4-Hydroxy-1-[2-(4-hydroxyphenoxy)ethyl]-4-(4-methylbenzyl)piperidine: A Novel, Potent, and Selective NR1/2B NMDA Receptor Antagonist

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A structure-based search and screen of our compound library identified *N*-(2-phenoxyethyl)-4-benzylpiperidine **(8)** as a novel *N*-methyl-D-aspartate (NMDA) receptor antagonist that has high selectivity for the NR1/2B subunit combination (IC_{50} = 0.63 μM). We report on the optimization of this lead compound in terms of potency, side effect liability, and in vivo activity. Potency was assayed by electrical recordings in *Xenopus* oocytes expressing cloned rat NMDA receptors. Side effect liability was assessed by measuring affinity for α_1-adrenergic receptors and inhibition of neuronal K^+ channels. Central bioavailability was gauged indirectly by determining anticonvulsant activity in a mouse maximal electroshock (MES) assay. Making progressive modifications to **8**, a hydroxyl substituent on the phenyl ring para to the oxyethyl tether **(10a)** resulted in a ∼25-fold increase in NR1A/2B potency (IC_{50} = 0.025 μM). *p*-Methyl substitution on the benzyl ring **(10b)** produced a ∼3-fold increase in MES activity (ED_{50} = 0.7 mg/kg iv). Introduction of a second hydroxyl group into the C-4 position on the piperidine ring **(10e)** resulted in a substantial decrease in affinity for α_1 receptors and reduction in inhibition of K^+ channels with only a modest decrease in NR1A/2B and MES potencies. Among the compounds described, **10e** (4-hydroxy-*N*-[2-(4-hydroxyphenoxy)ethyl]-4-(4-methylbenzyl)piperidine, Co 101244/PD 174494) had the optimum pharmacological profile and was selected for further biological evaluation.

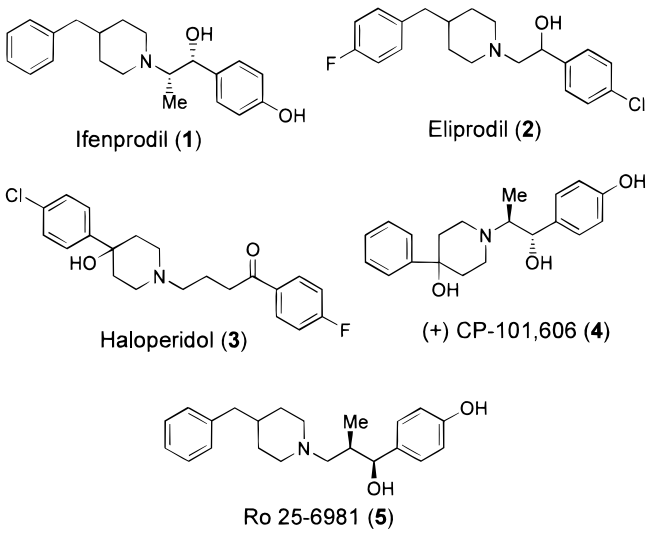
Introduction

Overactivation of *N*-methyl-D-aspartate (NMDA) receptors by glutamate is believed to play a role in numerous acute and chronic neurodegenerative disorders.[1,2] In the search for clinically effective neuroprotectants, a large variety of NMDA receptor antagonists have been identified and characterized.[3] Thus far, however, many NMDA antagonists tested clinically have been compromised by dose-limiting cardiovascular, behavioral, or neurotoxic side effects.[4]

Native NMDA receptors are heterooligomeric assemblies composed of two different types of subunits termed NMDA receptor 1 (NR1) and NR2.[5] NR1 subunits have eight different isoforms generated by alternative RNA splicing, and NR2 subunits have four distinct subtypes.[5] NMDA receptor subunits are differentially distributed across brain regions.[6] This raises the possibility that subtype-selective NMDA receptor antagonists could have therapeutic potential as neuroprotectants without the cardiovascular, behavioral, and neurotoxic side effects often associated with broad-spectrum antagonists.

Ifenprodil (**1**) was the first NMDA receptor antagonist shown to have pronounced subtype selectivity. Selectivity for this class of antagonist is directed toward the NR2B subunit.[7] A number of structurally related compounds have subsequently been identified as NR1/2B-selective NMDA receptor antagonists. Exemplary compounds (Chart 1) include eliprodil (**2**),[7b,8] haloperidol (**3**),[7b,9] CP-101,606 (**4**),[10] and Ro 25-6981 (**5**).[11] Parallel experiments have investigated the complex mechanism of allosteric inhibition and the actions of this class of antagonists on neuronal NMDA currents in situ.[11a,12,13]

Chart 1



Herein we report on a novel series of NR2B-selective antagonists. Structure−activity relationship (SAR) studies reveal how three simple structural modifications can

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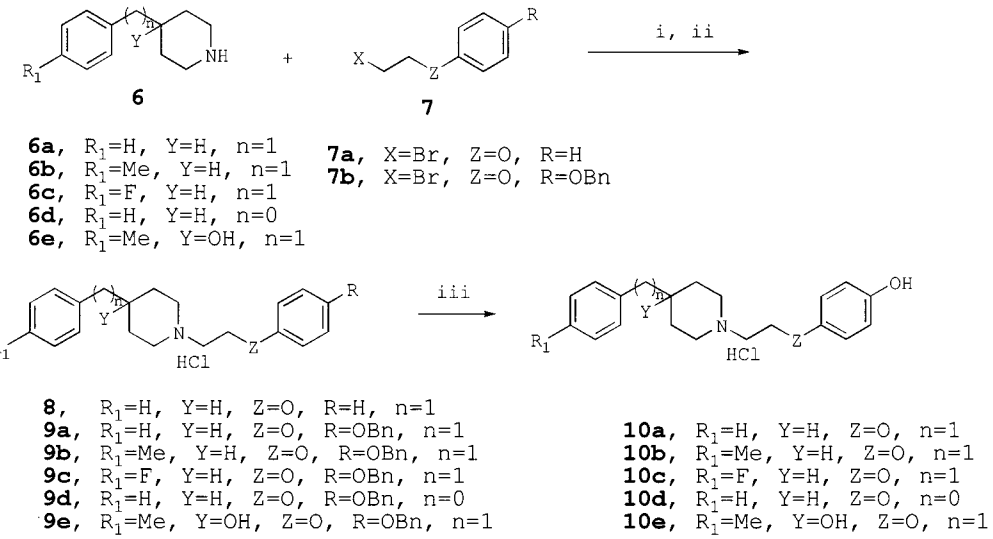
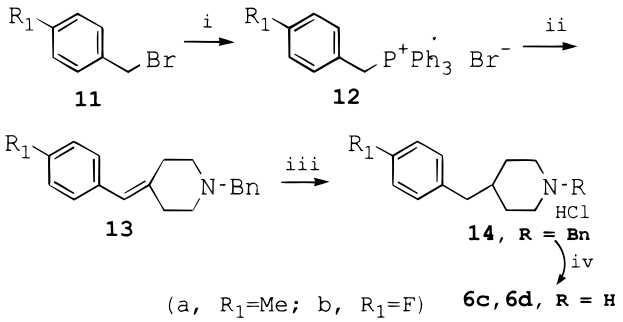
Scheme 1[a]



[a] (i) K_2CO_3/CH_3CN/reflux; (ii) 1 M HCl/MeOH; (iii) 10% Pd/C or 20% $Pd(OH)_2$/MeOH/H_2.

