Experimental Section

General chemical procedures can be found in reference 12a.

4-Ethyl quinoline (5). To a flame-dried 500-mL r.b. flask containing lepidine (10.0 g, 69.8 mmol) in 130 mL anhydrous THF at -78 °C under argon was added lithium diisopropylamide (42 mL of a 2.0 M solution in THF, 84 mmol, 1.2 equiv) dropwise over 15 min. The reaction mixture was stirred for 2.5 h before the addition of iodomethane (5.4 mL, 84 mmol, 1.2 equiv) to the then brown colored suspension. The reaction mixture was stirred at -78 °C for 2 h and then allowed to warm to rt overnight. The reaction was then quenched with saturated NH_4Cl (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by distillation under reduced pressure to yield 10.1 g (91%) of the desired 4-ethylquinoline **5** as a colorless oil [bp 155-160 °C/ 15 mm (lit 134 °C/ 9 mm)]. ^1H NMR 8.80 (d, 1H, J = 4.5, 2-H), 8.10 (d, 1H, J = 8.5, 5-H), 8.04 (d, 1H, J = 8.0, 8-H), 7.70 (dd, 1H, J = 8.5, 8.0, 7-H), 7.58 (dd, 1H, J = 8.5, 8.5, 6-H), 7.25 (d, 1H, J = 4.5, 3-H), 3.12 (q, 2H, J = 7.5, CH_2CH_3), 1.40 (t, 3H, J = 7.5, CH_2CH_3).

4-Ethyl-1,2,3,4-tetrahydroquinoline (6). To a flame-dried 500-mL 3-necked r.b. flask containing 4-ethylquinoline **5** (9.00 g, 57.2 mmol) and $NiCl_2 \cdot 6H_2O$ (13.6 g 57.2 mmol, 1.00 equiv) in anhydrous MeOH (200 mL) cooled to -5 °C using an ice-salt bath was added sodium borohydride (8.65 g , 288 mmol, 5.03 equiv) in small portions over 1.5 h. The reaction mixture was then allowed to warm to rt and concentrated under reduced pressure. The dark residue was treated with 300 mL 1N HCl and filtered. The filtrate was then basified with conc. NH_4OH and extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford a dark oil, which was purified by bulb to bulb distillation (180 °C/ 4 mm) to yield 8.8 g (95%) of the 4-ethyl-1,2,3,4-

tetrahydroquinoline **6** as a colorless oil (Rf 0.40, hexanes / EtOAc, 2:1). ^{1}H NMR 7.02 (d, 1H, J = 7.6, 8-H), 6.96 (ddd, 1H, J = 7.7, 7.7, 1.3, 7-H), 6.61 (ddd, 1H, J = 8.2, 8.2, 1.0, 6-H), 6.47 (d, 1H, J = 7.9, 5-H), 3.83 (br s, 1H, CH_2NH), 3.31 (ddd, 1H, J = 11.3, 11.3, 3.6, 2-H), 3.25 (ddd, 1H, J = 9.7, 9.7, 4.8, 2-H), 2.65 (dddd, 1H, J = 10.1, 5.1, 5.1, 5.1, 4-H), 1.92 (dddd, 1H, J = 9.6, 4.7, 4.7, 4.7, 3-H), 1.82 (m, 1H, 3-H), 1.74 (m, 1H, CH_2CH_3), 0.98 (t, 3H, J = 7.4, CH_2CH_3). These spectral data were in agreement with the reported values for 4-ethyl-1,2,3,4-tetrahydroquinoline.

