Synthesis of *N*-Substituted 4-(4-Hydroxyphenyl)piperidines, 4-(4-Hydroxybenzyl)piperidines, and (±)-3-(4-Hydroxyphenyl)pyrrolidines: Selective Antagonists at the 1A/2B NMDA Receptor Subtype

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Received August 23, 1999

Antagonists at the 1A/2B subtype of the NMDA receptor (NR1A/2B) are typically small molecules that consist of a 4-benzyl- or a 4-phenylpiperidine with an ω-phenylalkyl substituent on the heterocyclic nitrogen. Many of these antagonists, for example ifenprodil (**1**), incorporate a 4-hydroxy substituent on the ω-phenyl group. In this study, the position of this 4-hydroxy substituent was transferred from the ω-phenyl group to the benzyl or phenyl group located on the 4-position of the piperidine ring. Analogues incorporating pyrrolidine in lieu of piperidine were also prepared. Electrical recordings using cloned receptors expressed in *Xenopus* oocytes show that high-potency antagonists at the NR1A/2B subtype are obtained employing *N*-(ω-phenylalkyl)-substituted 4-(4-hydroxyphenyl)piperidine, 4-(4-hydroxybenzyl)piperidine, and (±)-3-(4-hydroxyphenyl)pyrrolidine as exemplified by **21** ($IC_{50} = 0.022\ \mu M$), **33** ($IC_{50} = 0.059\ \mu M$), and **40** ($IC_{50} = 0.017\ \mu M$), respectively. These high-potency antagonists are >1000 times more potent at the NR1A/2B subtype than at either the NR1A/2A or NR1A/2C subtypes. The binding affinities of **21** at α_1-adrenergic receptors ([^{3}H]prazosin, $IC_{50} = 0.54\ \mu M$) and dopamine D2 receptors ([^{3}H]raclopride, $IC_{50} = 1.2\ \mu M$) are reduced by incorporating a hydroxy group onto the 4-position of the piperidine ring and the β-carbon of the *N*-alkyl spacer to give (±)-**27**: IC_{50} NR1A/2B, 0.026; α_1, 14; D2, 105 μM. The high-potency phenolic antagonist **21** and its low-potency *O*-methylated analogue **18** are both potent anticonvulsants in a mouse maximal electroshock-induced seizure (MES) study (ED_{50} (iv) = 0.23 and 0.56 mg/kg, respectively). These data indicate that such compounds penetrate the blood−brain barrier but their MES activity may not be related to NMDA receptor antagonism.

Introduction

N-Methyl-D-aspartate (NMDA) receptor antagonists are being investigated as potential therapeutic agents for diseases associated with acute and chronic neuronal excitotoxicity such as focal ischemia, epilepsy, and Parkinson's disease.[1] However, undesired side effects such as neurotoxicity, sedation, and psychotomimetic behaviors have limited the usefulness of these antagonists in the clinic.[2] Subtype-selective NMDA receptor antagonists may offer one means to limit these side effects.[3] Native NMDA receptors are heterooligomeric assemblies of two classes of subunits. These subunits are NMDA receptor 1 (NR1) of which eight isoforms are known and NMDA receptor 2 (NR2) that consists of four distinct types (A−D), each of which is transcribed from a separate gene. The NR1 subunits are widely distributed throughout the brain, whereas the NR2 subunits exhibit distinct regional distribution patterns.[4] Hence, the activity of subtype-selective NR2 antagonists should be limited to specific regions in the brain. Regional specificity may improve the side effect profile associated with broad-spectrum NMDA receptor antagonists.

Many NR2B-selective antagonists reported in the literature (e.g. **1**,[5] **2**,[6] **3**,[7] and **4**[8]) are 4-benzyl- or 4-phenylpiperidines with an ω-(4-hydroxyphenyl)alkyl or ω-(4-hydroxyphenoxy)alkyl substituent on the heterocyclic nitrogen atom. Recently, we reported that the piperidine ring is not requisite for potent NR2B antagonism since open chain alkylamines, such as bis(phenylalkyl)amine **5**, are also potent antagonists.[9] Interestingly, even cinnamides **6** and **7** are moderate NR2B antagonists.[10] These amides are of special interest since antagonist potency is retained even though the *p*-hydroxy group, which is critical for potency in this series,[11] is located on opposite ends of the two molecules.

