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## Supporting Information

### Experimental Section:

$^1$H NMR spectra were recorded using a Varian Gemini 300 spectrometer (300 MHz) in $CDCl_3$ unless otherwise indicated. Mass spectra were recorded using VG-analytical 7070E organic mass spectrometer. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison NJ. Thin layer chromatography (TLC) was carried out using Whattman silica gel 60 A plates (0.25 mm). Flash chromatography was performed using E. Merck silica gel 60 (230-400 mesh).

**2-Bromo-3-hydroxy-5,5,8,8-tetramethyltetralin (4)** To a solution of 2-hydroxy-5,5,8,8-tetramethyltetralin (**3**, 700 mg, 3.43 mmol) in 1.5 mL of HOAc was added $Br_2$ (0.177 mL, 3.43 mmol). The reaction mixture was stirred at room temperature overnight. A stream of air was passed through the reaction mixture to remove the unreacted $Br_2$. The remaining solid was dissolved in a small amount of THF and purified by column chromatography (ethyl acetate/hexane = 1/9) to yield 747 mg (77%) of **4** as a white solid. $^1$H NMR δ 7.36 (s, 1H), 6.96 (s, 2H), 5.32 (b, 1H), 1.66 (s, 4H), 1.25 (s, 12H). Anal. ($C_{14}H_{20}BrO$) C, H.

**2-Bromo-3-methoxymethoxy-5, 5, 8, 8-tetramethyltetralin (5)** To a solution of **4** (600 mg, 2.12 mmol) and catalytic amount of tetrabutyl ammonium bromide in 20 mL of dry $CH_2Cl_2$ at 0 °C was added diisopropylethylamine (1.138 mL, 12.75 mmol), followed by chloromethyl methyl ether (0.484 mL, 6.39 mmol). The reaction mixture was heated at 45 °C for 12 h and cooled to room temperature. The reaction mixture was washed with 10% citric acid, saturated $NaHCO_3$ and brine and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by column chromatography (ethyl acetate/hexane = 1/9) to yield 680 mg (98%) of **5** as a white solid. $^1$H NMR δ 7.43 (s, 1H), 7.06 (s, 1H), 5.21 (s, 2H), 3.54 (s, 3H), 1.66 (s, 4H), 1.26 (s, 6H), 1.25 (s, 6H). Anal. ($C_{16}H_{24}BrO_2$) C, H.

**3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl Acid (6)** To a solution of **5** (655 mg, 2.00 mmol) in 9 mL of dry THF at -78 °C under Ar was added slowly 2.23 mL of t-BuLi (1.7 M in hexane, 4.59 mmol). The reaction mixture was stirred at -78 °C for 1 h and then $CO_2$ was bubbled through the solution for 1 h. After removal of the $CO_2$ stream, the reaction mixture was stirred for an additional hour at -78 °C and quenched with 3 mL of 10% HCl. After warming to room temperature, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with brine and dried over $Na_2SO_4$. After filtration and concentration under reduced pressure, the residue was purified by column chromatography (ethyl acetate/hexane = 1/1) to yield 155 mg (27%) of **6** as a white solid. $^1$H NMR δ 7.85 (s, 1H), 6.93 (s, 1H), 1.68 (s, 4H), 1.28 (s, 12H). Anal. ($C_{15}H_{21}O_3$) C, H.

**1-Bromo-2-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-3-yl Acid (7)** Using the same procedure as for the synthesis of **4**, **6** (700 mg, 2.82 mmol) afforded 792 mg (86%) of **7** as an off-white solid. $^1$H NMR δ 7.91 (s, 1H), 1.75 (m, 2H), 1.64 (m, 2H), 1.62 (s, 6H), 1.30 (s, 6H). Anal. ($C_{15}H_{20}BrO_3$) C, H.