Scheme 2[a]



[a] (i) Ph_3P/ether/rt; (ii) NaH/DMSO/80 °C, then 1-benzyl-4-piperidone; (iii) PtO_2/MeOH/H_2, then 1 M HCl/MeOH; (iv) 10% Pd/C, 95% EtOH/H_2.

transform the screening lead into a potent and specific inhibitor.[14]

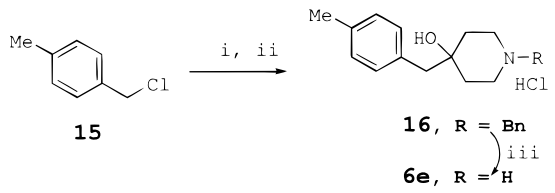
Chemistry

Compound **8** was prepared by *N*-alkylation of 4-benzylpiperidine (**6b**) with 2-phenoxyethyl bromide (**7a**). Compounds **10a**−**10e** were prepared by *N*-alkylation of the requisite piperidines **6a**−**6e** with bromide **7b** followed by debenzylation of the benzyloxy analogues **9a**−**9e** as shown in Scheme 1.

Those substituted 4-benzylpiperidines that were not commercially available were prepared from the appropriately substituted benzyl bromides through a Wittig reaction.[15] Briefly, reaction of substituted benzyl bromide **11** with triphenylphosphine afforded the corresponding phosphonium salt **12**. Treatment of **12** with sodium methylsulfinyl carbanion in dimethyl sulfoxide at 80 °C gave the ylide which reacted with 1-benzyl-4-piperidone to form the olefin **13**. Reduction of **13** with H_2 in the presence of PtO_2 gave compound **14**. Further debenzylation of **14** by hydrogenation in the presence of 10% Pd/C gave the desired piperidines **6c** and **6d** in quantitative yield (Scheme 2).

4-Hydroxy-4-(4-methylbenzyl)piperidine (**6e**) was prepared according to Scheme 3. Reaction of 4-methylbenzylmagnesium chloride, which was made in situ from

Scheme 3[a]



[a] (i) Mg/THF, then 1-benzyl-4-piperidone/−78 °C to rt; (ii) 1 M HCl/MeOH; (iii) 10% Pd/C, 95% EtOH/H_2.

4-methylbenzyl chloride (**15**) and magnesium, with 1-benzyl-4-piperidone in THF afforded the corresponding alcohol **16** in 93% yield. Debenzylation of compound **16** by hydrogenation in the presence of 10% Pd/C gave the desired piperidine **6e** in excellent yield.

Unsubstituted 2-phenoxyethyl bromide (**7a**) and 2-(4-benzyloxyphenoxy)ethyl bromide (**7b**) were synthesized from the reaction of the corresponding phenol with 1,2-dibromoethane.

Pharmacology

Compounds were tested for antagonism of cloned NMDA receptors expressed in *Xenopus* oocytes using standard two-electrode voltage clamp techniques.[16,17] IC_{50} values for inhibition of NMDA responses were determined by curve fitting.[18] Sample data for compound **10e** illustrating selectivity for NR1A/2B are given in Figure 1. Affinity for α_1-adrengeric receptors was deterimed by [^{3}H]prazocin binding assays.[19] Inhibition of voltage-gated K^+ currents was measured by whole-cell voltage clamp recordings from dissociated rat superior cervical ganglion neurons.[20] Mouse MES assays were done as reported previously.[21,22]

Results and Discussion

SARs of *N*-(2-phenoxyethyl)-4-benzylpiperidine **(8)** and related analogues are given in Figure 2 and Table 1. The screening lead **8** had an IC_{50} value of 0.63 μM at NR1A/2B receptors: roughly comparable in potency to the prototype compound eliprodil and 6-fold less active than ifenprodil. Like eliprodil and ifenprodil, **8** was >100-fold selective for NR1A/2B as compared to NR1A/

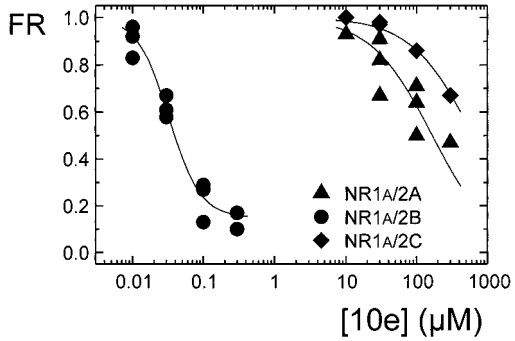


Figure 1. Inhibition of inward currents mediated by cloned NMDA receptors expressed in *Xenopus* oocytes by **10e** illustrating the effect of varying the NR2 subunit. Inhibition is plotted as a fraction (FR) of control responses elicited by saturating, or near-saturating, concentrations of agonists: NR1A/2B and NR1A/2C, glutamate (100 μM) and glycine (1 μM); NR1A/2A, glutamate (100 μM) and glycine (10 μM). Curve fitting is as described in the Experimental Section. Data are taken from three individual oocytes for NR1A/2B and two oocytes for NR1A/2A and NR1A/2C.

2A or NR1A/2C. In terms of potential side effects, **8** had submicromolar affinity for α_1-adrenergic receptors (IC_{50} = 0.82 μM), presenting a liability to produce hypotension. In addition, **8** inhibited neuronal voltage-gated K^+ channels by 65% at 10 μM, suggesting a potential for prolongation of cardiac QT interval, a dose-limiting clinical side effect for eliprodil (in our assay eliprodil inhibited neuronal K^+ channels by 67% at 10 μM). Like eliprodil, **8** was a potent anticonvulsant when administered intravenously (iv) to mice (ED_{50} = 2 mg/kg). Our goal was to modify **8** to improve NR2B potency while at the same time reducing α_1 affinity and K^+ channel inhibition while retaining in vivo activity.