Our objective herein is to determine whether the transposition of the hydroxy group with retention of potency that is observed for **6** and **7** can be extended to a piperidine or pyrrolidine series of antagonists. Therefore, selected *N*-substituted 4-(4-hydroxyphenyl)piperidines, 4-(4-hydroxybenzyl)piperidines, and (±)-3-(4-

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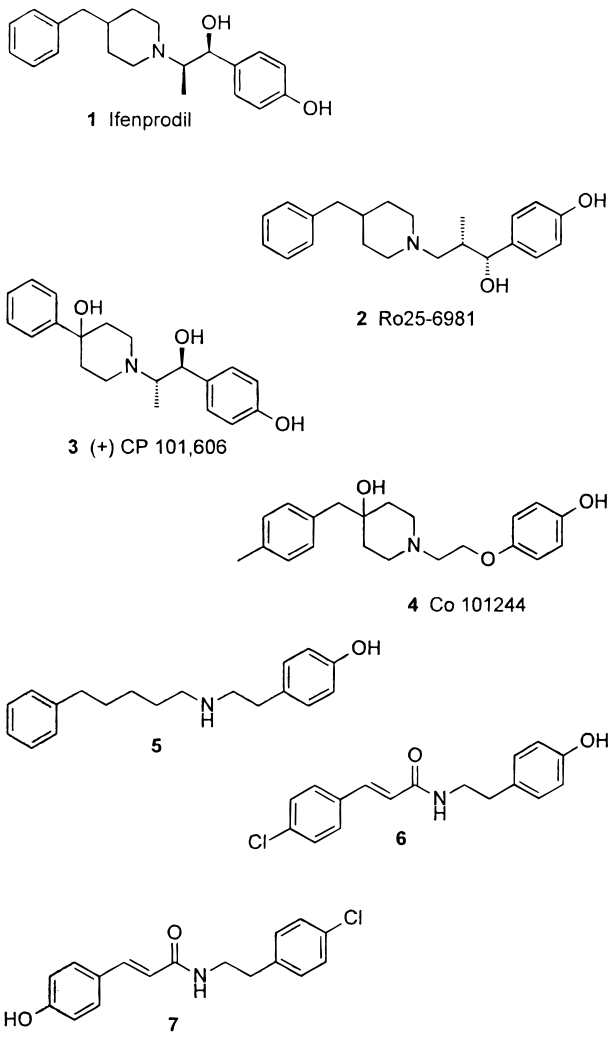
10.1021/jm990428c CCC: $19.00
Published on Web 02/15/2000



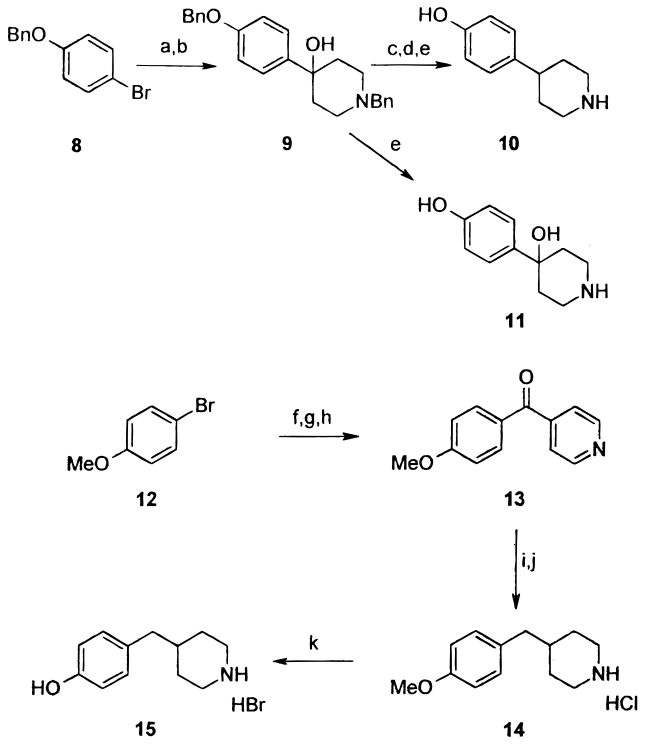
hydroxyphenyl)pyrrolidines were prepared and assayed for NMDA receptor antagonism employing the NR1A/2A, NR1A/2B, and NR1A/2C subtypes. Additionally, selected molecules were evaluated for α_1-adrenergic ([^{3}H]prazosin) and dopamine D2 ([^{3}H]raclopride) binding activity and for in vivo anticonvulsant activity.

