Supporting Information

A SERM Designed for the Treatment of Uterine Leiomyoma with Unique Tissue Specificity for Uterus and Ovaries in Rats.

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Chemical Synthesis: General Experimental Details

^{1}H NMR spectra were obtained on a Varian INOVA 400MHz spectrometer in the solvent indicated. Electrospray mass spectra were obtained on a Finnigan LCQ Duo instrument using a mobile phase of 50% acetonitrile, 25% methanol, and 25% 2mM aqueous ammonium acetate. Elemental analysis were determined by Schwarzkopf Microanalytical Laboratories and are within 0.4% of the theoretical values unless otherwise indicated. Analytical HPLC's were obtained on a Varian Prostar 210 instrument equipped with a PDA detector. A 5-cm YMC ODS-AQ column with a particle size of 3 microns was used as the stationary phase and 0.1% TFA in water was used as mobile phase A and 0.05% TFA in acetonitrile was used as mobile phase B. The standard method was a gradient of 30 to 95% B unless otherwise indicated. Preparative HPLC's were obtained on a Gilson Preparative System with Unipoint Software and dual wavelength detection at 220 and 254 mn as well as Finnigan aQa MS. A 20-mm x 250-mm ODS-AQ column with a particle size of 15 microns was used as the stationary phase. (Same A and B bottles). The standard method was a gradient of 30-95% B unless otherwise indicated. Also, preparative HPLC's were obtained on a Biotage ParallelFlex system with proprietary dual wavelength detection and software. A 30-mm x 150-mm or 19-mm x 250 mm Xterra column with a particle size of 10 microns was used as the stationary phase and 10mM $NH_4^+HCOO^-$/ 10mM NH_4OH was used as mobile phase A and 100% acetonitrile was used as a mobile phase B.

(2,6-Dimethoxy-naphthalen-1-yl)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone (**4**): 2,6-Dimethoxynaphthalene (1.0 eq.) was dissolved in CH_2Cl_2 (5 volume eq.) at ambient temperature in a dry round bottom flask equipped with stir bar, temperature probe and N_2 line. The solution was cooled to 0 ºC with an ice bath, and 4-(2-piperidin-1-yl-ethoxy)-benzoyl chloride (1.1 eq.) was added followed by aluminum chloride (2.0 eq.). Upon completion of the reaction, 1 N NaOH was added to quench the reaction and diluted with additional water and CH_2Cl_2. The aqueous layer was washed with CH_2Cl_2 (20 mL). The combined organic extracts were washed with brine and dried with Na_2SO_4. The crude product was recrystalized from methanol to give 68% of (2,6-dimethoxy-naphthalen-1-yl)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone. ^{1}H NMR ($CDCl_3$) δ 7.83 (d, *J* = 9.3 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 9.3 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 2.9 Hz, 1H), 7.05 (dd, *J* = 9.3, 2.4 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.61 (m, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.61 (d, *J*=11.7 Hz, 2H), 3.37 (m, 2H), 2.78 (m, 2H), 2.25 (m, 2H), 1.89 (m, 3H), 1.41 (m, 1H).

Trifluoro-methanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalen-2-yl ester (**5**): A 3-neck round bottom flask equipped with a pressure equalizing addition funnel, stirbar, and N_2 source was charged with (2,6-dimethoxy-naphthalen-1-yl)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone and dissolved in CH_2Cl_2 (**4**, 10 volume eq.). The flask was cooled in an ice/brine bath and 1.0 M BCl_3 solution in CH_2Cl_2 (1.2 eq.) was added dropwise. The reaction solution turned dark red and the temperature initially increased to 5 ºC. After about 1 hour, the reaction was quenched with methanol (5 eq.) and allowed to warm to room temperature. The organic solution was diluted with CH_2Cl_2 (one volume eq.) and a 1.0 M $NaHCO_3$ solution (5 volume eq.) was added and stirred for one hour. The layers were separated and the aqueous layer was washed CH_2Cl_2 (one volume). The combined organic layers were washed with saturated NH_4Cl and dried over Na_2SO_4. The product was purified via column chromatography (50/1 silica gel) eluting with CH_2Cl_2/hexanes (3/1) to yield 87% of (2-hydroxy-6-methoxy-naphthalen-1-yl)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone. ^{1}H NMR ($CDCl_3$) δ 7.80 (d, *J* = 9.3 Hz, 1H), 7.63 (m, 2H), 7.32 (d, *J* = 9.8 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 2.9 Hz, 1H), 6.88 (dd, *J* = 9.2, 2.9 Hz, 1H), 6.85 (m, 2H), 4.14 (t, *J* = 5.9 Hz, 2H), 3.88 (s, 3H), 2.78 (t, *J* = 6.1 Hz, 2H), 2.51 (bs, 4H), 1.60 (m, 4H), 1.44 (m, 2H). A three neck round bottom flask equipped with a stir bar and N_2 source and chilled to 0 ºC in an ice/brine bath was charged with (2-hydroxy-6-methoxy-naphthalen-1-yl)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone and dissolved in CH_2Cl_2 (10 volumes). Pyridine (1.3 eq.) was added followed by trifluoromethanesulfonyl chloride (1.2 eq.) via syringe over 15 minutes. After about 15 minutes, the reaction was quenched with H_2O (10 volumes), washed with 1 N aqueous HCl (5 volumes) and 1.0 N aqueous $NaHCO_3$, and dried over Na_2SO_4. The title compound was obtained in quantitative yield after concentration. ^{1}H NMR ($CDCl_3$) δ 7.90 (d, *J* = 9.3 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 9.3 Hz, 1H), 7.45 (d, *J* = 9.3 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.16 (dd, *J* = 9.3, 2.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.23 (t, *J* = 5.4 Hz, 2H), 3.93 (s, 3H), 2.95 (t, *J* = 5.4 Hz, 2H), 2.68 (bs, 4H), 1.70 (m, 4H), 1.50 (m, 2H).

