Supporting Information

Synthesis, Structure–Activity Relationships, and Characterization of Novel Nonsteroidal and Selective Androgen Receptor Modulators

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Chemistry

Experimental Section

All procedures were carried out under a nitrogen atmosphere unless otherwise indicated using anhydrous solvents purchased from commercial sources without further purification. The microwave-assisted reactions were carried out using a *SmithCreator*™ or *Initiator 60EXP*™ single mode cavity; producing continuous irradiation at 2450 MHz. Reaction temperatures and pressures were determined using the build in, on-line IR- and pressure sensors. Thin layer chromatography (TLC) was performed on precoated Merck Silica gel 60 F_{254}, which was visualized by UV light or by staining with a solution of $KMnO_4$ (1%) and Na_2CO_3 (5%). Flash chromatography was performed using SiO_2 60 (0.040-0.063 mm). All ^1H and ^{13}C-NMR spectra were recorded using a Varian XL 400MHz spectrometer. NMR spectra were recorded in CD_3OD, $CDCl_3$ or DMSO-d_6; chemical shifts are given in ppm relative to CH_3OH (^1H, 3.31 ppm; ^{13}C, 49.00±0.01 ppm), $CHCl_3$ (^1H, 7.26 ppm; ^{13}C, 77.16±0.06 ppm) or DMSO (^1H, 2.50 ppm; ^{13}C, 39.52±0.06 ppm), respectively. Liquid chromatography/mass spectroscopy was performed on a Waters/Micromass ZQ2000 LC/MS instrument consisting of a ZQ single quadropole mass spectrometer equipped with an electrospray ionization interface, and a Waters Alliance HT with a 2795 Separation Module and 996 Photodiode Array Detector (PDA). HPLC Method: *Mobile Phase:* A: 10mM NH_4OAc H_2O; B: 10mM NH_4OAc CH_3CN-H_2O (95:5). *Column:* Waters Xterra® MS C_{18} 3.5µm, 30x4.6mm ID with a guard column cartridge system. *Program:* 5 min. gradient starting at 30% B (initial hold for 0.5 min.), to 100% B, hold for 1.5 min., over 0.5 min. to 30% B, hold for 2.5 min. The flow rate was 1 mL/min. *PDA range:* 190-450nm. HRMS analyses were recorded in FAB(+) mode using direct inlet, at the University of Lund. Elemental analysis was determined on a "2400 CHN Elemental analyzer" by Perkin Elmer in the microanalytical laboratory of the Fakultät für Chemie, Universität Wien. The purity of compounds **1**-**14** are >98% based on HPLC analysis, and elemental analysis.

3-Bromo-2-chloro-6-fluorotoluene. 2-Chloro-6-fluorotoluene (5.00 g, 34.6 mmol) and iron (0.1 g, 0.17 mmol) were stirred at room temperature. Bromine (6.08 g, 38.1 mmol) was added slowly in 3 portions at 1 min intervals and the reaction was stirred for additional 15 min. Dichloromethane (50 mL) was added, the reaction mixture transferred to a separatory funnel and washed with a sodium thiosulphate solution (10%, 30 mL) until it was colorless. The layers were separated and the organic layer was washed with sat. sodium hydrogen carbonate (30 mL), dried over sodium sulfate, filtered and evaporated to give the title compound as a colorless oil (7.57 g, 98 %) containing 15% 3-bromo-5-chloro-2-fluorotoluene (determined by ^{1}H-NMR). The compound was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (dd, *J* = 5.5, 8.6 Hz, 1H), 7.07 (t, *J* = 8.6 Hz, 1H), 2.35 (d, *J* = 2.3 Hz, 3H). GCMS *m/z* 222 $[M+H]^+$.

2-Chloro-4-fluoro-3-methylbenzonitrile. 3-Bromo-2-chloro-6-fluorotoluene (173 mg, 0.78 mmol), zinc cyanide (91 mg, 0.78 mmol) and tetrakis(triphenylphosphine)palladium(0) (27 mg, 23 μmol) were charged into a vial, DMF (1 mL) was added, and the mixture was irradiated for 150 sec at 200 °C in a microwave oven. Diethyl ether (30 mL) was added and the reaction mixture washed with magnesium sulphate (4% solution, 3 x 20 mL) and brine (20 mL). The organic layer was dried over sodium sulfate, filtered and evaporated. The product was further purified by column chromatography on silica gel eluting with *n*-heptane/ethyl acetate (9:1) to give the title compound (55 mg, 42 %) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (dd, *J* = 5.6, 8.8 Hz, 1H), 6.87 (t, *J* = 8.8 Hz, 1H), 2.36 (d, *J* = 2.4 Hz, 3H). GCMS *m/z* 169 $[M+H]^+$.