Chemistry

Synthesis. The preparation of 4-(4-hydroxyphenyl)-piperidine[12] (**10**) was performed according to general literature procedures[13] starting from 4-benzyloxybromobenzene (**8**; Scheme 1). Treatment of **8** with *n*-BuLi followed by addition of 1-benzyl-4-piperidone gave alcohol **9**.[14] Heating **9** in a solution of aqueous ethanolic HCl resulted in elimination of the hydroxy group and removal of the *O*-benzyl protecting group (structure not shown). Conversion of this intermediate to the free base (NH_4OH, $MeOH/H_2O$) followed by reduction and concomitant *N*-debenzylation (H_2, Pd/C) gave **10**. The 4-hydroxypiperidine analogue **11**[14] was prepared by selective hydrogenolysis of **9**. Treatment of **14**, which was prepared from **12** by methods described in the patent literature,[15] with refluxing aqueous HBr gave the corresponding phenol **15**.

The synthesis of *N*-substituted 4-phenylpiperidines is shown in Scheme 2. *N*-Alkylation of **16**,[13] which was prepared as described for **10** but starting from 4-bromo-

Scheme 1[a]



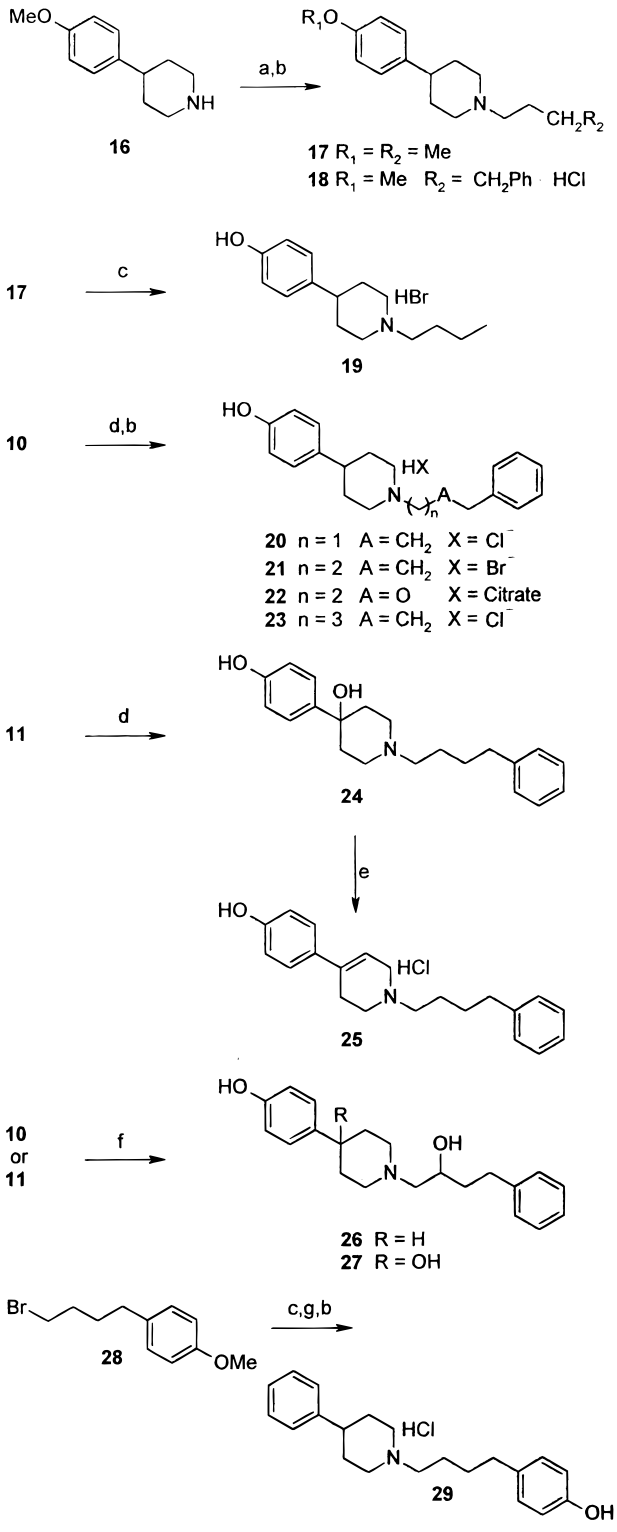
[a] (a) *n*-BuLi, THF, −78 °C; (b) 1-benzyl-4-piperidone, THF, −78 °C; (c) concd HCl in EtOH (1:1), reflux; (d) NH_4OH, $MeOH/H_2O$; (e) H_2, Pd/C (10%), EtOH, 25 °C; (f) *n*-BuLi, THF, −78 °C; (g) 4-cyanopyridine, THF, −78 to 0 °C; (h) aq HCl, 25 °C; (i) N_2H_4, KOH, ethylene glycol, 140 °C; (j) H_2, PtO_2, MeOH, aq HCl, 25 °C; (k) HBr (48% in H_2O), reflux.