7-Amino-4-ethyl-1,2,3,4-tetrahydroquinoline (7). A 25-mL r.b. flask containing tetrahydroquinoline **6** (340 mg, 2.1 mmol) was cooled to -10 °C, and conc. H_2SO_4 (5 mL) was slowly added. The resulting solution was warmed to rt to effect complete dissolution of the quinoline, then cooled again to -10 °C and stirred vigorously. Fuming HNO_3 (85 µL) was slowly added dropwise, and the reaction mixture became dark red. After 10 min, the reaction mixture was poured onto cracked ice and diluted with water (5 mL). Saturated $NaHCO_3$ (80 mL) was added, and the pH was adjusted to pH 9 with 3.0 M NaOH. The aqueous mixture was extracted with EtOAc (3 x 75 mL), and the combined organic extracts were dried (Na_2SO_4), and concentrated under reduced pressure to yield a dark red oil. This crude material was placed into a 250-mL r.b. flask with 1:1 EtOAc / EtOH (40 mL) and 10% Pd on C (approx. 1 mol %). The vessel was evacuated and flushed with N_2 three times, then stirred under an atmosphere of H_2 for 16 h, filtered, and concentrated under reduced pressure to yield a yellow oil, which was purified by flash chromatography (silica gel, CH_2Cl_2 / methanol, 9:1), affording 210 mg (57 %) of the desired product as a dark yellow oil (Rf 0.50, CH_2Cl_2 / MeOH, 9:1). ^{1}H NMR 6.81 (d, 1H, J = 8.1, 5-H), 6.02 (dd, 1H, J = 8.0, 2.2, 6-H), 5.84 (d, 1H, J = 2.3, 8-H), 3.48 (s, 2H, NH_2), 3.27 (ddd, 1H, J = 11.1, 11.1, 3.5, 2-H), 3.20 (ddd, 1H, J = 9.8, 5.3, 4.5, 2-H), 2.55 (dddd, 1H, J = 10.2, 5.2, 5.2, 5.2, 4-H), 1.90 (dddd, 1H, J = 9.6, 9.6, 9.6,

4.7, 3-H), 1.72 (m, 2H, 3-H, CH_2CH_3), 1.48 (m, 1H, CH_2CH_3), 0.96 (t, 3H, J = 7.4, CH_2CH_3).

4-Ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (8). To a flame-dried 100-mL r.b. flask containing aminotetrahydroquinoline **7** (210 mg, 1.19 mmol) in ethanol (20 mL) at rt, was added ethyl-4,4,4-trifluoroacetoacetate (190 μL, 1.31 mmol, 1.10 equiv) and $ZnCl_2$ (244 mg, 1.79 mmol, 1.50 equiv). The reaction mixture was heated to reflux for 6 h, at which time TLC analysis indicated complete consumption of starting material. The reaction mixture was cooled to rt, and the solvent was removed under reduced pressure. Dichloromethane (20 mL) was added and the organic phase was washed with saturated $NaHCO_3$ (2 x 10 mL) and brine (1 x 10 mL), then dried (Na_2SO_4), and concentrated under reduced pressure. This crude product was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH, 15:1), affording 24.4 mg (82%) of the desired product as a yellow solid (Rf 0.37, CH_2Cl_2 / MeOH, 9:1). Recrystallization from EtOAc provided an analytically pure sample as yellow needles (mp 264-265 °C). ^{1}H NMR (CD_3OD) 7.31 (s, 1H, 5-H), 6.47 (s, 1H, 7-H), 6.37 (s, 1H, 10-H), 3.34 (m, 2H, 2-H), 2.70 (m, 1H, 4-H), 1.88 (m, 2H, 3-H), 1.62 (m, 2H, CH_2CH_3), 1.00 (t, 3H, J = 7.5, CH_2CH_3). ^{13}C NMR (CD_3OD) 164.3, 150.3, 141.7, 140.4 (q, J = 30.6), 125.6, 124.6, 124.5 (q, J = 274.5), 112.6 (q, J = 5.7), 106.2, 97.4, 39.1, 38.6, 29.3, 26.2, 11.8. IR (thin film) 3358 (br, m), 2970 (m), 1664 (s), 1281 (br, s), 1124 (s). Anal. Calcd for $C_{15}H_{15}F_3N_2O$: C, H, N.

Biological Methods.

Cotransfection and Receptor Binding Assays. These in vitro assays were performed as previously described in reference 12a.

Two-week LH Suppression Assay in Rats. Mature male Sprague-Dawley rats (6-7 weeks old) were obtained from Harlan and castrated via the scrotal route under

isoflurane anesthesia. Two weeks after castration, the animals were divided into groups (four rats/group) and treated daily for two weeks with one of the following: (1) control vehicle (10% polyethylene glycol and 0.05% Tween-80 in 1% carboxymethyl cellulose, PEG/CMC, orally); (2) testosterone propionate (TP, 1 mg/kg, subcutaneous injection in sesame oil); (3) Compound **8** (20 mg/kg in PEG/CMC formulation, orally). The fourth group of animals were kept as intact control without surgery and treated with vehicle as with group 1. The animals were sacrificed 24 hours after the last treatment. The serum samples were collected for measuring luteinizing hormone (LH) by RIA with a kit purchased from Amersham using NIH standards (NIADDK-rat-LH-RP2).