2-Chloro-4-(3-*endo*-hydroxy-3-*exo*-methyl-8-aza-bicyclo[3.2.1]oct-8-yl)-3-methylbenzonitrile; hydrochloride (1). 2-Chloro-4-fluoro-3-methylbenzonitrile (2.48 g, 14.6 mmol), *endo*-3-*exo*-methyl-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (**15**) (3.37 g, 19.0 mmol), and K_2CO_3 (6.67 g, 48.2 mmol) were dissolved in dimethyl sulfoxide (40 mL), and the mixture stirred under argon at 80 °C for 18 hours. The reaction mixture was poured into water (200 mL) and stirred for 30 min. The off-white solid was filtered off and recrystallized twice from toluene, giving a white powder (1.53 g). The mother liquor was

evaporated and the residue recrystallized to yield a second batch of compound (210 mg), giving an overall yield of 40 %. The hydrochloride salt was prepared by dissolving the product in diethyl ether and adding HCl (1 equiv, 4 M solution in 1,4-dioxane). The mixture was allowed to stir for 15 min and the precipitated salt was filtered off, washed with diethyl ether and dried. The title compound was obtained as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, *J* = 8.6 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 3.82 (m, 2H), 2.36 (s, 3H), 2.32–2.22 (m, 2H), 2.17–1.98 (m, 2H), 1.92–1.77 (m, 4H), 1.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.8, 138.4, 132.0, 129.7, 117.9, 115.5, 105.1, 69.6, 59.3, 45.9, 34.7, 27.4, 17.9. LCMS *m/z* 291 $[M+H]^+$. Anal. ($C_{16}H_{19}ClN_2O$): C, H, N.

4-(3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (2). 1-Cyano-4-fluoronaphthalene (104 mg, 0.6 mmol), nortropanol (305 mg, 2.4 mmol) and pyridine (93 mL, 0.6 mmol) were added to a Pyrex tube. The tube was capped and the reaction tube was exposed to microwave irradiation (220°C, 5 min). The mixture was transferred to a separation funnel with ethyl acetate and with 2M HCl, the layers separated, and the organic phase was then washed with brine. The organic layer was collected, dried over Na_2SO_4, filtered and concentrated to yield the title compound (157 mg, 92%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21-8.16 (m, 2H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.66-7.62 (m, 1H), 7.56-7.52 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 4.32 (t, *J* = 5.1 Hz, 1H), 4.14-4.11 (m, 2H), 2.51-2.45 (m, 2H), 2.34-2.28 (m, 2H), 2.02-1.96 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.0, 134.4, 133.6, 128.3, 127.8, 126.0, 125.8, 125.4, 119.0, 110.9, 102.0, 65.2, 60.0 (2C), 40.7 (2C), 27.3 (2C). LCMS *m/z* 279 $[M+H]^+$. Anal. ($C_{18}H_{18}N_2O$) C, H, N.

1-(4-nitronaphthalen-1-yl)pyrrolidine (3). Commercially available, LCMS purity (>98%).

4-Pyrrolidin-1-ylnaphthalene-1-carbonitrile (4). 1-Cyano-4-fluoronaphthalene (2.0 g, 11.7 mmol) was added to pyrrolidine (4.0 mL) and the reaction mixture stirred for 15 min during which the crude product precipitated out. The reaction mixture was concentrated under reduced pressure and the solid was recrystallized in methanol and the crystals washed with ethanol and dried to afford the title compound (1.6 g, 62%) as a pale yellow solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.38-8.35 (m, 1H), 8.05-

8.02 (m, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.64-7.60 (m, 1H), 7.51-7.45 (m, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 3.65-3.61 (m, 4H), 2.07-2.03 (m, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 151.5, 134.3, 134.1, 128.4, 126.5, 124.6, 124.5, 124.4, 119.6, 107.6, 95.7, 52.7 (2C), 25.6 (2C). LCMS *m/z* 223 $[M+H]^+$. Anal. ($C_{15}H_{14}N_2$) C, H, N.

4-(3-Oxo-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (5). A solution of **2** (647 mg, 2.32 mmol) in dry dichloromethane (7 mL) was added dropwise to a cold reaction mixture, prepared as follows: A solution of oxalyl chloride (440 mL, 5.11 mmol) in anhydrous dichloromethane (3 mL) was added dropwise to a cold solution of dry dimethylsulfoxide (726 mL, 10.22 mmol) in dichloromethane (5 mL) at –60 °C under argon atmosphere. The mixture was allowed to warm up to -40°C over 50 min. Afterwards the mixture was cooled to -60 °C and triethylamine (1.90 mL, 13.92 mmol) was added dropwise. The mixture was allowed to warm up slowly to rt and stirring was continued overnight at rt. The mixture was partitioned between dichloromethane and water. The organic layer was dried over sodium sulphate, filtered and evaporated to dryness. Purification of the residue by flash chromatography on silica gel, eluting with a mixture of ethyl acetate and *n*-heptane (1:1), afforded the desired compound (0.55 g, 86%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27-8.21 (m, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.68 (m, 1H), 7.61 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 4.39 (m, 2H), 3.03 (m, 2H), 2.53 (m, 2H), 2.20 (m, 2H), 1.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.1, 151.8, 134,2. 133.4, 128.3, 127.8, 126.0, 125.8, 125.4, 119.2, 110.9, 102.0, 60.0, 49.7 , 28.3. LCMS *m/z* 277 $[M+H]^+$. Anal. ($C_{18}H_{16}N_2O$).