[2-(4-Methanesulfonyl-phenyl)-6-methoxy-naphthalen-1-yl]-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone (**7**): Trifluoro-methanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalen-2-yl ester (**5**, 555 mg, 1.0 mmol), 4-methansulfonylphenylboronic acid (**6**, 310 mg, 1.55 mmol), $Pd(OAc)_2$ (23.9 mg, 0.11 mmol), Ph_3P (54.2 mg, 0.21 mmol) and Na_2CO_3 (2.5 mL, 2M in water) were dissolved in ethyleneglycol dimethyl ether (DME, 30 mL). The mixture was refluxed for 2 hours and additional $Pd(OAc)_2$ (25.2 mg) and Ph_3P (58.9 mg) were added. The mixture was refluxed for 2 more hours then diluted with water and extracted with chloroform. The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude material was purified by loading on an SCX column and eluting with 2M NH_3/MeOH to afford 569 mg of **7** (quantitative). LCMS: m/z = 544 (M+H)+. 1H NMR ($CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.58 (m, 5H), 7.48 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 2.6 Hz, 1H), 7.12 (dd, J = 9.1, 2.6 Hz, 1H), 6.74 (d, J = 9.2 Hz, 2H), 4.09 (t, J = 6.1 Hz, 2H), 3.95 (s, 3H), 3.00 (s, 3H), 2.76 (t, J = 5.9 Hz, 1H), 2.5 (bs, 4H), 1.61 (m, 4H), 1.45 (m, 2H).

[2-(4-Methanesulfonyl-phenyl)-6-methoxy-naphthalen-1-yl]-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methane (**8**): A round bottom flask was charged with [2-(4-methanesulfonyl-phenyl)-6-methoxy-naphthalen-1-yl]-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone (**7**, 200 mg, 0.37 mmol) and dissolved in THF (30 mL). Lithium aluminum hydride (LAH, 70.3 mg) was added. After completion the reaction was quenched with ice and water and acidified with 1M aqueous HCl. The solution was then neutralized with aqueous $NaHCO_3$ and extracted with 25% i-PrOH in $CHCl_3$. After concentration, the crude product was purified using an SCX column eluting with 2M NH_3/MeOH to afford 185 mg of the title compound (92%) LCMS: m/z = 546 (M+H)+ which was carried onto the next step. A round bottom flask was charged with [2-(4-methanesulfonyl-phenyl)-6-methoxy-naphthalen-1-yl]-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanol (185.2 mg, 0.33 mmol), Et_3SiH (0.3 mL, 1.88 mmol) and TFA (0.3 mL, 3.8 mmol) and dissolved with CH_2Cl_2 (30 mL). The reaction was stirred at room temperature for 1 hour and then quenched with saturated aqueous $NaHCO_3$ and extracted with 25% i-PrOH in CH_2Cl_2. The organic layer was dried over Na_2SO4, filtered, and concentrated. The crude material was purified by flash chromatography (0 – 5% MeOH/CH_2Cl_2 to afford 1.18 g of **8** (63%). LCMS: m/z = 530 (M+H)+. 1H NMR ($CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 9.3 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.3 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.11 (dd, J = 9.2, 2.4 Hz, 1H), 6.86 (m, 2H), 6.75 (m, 2H), 4.29 (s, 2H), 4.07 (t, J = 5.9 Hz, 2H), 3.94 (s, 3H), 3.09 (s, 3H), 2.77 (m, 2H), 2.53 (bs, 4H), 1.62 (m, 4H), 1.45 (m, 2H).

6-(4-Methanesulfonyl-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol hydrochloride (**9**): Pyridine hydrochloride (4 g, 34 mmol) was added to a flask containing [2-(4-methanesulfonyl-phenyl)-6-methoxy-naphthalen-1-yl]-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methane (**8**, 110 mg, 0.21 mmol). The flask was purged with nitrogen, capped and heated to 200 °C for 2 hours. The reaction mixture was cooled to room temperature and diluted with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (0-10% MeOH/CH_2Cl_2). The product was dissolved in 1:1 CH_3CN/1M aqueous HCl and lyophilized to afford 92 mg of **9** (80%). LCMS: m/z = 516 (M+H)+-HCl. 1H NMR (d_6-DMSO) δ 10.16 (bs, 1H), 9.85 (bs, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.68 (dd, J = 9.1, 6.9 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 2.2 Hz, 1H), 6.99 (dd, J = 9.1, 2.2 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 4.22 (s, 4H), 3.30-3.50 (m, 6H), 3.21 (s, 3H), 2.89 (m, 2H), 1.55-1.75 (m, 5H), 1.26 (m, 1H). Analysis calculated for $C_{31}H_{33}NO_4S.HCl$: C, 67.44; H, 6.21; N, 2.54. Found: C, 65.98; H, 6.26; N, 2.46.