Introduction of a hydroxyl group on the 4-position of the phenyl ring, which is attached to the tether connecting to the nitrogen atom of the piperidine ring, led to compound **10a** and increased NR2B potency by 25 times. As described in other series of compounds,[10,18,23] this emphasizes the importance of having a hydrogen-bond-donating group at this position for interaction with the NMDA receptor. Though NR2B potency was increased in **10a**, the α_1 activity remained less than 1 μM.

Removing the methylene group from the spacer connecting the C-4 phenyl group to the piperidine ring gave compound **10d** and unexpectedly resulted in a 200-fold drop in potency. In this instance, the SAR did not follow that described previously for compounds such as CP-101,606 where phenylpiperidines are optimal.[10]

Simple substitution on the benzyl ring of **10a**, such as 4-methyl (**10b**) and 4-fluoro (**10c**), had little effect on NR1A/2B potency or on the potential side effects profile. However, the in vivo potency of **10b** was increased roughly 3 times (MES ED_{50} = 0.7 mg/kg) compared to that of **10a**, while the in vivo potency of **10c** was slightly reduced (MES ED_{50} = 3 mg/kg). This

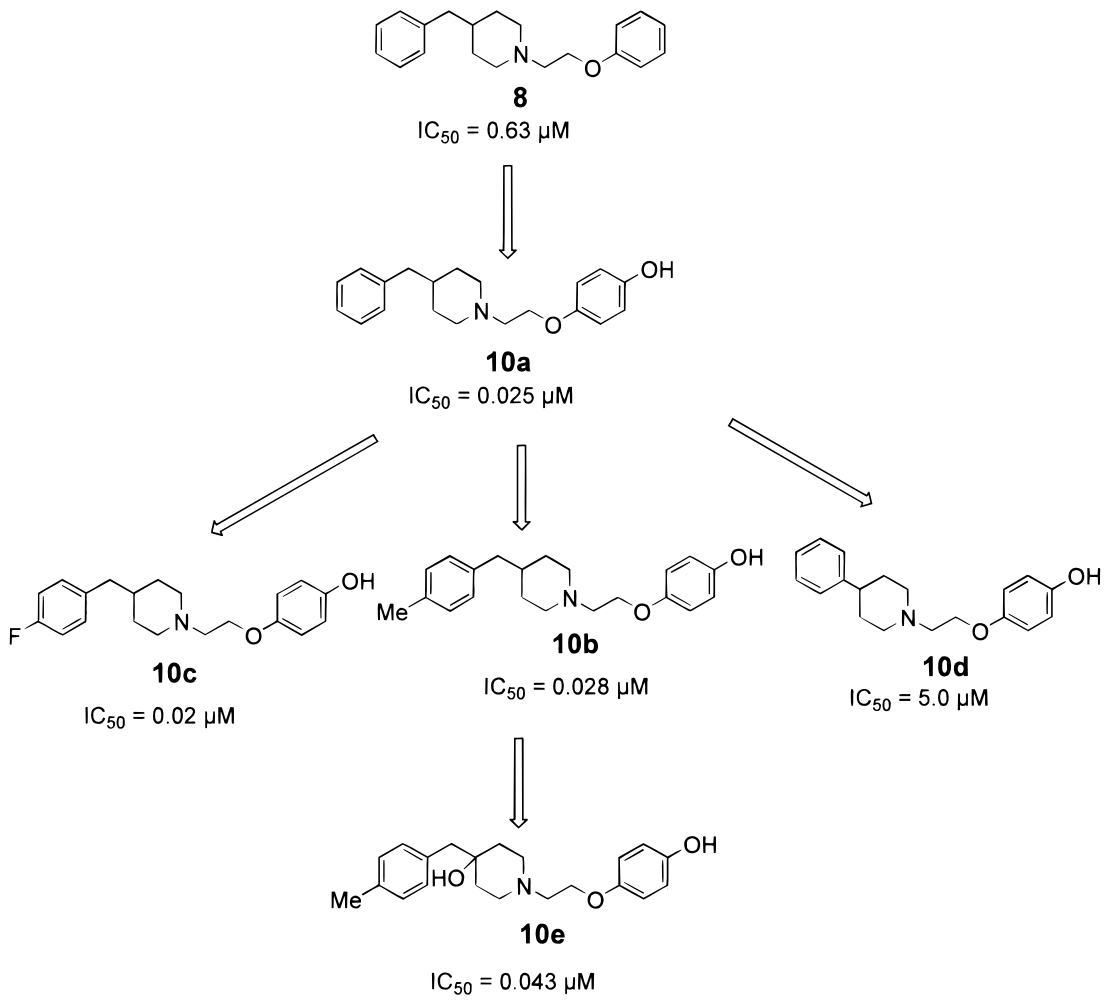


Figure 2. SAR of the substituted benzylpiperidines at the NR1A/2B subtype.

Table 1. In Vitro and in Vivo Profiles of Substituted Benzylpiperidines[a]

	cloned NMDA receptors expressed in oocytes: IC_{50} (μM)					
no.	NR1A/2A	NR1A/2B	NR1A/2C	α_1: IC_{50} (μM)	K^+ channels: % inhib at 10 μM	MES: ED_{50} (mg/kg)
1	20 ± 6	0.11 ± 0.01	>100	0.22	54 ± 7.7	7.0
2	100.0	1.40	100.0	3.30	67 ± 6.2	1.0
8	>100	0.63 ± 0.10	>100	0.82	65 ± 4.3	2.0
10a	>100	0.025 ± 0.009	>100	0.47	46 ± 2.9	2.0
10b	>100	0.028 ± 0.004	>100	1.80	67 ± 5.2	0.7
10c	21 ± 4	0.05 ± 0.017	>100	1.60	53 ± 8.9	3.0
10d	110 ± 19	7.7 ± 1.5	>100	nd	nd	nd
10e	>100	0.043 ± 0.004	>100	27	23 ± 5.6	1.5

[a] IC_{50} values for inhibition of NMDA responses at cloned NMDA receptors expressed in *Xenopus* oocytes, as illustrated in Figure 1. Data are presented as mean ± SEM. Values were obtained from at least three oocytes for NR1A/2B and at least two oocytes for the other subunits. nd, not determined.

suggests that substitutions on the benzyl ring can have significant effects on in vivo potency.

Introduction of a hydroxyl group into the C-4 position of the piperidine ring of **10b** led to **10e** and resulted in a modest reduction in NR2B potency (IC_{50} = 0.043 μM). However, this substitution greatly improved the side effects profile: α_1 activity was reduced by 15-fold (IC_{50} = 27 μM), and K^+ channel inhibition was reduced to only 23% at 10 μM. A similar reduction in α_1 activity has been reported with 4-hydroxy substitution into phenylpiperidines such as CP-101,606.[10] The in vivo activity of **10e** was not greatly compromised (MES ED_{50} = 1.5 mg/kg) giving a molecule with the desired pharmacological properties.