anisole, gave methoxyphenylpiperidines **17** and **18**. Demethylation of **17** with BBr_3 in CH_2Cl_2 gave **19**. Subsequently, it was found more convenient to directly *N*-alkylate phenolic piperidine **10** employing an alkylating agent with $NaHCO_3$ in DMF. This procedure did not result in any observable *O*-alkylation and was used to prepare **20**−**23**. In a similar manner, alkylation of **11** gave 4-hydroxypiperidine **24**. Treatment of **24** with aqueous HCl in refluxing EtOH gave tetrahydropyridine **25**. Racemic alcohols **26** and **27** were prepared by reaction of 4-phenylbutane 1,2-epoxide[16] with piperidine **10** or **11** in DMF. Compound **29** was prepared by demethylation of **28**[17] (BBr_3, CH_2Cl_2) followed by reaction of the corresponding phenol (not shown) with 4-phenylpiperidine. Where appropriate, amine free bases were converted to salts by treatment with an acid in MeOH.

N-Substituted 4-(4-hydroxybenzyl)piperidines were synthesized as shown in Scheme 3. Phenol **30** was prepared by *N*-alkylation of methoxybenzylpiperidine **14** followed by demethylation. Acetylenes **31** and **32** were synthesized by *N*-alkylation of **15** with either 3-tosyloxy-1-propyne or 4-tosyloxy-1-butyne,[18] respectively, followed by a Pd-catalyzed coupling of the resulting terminal alkynes (not shown) with iodobenzene. Hydrogenation of **31** gave **33**.

The synthesis of (±)-3-(4-hydroxyphenyl)pyrrolidines is shown in Scheme 4. Maleic acid diethyl ester **35** was prepared via the general method of Dean and Blum[19] by the initial treatment of 4-methoxybenzylcyanide (**34**) with glyoxylic acid followed by ethanolysis of the resulting nitrile (not shown). Hydrogenation of **35** to the

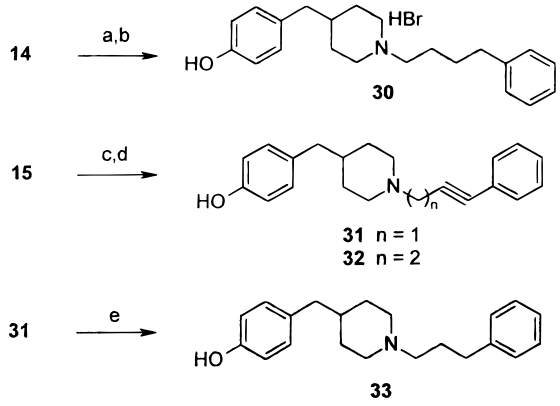
Scheme 2[a]



[a] (a) 1-Bromobutane or 1-phenyl-4-tosyloxybutane, K_2CO_3, MeCN, reflux; (b) HBr or HCl or citric acid, MeOH, 25 °C; (c) BBr_3, CH_2Cl_2, 0−25 °C; (d) 1-bromo-3-phenylpropane or 1-phenyl-4-tosyloxybutane or 2-benzyloxyethyl mesylate or 1-phenyl-5-tosyloxypentane, $NaHCO_3$, DMF, 80 °C; (e) concd HCl in EtOH (1:1), reflux; (f) 4-phenylbutane 1,2-epoxide, DMF, 80 °C; (g) 4-phenylpiperidine, $NaHCO_3$, MeCN, reflux.

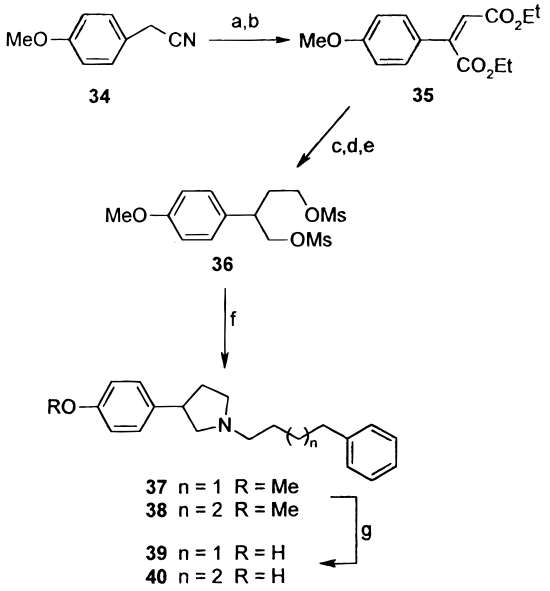
succinate, followed by ester reduction ($LiAlH_4$) and mesylation of the resulting diol, yielded dimesylate **36**. The reaction of **36** with neat 4-phenylbutylamine or 5-phenylpentylamine[20] gave methoxyphenylpyrrolidines