4-(8-Azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (6). To a mixture of ketone **5** (500 mg, 1.81 mmol) in absolute ethanol (6 mL) was added *p*-toluenesulfonylhydrazine (405 mg, 2.17 mmol) and the reaction mixture was refluxed under stirring for 1 h. The mixture was then cooled to ambient temperature, the precipitated white solid was filtered, washed with absolute ethanol and dried to yield *N'*-((1R,5S)-8-(4-cyanonaphthalen-1-yl)-8-azabicyclo[3.2.1]octan-3-ylidene)-4-methylbenzenesulfonohydrazide (738 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.258-8.156 (m, 2H), 7.88 (d, J = 8.3, 2H), 7.77 (d, J = 8.0, 1H), 7.73-7.63 (m, 1H), 7.63-7.53 (m, 1H), 7.35 (d, *J* = 8.0 Hz,

2H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.32-4.19 (m, 2H), 3.01-2.88 (m, 1H), 2.82-2.69 (m, 1H), 2.69-2.49 (m, 2H), 2.46 (s, 3H), 2.11.1.96 (m, 2H9, 1.79-1.66 (m, 1H), 1.62-1.48 (m, 1H). To a solution of *N'*-((1R,5S)-8-(4-cyanonaphthalen-1-yl)-8-azabicyclo[3.2.1]octan-3-ylidene)-4-methylbenzenesulfonohydrazide (400 mg, 0.90 mmol) in DMF/sulfolane (1:1, 5.0 mL) and cyclohexane (5.0 mL) was added sodium cyanoborohydride (226 mg, 3.60 mmol) and *p*-toluenesulfononic acid monohydrate (45 mg, 0.24 mmol), and the reaction mixture was stirred at 110 °C for 7 h. The reaction mixture was diluted with water and extracted three times with cyclohexane. The cyclohexane solution was washed twice with water, dried over Na_2SO_4, filtered and evaporated to give a crude product, which was purified by flash chromatography on silica gel using heptane/ethyl acetate (8:2) as the eluent, to give the title compound (94 mg, 40%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.28 (d, *J* = 8.3 Hz, 1H), 8.18 (d, *J* = 8.9 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.71-7.61 (m, 1H), 7.61-7.51 (m, 1H), 6.90 (d, *J* =8.1 Hz, 1H), 4.28-4.02 (m, 2H), 2.28-1.92 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.6, 134.7, 133.9, 128.5, 128.0, 126.1, 126.0, 125.9, 119.4, 111.0, 101.9, 61.6, 32.6, 27.5, 17.5. LCMS *m/z* 263 $[M+H]^+$. Anal. ($C_{18}H_{18}N_2$) C, H, N.

4-(*endo*-3-Methoxy-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (7). Sodium hydride (50% suspension in an mineral oil, 10 mg, 0.21 mmol) was added to solution of compound **2** (50 mg, 0.18 mmol) at ambient temperature in DMF (4 mL). After stirring for 15 minutes at ambient temperature a solution of methyl iodide (22 mL, 0.36 mmol) in DMF was added to the mixture and stirring was continued overnight at 60 °C. The mixture was allowed to cool down to ambient temperature and partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica, ethyl acetate and *n*-heptane (50:50), affording the desired compound (4.4 mg, 8%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20-8.15 (m, 2H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.65-7.60 (m, 1H), 7.54-7.50 (m, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.08 (m, 2H), 3.64 (t, *J* = 5.0 Hz, 1H), 3.33 (s, 3H), 2.32-2.27 (m, 2H), 2.18-2.09 (m, 4H), 1.95-1.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 134.2, 133.4, 128.1, 127.6, 125.7, 125.6,

125.2, 118.9, 110.6, 101.6, 74.3, 59.9, 56.4 (2C), 36.5 (2C), 27.0 (2C). LCMS *m/z* 293 $[M+H]^+$. Anal. ($C_{19}H_{20}N_2O$) C, H, N.

4-(3-*exo*-Hydroxy-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (8). Diisopropylazadicarboxylate (1.62 g, 8.01 mmol) was added at 0 °C over 10 min to a solution of tropanol **2** (0.56 g, 2.00 mmol), triphenylphosphine (2.10 g, 8.00 mmol) and 4-nitrobenzoic acid (1.34 g, 8.02 mmol) in tetrahydrofuran (15 mL) under argon atmosphere. The reaction was stirred overnight at rt, then for additional 3 h at 40 °C before partitioning the mixture between diethylether (150 mL) and sat. aq. sodium bicarbonate solution (150 mL). The aqueous phase was extracted with diethylether (100 mL), *n*-heptane (300 mL) was added to the combined ether extracts and the resulting solution was passed through a pad of silica. The title compound crystallized upon standing as long yellow needles which were collected by filtration and dried under reduced pressure to afford 8-(4-cyanonaphthalen-1-yl)-3-*exo*-8-azabicyclo[3.2.1]octan-3-yl 4-nitrobenzoate (435 mg, 50%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35-8.25 (m, 6H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.70-7.55 (m, 2H), 6.82 (d, *J* = 7.5 Hz, 1H), 5.53 (m, 1H), 4.12 (br s, 2H), 2.42-1.88 (m, 8H). 8-(4-cyanonaphthalen-1-yl)-3-*exo*-8-azabicyclo[3.2.1]octan-3-yl 4-nitrobenzoate (280 mg, 0.65 mmol), lithium hydroxide (2 M, 30 mL) and THF (30 mL) were stirred overnight at rt, the mixture extracted with dichloromethane (3 x 100 mL), and the combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0-50% ethyl acetate in *n*-heptane, to give the title compound (162 mg, 89%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28-8.16 (m, 2H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.71-7.53 (m, 2H), 6.82 (d, *J* = 8.1, 1H), 4.21 (m, 3H), 2.22-1.79 (m, 6H), 1.38-0.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5, 134.4, 134.0, 128.4, 128.0, 126.5, 126.0, 125.6, 119.0, 110.8, 102.0, 65.2, 60.1, 42.0, 27.8. LCMS *m/z* 279 $[M+H]^+$. Anal. ($C_{18}H_{18}N_2O$) C, H, N.