2-Benzyloxy-1-bromo-6-methoxy-naphthalene (**11**): 6-Methoxynaphthalene-2-ol (**10**, 20 g, 114.8 mmol) was dissolved in dimethylformamide (DMF, 250 mL) at ambient temperature. N-Bromosuccinimide (NBS, 21.5 g, 120 mmol) was added over a 30 minute period. After 45 minutes, the reaction was diluted with water (800 mL), the precipitate was collected and dried to provide 25.5 g (87%) of 1-bromo-6-methoxy-naphthalen-2-ol: 1H NMR (CDCl3) δ 7.94 (d, 1H), 7.62 (d, 1H), 7.23 (dd, 1H), 7.22 (d, 1H), 7.11 (d, 1H), 5.72 (s, 1H), 3.91 (s, 3H). HPLC Rt = 2.86 min. 1-Bromo-6-methoxy-naphthalen-2-ol (66.7 g, 264 mmol), potassium carbonate (K_2CO_3, 40.0 g, 290 mmol) and benzyl bromide (49.6 g, 290 mmol) were added to a flask containing DMF (800 mL). The mixture was stirred at ambient temperature for 1 hour. Water (400 mL) was added to precipitate the product. The precipitate was collected and washed with heptane (3 X 125 mL) then dried to provide 83.7 g of 2-benzyloxy-1-bromo-6-methoxy-naphthalene (**11**, 86 %): ^{1}H NMR ($CDCl_3$) δ 8.15 (d, 1H), 7.64 (d, 1H), 7.49-7.54 (m, 2H), 7.35-7.42 (m, 2H), 7.33 (d, 1H), 7.20-7.26 (m, 2H), 7.07 (br s, 1H), 5.25 (s, 2H), 3.90 (s, 3H). HPLC R_t = 3.43 min.

1-{2-[4-(2-Benzyloxy-6-methoxy-naphthalen-1-yloxy)-phenoxy]-ethyl}-piperidine (**13**): Toluene (200 mL), 2-benzyloxy-1-bromo-6-methoxy-naphthalene (**11**, 30 g, 87.4 mmol), 4-(2-piperidin-1-yl-ethoxy)phenol (**12**, 23.2 g, 105 mmol) and cesium carbonate (34.4 g, 105 mmol), were combined and heated to reflux. A portion of the toluene was distilled (100 mL) and ethyl acetate (390 mg, 4.37 mmol) and copper triflate benzene complex (2.20 g, 4.37 mmol) were added to the reaction mixture and stir for 5 minutes. The solvent was removed by distillation and the resulting residue was heated to 174°C for 1.5 hours. The residue was cooled and dissolved in a mixture of ethyl acetate (200 mL) and aqueous HCl (1 N, 90 mL). The organic layer was separated and concentrated. The residue was purified by column chromatography to give 12.4 g of 1-{2-[4-(2-benzyloxy-6-methoxy-naphthalen-1-yloxy)-phenoxy]-ethyl}-piperidine (**13**, 30%): m/z = 484.4 (M+1); ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1H), 7.53 (d, 1H), 7.28 (d, 1H), 7.22-7.26 (m, 3H), 7.16-7.20 (m, 2H), 7.01-7.12 (m, 2H), 6.75-6.83 (m, 4H), 5.10 (s, 2H), 4.03 (t, 2H), 3.87 (s, 3H), 2.73, (t, 2H), 2.42-2.57 (br s, 4H), 1.55-1.65 (m, 4H), 1.39-1.48 (m, 2H); HPLC R_t (Purity @ 254 nm) = 2.43 min (96%).

Trifluoro-methanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (**14**): 1-{2-[4-(2-Benzyloxy-6-methoxy-naphthalen-1-yloxy)-phenoxy]-ethyl}-piperidine (**13**, 12.4 g, 25.5 mmol) was added to a methanol/ethyl acetate mixture (1:1, 490 mL) and heated to form a solution. The heat was removed and ammonium formate (4.83 g, 76.6 mmol) and $Pd(OH)_2$ on Carbon (20 % ww, 1.58 g, 1.12 mmol) were added. The mixture was refluxed for 50 minutes then filtered. The filtrate was concentrated to provide 9.9 g of 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalene-2-ol (98 %): ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H), 7.62 (d, 1H), 7.52, (d, 1H), 7.30 (d, 1H), 7.10 (d, 1H), 7.03 (dd, 1H), 6.78-6.80 (m, 2H), 6.64-6.69 (m, 2H), 4.03 (t, 2H), 3.87 (s, 3H), 3.08 (t, 2H), 2.88-2.96 (bs, 4H), 1.73-1.81 (m, 4H), 1.48-1.55 (bs, 2H). Dichloromethane (290 mL), triethylamine (3.08 g, 30.4 mmol) and 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalene-2-ol (9.2 g, 23.4 g) were cooled to –50 °C and trifluoromethanesulfonic acid anhydride (7.26 g, 25.7 mmol) was added. The resulting mixture was stirred at –50 °C for 2 hours then allowed to warm to ambient temperature before stirring an additional hour. Brine (150 mL) was added and the phases separated. The