Scheme 3[a]



[a] (a) 1-Phenyl-4-tosyloxybutane, K_2CO_3, MeCN, reflux; (b) BBr_3, CH_2Cl_2, 0−25 °C; (c) 3-tosyloxy-1-propyne or 4-tosyloxy-1-butyne, DMF, $NaHCO_3$, 80 °C; (d) iodobenzene, $Pd(PPh_3)_4$, pyrrolidine, 25 °C; (e) H_2, Pd/C (20%), THF:MeOH (1:1), 25 °C.

Scheme 4[a]



[a] (a) Glyoxylic acid, K_2CO_3, MeOH, reflux; (b) H_2SO_4, EtOH, reflux; (c) H_2, Pd/C (10%), EtOH, 25 °C; (d) $LiAlH_4$, THF, reflux; (e) methanesulfonyl chloride, TEA, DMAP, CH_2Cl_2, 25 °C; (f) 4-phenylbutylamine (neat) or 5-phenylpentylamine (neat), 100 °C; (g) BBr_3, CH_2Cl_2, 25 °C.

37 and **38**, respectively. Demethylation of **37** and **38** gave the corresponding phenols **39** and **40**.

Electrophysiology in *Xenopus* Oocytes. Potency and subunit selectivity (see Table 1) were determined by electrical recordings under steady-state conditions in *Xenopus* oocytes expressing three binary combinations of cloned rat NMDA receptor subunits (NR1A expressed in combination with either NR2A, NR2B, or NR2C). The IC_{50} values were derived by curve fitting the concentration−inhibition data pooled from 1−7 separate experiments (see ref 9a for details).

Radioligand Binding Studies. Selected compounds were assayed for α_1-adrenergic and dopamine D2 activity employing [^{3}H]prazosin[21] and [^{3}H]raclopride[22] binding assays, respectively (see Table 2). Test compounds were evaluated at nine concentrations in duplicate (see Experimental Section for details). IC_{50} values were determined by fitting the data to the sigmoidal equation in Prism.

Table 1. Functional Antagonism of *N*-Substituted 4-Phenylpiperidines, 4-Benzylpiperidines, and (±)-3-Phenylpyrrolidines at NMDA Receptor Subtypes

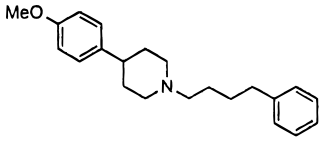
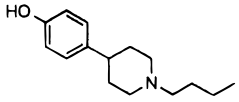
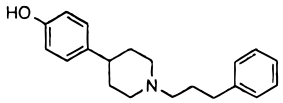
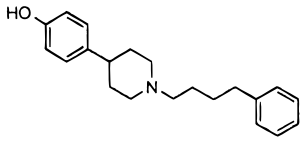
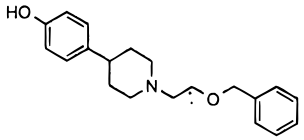
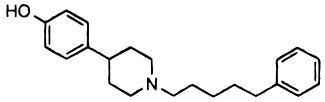
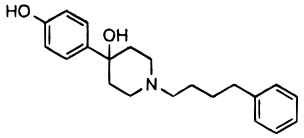
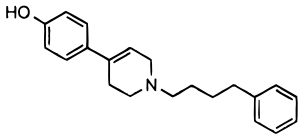
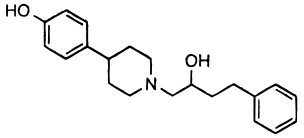
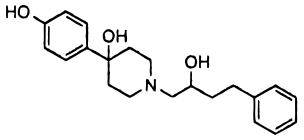
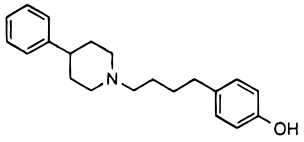
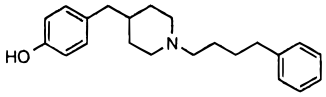
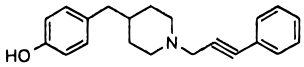
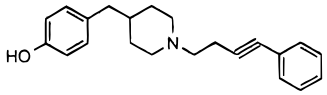
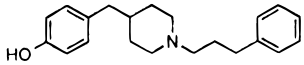
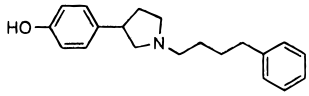
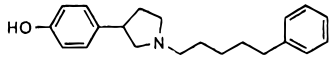
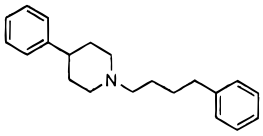
			IC_{50} (μM)[a]		
compd no.	Structure	Salt	NR1A/2A	NR1A/2B	NR1A/2C
18		HCl	>100	>100	>100
19		HBr	>100	61± 22	>100
20		HCl	51	0.074 ± 0.01	>100
21		HBr	>100	0.022 ± 0.003	>100
22		Citrate	59	0.019 ± 0.001	>100
23		HCl	>100	0.075 ± 0.02	>100
24		-	62	0.012 ± 0.001	>100
25		HCl	>100	0.011 ± 0.002	>100
26		-	>100	0.019 ± 0.003	>100
27		-	93	0.026 ± 0.004	>100