General procedure (GP) for compounds **9a**-**9g**: In a flame-dried Schlenk flask under argon atmosphere was placed a $CeCl_3$*2LiCl solution in anhydrous THF (ca. 0.6 M, 1.0 mL, 0.6 mmol). Ketone **5** (0.50 mmol) was added neat, and the resulting mixture stirred for 1 h at rt. The reaction mixture was cooled to 0 ^oC, Grignard reagent (0.6 mmol) was added dropwise, and the reaction mixture was allowed to stir at the same temperature. Upon full conversion of starting material (checked by TLC and/or analytical HPLC/MS), saturated ammonium chloride (1.0 mL) and ethyl acetate (2.0 mL) were added. The aqueous layer was extracted with more ethyl acetate (2 x 10 mL) and the combined extracts were dried over sodium sulfate, filtered and concentrated to dryness. The residues were purified by column chromatography on silica gel to give pure products.

4-(3-*endo*-Hydroxy-3-*exo*-methyl 8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (9a). The title compound was prepared according to GP from 4-(3-oxo-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (**5**) (138 mg, 0.50 mmol) and methylmagnesium bromide (3.0 M in diethylether, 0.2 mL, 0.6 mmol). The crude product was purified by preparative TLC (DCM/EtOAc 3:1, 2 runs) to yield the title compound (42 mg, 29%) as a colorless solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.66-7.59 (m, 1H), 7.56-7.49 (m, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 4.17-4.08 (m, 2H), 2.35-2.23 (m, 4H), 2.02-1.88 (m, 4H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.0, 134.6, 133.8, 128.5, 128.0, 126.2, 126.1, 125.6, 119.3, 111.2, 102.2, 69.9, 60.6, 46.2, 34.7, 26.9. LCMS *m/z* 293 $[M+H]^+$. Anal. ($C_{19}H_{20}N_2O$) C, H, N.

4-(3-*endo*-Hydroxy-3-*exo*-ethyl 8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (9b). The title compound was prepared according to GP from 4-(3-oxo-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (**5**) (38 mg, 0.5 mmol) and ethylmagnesium bromide (3.0 M in diethylether, 0.2 mL, 0.6 mmol) and purified by reverse phase preparative HPLC to yield the title compound (96 mg, 63%) as a pale yellow solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.16 (dd, *J* = 1.1, 8.6 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.65–7.59 (m, 1H), 7.56–7.49 (m, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 4.17-4.11 (m, 2H), 2.34–2.25 (m, 2H), 2.22 (dd, *J* = 3.6, 14.3 Hz, 2H), 1.99–1.90 (m, 2H), 1.89-1.83 (m, 2H), 1.54 (q, *J* = 7.5 Hz, 2H), 1.17 (s, 1H, OH), 0.97 (t, *J* = 7.5, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8, 134.2, 133.4, 128.1, 127.6, 125.8,

125.6, 125.2, 118.9, 110.7, 101.6, 71.1, 60.1, 44.2, 39.1, 26.7, 7.1. LCMS *m/z* 307 $[M+H]^+$. Anal. ($C_{20}H_{22}N_2O$) C, H, H.

4-(3-*endo*-Hydroxy-3-*exo*-vinyl 8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (9c). The title compound was prepared according to GP from 4-(3-oxo-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (**5**) (138 mg, 0.50 mmol) and vinylmagnesium bromide (1.0 M in THF, 0.6 mL, 0.6 mmol). Purification by reverse phase preparative HPLC yielded the title compound (48 mg, 32%) as a pale yellow powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19-8.14 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.64–7.59 (m, 1H), 7.55-7.51 (m, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 5.98 (dd, *J* = 10.6 Hz, 17.2, 1H), 5.30 (dd, *J* = 0.6, 17.2 Hz, 1H), 5.07 (dd, *J* = 0.5, 10.6 Hz, 1H), 4.18-4.13 (m, 2H), 2.42-2.33 (m, 4H), 2.02–1.91 (m, 2H), 1.84 (d, *J* = 14.0 Hz, 2H), 1.44 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8, 147.7, 134.3, 133.6, 128.3, 127.7, 126.0, 125.8, 125.3, 119.0, 111.2, 110.8, 101.9, 71.8, 60.1, 44.6, 26.8. LCMS *m/z* 305 $[M+H]^+$. Anal. ($C_{20}H_{20}N_2O$) C, H, N.

4-(3-*exo*-Ethynyl-3-*endo*-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (9d). The title compound was prepared according to GP from 4-(3-oxo-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (**5**) (138 mg, 0.50 mmol) and ethynyl magnesium bromide (0.5 M in THF, 1.2 mL, 0.60 mmol). Purification by reverse phase preparative HPLC afforded the title compound (89 mg, 59%) as a colorless solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.99 (dd, *J* = 0.8, 8.3 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.72 (ddd, *J* = 1.2, 6.9, 8.2 Hz, 1H), 7.63 (ddd, *J* = 1.3, 6.9, 8.3 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 5.45 (s, 1H), 4.12-4.07 (m, 2H), 2.40 (dd, *J* = 3.3, 14.2 Hz, 2H), 2.21–2.11 (m, 4H), 1.83-1.76 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.7, 134.4, 133.8, 129.1, 127.2, 126.7, 125.8, 125.1, 118.9, 111.6, 100.6, 91.2, 72.1, 64.4, 59.8, 45.7, 26.6. LCMS *m/z* 303 $[M+H]^+$. Anal. ($C_{20}H_{18}N_2O$) C, H, N.