**1-Bromo-2-methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-3-yl Acid (8)** To a solution of **7** (233 mg, 0.71 mmol) in 6 mL of $CH_2Cl_2$ was added chloromethyl methyl ether (0.162 mL, 2.1 mmol), diisopropylethyl amine (0.764 mL, 4.2 mmol) and a catalytic amount of tetrabutylammonium bromide. The reaction mixture was heated to 45 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (ethyl acetate/hexane = 1/9) to yield 200 mg of the methoxymethyl ester of **8** as a white solid. This white solid was dissolved in 20 mL of EtOH and treated with an aqueous solution of NaOH (0.5 mL, 1M). The reaction mixture was stirred at room temperature overnight. The EtOH was removed and the residue was treated with 2 mL of ethyl acetate and 3 mL of water. This mixture was very slowly acidified with 10% HCl to pH = 7. The ethyl acetate layer was separated and washed with brine and dried over $Na_2SO_4$. After filtration and concentration under reduced pressure, 153 mg (58%) of **8** was obtained as a white solid. $^1$H

NMR δ 7.99 (s, 1H), 5.20 (s, 2H), 3.66 (s, 3H), 1.74 (m, 2H), 1.67 (m, 2H), 1.60 (s, 6H), 1.32 (s, 6H). Anal. ($C_{17}H_{24}BrO_4$) C, H.

**Ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-5', 6', 7', 8'-tetrahydro-5', 5', 8', 8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoate (9)** To a solution of **8** (80 mg, 0.22 mmol) in 4 mL of $CH_2Cl_2$ was added DMAP (60 mg, 0.26 mmol), **13** (43 mg, 0.24 mmol) and EDC (50 mg, 0.26 mmol). The reaction mixture was stirred at room temperature overnight and then concentrated to dryness. The residue was purified by column chromatography (ethyl acetate/hexane = 1/3) to yield 45.2 mg (39%) of **9** as a clear oil. $^1$H NMR δ 9.92 (b, 1H), 8.10 (s, 1H), 7.94 (t, J = 8.4 Hz, 1H), 7.81 (dd, J = 12.9; 1.9 Hz, 1H), 7.35 (dd, J = 8.5; 1.8 Hz, 1H), 5.20 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.61 (s, 3H), 1.74 (m, 2H), 1.64 (m, 2H), 1.60 (s, 6H), 1.40 (t, J = 7.1 Hz, 3H), 1.34 (s, 6H).

**Ethyl 2,6-difluoro-4-[(3'-methoxymethoxy-4'-bromo-5', 6', 7', 8'-tetrahydro-5', 5', 8', 8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoate (10)** Using the same procedure as for the synthesis of compound **9**, **6** (80 mg, 0.22 mmol), DMAP (60 mg, 0.26 mmol), **16** (52 mg, 0.24 mmol) and EDC (50 mg, 0.26 mmol) afforded 26 mg (22%) of **10** as a clear oil. $^1$H NMR δ 10.01 (b, 1H), 8.11 (s, 1H), 7.42 (d, J = 10.0 Hz, 2H), 5.2 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.63 (s, 3H), 1.75 (m, 2H), 1.65 (m, 2H), 1.61 (s, 6H), 1.40 (t, J = 7.1 Hz, 3H), 1.35 (s, 6H); Anal. ($C_{26}H_{30}BrF_2NO_5$) C, H, N.

**2-Fluoro-4-[(3'-hydroxy-4'-bromo-5', 6', 7', 8'-tetrahydro-5', 5', 8', 8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic Acid (1)** To a solution of **9** (45 mg, 0.084 mmol) in 1 mL of EtOH was added 1 mL of aqueous solution of NaOH (1M). The reaction mixture was stirred at room temperature overnight and acidified to pH = 1 with 10% HCl. EtOH was removed and ethyl acetate and water were added to the residue. The organic layer was separated and washed with saturated $NaHCO_3$, brine and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the reaction yielded 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-5', 6', 7', 8'-tetrahydro-5', 5', 8', 8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic acid as a white solid. The methoxymethyl group was removed by dissolving the resulting white solid in 2 mL of MeOH and treating with 3 drops of conc. HCl. After stirring overnight, the reaction mixture was concentrated to dryness. The residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated $NaHCO_3$, brine and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the white solid was purified by a mini pipette column (ethyl acetate/hexane = 1/1) to give 5.00 mg (20%) of **1** as a white solid. $^1$H NMR δ (acetone-$d_6$) 10.19 (b, 1H), 8.01 (s, 1H), 7.96 (t, J = 8.6 Hz, 1H), 7.76 (dd, J = 11.2; 2.0 Hz, 1H), 7.54 (dd, J = 8.8; 2.0 Hz, 1H), 1.75 (m, 2H), 1.65 (m, 2H), 1.61 (s, 6H), 1.32 (s, 6H); Ms (m/z) 465, 463, 309, 231, 138 (base peak); Anal. ($C_{22}H_{23}BrFNO_4 \cdot 0.4H_2O$) C, H, N.