Table 1 (Continued)

compd no.	Structure	Salt	IC_{50} (μM)[a] NR1A/2A	NR1A/2B	NR1A/2C
29		HCl	43	0.23 ± 0.05	>100
30		HBr	>100	0.071 ± 0.01	>100
31		-	>100	0.18 ± 0.02	>100
32		-	>100	0.80 ± 0.09	>100
33		-	>100	0.059 ± 0.01	>100
39		-	52	0.13 ± 0.01	>100
40		-	41	0.017 ± 0.002	>100
41		Maleate	>100	2.2 (1.5-2.8)[b]	>100

[a] IC_{50} values (±SEM) were determined by electrical recordings in *Xenopus* oocytes expressing the various NMDA receptor combinations. For all compounds $n \geq 3$ at NR1A/2B. With the exception of **29**, $n \geq 2$ at other subunit combinations. For **29**, $n = 1$ at NR1A/2A. [b] The data for **41** are presented with 95% confidence limits; see ref 25.

Table 2. α_1-Adrenergic and Dopamine D2 Receptor Potencies and Mouse MES Activity for *N*-Substituted 4-Phenylpiperidines and 4-Hydroxy-4-phenylpiperidines

compd no.	IC_{50} (μM) α_1[a]	D2[b]	ED_{50} (mg/kg) mouse MES[c]
18	1.7[d]	0.41	0.56 (0.33−0.94)
21	0.54	1.2	0.23 (0.10−0.51)
24	2.2	22	2.3 (1.3−4.1)
26	1.4	5.9	0.46 (0.25−0.84)
27	14	105	5.7 (3.8−8.7)

[a] Inhibition of [^{3}H]prazosin binding in rat brain cortical membranes. [b] Inhibition of [^{3}H]raclopride binding in rat brain striatal membranes. [c] ED_{50} values and 95% confidence limits for protection against MES seizures in mice. A minimum of 24 animals were employed for each test compound.

In Vivo Measurements. Anticonvulsant effects for five compounds were measured using a mouse MES model.[23] Seizure protection was measured 2 min after iv administration. ED_{50} values (95% confidence limits) are given in Table 2 (see Experimental Section for details).

Results and Discussion

Antagonist Potency at NMDA Receptor Subtypes. The goal of this study was to determine if high-potency antagonists for the NR1A/2B subtype could be obtained by tethering a 4-hydroxyphenyl or 4-hydroxybenzyl substituent onto the 4-position of an *N*-(ω-phenylalkyl)piperidine or the 3-position of an *N*-(ω-phenylalkyl)pyrrolidine. As a starting point, we chose to prepare derivatives of 4-phenyl-1-(4-phenylbutyl)-piperidine (PPBP, **41**), a potent σ receptor ligand.[24a] Compound **41** is an unsubstituted analogue of the NR2B and D2 antagonist haloperidol[25a] and decreases brain injury after focal ischemia in cats.[24b] Like haloperidol, compound **41** is a moderately potent NR1A/2B antago-

nist (IC_{50} = 2.2 μM, Table 1).[25b] Each phenyl group of **41** was separately substituted at the *para* position with a hydroxy group to give either **21** or **29**. Compound **21** (IC_{50} = 0.022 μM) is 100 times more potent at NR1A/2B than **41,** while compound **29** (IC_{50} = 0.23 μM) is 10-fold more potent than **41**. The increased potency of both **21** and **29** relative to **41** suggests that such 4-phenylpiperidines may orientate in opposite directions within the receptor pocket in order to take advantage of a putative hydrogen bond interaction. Alternatively, these data may also indicate that the receptor pocket possesses two independent phenolic binding domains, one of which may accommodate **21** and the other **29**. This latter possibility seems unlikely in the case of the *N*-(phenylalkyl)cinnamide series of NR1A/2B antagonists,[10b] which exhibits a SAR similar to those of the piperidine- and bis(phenylalkyl)amine-based antagonists.[9b] The dihydroxycinnamide resulting from replacement of the Cl of **7** by OH is about 170-fold less potent than **7**,[10b] indicating that a second OH group is detrimental to potency.