4-(3-*endo*-Hydroxy-3-*exo*-cyclopropyl 8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (9e). The title compound was prepared according to GP from 4-(3-oxo-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (**5**) (138 mg, 0.50 mmol) and cyclopropylmagnesium bromide (0.5 M in THF, 1.2 mL, 0.60 mmol). Purification by reverse phase preparative HPLC yielded the title compound

(39 mg, 25%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19–8.14 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.63 (ddd, *J* = 1.2, 6.9, 8.4 Hz, 1H), 7.57–7.50 (m, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 4.17-4.12 (m, 2H), 2.31-2.22 (m, 4H), 1.98-1.91 (m, 2H), 1.80 (dd, J = 1.8, 15.7, 2H), 1.02-0.95 (m, 2H), 0.46–0.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 134.4, 133.6, 128.3, 127.7, 125.9, 125.8, 125.4, 119.1, 110.8, 101.8, 70.0, 60.1, 44.1, 26.9, 24.7, 0.15. LCMS *m/z* 319 $[M+H]^+$. Anal. ($C_{21}H_{22}N_2O$) C, H, N.

4-(3-*endo*-Hydroxy-3-*exo*-isopropyl 8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (9f). The title compound was prepared according to GP from 4-(3-oxo-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (**5**) (138 mg, 0.50 mmol) and isopropylmagnesium chloride (2.0 M in THF, 0.3 mL, 0.6 mmol). The crude mixture was purified by reverse phase preparative HPLC to yield the title compound (44 mg, 28%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.66–7.59 (m, 1H), 7.57–7.50 (m, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 4.18-4.13 (m, 2H), 2.31–2.17 (m, 4H), 1.99–1.90 (m, 2H), 1.86 (d, *J* = 13.8 Hz, 2H), 1.59 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 134.4, 133.6, 128.2, 127.7, 125.9, 125.8, 125.3, 119.1, 110.9, 101.7, 72.7, 60.2, 43.4, 40.9, 26.9, 16.2. LCMS *m/z* 321 [M+H]+. Anal. ($C_{21}H_{24}N_2O$) C, H, N.

4-(3-*endo*-Hydroxy-3-*exo*-*n*-propyl-8-azabicyclo[3.2.1.]oct-8-yl)naphthalene-1-carbonitrile (9g). The title compound was prepared according to GP from 4-(3-oxo-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (**5**) (138 mg, 0.50 mmol) and *n*-propylmagnesium chloride (2.0 M in diethylether, 0.3 mL, 0.6 mmol). Purification by reverse phase preparative HPLC yielded the title compound (38 mg, 23%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.66-7.59 (m, 1H), 7.56-7.50 (m, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 4.17-4.09 (m, 2H), 2.35–2.18 (m, 4H), 2.02–1.91 (m, 2H), 1.87 (d, J = 13.8, 2H), 1.55–1.37 (m, 4H), 1.11 (s, 1H), 0.97 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 134.4, 133.6, 128.3, 127.8, 125.9, 125.8, 125.4, 119.1, 110.9, 101.8, 71.3, 60.2, 49.4, 44.8, 26.8, 16.2, 14.7. LCMS *m/z* 321 $[M+H]^+$. HRMS (Ion Mode: FAB^+) Calcd, $C_{21}H_{25}N_2O$ (M+H): 321.1967; found: 321.1974.

4-(*endo*-spiro[8-Azabicyclo[3.2.1]octane-3,2'-oxiran]-8-yl)naphthalene-1-carbonitrile (10). Trimethylsulfoxonium iodide (359 mg, 1.63 mmol) was added to a suspension of sodium hydride (55%, 71 mg, 1.63 mmol) in dry DMSO (1.5 mL) at rt under argon atmosphere. After stirring at rt for 1 h, a solution of 4-(-3-oxo-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (**5**) (300 mg, 1.08 mmol) in DMSO (4.0 mL) was added to the reaction mixture at rt and the stirring was continued overnight at rt. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with 4% (w/v) aqueous magnesium sulfate, dried over sodium sulfate, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (30-45% ethyl acetate in *n*-heptane) affording the title compound (194 mg, 61%) as a colorless solid. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.71-7.62 (m, 1H), 7.61-7.52 (m, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 4.33-4.16 (m, 2H), 2.85-2.71 (m, 2H), 2.58 (s, 2H), 2.36-2.17 (m, 2H), 2.15-1.97 (m, 2H) 1.55-1.41 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 134.6, 133.8, 128.6, 128.1, 126.5, 126.1, 125.5, 119.2, 111.6, 102.7, 61.0, 55.1, 48.7, 40.9, 27.3. LCMS *m/z* 291 $[M+H]^+$. Anal. ($C_{19}H_{18}N_2O$) C, H, N.

4-(3-*endo*-Hydroxy-3-*exo*-hydroxymethyl-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (11). Aqueous sulfuric acid (0.2 M, 2.5 mL) was added dropwise to a solution of compound **10** (60 mg, 0.21 mmol) in THF (2.5 mL) at rt. After stirring for 3 h at rt, the reaction mixture was neutralized with saturated sodium bicarbonate. The solvent was evaporated and the residue passed over an acidic ion-exchange SPE cartridge. The obtained product was purified by flash chromatography using ethyl acetate as eluent to yield the title compound (20 mg, 31%) as colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (d, *J* = 8.0 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.73-7.60 (m, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 4.31-4.20 (m, 2H), 3.61 (s, 2H), 2.59-2.48 (m, 2H), 2.20-1.69 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.0, 134.1, 133.4, 128.3, 127.8, 126.0, 125.8, 125.4, 118.7, 110.9, 103.4, 70.3, 65.2, 58.4, 42.1, 28.3. LCMS *m/z* 309 $[M+H]^+$. HRMS (Ion Mode: FAB^+) Calcd, for $C_{19}H_{21}N_2O_2$ (M+H): 309.1603; found: 309.1605.