organics were washed with $NaHCO_3$ then dried with Na_2SO_4 before concentrating to a residue. The residue was crystallized with ethyl ether – hexanes to provide 11.2 g of **14** (91%): mass spectrum (ion spray): m/z = 526.2 (M+1); ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1H), 7.66 (d, 1H), 7.40 (d, 1H), 7.26 (d, 1H), 7.14-7.20 (m, 2H), 6.74-6.82 (m, 4H), 4.03 (t, 2H), 3.93 (s, 3H), 2.74 (t, 2H), 2.44-2.52 (m, 4H), 1.56-1.62 (m, 4H), 1.40-1.47 (m, 2H); HPLC R_t (Purity @ 254 nm) = 2.39 min (97%).

1-(2-{4-[2-(4-Methanesulfonyl-phenyl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine (**15**): A 500 mL flame-dried flask fitted with a reflux condenser was charged with 4-(methanesulfonyl)phenylboronic acid (**6**, 6.8 g, 34 mmol), trifluoro-methanesulfonic acid 6-methoxyoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (**14**, 6.6 g, 12.6 mmol), cesium fluoride (17.2 g, 113 mmol), and acetonitrile (130 mL). In a separate flask, palladium(II) acetate (283 mg, 1.26 mmoL) and tricyclohexylphosphine (530 mg, 1.9 mmol) were charged. Acetonitrile (65 mL) was added and sonicated for 10 minutes under nitrogen. The catalyst slurry was added to the mixture of substrates and heated in a 90 °C oil bath for 30 minutes. The suspension was cooled to room temperature and filtered through packed celite. The celite was rinsed with ethyl acetate and the filtrate was washed with a 50:50 mixture of water and sat. aq. Na_2CO_3, sat. aq. NH_4Cl, and sat. aq. NaCl. The organic layer was dried with Na_2SO_4, filtered and evaporated to obtain 10 grams of crude material. The crude material was treated with a solution of 1% MeOH in CH_2Cl_2 and the resulting white solid impurity (400 mg) was removed by filtration. The filtrate was concentrated and the crude product pre-adsorbed onto silica gel. The residue was chromatographed on a SiO_2 column eluting the material with methanol in dichloromethane (0 to 10%) to give 5.2 grams (78%) of **15** as an off-white solid. The crude fractions were concentrated and recrystallized from ethyl acetate to obtain another 1.2 grams (18%) of the desired material: mass spectrum (ion spray): m/z = 532.3 (M+H); ^{1}H NMR ($CDCl_3$) δ 7.86-7.91 (m, 3H), 7.72-7.78 (m, 3H), 7.51 (d, J = 8.7 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.13 (dd, J = 9.3, 2.4 Hz, 1H), 6.62-6.67 (m, 2H), 6.55-6.60 (m, 2H), 4.11 (t, J = 5.2 Hz, 2H), 3.95 (s, 3H), 3.06 (obs t, 2H), 3.05 (s, 3H), 2.83-2.91 (m, 4H), 1.74-1.81 (m, 4H), 1.50-1.57 (m, 2H); HPLC R_t (Purity @ 223 nm) = 1.91 min (100%).