In conclusion, **10e** (4-hydroxy-*N*-[2-(4-hydroxyphenoxy)ethyl]-4-(4-methylbenzyl)piperidine, Co 101244/PD 174494) has the best overall profile of the compounds described, one that rivals or exceeds that of previously reported NR2B antagonists. In addition, **10e** has the advantage of achieving the desired profile without introduction of stereocenters. The SAR leading to **10e** illustrates some of the key features necessary for designing potent, highly specific NR2B antagonists. Compound **10e** is currently undergoing pharmacological evaluation for a variety of therapeutic applications including stroke and Parkinson's disease.[24]

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. The ^{1}H NMR spectra were recorded at 300 MHz. Chemical shifts are reported in ppm (δ), and *J* coupling constants are reported in Hz. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Mass spectra (MS) were obtained with a VG 12-250 or VG ZAB-2FHF mass spectrometer. Reagent grade solvents were used without further purification unless otherwise specified. TLC was performed using TLC plates GF_{254}. Column chromatography was performed on silica gel (230−400 mesh). Reverse-phase HPLC analyses were obtained at 254 nm on a 4.6- × 250-mm microsorb-MV C18 column, using 0.1% trifluoroacetic acid in water (A) and 0.1% trifluoroacetic acid in acetonitrile (B) as solvents. The linear gradient was 20% B in A to 95% B in A with a flow rate of 1 mL/min.

4-Benzyl-1-(2-phenoxyethyl)piperidine Hydrochloride (8). A mixture of 4-benzylpiperidine (35 g, 0.20 mol), 1-bromo-2-phenoxyethane (42 g, 0.21 mol), and potassium carbonate (111 g, 0.80 mol) in 400 mL of methyl ethyl ketone was heated at reflux with vigorous stirring for 12 h. The reaction mixture was filtered, and the filtrate was evaporated. The residue was extracted with water/ether, and the ether layer was washed with 2 N hydrochloric acid. The amine hydrochloride salt separated from the aqueous layer was collected by filtration. The salt was treated with 2 N aqueous NaOH solution (150 mL) and extracted with ether. The extract was dried over $MgSO_4$ and treated with Norite. After filtration, the ether was removed, and the product was vacuum-distilled (45.6 g, bp = 159−162 °C at 0.1 mmHg, 75% yield). The hydrochloride salt was formed in 2-propanol/HCl and recrystallized from ethyl acetate to give **8** as colorless crystals: mp 170−172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 3 H), 1.82 (m, 2 H), 2.10 (m, 2 H), 2.80 (m, 2 H), 3.39 (m, 2 H), 3.65 (m, 2 H), 4.54 (m, 2 H), 6.85−7.31 (m, 10 H), 12.50 (brs, 1 H). Anal. ($C_{20}H_{26}ClNO$) C, H, N.

2-(4-Benzyloxyphenoxy)ethyl Bromide (7b). A mixture of 4-benzyloxyphenol (10 g, 0.05 mol) and potassium carbonate (17.3 g, 0.125 mol) in 50 mL of acetonitrile and 21.6 mL of 1,2-dibromoethane was refluxed with stirring for 24 h. The inorganic salt was removed by filtration through a short column of silica gel which was washed with ethyl acetate (3 × 25 mL). The combined filtrate was evaporated in vacuo, and the residue was further purified by flash chromatography (5% EtOAc in hexane) to give 12 g (79%) of the title product as a white solid: mp 75−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (t, *J* = 6.2 Hz, 2 H), 4.24 (t, *J* = 6.2 Hz, 2 H), 5.02 (s, 2 H), 6.87 (m, 4 H), 7.38 (m, 5 H).

4-Benzyl-1-[2-(4-benzyloxyphenyl)ethoxy]piperidine Hydrochloride (9a). A mixture of 2-(4-benzyloxyphenoxy)-ethyl bromide (**7b**) (1.44 g, 4.7 mmol), 4-benzylpiperidine (0.876 g, 5.0 mmol), potassium carbonate (1.725 g, 12.5 mmol), and 50 mL of acetonitrile was refluxed for 24 h. The inorganic salt was removed by filtration through a short column of silica gel which was washed with ethyl acetate (3 × 25 mL). The combined filtrate was evaporated in vacuo, and the residue was further purified by flash chromatography (50% EtOAc in hexane), giving 1.62 g (86%) of the free amine. The amine was dissolved in 50 mL of methanol and treated with 1 N HCl in methanol (6 mL). The solution was evaporated in vacuo and titratuted with ether (100 mL). The white solid was collected by filtration and dried in vacuo, giving the title HCl salt in 100% yield: mp 164−166 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51 (m, 1 H), 1.68 (d, *J* = 12.3 Hz, 2 H), 2.46 (m, 4 H), 2.94 (m, 2 H), 3.35 (m, 2 H), 3.45 (d, *J* = 11.7 Hz, 2 H), 4.26 (s, 2 H), 5.01 (s, 2 H), 6.89 (m, 4 H), 7.18−7.40 (m, 10 H), 10.2 (brs, 2 H); EIMS *m/e* 311 (M^+, 5), 202 (10), 188 (100), 91 (30).

4-Benzyl-1-[2-(4-hydroxyphenyl)ethoxy]piperidine Hydrochloride (10a). To a solution of 4-benzyl-1-[2-(4-benzyloxyphenyl)ethoxy]piperidine (**9a**) (401 mg, 1.0 mmol) in 25 mL of ethanol were added 1.0 mL of 1 M HCl in methanol and 100 mg of 10% Pd/C. The resulting mixture was hydrogenated at 30 psi of H_2 for 2 h. The catalyst was removed by filtration through a short column of Celite (5 g) and washed with methanol (3 × 15 mL). The combined filtrate was evaporated in vacuo to give an oil, and then ether (30 mL) was added to the residue. The resulting mixture was stirred at room temperature overnight. The white solid was collected by filtration and dried in vacuo, giving 330 mg (100%) of the title compound: mp 212−215 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 1.66 (m, 3 H), 1.83 (m, 2 H), 2.43 (s, 2 H), 2.63 (m, 2 H), 3.19 (m, 2 H), 3.40 (brs, 1 H), 4.25 (s, 2 H), 6.55 (m, 4 H), 6.94−7.09 (m, 5 H), 12.0 (brs, 1 H); EIMS *m/e* 311 (M^+, 5), 202 (10), 188 (100), 91 (30). Anal. ($C_{20}H_{26}ClNO_2$) C, H, N.