**2,6-Difluoro-4-[(3'-hydroxy-4'-bromo-5', 6', 7', 8'-tetrahydro-5', 5', 8', 8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic Acid (2)** Using the same procedure as for the synthesis of compound **1, 10** (26 mg, 0.047 mmol) afforded 12 mg (54%) of **2** as a white solid. $^1$H NMR δ (acetone-$d_6$) 10.23 (b, 1H), 8.01 (s, 1H), 7.52 (d, J = 10.2 Hz, 2H), 4.8 (b, 1H), 1.75 (m, 2H), 1.65 (m, 2H), 1.60 (s, 6H), 1.31 (s, 6H); Ms (m/z) 483, 481, 439, 437, 401 (base peak), 357, 339; Anal. ($C_{22}H_{22}BrF_2NO_4$) C, H, N.

**Ethyl 2-fluoro-4-nitrobenzoate (12)** To a mixture of **11** (2.0 g, 12.8 mmol, Aldrich) and $Na_2Cr_2O_7$ (5.48 g, 16.8 mmol) in 27 mL of HOAc was added slowly 13.7 mL of conc. $H_2SO_4$. This mixture was slowly heated to 90 °C for 1 h to give a green suspension. The mixture was cooled to room temperature and diluted with ethyl acetate. The solution was adjusted to pH = 4 with aqueous NaOH. The mixture was extracted with more ethyl acetate and the organic layer was washed with saturated $NaHCO_3$ and brine and dried over $Na_2SO_4$. After filtration, the solution was concentrated to dryness and the residue was dissolved in 12 mL of $SOCl_2$. The solution was heated at 80 °C for 1 h. The excess $SOCl_2$ was removed under reduced pressure and the residue was dissolved in 22 mL of $CH_2Cl_2$, 2 mL of EtOH and 4 mL of pyridine. The

mixture was stirred at room temperature for 2 h and concentrated to dryness. After column chromatography (ethyl acetate/hexane = 1/9), 2.0 g (73%) of **12** was obtained as a white solid. $^1$H NMR δ 8.15 (m, 2H), 8.02 (dd, $J_1$ = 2.0, $J_2$ = 9.9 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H). Anal. ($C_9H_8FNO_4$) C, H, N.

**Ethyl 4-amino-2-fluorobenzoate (13)** To a solution of **12** (474 mg, 2.23 mmol) in 15 mL of ethyl acetate (purged with Ar) was added Pd/C (30 mg, 10% w/w). The reaction mixture was stirred at room temperature for 4 h under a $H_2$ atmosphere maintained with a hydrogen balloon. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane = 1/3) to yield 406 mg (100%) of **13** as a white solid. $^1$H NMR δ 7.77 (t, J = 8.4 Hz, 1H), 6.41 (dd, $J_1$ = 8.6, $J_2$ = 2.2 Hz, 1H), 6.33 (dd, $J_1$ = 13.0, $J_2$ = 2.2 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.3 (b, 2H), 1.37 (t, J = 7.1 Hz, 3H). Anal. ($C_9H_{10}FNO_2$) C, H, N.

**Ethyl 2, 4, 6-trifluorobenzoate (15)** A solution of **14** (562 mg, 3.19 mmol, Aldrich) in 2 mL of $SOCl_2$ was refluxed for 30 min. After cooling to room temperature, the excess $SOCl_2$ was removed under reduced pressure and the residue was dissolved in 5 mL of $CH_2Cl_2$ and 1 mL of EtOH. To this solution was added triethylamine (0.53 mL, 3.8 mmol) and the reaction was stirred at room temperature for 30 min. The reaction was concentrated and the residue was treated with 3 mL of ether. The white precipitate was removed by filtration through celite and the filtrate was concentrated under reduced pressure to a colorless oil. This oil was purified by column chromatography (ethyl acetate/hexane = 1/9) to give 638 mg (98%) of **15** as a colorless oil. $^1$H NMR δ 6.72 (t, J = 7.76 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H).