6-(4-Methanesulfonyl-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol hydrochloride (**16**): 1-(2-{4-[2-(4-Methanesulfonyl-phenyl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine (**15**, 6.4 g, 12.1 mmol) was dissolved in a mixture of ethyl acetate, dichloromethane, and methanol (300 mL; 2.5:2.5:1). The resulting solution was cooled in an ice-bath and treated with 2M HCl in diethyl ether (9.1 mL, 18.2 mmol). The solution was concentrated in vacuo and dried at 50 °C (<2mm of Hg) for 18 hours to give 6.6 grams (96%) of 6-(4-Methanesulfonyl-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol as an off-white amorphous solid: mass spectrum (ion spray): m/z = 532.3 (M+1-HCl); ^{1}H NMR (d_6-DMSO) δ 9.20 (bs, 1H), 7.86-7.94 (m, 5H), 7.76 (d, J = 9.3 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.20 (dd, J = 9.3, 2.3 Hz, 1H), 6.79-6.83 (m, 2H), 6.62-6.67 (m, 2H), 4.17 (t, J = 4.8 Hz, 2H), 3.91 (s, 3H), 3.38-3.48 (m, 4H), 3.24 (s, 3H), 2.89-2.99 (m, 2H), 1.75-1.82 (m, 2H), 1.58-1.70 (m, 3H), 1.31-1.41 (m, 1H); HPLC R_t (Purity @ 254 nm) = 1.91 min (>99%); Analysis calculated for $C_{30}H_{32}ClNO_5S$ HCl: C, 56.48; H, 5.58; N, 2.12. Found: C, 56.38; H, 5.39; N, 1.78. 1-(2-{4-[2-(4-Methanesulfonyl-phenyl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine (6.45 g, 11.4 mmol) was dissolved in dichloromethane (200 mL) and cooled to 3 °C in an ice-bath. This solution was treated with neat BBr_3 (5.4 mL, 57 mmoL), dropwise over 5 minutes, and stirred for 3 hours at 0 to 10 °C. The reaction was slowly poured into a 1-liter sep. funnel containing sat. aq. $NaHCO_3$ (300 mL) and ice. The two-phase mixture was diluted with a solution of 7.5% MeOH in EtOAc (400mL) and sat. aq. NaCl (100 mL). The layers were separated and the aqueous layer was extracted with 5% MeOH in EtOAc (2 X 150mL). The combined organic layers were washed with sat. aq. NaCl (100 mL), dried (Na_2SO_4), filtered and evaporated to obtain 5.3 g of a light yellow foam. The residue was purified on a SiO_2 column eluting the material with methanol in dichloromethane (2.5 to 12%) to give 4.99 grams (85%) 6-(4-methanesulfonyl-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol (2.8 g, 5.4 mmoL) as a light yellow amorphous solid which was dried at 45 °C (<2 mm of Hg) for 18 hours: mass spectrum (ion spray): m/z = 518.3 (M+1); ^{1}H NMR ($CDCl_3$) δ 7.85-7.89 (m, 2H), 7.79 (d, J = 8.9 Hz, 1H), 7.67-7.71 (m, 2H), 7.58 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.9 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H), 7.02 (dd, J = 9.1, 2.3 Hz, 1H), 6.42 (s, 4H), 4.00 (t, J = 5.7 Hz, 2H), 3.06 (s, 3H), 2.84 (t, J = 5.7 Hz, 2H), 2.61-2.68 (m, 4H), 1.66-1.73 (m, 4H), 1.46-1.53 (m, 2H); HPLC R_t (Purity @ 254 nm) = 1.22 min (98%); Analysis calculated for $C_{30}H_{31}NO_5S$ C, 67.42; H, 5.89; N, 2.60. Found: C, 67.32; H, 5.79; N, 2.48. 6-(4-Methanesulfonyl-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol (2.8 g, 5.4 mmoL) was slurried in a mixture of ethyl acetate, ethyl ether, and methanol (50 mL; 5:1:4) and cooled in an ice bath. 2M HCl in diethyl ether (4.1 mL, 8.2 mmol) was added. The resulting solid was collected on filter paper, rinsed with diethyl ether and dried at 45 °C (<2mm of Hg) for 18 hours to give 2.84 grams (95%) of **16** as an off-white solid: mass spectrum (ion spray): m/z = 518.3 (M+1-HCl); ^{1}H NMR (d_6-DMSO) δ 10.14 (s, 1H), 10.07 (br s, 1H), 7.89-7.93 (m, 2H), 7.84-7.87 (m, 2H), 7.78 (d, J = 8.9 Hz, 1H), 7.72 (d, J = 9.1 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.27 (d, J = 2.4 Hz, 1H), 7.12 (dd, J = 9.0, 2.3 Hz, 1H), 6.78-6.82 (m, 2H), 6.61-6.66 (m, 2H), 4.17-4.24 (m, 2H), 3.29-3.48 (m, 4H), 3.23 (s, 3H), 2.84-2.98 (m, 2H), 1.60-1.78 (m, 5H), 1.28-1.42 (m, 2H); HPLC R_t (Purity @ 254 nm) = 1.22 min (98%); Analysis calculated for $C_{30}H_{32}ClNO_5S$: C, 63.91; H, 6.18; N, 2.26. Found: C, 63.77; H, 5.80; N, 2.34.

6-(4-fluorophenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol hydrochloride (**17**): A 50 mL flask fitted with a reflux condenser was charged with 4-fluorophenylboronic acid (0.20 g, 1.43 mmol), trifluoro-methanesulfonic acid 6-methoxyoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (**16**, 0.25 g, 0.48 mmol), cesium fluoride (0.65 g, 4.28 mmol) palladium(II) acetate (20 mg, 0.09 mmoL), tricyclohexylphosphine (31 mg, 0.11 mmol) and acetonitrile (6 mL). The resulting mixture was heated in a 90 °C oil bath for 30 minutes. The reaction suspension was cooled to room temperature and filtered through packed celite. The celite was rinsed with ethyl acetate and the filtrate was washed with a