Trifluoromethanesulfonic acid 2,3-dimethyl-4-nitrophenyl ester. Trifluoromethanesulfonic anhydride (1.57 mL, 8.77 mmol) was added to 2,3-dimethyl-4-nitrophenol (1.12 g, 6.70 mmol) and triethylamine (2.5 mL, 17.9 mmol) in dichloromethane (40 mL) at 0 °C under argon atmosphere and the resulting mixture was allowed to stir overnight at rt. HCl (2 M, 50 mL) was added and the solution was extracted with dichloromethane (3 x 100 mL). The organic extracts were combined, washed with saturated aqueous sodium bicarbonate (100 mL), diluted with *n*-heptane (200 mL), and passed through a pad of silica gel to give the title compound (1.96 g, 98 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 1H), 2.48 (s, 3H), 2.41 (s, 3H). GCMS *m/z* 299 $[M]^+$.

***endo*-8-(2,3-Dimethyl-4-nitro-phenyl)-8-azabicyclo[3.2.1]octan-3-ol (12).** A mixture of trifluoromethanesulfonic acid 2,3-dimethyl-4-nitrophenyl ester (793 mg, 2.65 mmol), nortropine (1.01 g, 7.96 mmol), and pyridine (2.5 mL) were heated to 110 °C for 16 h. The crude material was cooled to rt, poured into water (200 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over sodium sulfate, concentrated under reduced pressure, and the residue purified by preparative TLC (ethyl acetate/*n*-heptane 1:8) to give the title compound (49.7 mg, 6.8 %) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, *J* = 9.0 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 1H), 4.25 (t, *J* = 4.5 Hz, 1H), 3.79 (br s, 2H), 2.47 (s, 3H), 2.49-2.25 (m, 4H) 2.32 (s, 3H), 1.98-1.85 (m, 4H). HRMS (Ion Mode: FAB^+) Calcd for $C_{15}H_{20}N_2O_2$ ($M+H^+$): 277.1552, found: 277.1536.

2-Chloro-4-(3-*endo*-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)benzonitrile (13). Nortropine (269 mg, 2.12 mmol) and 2-chloro-4-fluorobenzonitrile (100 mg, 0.643 mmol) were dissolved in pyridine (2 mL). The mixture was heated to 110 °C in a sealed flask for 20 h and then concentrated. The residue was dissolved in HCl (2 M, 20 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic phases were dried over sodium sulfate, filtered and evaporated, and the resulting oil was purified by preparative TLC (eluent: dichloromethane) to afford the title compound (107 mg, 63%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, *J* = 8.8 Hz, 1H), 6.70 (d, *J* = 2.3 Hz, 1H), 6.56 (dd, *J* = 2.4 Hz, 8.8, 1H), 4.33-4.14 (m, 2H), 4.13-3.97 (m, 1H), 2.48-2.29 (m, 2H), 2.22-1.94 (m, 4H), 1.83 – 1.66

(m, 2H), 1.64 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.8, 138.4, 135.2, 117.9, 114.3, 112.3, 98.3, 65.3, 53.7, 35.7, 28.2. LC/MS *m/z* 263 $[M+H]^+$. Anal. ($C_{14}H_{15}ClN_2O$) C, H, N.

2-Chloro-4-(3-*endo*-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-methylbenzonitrile (14). 2-Chloro-4-fluoro-3-methylbenzonitrile (55 mg, 0.32 mmol) and nortropine (165 mg, 1.29 mmol) were dissolved in pyridine (2 mL) and the mixture irradiated at 220°C for 2 hours in a microwave oven. The reaction was allowed to cool to ambient temperature, dichloromethane (50 mL) was added and the mixture washed with hydrochloric acid (0.4 M, 2 x 30 mL) followed by sat. sodium hydrogen carbonate (20 mL). The organic layer was dried over sodium sulfate, filtered and evaporated. The product was further purified by column chromatography eluting with dichloromethane to give the title compound (16.2 mg, 18 %) as colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 4.20 (m, 1H), 3.80 (m, 2H), 2.37 (s, 3H), 2.32-2.22 (m, 4H), 1.98-1.81 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.8, 138.4, 131.8, 129.9, 117.0, 115.9, 105.0, 67.6, 61.3, 41.9, 27.4, 18.5. LCMS *m/z* 277 $[M+H]^+$. HRMS (Ion Mode: FAB^+) Calcd for $C_{15}H_{18}ClN_2O$ (M+H): 277.1108, found: 277.1096.