Removing the phenyl group from the butyl chain of **21** (i.e., **19**) reduces the potency approximately 3000-fold. The reduction in potency is likely the result of a reduced hydrophobic interaction that is important for docking the ligand to the receptor pocket. Decreasing the alkyl spacer length of **21** to three carbons (**20**) or increasing it to five carbons (**23**) results in a 3−4-fold drop in potency relative to **21**. Placing a methyl group on the phenolic oxygen of **21** gives **18** (IC_{50} >100 μM), which is essentially inactive. In light of the moderate potency of **41** (vide supra), the inactivity of **18** is surprising and implies severe steric constraints for this series. The effect of replacing the phenolic oxygen with other substituents, such as a fluorine or chlorine atom, was not investigated. Various other modifications to **21** have little effect on the NR1A/2B potency. These include (1) incorporation of an oxygen atom into the alkyl spacer (**22**); (2) addition of a hydroxy group to the 4-position of the piperidine ring and/or to the alkyl spacer β to the piperidine nitrogen (**24**, **26,** and **27**); (3) placement a double bond between C3 and C4 of the piperidine ring (**25**).

The 4-benzylpiperidine analogue of **21** (i.e., **30**) shows a 3−4-fold drop in potency. Decreasing the alkyl spacer length of **30** by one carbon atom (i.e., **33**) increases potency relative to **30** but not to the same level as that of 4-phenylpiperidine **21**. The alkynyl analogues **31** and **32** show decreased potency relative to their reduced counterparts **33** and **30**. Apparently, the added rigidity imposed by the triple bond does not allow for optimal interaction with the receptor.

Changing the piperidine ring of **21** to a pyrrolidine ring (i.e., **39**) reduces the potency approximately 6-fold. However, increasing the alkyl spacer length to five carbons (**40**) restores the potency to that of **21**.

The potency data at NR1A/2B for these three series of molecules suggest that one factor for optimal receptor site binding is the length of the antagonist. This length dependence may be due to the optimization of factors such as the fit of the ligand within the receptor pocket or the optimization of hydrophobic interactions between the ligand and its receptor site. Previous modeling studies have calculated the overall length (distance measured from the *para* carbon of one phenyl ring to the hydroxyl oxygen of the other ring) of several NR1A/2B antagonists in a fully extended, energy-minimized conformation.[9b] For piperidine-based antagonists, the length ranged from 13.9 Å for **1** (NR1A/2B IC_{50} = 0.11 μM) to 15 Å for **2** (NR1A/2B IC_{50} = 0.009 μM). The calculated lengths for 4-phenylpiperidine **21**, 4-benzylpiperidine **33,** and 4-phenylpyrrolidine **40** (15.6, 14.0, and 15.8 Å, respectively) are similar. By way of comparison, the length of the most potent of the *N*-(phenylalkyl)cinnamides tested, namely, *N*-(4-phenylbutyl)-4-hydroxycinnamide (NR1A/2B IC_{50} = 0.077 μM), is 17.5 Å.[10b]

The new NR1A/2B antagonists herein described generally show little or no antagonist potency at the NR1A/2A and NR1A/2C subtypes. With the exception of **20**, all compounds having potency less than 0.1 μM at NR1A/2B are at least 1000-fold more selective versus either NR1A/2A or NR1A/2C. For **20**, the selectivity for NR1A/2B is approximately 700 times that for NR1A/2A.

Interaction at Other Receptor Types. Selected molecules were screened for activity at α_1-adrenergic and dopamine D2 receptors using radioligand binding assays (see Table 2). Activity at these sites was viewed as a liability for a clinically useful drug. Compound **21** shows moderate affinity for these receptors. The affinities may be decreased by placing a hydroxy group on the 4-position of the piperidine ring (**24**) or on the β-carbon of the *N*-alkyl spacer (**26**). Further reduction is obtained by placing hydroxy groups at both positions (**27**). The lessened affinities at α_1 and D2 receptors come without loss of potency at NR1A/2B. Similar observations have been made for certain other NR1A/2B antagonists.[7]

Compound **21** was assayed by Novascreen.[26] In a nonselective σ receptor assay, compound **21** exhibited 98.5% inhibition of [^{3}H]DTG binding at 1 μM. The activity of **21** at σ receptors is not surprising since it is a structural analogue of **41**, a known σ ligand.[24a]

In Vivo Activity. Selected molecules were assayed for in vivo anticonvulsant activity employing a mouse MES model. The highly potent NR1A/2B antagonist **21** and the low-potency antagonist **18** are both potent anticonvulsants (see Table 2) when administered iv indicating their ability to penetrate the blood−brain barrier. The lack of correlation between NR1A/2B potency and MES activity for these two compounds leaves the mechanism for this activity in question.