50:50 mixture of water and sat. aq. Na_2CO_3, sat. aq. NH_4Cl, water and sat. aq. NaCl. The organic layer was dried with Na_2SO_4, filtered and evaporated. The crude material was taken up in minimal dichloromethane and loaded onto a 10 gram SCX column. The column was treated with 100% dichloromethane (50 mL) followed by a 30% methanol/dichloromethane solution (50 mL). The product was flushed off the column with 100 mL of a 2 Molar ammonia/methanol solution. The filtrate was concentrated and the crude residue was chromatographed on SiO_2 eluting the material with a 1-3% gradient of a 2 Molar ammonia/methanol solution in 30% ethyl acetate/hexane to give 178 mg (79%) of the title compound as an off-white solid: mass spectrum (ion spray): m/z = 472.2 (M+H); ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.8Hz, 1H), 7.48-7.52 (m, 3H), 7.19 (d, J = 2.9 Hz, 1H), 7.10 (dd, J = 9.1, 2.9 Hz, 1H), 7.00 (app t, J = 9.1 Hz, 2H), 6.65 (d, J = 9.1Hz, 2H), 6.57 (d, J = 9.1 Hz, 2H), 3.96 (t, J = 6.3 Hz, 2H), 3.93 (s, 3H), 2.68 (t, J = 6.1 Hz, 2H), 2.43-2.47 (m, 4H), 1.54-1.60 (m, 4H), 1.39-1.45 (m, 2H); LC/MS R_t (Purity @ 214 nm) = 5.70 min (100%); Analysis calculated for $C_{30}H_{30}FNO_3$: C, 76.41; H, 6.41; N, 2.97. Found: C, 77.36; H, 6.58; N, 3.11. 1-(2-{4-[2-(4-fluorophenyl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine. (0.170 g, 0.38 mmol) was dissolved in a mixture of dichloromethane, and methanol (10 mL; 1:1). The resulting solution was treated with 1M HCl in diethyl ether (0.4 mL, 0.4 mmol). The solution was stirred for 5 min at room temperature then concentrated to give 0.183 g (100%) of the hydrochloride salt of 1-(2-{4-[2-(4-fluorophenyl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine as an off-white crystalline solid: mass spectrum (ion spray): m/z = 472.2 (M+1-HCl); ^{1}H NMR (d_6-DMSO) δ *10.23 (bs, 1H), 7.84 (d,* J = 8.8 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.57-7.61 (m, 3H), 7.43-7.45 (m, 1H), 7.13-7.21 (m, 3H), 6.78 (d, J = 8.6Hz, 2H), 6.59 (d, J = 8.6 Hz, 2H), 4.20-4.24 (m, 2H), 3.88 (s, 3H), 3.30-3.44 (m, 4H), 2.86-2.96 (m, 2H), 1.61-1.77 (m, 5H), 1.28-1.38 (m, 1H); LC/MS R_t (Purity @ 214 nm) = 5.71 min (100%); Analysis calculated for $C_{30}H_{30}FNO_3 \cdot 1.2HCl$: C, 69.92; H, 6.10; N, 2.72. Found: C, 69.62; H, 5.98; N, 2.85. The HCl salt of 1-(2-{4-[2-(4-fluorophenyl)-6-methoxy-naphthalen-1-yloxy]-phenoxy}-ethyl)-piperidine (0.173 g, 0.34 mmol) was dissolved in dichloromethane (5.0 mL) and cooled in an ice-bath. This solution was treated with a 1M dichloromethane solution of BBr_3 (1.10 mL, 1.10 mmoL) and stirred for 2 hours at 0 to 20 °C. The reaction was quenched with ice-cooled sat. aq. $NaHCO_3$ (15 mL). To the resulting mixture was added THF (7.5 mL) to dissolve any remaining solids. The subsequent two phase mixture was separated and the aqueous layer was extracted with EtOAc (3 X 15 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (15mL), H_2O (15mL) and sat. aq. NaCl (100 mL), dried (Na_2SO_4), filtered and evaporated *in* vacuo. The resulting residue was purified on SiO_2 eluting the material with a 1-3% gradient of a 2M ammonia/methanol solution in 30% ethyl acetate/hexane to give 178 mg (84%) of 6-(4-fluorophenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol as an off-white crystalline solid: mass spectrum (ion spray): m/z = 458.1 (M+1); ^{1}H NMR (d_6-DMSO) δ 9.92 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 2.2 Hz, 1H), 7.05 (dd, J = 9.1, 2.3 Hz, 1H), 6.70 (d, J = 9.1 Hz,2 H), 6.54 (d, J = 9.1 Hz), 3.86 (t, J = 5.9 Hz, 2H), 2.53 (t, J = 5.9 Hz, 2H), 2.32-2.36 (m, 4H), 1.40-1.46 (m, 4H), 1.30-1.35 (m, 2H); LC/MS R_t (Purity @ 214 nm) = 5.19 min (100%); Analysis calculated for $C_{30}H_{31}FNO_3$: C, 67.42; H, 5.89; N, 2.60. Found: C, 67.32; H, 5.79; N, 2.48. 6-(4-fluorophenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol (0.119 g, 0.26 mmoL) was dissolved in a mixture of dichloromethane and methanol (7.5 mL; 1:1) and 2M HCl in diethyl ether (4.1 mL, 8.2 mmol) was added. The resulting solution was stirred at room temperature for 5 min at which time it was concentrated *in-vacuo* to give 0.128 grams (100%) of **17** as an off-white solid: mass spectrum (ion spray): m/z = 458.1 (M+1-HCl); ^{1}H NMR (d_6-DMSO) δ 10.17 (br s, 1H), 9.98 (s, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 9.1 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.20 (d, J = 2.2 Hz, 1H), 7.14 (app. t, J = 8.9 Hz, 2H) 7.04 (dd, J = 9.0, 2.3 Hz, 1H), 6.76 (d, J = 9.1 Hz, 2H), 6.57 (d, J = 9.1 Hz, 2H), 4.19 (app. t, J = 5.0 Hz, 2H), 3.36-3.41 (m, 2H), 3.31-3.35 (m, 2H), 2.85-2.94 (m, 2H), 1.59-1.74 (m, 5H), 1.26-1.35 (m, 1H); LC/MS R_t (Purity @ 214 nm) = 4.85 min (100%); Analysis calculated for $C_{29}H_{28}FNO_3$.HCl: C, 70.51; H, 5.92; N, 2.84. Found: C, 70.82; H, 6.09; N, 2.91.