3-*endo*-Hydroxy-3-*exo*-methyl-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester. Trimethylsulfoxonium iodide (7.33 g, 33.3 mmol) was slowly added to a suspension of sodium hydride (55-65% dispersion in mineral oil, 1.45 g, 33.3 mmol) in DMSO (20 mL) and the reaction mixture was stirred for 1 h. A solution of *N*-Boc-tropinone (5.0 g, 22.2 mmol) was added and the mixture was stirred at rt for 20 h. The mixture was partitioned between ethyl acetate and water, the organic layer was dried over magnesium sulfate, filtered and evaporated, affording the crude title compound, which was used in the next step without further purification. To a solution of the crude oxirane product (5.3 g, 22.2 mmol) in dry THF (10 mL) under cooling with a water bath, Super-Hydride® (1.0 M THF solution, 29.0 mmol, 29.0 mL) was added, and the reaction mixture was stirred at rt. After 1 h the mixture was cooled again (ice bath), slowly quenched with water (10 mL), the aqueous phase was saturated with K_2CO_3, and the reaction mixture was extracted with diethylether. The organic phase was dried over sodium sulfate, filtered and evaporated to give the crude product which was taken up in ethyl acetate (200 mL) and filtered through a silica pad to give the title compound as a colorless oil (4.11 g, 77%). ^{1}H NMR

($CDCl_3$, 400 MHz) 4.19 (m, 2H), 2.18-2.12 (m, 2H), 1.95-1.89 (m, 4H), 1.66 (d, *J* = 14.3 Hz, 2H), 1.46 (s, 9H), 1.17 (s, 3H). GCMS *m/z* 241.

***endo*-3-*exo*-Methyl-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (15).** 4 M HCl solution in dioxane (40 mL) was added to solution of 3-*endo*-hydroxy-3-*exo*-methyl-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (3.81 g, 15.8 mmol) in diethylether (40 mL). The reaction mixture was stirred for 2 h, then evaporated to give a white solid, which was filtered, washed with *n*-heptane (70 mL), and dried to give the title compound as a colorless solid (2.17 g, 77%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.87 (br s, 2H), 2.27 (d, J = 7.3, 2H), 2.00 (dd, *J* = 14.9, 3.2 Hz, 2H), 1.87-1.83 (m, 2H), 1.74 (d, *J* = 14.6 Hz, 2H), 1.07 (s, 3H).

Biology

Materials and methods

Constructs

The sequence encoding the wild-type human AR (Genbank NM 000044) was cloned by PCR into a modified PSI vector (Promega). The mutant T877A was generated by site-directed mutagenesis of the wild type human AR using the commercially available kit QuickChange according to manufacturer's instructions (Stratagene). The sequences of the oligonucleotides were as follows:
5_ T877A CATCAGTTCGCTTTTGACCTGCTAATCAAG,
3_ T877A CAGGTCAAAAGCGAACTGATGCAGCTCTCT.
All mutants were confirmed by sequencing.

Reagents
DHT, testosterone and testosterone propionate (TP) were purchased from Sigma.

R-SAT assays
Receptor selection and amplification technology (R-SAT) is a functional cell-based assay that allows one to monitor receptor-dependent proliferative responses of various receptor classes including nuclear receptors. Its principle resides in the genetic selection and amplification of nuclear receptors in a ligand-dependent manner. This process is achieved by partial cellular transformation via loss of contact inhibition and growth factor dependency. Monitoring is achieved by transfecting the cells with a β-galactosidase reporter gene vector whose expression is under a constitutively active promoter. Briefly, mouse NIH-3T3 fibroblasts were plated overnight in 96-well plates in DMEM 10% calf serum (Hyclone) and grown to 60–70% confluency prior to transfection. Transient transfections were performed using Polyfect (Qiagen) according to manufacturer's instructions. Typically a transfection mix would consist of expression vectors encoding the androgen receptor (200 ng), β-galactosidase (500 ng) and the co-activators SRC1, DRIP205 and GRIP1 (10 ng each). Such a transfection mix would be sufficient to transfect 30 96-wells. Sixteen hours posttransfection, cells were incubated with different doses of ligand in DMEM containing 30% ultraculture (Hyclone) and 0.4% calf serum (Hyclone) to generate a dose–response curve. After 5 days, plates were developed by adding onto the washed cells a solution containing the β-galactosidase substrate *o*-nitrophenyl β-galactose (ONPG) (in phosphate-buffered saline with 5% Nonidet P-40 detergent). Plates were read using a microplate reader at 420 nm. Data from R-SAT assays were fit to the equation: $r = A + B(x/(x + c))$, where A = minimum response, B = maximum response minus minimum response, c = EC50, r = response, and x = concentration of ligand. Curves were generated using the curve fitting softwares Excel Fit and GraphPad Prism (San Diego, CA).

Luciferase reporter gene assays
Human breast carcinoma MDA-kb2 cells (which are stably transfected with the mouse mammary tumor virus (MMTV) promoter linked to luciferase, and express endogeneous AR) were grown in DMEM charcoal-stripped 10% FBS (Gibco BRL), plated at 10,000 cells per 96-well (100 µl/well) onto luciferase assay plates. The day after plating, the medium was replaced with fresh one and varying concentrations of ligand. After 24 h, the media was removed from plates and cell extracts were then lyzed and luciferase activity measured using a commercially available kit (Promega).

Binding assays
Hamster DDT cells were grown in DMEM 5% charcoalstripped FBS in presence of 10nM testosterone. Cells were plated at 25,000 cells/well in a 24-well plate (500 µl/well) and grown to 80% confluency

(typically 3 days). At that stage, the media was replaced and 3H-DHT added to a final concentration of 2 nM, along with varying concentrations of the test ligands. Cells were incubated for an additional 24-h period. Cells were then washed multiple times with ice-cold HBSS (Hank's balanced salt solution) then resuspended in 100% ethanol (100µl/well). Plates were then sealed and shaken for 6 h. Extracts were then quantified in a Beckman scintillation counter.

