), 4.16 (t, J = 6.0 Hz, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 2.81 (t, J = 6.0 hz, 2H), 2.53 (m, 4H), 1.5−1.7 (m, 4H), 1.4−1.5 (m, 2H); MS (FD) *m/e* 508 (M^+); Anal. $C_{32}H_{32}N_2O_4$: C, H, N.

2,8-Dimethoxy-5-[4-[2-(1-piperidinyl)ethoxy]phenyl]-6*H*-benzo[*c*]phenanthridine (10d). A solution of **10b** (3.82 g, 7.51 mmol) in THF (250 mL) was treated with lithium aluminum hydride (1.43 g, 37.5 mmol) resulting in a moderate exotherm. After the exotherm ceased, the mixture was warmed to reflux overnight, cooled to room temperature, and quenched cautiously with ethyl acetate (200 mL) followed by 1 N NaOH (200 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (2 × 200 mL), and the combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), and concentrated. The residue was recrystallized from hexane:ethyl acetate to provide 3.24 g (87%) of the title compound as an off-white solid, mp 136−137: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 2.5 Hz, 1H), 6.95 (dd, J = 9.2, 2.6, 1H), 6.91 (dd, J = 8.5, 2.6 Hz, 1H), 6.6−6.8 (m, 5H), 4.75 (s, 2H), 3.95 (t, J = 6.1 Hz, 2H), 3.90 (s, 3H), 3.79 (s, 3H), 2.68 (t, J = 6.1 Hz, 2H), 2.44 (m, 4H), 1.5−1.7 (m, 4H), 1.4−1.5 (m, 2H); MS (FD) *m/e* 494 (M^+); Anal. $C_{32}H_{34}N_2O_3$: C, H, N.

2,8-Dihydroxy-5-[4-[2-(1-piperidinyl)ethoxy]phenyl]-6*H*-benzo[*c*]phenanthridine (4d). A solution of **10d** (3.2 g, 6.4 mmol) in CH_2Cl_2 (150 mL) was treated with ethanethiol (3.2 g, 3.6 mL, 51 mmol) and aluminum chloride (5.1 g, 38.2 mmol). After being stirred for 4 h at ambient temperature, the mixture was quenched carefully with THF (150 mL) and saturated $NaHCO_3$ (150 mL). The layers were separated, the aqueous layer was extracted with THF (150 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (1:1 hexane:ethyl acetate, 10−20% methanol, 0.1% NH_4OH) and then recrystallized from methanol to provide 2.7 g (90%) of the title compound as an off-white powder, mp 260−270 °C: ^{1}H NMR (300 MHz, DMF-d_7) δ 9.92 (br s, 1H), 9.74 (br s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 6.98 (dd, J = 9.0, 2.1 Hz, 1H), 6.84 (dd, J = 8.4, 2.1 Hz, 1H), 6.73 (m, 5H), 3.92 (t, J = 5.9 Hz, 2H), 2.57 (t, J = 5.9 Hz, 2H), 2.38 (m, 4H), 1.4−1.5 (m, 4H), 1.3−1.4 (m, 2H); IR (KBr) 3560, 3490 cm^{-1}; MS (FD+) *m/e* 466 (M^+); Anal. $C_{30}H_{30}N_2O_3 \cdot 0.5H_2O$: C, H, N.

Biological Assays. Methods utilized for the ER binding, MCF-7 proliferation, OVX rat, and immature rat assays have been recently described.[13,14]

Supporting Information Available: Detailed procedures for the syntheses of compounds **4a**, **4c**, **10a**, and **10c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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