4-Methylbenzyltriphenylphosphonium Bromide (12a). To a solution of triphenylphosphine (35.45 g, 0.135 mol) in 100 mL of ether was added 4-methylbenzyl bromide (**11a**) (25 g, 0.135 mol). The resulting solution was stirred at room temperature overnight. The white solid was collected by filtration and dried to give 60.0 g (98%) of the title product as a white solid: mp 256−258 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3 H), 5.27 (d, J = 14.4 Hz, 2 H), 6.93 (m, 4 H), 7.59−7.76 (m, 15 H).

1-Benzyl-4-(4-methylbenzylidene)piperidine (13a). A suspension of sodium hydride (1.20 g, 0.03 mol, 60% in mineral oil) in 20 mL of dry DMSO was heated at 80 °C under N_2 for 1 h. The resulting solution was cooled in an ice−water bath and treated with a suspension of 4-methylbenzyltriphenylphosphonium bromide (**12a**) (13.41 g, 0.03 mol) in 120 mL of warm DMSO. The resulting solution was stirred at 0 °C for 10 min and then at room temperature for 15 min, to which 1-benzyl-4-piperidone (5.67 g, 0.03 mol) was then added dropwise under N_2. The resulting mixture was stirred at 80 °C overnight, then poured over ice (400 g), and extracted with ether (3 × 200 mL). The combined extracts were dried over sodium sulfate. The solvent was evaporated in vacuo and further purified by flash chromatography (eluent 5% EtOAc in hexanes), giving 7.0 g (84%) of the title compound as a pale-yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3 H), 2.32 (m, 4 H), 2.43 (m, 4 H), 3.45 (s, 2 H), 6.16 (s, 1 H), 7.03 (m, 4 H), 7.18−7.26 (m, 5 H).

1-Benzyl-4-(4-methylbenzyl)piperidine Hydrochloride (14a). To a solution of 1-benzyl-4-(4-methylbenzylidene)-piperidine (**13a**) (4.16 g, 15 mmol) in 100 mL of methanol was added 200 mg of PtO_2. The resulting mixture was hydrogenated at 40 psi for 8 h. The catalyst was removed by filtration through a short column of Celite (10 g) and washed with methanol (3 × 20 mL). The filtrate was evaporated in vacuo, redissolved into 20 mL of methanol, and treated with 30 mL of 1 M solution of HCl in methanol. The resulting solution was evaporated in vacuo and triturated with 60 mL of ether. An off-white solid was collected by filtration and dried to give 4.6 g (97%) of the title product: mp 190−192 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (m, 1 H), 1.75 (m, 2 H), 2.07 (m, 2 H), 2.29 (s, 3 H), 2.54 (m, 4 H), 3.40 (d, J = 10.5 Hz, 2 H), 4.09 (d, J = 4.8 Hz, 2 H), 6.99 (d, J = 7.8 Hz, 2 H), 7.05 (d, J = 7.8 Hz, 2 H), 7.42 (m, 3 H), 7.60 (m, 2 H), 12.40 (brs, 1 H).

4-(4-Methylbenzyl)piperidine Hydrochloride (6c). A mixture of 1-benzyl-4-(4-methylbenzyl)piperidine hydrochloride (**14a**) (4.1 g, 13 mmol) and 1.02 g of 10% Pd/C in 100 mL of 95% ethanol was hydrogenated at 60 psi for 12 h. The catalyst was removed by filtation through a short column of Celite (10 g) and washed with methanol (3 × 20 mL). The filtrate was evaporated in vacuo and triturated with ether (50 mL). A white solid was collected by filtration and dried in vacuo, giving 2.8 g (98%) of the title product: mp 209−211 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.70 (m, 3 H), 1.82 (m, 2 H), 2.32 (s, 3 H), 2.55 (m, 2 H), 2.78 (m, 2 H), 3.44 (d, J = 8.7 Hz, 2 H), 6.99 (d, J = 7.8 Hz, 2 H), 7.05 (d, J = 7.8 Hz, 2 H), 9.30 (brs, 1 H), 9.60 (brs, 1 H).

1-[2-(4-Benzyloxyphenyl)ethoxy]-4-(4-methylbenzyl)-piperidine Hydrochloride (9b). A mixture of 2-(4-benzyloxyphenoxy)ethyl bromide (**7b**) (0.61 g, 2.0 mmol), 4-(4-methylbenzyl)piperidine hydrochloride (**6c**) (0.45 g, 2.0 mmol), and potassium carbonate (0.69 g, 5.0 mmol) in 20 mL of acetonitrile was refluxed for 24 h. The inorganic salt was removed through a short column of silica gel and washed with ethyl acetate (3 × 25 mL). The combined filtrate was evaporated in vacuo to give a crude mixture, which was purified by flash chromatography (20% methanol in ethyl acetate), giving a pale-yellow oil. A solution of this oil in 10 mL of methanol was treated with 3 mL of 1 M HCl in methanol. The resulting solution was evaporated in vacuo and triturated with 50 mL of ether. A white solid was collected by filtration and dried in vacuo, giving 650 mg (72%) of the title product: mp 194−196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (m, 1 H), 1.80 (m, 2 H), 2.02 (m, 2 H), 2.31 (s, 3 H), 2.57 (d, J = 6.9 Hz, 2 H), 2.72 (m, 2 H), 3.34 (m, 2 H), 3.63 (d, J = 11.4 Hz, 2 H), 4.49 (s, 2 H), 5.01 (s, 2 H), 6.81 (d, J = 10.8 Hz, 2 H), 6.88 (d, J = 10.8 Hz, 2 H), 6.99 (d, J = 7.8 Hz, 2 H), 7.08 (d, J = 7.8 Hz, 2 H), 7.32−7.39 (m, 5 H), 12.51 (brs, 1 H).

1-[2-(4-Hydroxyphenyl)ethoxy]-4-(4-methylbenzyl)-piperidine Hydrochloride (10b). To a solution of 1-[2-(4-benzyloxyphenyl)ethoxy]-4-(3-methylbenzyl)piperidine hydrochloride (**9b**) (250 mg, 0.55 mmol) in 25 mL of ethanol was added 60 mg of 20% $Pd(OH)_2$. The resulting mixture was hydrogenated at 30 psi of hydrogen for 2 h. The catalyst was removed through a short column of Celite (5 g) and washed with methanol (3 × 15 mL). The combined filtrate was evaporated in vacuo and triturated with 30 mL of ether. The white solid was collected by filtration and dried in vacuo, giving 140 mg (88%) of the title product: mp 198−200 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.60 (m, 2 H), 1.88−1.92 (m, 3 H), 2.29 (s, 3 H), 2.57 (d, J = 6.6 Hz, 2 H), 3.06 (m, 2 H), 3.47 (m, 2 H), 3.61 (m, 2 H), 4.24 (t, J = 5.1 Hz, 2 H), 6.71 (dd, J_1 = 2.4 Hz, J_2 = 6.6 Hz, 2 H), 6.83 (dd, J_1 = 2.4 Hz, J_2 = 6.6 Hz, 2 H), 7.70 (m, 4 H). Anal. ($C_{21}H_{28}ClNO_2$) C, H, N.