**Ethyl 4-amino-2,6-difluorobenzoate (16)** To a solution of **15** (638 mg, 3.13 mmol) in 7 mL of acetonitrile was added $NaN_3$ (250 mg, 3.85 mmol) in 2 mL of water. The resulting solution was refluxed for 3 days. The reaction was poured into ice-water and then extracted with ethyl acetate. The organic layer was dried over $Na_2SO_4$ and concentrated to an oil which was a mixture of **16** and ethyl 4-azido-2,6-difluorobenzoate. $^1$H NMR δ 6.62 (d, J = 8.61 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H). This mixture was dissolved in 10 mL of ethyl acetate. The solution was purged with $N_2$ and treated with Pd/C (50 mg, 10% w/w). The solution was maintained under a hydrogen atmosphere for 12 h. The catalyst was removed by filtration and the filtrate was concentrated to an oil. After column chromatography (ethyl acetate/hexane = 1/3), 97 mg (40%) of **16** was obtained as a white solid along with 391 mg (60% recovered) of **15** as a colorless oil. $^1$H NMR δ 6.18 (d, J = 10.44 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); Anal. ($C_9H_9F_2NO_2$) C, H, N.

Binding Assay:

Each receptor subtype was expressed in Baculovirus. Stock solutions of all compounds were prepared as 10 mM ethanol solutions and serial dilutions carried out into 1:1 DMSO:glycerol, 120 mM KCl, 8 mM Tris, 5 mM CHAPS, 4 mM DTT, and 0.24 mM PMSF, at PH = 7.4 at room temperature.

The final assay volume was 250 μL and contained 10-40 μg of extract protein along with 5 nM of [$^3$H] all-*trans* retinoic acid and varying concentrations of competing ligand at that ranged from 0-$10^{-5}$ M. The assays were run using a Biomek formatted for a 96 well minitube system. Incubations were carried out at 4 °C until equilibrium was achieved. Non-specific binding was defined as that binding remaining in the presence of 1000 nM of unlabeled RA. At the end of the incubation period, 50 μL of 6.25% hydroxyapitite was added in a wash buffer which consisted of 100 nM KCl, 10 mM Tris, and 0.5% Triton X-100. The mixture was vortexed and incubated for 10 minutes at 4 °C, centrifuged and the supernatant removed. The hydroxyapitite was washed three more times with the buffer and the amount of receptor-ligand complex determined by liquid scintillation counting of the pellet.

After correcting for non-specific binding, $IC_{50}$ values were determined graphically from a log-logit plot of the data. The $K_d$ values were determined by application of the Cheng-Prussof equation to the $IC_{50}$ values, the labeled ligand concentration, and the $K_d$ of the labeled ligand.

Transactivation assays

$4 \times 10^4$ Green monkey CV-1 cells in 1 mL of D-MEM growth medium containing 10% fetal calf serum (Gibco-BRL) were transfected in 12-well multiwell-plates (Costar) via calcium-phosphate precipitation (Chen and Okayama 1987) using 0.5 ug ERE-*tk*-Luc reporter plasmid and 0.1 ug of chimeric ER-RAR expression plasmid. ERE-tk-Luc consists of the region -397 to -87 of the estrogen responsive 5'-flanking region of the Xenopus vitellogenin A2 gene (Klein-Hitpass et al. 1986) cloned upstream from the herpes simplex virus thymidine kinase promoter of the luciferase reporter plasmid *tk*-luc (Glass *et al.* 1989). Estrogen receptor DNA binding domain-retinoid receptor hormone binding domain chimeric receptors, ER-RARα, ER-RARβ ,ER-RARγ (Graupner *et al* 1991) were expressed from the SV-40 based expression vector pECE (Ellis *et al.* 1986).

Eighteen hours after introduction of the DNA precipitants, cells were rinsed with phosphate buffered saline (PBS) and fed with D-MEM (Gibco-BRL) containing 10% activated charcoal extracted fetal bovine serum (Gemini Bio-Products). Cells were dosed with appropriate dilution of ATRA or Am 580, **1, 2** in ethanol or ethanol alone for 18 hours after which they were rinsed in PBS, then lysed and harvested in 0.1 M $K_3PO_4$ (pH 7.8), 1.0% Triton X-100, 1.0 mM DTT, 2 mM EDTA. Luciferase activity was measured as previously described (de Wet et al. 1987) using firefly luciferin (Analytical Luminescence Laboratory) and an EG&G Berthold 96-well plate luminometer. Luciferase values represent the mean ± SEM of triplicate determinations.

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