Elemental Analyses for Target Compounds

Cmpd	Elemental Results
9	Analysis calculated for $C_{31}H_{33}NO_4S$.HCl: C, 67.44; H, 6.21; N, 2.54. Found: C, 65.98; H, 6.26; N, 2.46.
16	Analysis calculated for $C_{30}H_{32}ClNO_5S$: C, 63.91; H, 6.18; N, 2.26. Found: C, 63.77; H, 5.80; N, 2.34.
17	Analysis calculated for $C_{29}H_{28}FNO_3$.HCl: C, 70.51; H, 5.92; N, 2.84. Found: C, 70.82; H, 6.09; N, 2.91

Biological Assay Protocols

ER binding. The competition binding assay was run in a buffer containing 50mM Hepes, pH 7.5, 1.5mM EDTA, 150mM NaCl, 10% glycerol, 1mg/mL ovalbumin and 5mM DTT, using 0.025 µCi per well ^{3}H-estradiol (NEN #NET517 at 118 Ci/mmol, 1.5 nM E2) (NEN/PerkinElmer, Boston, MA) 10 ng/well ERα or ERβ receptor (PanVera/Invitrogen, Carlsbad, CA). Nonspecific binding was determined in the presence of 1µM of 17-β estradiol (E2). The binding reaction was incubated for 4 hours at room temperature, and then cold DCC buffer was added to each reaction (DCC buffer contains per 50 ml of assay buffer, 0.75 g of charcoal (Sigma, St Louis, MO) and 0.25 g of dextran (Pharmacia, Uppsala, Sweden). Plates were mixed 8 minutes on an orbital shaker at 4°C, then centrifuged at 3,000 rpm at 4°C for 10 minutes. An aliquot of the mix was added to Wallac Optiphase "Hisafe 3" scintillation fluid, incubated for 2.5 hr, and read in a Wallac Microbeta counter. The K_d for ^{3}H-estradiol was determined by saturation binding to ER-alpha and ER-beta receptors. The IC_{50} values for compounds were converted to K_i using Cheng-Prusoff equation.

Ishikawa Assay. Estrogenic stimulation and antagonism were measured in Ishikawa human endometrial tumor cells by alkaline phosphatase quantitation. The cells were incubated in DMEM/F-12 (3:1) supplemented with 5% dextran coated charcoal stripped fetal bovine serum (DCC-FBS) (Hyclone, Logan, UT), L-Glutamine (2mM), MEM sodium pyruvate (1 mM), HEPES (2mM) all from Gibco BRL (Gaithersburg, MD). For the agonist mode, plates received diluted compounds only, while antagonist mode plates additionally received 1 nM estradiol (17β-Estradiol, Sigma, St. Louis, MO). Cells were incubated for 48 h then fresh compounds were added for an additional 72 h. The assay was quenched by removing medium, rinsing plates twice in PBS, and the plates were dried for 5 minutes and frozen at -70°C. After thawing, 100 µL of 1-Step™ PNPP (Pierce Chemical Company, Rockford, IL) was added for 20 min and plates were read on a spectrophotometer at 405 nm. For the agonist mode, a percentage increase over control was calculated. The data were fitted to a linear interpolation to derive IC_{50} values for the antagonist mode and a percentage efficacy was calculated that blocks the 17β-estradiol (1nM) stimulus.

MCF-7 Assay. MCF-7 breast adenocarcinoma cells (ATCC HTB 22) were grown in assay medium MEM (phenol red-free, Gibco BRL, Gaithersburg, MD) supplemented with 10% DCC-FBS. Cells were assayed by plating 8,000 cells in each well of 96 well Cytostar T scintillation plates (Amersham, Piscataway, NJ) and incubated at 37°C for 24 hours before adding compounds. For antagonist mode, 10 pM of E2 was added along with dilutions of compound for 48 h, then medium containing 0.01 µCi of ^{14}C-thymidine (52 mCi/mmol, 50 µCi/ul, Amersham, Piscataway, NJ) was added to each well. The plates were incubated overnight and then quantitated on a Wallac Microbeta counter. The data were averaged to calculate an IC_{50} and % inhibition at 1µM compound.