4-Fluorobenzyltriphenylphosphonium Bromide (12b). To a solution of triphenylphosphine (26.2 g, 0.1 mol) in 100 mL of ether was added 4-fluorobenzyl bromide (**12b**) (18.9 g, 0.1 mol). The resulting solution was stirred at room temperature overnight. The white solid was collected by filtration and dried to give 37.0 g (82%) of the product as a white solid: mp 280−282 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.49 (d, J = 14.4 Hz, 2 H), 6.77 (d, J = 8.7 Hz, 2 H), 7.12 (m, 2 H), 7.60 (m, 6 H), 7.75 (m, 9 H).

1-Benzyl-4-(4-fluorobenzylidene)piperidine (13b). A suspension of sodium hydride (1.44 g, 0.036 mol, 60% in mineral oil) in 20 mL of dry DMSO was heated at 80 °C under N_2 for 1 h. The resulting solution was cooled in an ice−water bath and treated with a suspension of 4-fluorobenzyltriphenylphosphonium bromide (**12b**) (16.2 g, 0.036 mol) in 120 mL of warm DMSO. The resulting solution was stirred at 0 °C for 10 min and then at room temperature for 15 min, to which 1-benzyl-4-piperidone (5.67 g, 0.03 mol) was then added dropwise under N_2. The resulting mixture was stirred at 80 °C overnight and then poured over ice (400 g) and extracted with ether (3 × 200 mL). The combined extracts were dried over sodium sulfate. The solvent was evaporated in vacuo and further purified by flash chromatography (eluent 5% EtOAc in hexanes), giving 7.0 g (83%) of the title compound as a pale-yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.36−2.54 (m, 8 H), 3.53 (s, 2 H), 6.22 (s, 1 H), 6.98 (m, 2 H), 7.14 (m, 2 H), 7.26−7.34 (m, 5 H).

1-Benzyl-4-(4-fluorobenzyl)piperidine Hydrochloride (14b). To a solution of 1-benzyl-4-(4-fluorobenzylidene)piperidine (**13b**) (4.22 g, 15 mmol) in 100 mL of methanol was added 200 mg of PtO_2. The resulting mixture was hydrogenated at 40 psi for 8 h. The catalyst was removed through a short column of Celite (10 g) and washed with methanol (3 × 20 mL). The filtrate was treated with 30 mL of 1 M HCl in methanol. The resulting solution was evaporated in vacuo and triturated with 100 mL of ether. An off-white solid was collected by filtration and dried to give 4.6 g (96%) of the title product: mp 168−170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.63 (m, 2 H), 1.73 (m, 2 H), 2.09 (q, J = 12.3 Hz, 2 H), 2.56 (m, 3 H), 3.41 (d, J = 11.1 Hz, 2 H), 4.10 (d, J = 5.1 Hz, 2 H), 6.94 (m, 2 H), 7.05 (m, 2 H), 7.43 (m, 3 H), 7.61 (m, 2 H), 12.41 (s, 1 H).

4-(4-Fluorobenzyl)piperidine Hydrochloride (6d). A mixture of 1-benzyl-4-(4-fluorobenzyl)piperidine hydrochloride (**14b**) (4.5 g, 14 mmol) and 1.93 g of 10% Pd/C in 100 mL of 95% ethanol was hydrogenated at 60 psi for 12 h. The catalyst was removed through a short column of Celite (10 g) and washed with methanol (3 × 20 mL). The filtrate was evaporated in vacuo and triturated with 80 mL of ether. A white solid was collected by filtration and dried in vacuo, giving 3.2 g (98%) of the title product: mp 158−160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.70−1.81 (m, 5 H), 2.57 (m, 2 H), 2.79 (m, 2 H), 3.45 (m, 2 H), 6.98 (m, 2 H), 7.05 (m, 2 H), 9.45 (brs, 2 H).

1-[2-(4-Benzyloxyphenyl)ethoxy]-4-(4-fluorobenzyl)-piperidine (9c). A mixture of 2-(4-benzyloxyphenoxy)ethyl bromide (**7b**) (3.50 g, 11.4 mmol), 4-fluorobenzylpiperidine

hydrochloride (**6c**) (2.6 g, 11.4 mmol), and potassium carbonate (3.91 g, 28 mmol) in 60 mL of acetonitrile was refluxed for 12 h. The inorganic salt was removed by filtration through a short column of silica gel and washed with ethyl acetate (3 × 25 mL). The combined filtrate was evaporated in vacuo to give a crude mixture, which was purified by flash chromatography (20% methanol in ethyl acetate), giving 4.0 g (84%) of the title product as a pale-yellow solid: mp 73−75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (m, 3 H), 1.62 (m, 1 H), 2.01 (m, 2 H), 2.47 (d, J = 6.9 Hz, 2 H), 2.73 (t, J = 6.0 Hz, 2 H), 2.93 (m, 2 H), 4.02 (t, J = 5.7 Hz, 2 H), 4.99 (s, 2 H), 6.78−6.96 (m, 7 H), 7.07 (m, 2 H), 7.29−7.41 (m, 4 H).

4-(4-Fluorobenzyl)-1-[2-(4-hydroxyphenyl)ethoxy]-piperidine Hydrochloride (10c). To a solution of 1-[2-(4-benzyloxyphenyl)ethoxy]-4-(4-fluorobenzyl)piperidine (**9c**) (4.0 g, 9.5 mmol) in 100 mL of methanol was added 1.0 g of 5% Pd/C. The resulting mixture was hydrogenated at 35 psi of hydrogen for 4 h. The catalyst was removed through a short column of Celite (5 g) and washed with methanol (3 × 15 mL). The combined filtrate was treated with 15 mL of 1 M HCl in methanol. The solution was evaporated in vacuo and triturated with 100 mL of ether. An off-white solid was collected by filtration and dried in vacuo, giving 3.2 g (95%) of the title product: mp 196−198 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.58 (m, 2 H), 1.89 (m, 3 H), 2.60 (d, J = 6.3 Hz, 2 H), 3.08 (m, 2 H), 3.49 (t, J = 5.1 Hz, 2 H), 3.62 (m, 2 H), 4.25 (t, J = 5.1 Hz, 2 H), 6.77 (d, J = 9.3 Hz, 2 H), 7.02 (m, 2 H), 7.20 (m, 2 H). Anal. ($C_{20}H_{25}ClFNO_2$) C, H, N.