Anabolic and androgenic study using Osmotic pumps

Male rats were orchidoepididyectomized by vendor on Day 36 of age and shipped for experimentation on Day 41 of age. At approximately Day 50 of age, animals were surgically implanted with a subcutaneous osmotic mini pump, inserted between the scapula with the flow moderator away from the incision site. Twenty-four hours prior to implantation, animals were weighed and alzet osmotic pumps (Model 2ML2, Durect Corporation) prepared. The pumps were loaded with compound (concentration based upon group average animal body weight), placed into a sterile water bath (set at 37ºC) and allowed to prime the length of the dosing flow moderator. Test material was formulated in 100% Propylene Glycol and prepared at concentrations of 1.41 and 5.63 mg/mL. Dose delivery volume was 5µL/hr. Blood specimens were collected via lateral tail vein at specific timepoints, post implant (T=2, 4, 24, 48, 72, 168 and 336 hr) to verify the compound concentrations in the plasma. The blood was collected with sodium heparin (15 µL/mL whole blood) and centrifuge (2000 x g for 6 min). Additionally, blood specimens were collected at T=168 and 336 hr post implant, allowed to clot and processed for plasma. Both plasma and serum specimens were transferred into eppendorph tubes and stored at -80°C.

The purpose of the bioanalytical part of this study was to determine the plasma concentrations over 14 days of **1** and testosterone propionate (**TP)**. The test compound **1** was administered at three doses 0.3, 1.0 and 3.0 mg/pk/day via osmotic pump. TP was dosed at 0.75 mg/pk/day. Rat plasma was collected four times during the study: day1, 6, 9 and 13. The concentrations of **1**, increased with the increasing dose; however, the increase in exposure was not proportional to the plasma concentration.

The plasma concentrations for each group are summarized in the following table.

Group Number (n=10)	Average (ng/mL)	Stdev
TP (0.75 mg/pk/day)	1.3	.3
1 (0.3 mg/pk/day)	10.9	1.4
1 (1.0 mg/pk/day)	16.0	3.3
1 (3.0 mg/pk/day)	29.2	7.7

Data analysis

The *in vitro* data (i.e. R-SAT and luciferase) was normalized to the response seen with DHT. Specifically, the dose–response curve was used to define the 0% and 100% efficacy values: 0% was defined as the value determined by the bottom part of the agonist curve, whereas 100% was defined as the value represented by the top plateau of the curve. The animal data were analysed by one-way ANOVA, followed by an unpaired *t*-test. A *p*-value of <0.05 was required to achieve statistical significance. ED50s were determined relative to the effects seen with TP (1 mg/kg) defined as 100%. Data from the 2-week study were normalized to testosterone using the following definitions: the effects seen in castrated rats treated with vehicle were defined as 0%, while the effects seen in castrated rats treated with testosterone propionate (TP at 1 mg/kg) were defined as 100%.

Animals

All animal studies were conducted in accordance with the policies and recommendations of the National Institutes of Health guidelines for the handling and use of laboratory animals and received approval from the Institutional Animal Care and Use Committee of ACADIA Pharmaceuticals.

Two-week study in castrated rats

Male Sprague–Dawley rats (200–225 g) were either castrated or sham-operated and allowed to recover for 5 days. Thereafter, castrated animals (n = 8 per group) were treated once daily with vehicle, testosterone propionate (TP 1 mg/kg) or **1** (3, 10 and 30 mg/kg) administered subcutaneously or po for 14 consecutive days. Twenty-four hours following the last injection, animals were sacrificed. The plasma samples were then obtained and the organs harvested. The levator ani muscle, the prostate glands and the seminal vesicles were dissected free of adipose tissue, blotted dry and their respective weights determined. Plasma levels of luteinizing hormone (LH) were quantified using a commercially available ELISA kit according to manufacturer's instructions (Amersham).

PK studies in Rat and Dog for compound 1

Rat

	Plasma Concentrations (ng/mL)								
Rat	**Time (min)**								
	1	**10**	**30**	**60**	**120**	**240**	**360**	**480**	
IV (1 mg/Kg)	824.4	447.4	234.1	137.1	74.3	45.4	23.5	14.9	
PO (10 mg/Kg)	0.0	147.7	314.2	262.8	237.6	353.3	350.1	252.8	

Average of three rats in each group.

Mean Pharmacokinetic Parameters in Rats for 1

Route	AUC_{8h} (min∗ng/mL)		C_{max} (ng/mL)		$T_{½}$ (min)		Vss ($mLkg^{-1}$)		CL ($mLmin^{-1}Kg^{-1}$)	
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
IV	37836.8	2964.6	882.5	267.5	147.5	11.2	3907.6	834.7	24.4	1.3
PO	142046.9	12503.9	420.7	62.5	ND	ND	ND	ND	ND	ND

Bioavailability PO = 38%

Pharmacokinetic Parameters of **1** following single dose administration (Beagle dogs)

	Dose (mg/Kg)	C_{max} (ng/mL)	$AUC_{(0\text{-inf})}$ (ng∗hr/mL)	$T_{½}$ (hr)	CL ($mLmin^{-1}Kg^{-1}$)	Vss (Lkg^{-1})	F %
IV	1	357	394	2.1	42	6.1	
PO	10	835	2212				56

	Plasma Concentrations (ng/mL)								
Dog	**Time (hr)**								
	0.08	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**8**	**24**

IV (1 mg/Kg)	356.9	231.2	189.6	89.3	49.5	18.5	9.5	5.5	0.3
PO (10 mg/Kg)	ND	835.4	591.6	408.1	270.3	158.9	103.5	60.6	3.2