3-Day Rat Uterine Antagonist. All rat experiments were conducted in accord with accepted standards of humane animal care and in accordance of the Animal Care and Use Committee at Eli Lilly and Company. Female Sprague Dawley (SD) rats, 6 per group and 19-21 days of age, were orally treated with ethynyl estradiol (EE; 0.1 mg/kg) and 10, 1.0, 0.1 or 0.01mg/kg SERM for 3 days. Test compounds were dissolved in 20% w/v β-hydroxycyclodextrin in water and administered by oral gavage in a volume of 0.2 ml daily (15 min prior to the EE gavage). Groups of 6 rats were also given vehicle as a negative control, EE alone as a positive control and EE plus LY117018 as a standard antagonist control. The animals were fasted overnight following the final dose. On the following morning, the animals were weighed and then euthanized (by carbon dioxide asphyxiation) and the uteri were rapidly collected (via a mid-line ventral incision), stripped of adipose tissue, removed luminal fluid by blotting onto absorbant paper, and weighed. Uterine weight/body weight ratios (UWR) were calculated for each animal. The percentage inhibition of the estrogen-induced response was then calculated by the following formula: percent inhibition = $100 \times (UWR_{E2} - UWR_{test\ compound}/UWR_{E2} - UWR_{control})$. ED_{50} values were derived from a semi-log regression analysis of the linear aspect of the dose response curve.

10-day Hormone Assay. Female Fischer 344 rats (9-10 weeks old) were dosed with 30X the ED_{50} dose value derived from the 3-Day Rat Uterine Antagonist model. Trunk blood was collected 2 hours after the final dose. Serum levels of estradiol were measured by RIA, using an assay kit from DiaSorin (Saluggia, Italy).

35-day Intact Rat Uterine Efficacy. Mature, virgin 3-month (14-day assay) or 6-month- old (35-day assay) SD rats were administered compound by oral gavage daily. Animals were euthanized and the uteri collected and weighed as described for the 3-Day Rat Uterine Antagonist assay. For histology and morphometry in the 35-day study: Uteri and ovaries were removed, weighed, and fixed in 10% neutral buffered formalin. Tissues were trimmed, processed, and embedded in paraffin blocks for histology. For trimming, transverse sections of the ovary and the midpoint of the left uterine horn were taken. Five-micron sections were stained with hematoxylin and eosin and evaluated by a board certified veterinary pathologist for histologic changes. Qualitative severity scores were as assigned as follows: 1 = minimal, 2 = slight, 3 = moderate, 4 = marked. Mean group lesion scores for individual groups, were calculated by adding the individual animal severity scores and dividing by the total number of animals. Morphometry was done on the uteri from all control (n=6) and 0.5 mg/kg LY2066948-treated (n=7) rats. Uteri were imaged at 25x magnification using a Spot digital camera attached to a Leica DMLB microscope. Cross sectional area (square microns) of the uterine wall, endometrium, and myometrium were measured using Spot morphometry software. LH was measured by RIA as described in (12), P4 was measured by Active® Progesterone radioimunoassay, Diagnostic Systems Laboratories Inc., Webster TX. For the progesterone assay, the upper limit of detection was 60 ng/mL and the lower limit of detection was 0.3 ng/mL for a 25-microliter sample volume.

X-ray Cystallography Material and Methods:

ERα Expression and Purification. For crystallographic studies the human ERαLBD (residues 304-550 with three mutations: C381S, C417S and C530S) was overexpressed as an N-terminally His_6-tagged protein in BL21(DE3) cells using expression vector pET19 (Novagen) and purified by PanVera (Madison, WI).

Crystallization and Data Collection. The protein was concentrated to ~5 mg/ml in solution containing 20 mM Tris HCl (pH=8.0), 100 mM NaCl, 100 μM ligand. Crystallization was carried out by the hanging drop vapor diffusion method at room temperature. The reservoir solution is 100 mM MES (pH=6.8), 0.5 M $MgCl_2$, 15% w/v PEG 4000 and 10% Ethylene glycol. Crystals of ERα–**16** belong to space group P6(5)22 with unit cell parameters a=58.87 Å, b=58.87 Å, c=276.01 Å. There is one molecule of the complex per asymmetric unit.The crystal was cooled at 100K, using 15-20% ethylene glycol plus the mother liquor as cryo-protectant, before data collection. X-ray diffraction data sets were collected on IMCA (Industrial Macromolecular Crystallography Association) beam lines and processed using HKL2000. The resolution of the data sets used for structure refinement is 1.9 Å for ligand **16**.

Structure Determination and Refinement. The crystal structure was determined by the method of molecular replacement with AMORE using an internal ERαLBD structures as a search model. The program suite QUANTA 2000 (Accelrys, Inc., San Diego, CA) was used for model building between rounds of refinement. Structure refinement was carried out by CNX2000 using rigid-body, positional and individual B factor refinements with bulk solvent correction. The refinement R-factors are R_{work}=0.2292, R_{free}=0.2596. The coordinates have been deposited in the Protein Data Bank (PDB ID code = 2AYR).