1-[2-(4-Benzyloxyphenyl)ethoxy]-4-phenylpiperidine Hydrochloride (9d). A mixture of 2-(4-benzyloxyphenoxy)-ethyl bromide (**7b**) (0.377 g, 1.23 mmol), 4-phenylpiperidine hydrochloride (**6a**) (0.20 g, 1.23 mmol), and potassium carbonate (0.42 g, 3.07 mmol) in 20 mL of acetonitrile was refluxed for 12 h. The inorganic salt was removed through a short column of silica gel and washed with ethyl acetate (3 × 25 mL). The combined filtrate was evaporated in vacuo to give a crude mixture, which was purified by flash chromatography (20% methanol in ethyl acetate) to give a residue, a solution of which in 10 mL of methanol was treated with 3 mL of 1 M HCl in methanol. The resulting solution was evaporated in vacuo and triturated with 50 mL of ether. A white solid was collected by filtration and dried in vacuo, giving 455 mg (88%) of the title product: mp 163−165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (d, J = 13.5 Hz, 3 H), 2.62 (m, 3 H), 2.98 (m, 2 H), 3.44 (m, 2 H), 3.79 (m, 2 H), 4.54 (m, 2 H), 5.02 (s, 2 H), 6.83 (d, J = 8.7 Hz, 2 H), 6.90 (d, J = 8.7 Hz, 2 H), 7.32 (m, 10 H), 12.80 (brs, 1 H).

1-[2-(4-Hydroxyphenyl)ethoxy]-4-phenylpiperidine Hydrochloride (10d). To a solution of 1-[2-(4-benzyloxyphenyl)-ethoxy]-4-phenylpiperidine hydrochloride (**9d**) (254 mg, 0.60 mmol) in 25 mL of methanol was added 85 mg of 20% $Pd(OH)_2$. The resulting mixture was hydrogenated at 20 psi of hydrogen for 2 h. The catalyst was removed through a short column of Celite (5 g) and washed with methanol (3 × 15 mL). The combined filtrate was evaporated in vacuo and triturated with 30 mL of ether. The white solid was collected by filtration and dried in vacuo, giving 180 mg (90%) of the title product: mp 198−200 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 2.11 (m, 4 H), 2.85 (m, 1 H), 3.30 (m, 2 H), 3.59 (m, 2 H), 3.77 (d, J = 10.5 Hz, 2 H), 4.31 (d, J = 5.1 Hz, 2 H), 6.73 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 7.29(m, 5 H). Anal. ($C_{19}H_{24}ClNO_2 \cdot 0.3H_2O$) C, H, N.

1-Benzyl-4-hydroxy-4-(4-methylbenzyl)piperidine (16). To a suspension of 2.31 g (0.095 mol) of Mg turnings in 15 mL of anhydrous THF was added a solution of 1,2-dibromoethane (0.489 g, 2.65 mmol) in 5 mL of THF dropwise at room temperature under N_2. After the addition, the THF was removed and the residue was rinsed with THF (2 × 5 mL). To this residue was added a solution of 4-methylbenzyl chloride (**15**) (13.0 g, 92.6 mmol) in 50 mL of THF dropwise at 0 °C. After the addition, the solution was stirred at room temperature for 2 h and another 50 mL of THF was added. After the mixture cooled to −35 to −40 °C, a solution of 4-benzylpiperidone (5.0 g, 26.5 mmol) in 20 mL of THF was added dropwise. After the addition was complete, the reaction mixture was stirred at room temperature for 3 h and stood overnight. The reaction mixture was treated with 100 mL of saturated aqueous NH_4Cl solution at 0 °C and then extracted with dichloromethane (2 × 50 mL). The combined organic phases were evaporated in vacuo to give an oil, which was redissolved in 200 mL of dichloromethane, washed with saturated aqueous NH_4Cl solution (2 × 30 mL) and brine (50 mL), and then dried over sodium sulfate. Evaporation of solvent followed by flash chromatography (EtOAc, R_f = 0.25) gave 7.5 g (96%) of the product as a pale-yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (m, 2 H), 1.73 (m, 2 H), 2.05 (s, 1 H), 2.32 (m, 5 H), 2.61 (m, 2 H), 2.71 (s, 2 H), 3.51 (s, 2 H), 7.09 (m, 4 H), 7.30 (m, 5 H).

4-Hydroxy-4-(4-methylbenzyl)piperidine Hydrochloride (6e). A mixture of 1-benzyl-4-hydroxy-4-(4-methylbenzyl)-piperidine (**16**) (2.8 g, 9.5 mmol) and 700 mg of 10% Pd/C in 100 mL of 95% ethanol was hydrogenated at 50 psi for overnight. The catalyst was removed by filtration through a short column of Celite (10 g) and washed with methanol (3 × 15 mL). The filtrate was treated with 12 mL of 1 M HCl in methanol. The resulting solution was evaporated in vacuo and triturated with 30 mL of ether. A white solid was collected by filtration, giving 2.1 g (92%) of the title product: mp 183−185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (m, 2 H), 2.10 (m, 2 H), 2.34 (s, 3 H), 2.78 (s, 2 H), 3.24 (m, 5 H), 7.05 (d, J = 7.5 Hz, 2 H), 7.14 (d, J = 7.5 Hz, 2 H), 9.30 (brs, 1 H), 9.52 (brs, 1 H).

1-[2-(4-Benzyloxyphenoxy)ethyl]-4-hydroxy-4-(4-methylbenzyl)piperidine Hydrochloride (9e). A mixture of 2-(4-benzyloxyphenoxy)ethyl bromide (**7b**) (368 mg, 1.2 mmol), 4-hydroxy-4-(4-methylbenzyl)piperidine hydrochloride (**6e**) (290 mg, 1.2 mmol), and potassium carbonate (414 mg, 3 mmol) in 30 mL of acetonitrile was refluxed for 12 h. The inorganic salt was removed through a short column of silica gel and washed with ethyl acetate (3 × 25 mL). The combined filtrate was evaporated in vacuo to give a crude mixture, which was purified by flash chromatography (5% methanol in ethyl acetate), giving a pale-yellow oil, a solution of which in 10 mL of methanol was treated with 4 mL of 1 M HCl in methanol. The resulting solution was evaporated in vacuo and triturated with 50 mL of ether. A white solid was collected by filtration and dried in vacuo, giving 420 mg (75%) of the title product: mp 179−181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 2 H), 1.73 (d, J = 14.1 Hz, 2 H), 2.33 (s, 3 H), 2.45 (m, 2 H), 2.81 (s, 2 H), 3.22 (m, 2 H), 3.36 (s, 1 H), 3.46 (d, J = 8.4 Hz, 2 H), 4.49 (s, 2 H), 5.01 (s, 2 H), 6.82 (d, J = 9.0 Hz, 2 H), 6.90 (d, J = 9.0 Hz, 2 H), 7.08 (d, J = 7.5 Hz, 2 H), 7.17 (d, J = 7.5 Hz, 2 H), 7.38 (m, 5 H), 12.40 (brs, 1 H).

4-Hydroxy-1-[2-(4-hydroxyphenoxy)ethyl]-4-(4-methylbenzyl)piperidine Hydrochloride (10e). To a solution of 1-[2-(4-benzyloxyphenoxy)ethyl]-4-hydroxy-4-(4-methylbenzyl)-piperidine (**9e**) (0.25 g, 0.53 mmol) in 30 mL of methanol was added 62.5 mg of 20% $Pd(OH)_2$. The resulting mixture was hydrogenated at 20 psi of hydrogen for 3 h. The catalyst was removed through a short column of Celite (5 g) and washed with methanol (3 × 15 mL). The filtrate was evaporated in vacuo and triturated with 30 mL of ether. A white solid was collected by filtration and dried in vacuo, giving 200 mg (100%) of the title product: mp 133−135 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.58 (m, 2 H), 1.75 (m, 2 H), 2.12 (s, 3 H), 2.62 (s, 2 H), 3.20−3.30 (m, 6 H), 4.06 (m, 2 H), 6.53 (d, J = 9.0 Hz, 2 H), 6.65 (d, J = 9.0 Hz, 2 H), 6.94 (s, 4 H). Anal. ($C_{21}H_{28}ClNO_3$) C, H, N.

Oocyte Electrophysiology. Oocytes were obtained from mature female *Xenopus* laevis and were prepared as described previously.[16] Individual oocytes were microinjected with a mixture of NMDA receptor-encoding cRNAs, provided by Dr. P. H. Seeburg (Heidelberg University, Heidelberg, Germany).[5d] NR1A and NR2A were injected at a 1:4 ratio; all other binary subunit combinations were injected 1:1 (1−10 ng of each subunit). Oocytes were stored in Barth's medium containing (in mM): NaCl, 88; KCl, 1; $CaCl_2$, 0.41; $Ca(NO_3)_2$, 0.33; $MgSO_4$, 0.82; $NaHCO_3$, 2.4; Hepes, 5; pH 7.4, with 0.1 mg/mL gentamycin sulfate. Standard voltage clamp recordings were made

at −70 mV in nominally Ca^{2+}-free Ringer solution (in mM): NaCl, 115; KCl, 2; $BaCl_2$, 1.8; Hepes, 5; pH 7.4.[17] Drugs were diluted in Ca^{2+}-free Ringer solution and applied by bath perfusion (7−10 mL/min) in a conventional flow-through chamber (volume ∼0.2 mL). Test drugs were dissolved in DMSO and diluted into Ringer just prior to application (final [DMSO] = 0.1−1%). IC_{50} values were obtained from partial (3−5 points) concentration−inhibition curves using the equation:

$$I/I_{control} = \{(1 - min)/\{1 + ([antagonist]/IC_{50})^n\}\} + min$$

where $I_{control}$ is the current in the absence of antagonist, min (minimum) is the residual fractional response at a saturating concentration of antagonist, n is the slope factor, and IC_{50} is the concentration of drug that produces one-half this level of inhibition. To fit the curves for NR1A/2B, 'min' was fixed at 0.15.[17] Data in the text are mean ± standard error (SE).

α_1-Adrenergic Receptor Binding. Test compounds were evaluated at nine concentrations in duplicate added in 5-mL aliquots (1% DMSO final) to 96-well, 1.0-mL volume assay plates and incubated in a total volume of 500 mL for 60 min at room temperature as described below. Assays were terminated by filtration through GF/B filter plates (Packard, Meriden, CT), and the filter plates were rinsed three times with ∼0.8 mL of assay buffer/well. Microscint-20 scintillation cocktail (50 mL/well; Packard) was added to the dried filter plates, which were then counted on a TopCount (Packard) scintillation counter for 8 min/well. IC_{50} values were determined by fitting the data to the sigmoidal equation using Prism (GraphPad, San Diego, CA). The [^{3}H]prazosin binding assay was modified from previously described methods.[19] Frozen Sprague−Dawley rat cortices obtained from ABS (Wilmington, DE) were thawed, homogenized in 10 volumes of ice-cold 0.25 M sucrose/10 mM Tris-HCl (pH 7.4) buffer, and centrifuged at 1000*g* for 10 min at 4 °C. The supernatant was centrifuged at 40000*g* for 30 min; the pellet was resuspended in 10 volumes of ice-cold 140 mM NaCl/5 mM $MgCl_2$/50 mM Tris-HCl (pH 7.4) buffer (prazosin binding buffer) and centrifuged at 40000*g* for 30 min. The pellet was resuspended in prazosin binding buffer and centrifuged twice more for a total of three wash steps, and the final pellet was stored at −80 °C. On the day of the binding assay, the membrane pellets were thawed and resuspended in prazosin binding buffer, and 200 mg of membrane protein was incubated with 0.8 nM [^{3}H]-prazosin (∼80 Ci/mmol; NEN, Boston, MA). Nonspecific binding was determined in the presence of 10 mM phentolamine.

K^+ Channel Electrophysiology. Superior cervical ganglion (SCG) neurons from 1−4-day-old rat pups were dissociated and plated into 35-mm dishes using standard techniques. Whole-cell voltage clamp recordings of K^+ channel currents were made 24−48 h later.[20] The external solution contained NaCl (150 mM), KCl (5 mM), $MgCl_2$ (1.1 mM), $CaCl_2$ (2.6 mM), Hepes (10 mM), and glucose (10 mM), with pH adjusted to 7.4 with NaOH. The internal solution contained KCl (80 mM), potassium aspartate (50 mM), EGTA (10 mM), and Hepes (10 mM), with pH adjusted to 7.3 with KOH. Test compounds were dissolved in DMSO at a concentration of 10 mM with final concentrations obtained by serial dilution in the external solution. Neurons were voltage-clamped at a potential of −60 mV, and 30-ms steps to +50 mV elicited K^+ channel currents. Control responses were obtained before application of drug to neurons by local perfusion. Data were expressed as a percent inhibition of sustained K^+ current.

MES Assays. Procedures for the mouse MES assay were as reported previously.[21,22] Compounds were dissolved in 0.05 M Tris and tested for anticonvulsant effect at the peak of activity which occurred 2 min after iv adminstration. ED_{50} values were determined by Litchfield and Wilcoxon analysis.

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