Hydroxylation of **21** either at the 4-position of the piperidine ring (i.e., **24**) or at the β-position of the alkyl spacer (i.e., **26**) reduces MES activity 10- and 2-fold, respectively. Hydroxylation of both positions (**27**) reduces MES activity approximately 25-fold. The reduction of MES activity may result from a reduced ability of these antagonists to penetrate the blood−brain barrier and/or reduced activity at the site(s) responsible for anticonvulsant activity.

Conclusion

Selected *N*-substituted 4-(4-hydroxyphenyl)piperidines, 4-(4-hydroxybenzyl)piperidines, and (±)-3-(4-hydroxyphenyl)pyrrolidines were prepared and assayed for NMDA receptor antagonism. All are selective for the NR1A/2B subtype. We demonstrate that the phenolic

hydroxy group, which is present in **1**−**4**, may be transposed to the other benzene ring while retaining high potency, as exemplified by **21**, **33**, and **40**. This work provides novel insights for the design of NR2B-selective antagonists.

Experimental Section

Chemistry. All starting materials were commercially available and used as received unless otherwise noted. Melting points were measured on a Thomas-Hoover or a Mel-Temp melting point apparatus and are uncorrected. CH_2Cl_2 was distilled from CaH and THF from Na/benzophenone immediately prior to use. Solvent removal was routinely performed on a rotoevaporator at 30−40 °C. All reactions were performed under an inert atmosphere (Ar or N_2) unless otherwise noted. TLC analyses were performed on plastic or glass backed F-254 silica gel plates. ^{1}H NMR spectra were measured on a Varian Inova or Varian Gemini spectrometer (300 or 400 MHz). Chemical shifts are reported in δ units referenced to the residual ^{1}H signal of the deuterated solvent ($CHCl_3$, δ 7.26; CD_3SOCD_2H, δ 2.49; CD_2HOD, δ 3.31). Microanalyses were performed by Desert Analytics Laboratory, Tuscon, AZ, Roberts Microlit Laboratories, Madison NJ, and Parke-Davis Pharmaceutical Research, Ann Arbor, MI.

1-Benzyl-4-(4-benzyloxyphenyl)-4-hydroxypiperidine (9). A solution of *n*-BuLi in hexanes (1.6 M, 68.8 mL, 110 mmol) was added to a stirred, dry ice/acetone (−78 °C) cooled solution of 4-benzyloxybromobenzene (**8**; 26.5 g, 101 mmol) in THF (300 mL) to give a suspension. The suspension was stirred at −78 °C for 30 min and a solution of 1-benzyl-4-piperidone (19.1 g, 101 mmol) in THF (80 mL) was added over 30 min to give a yellow solution. The solution was stirred at −78 °C for 2 h. The cold reaction solution was added to an ice-cold solution of NH_4Cl (50 g) in H_2O (350 mL). The layers were separated and the aqueous portion was extracted with ether (2 × 100 mL). The organic portion was washed with H_2O (2 × 100 mL) and brine (100 mL) and filtered. The filtrate was dried ($MgSO_4$) and the solvent was removed to give a liquid that turned to a paste upon standing. The paste was triturated with hexanes to give a powder. The powder was crystallized from CH_2Cl_2/hexanes to yield **9** as a colorless crystalline solid (24.4 g, 65%): mp 100−101 °C (lit.[14] mp 104−107 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 1H), 1.75 (dd, J = 12, 2.1 Hz, 2H), 2.16 (td, J = 12, 3.6 Hz, 2H), 2.50 (t, J = 11 Hz, 2H), 2.80 (d, J = 12 Hz, 2H), 3.60 (s, 2H), 5.06 (s, 2H), 6.96 (d, J = 9.0 Hz, 2H), 7.24−7.47 (m, 12H).

4-(4-Hydroxyphenyl)piperidine (10). Concentrated HCl (100 mL) was added in one portion to a stirred, boiling solution of **9** (5.00 g, 13.4 mmol) in 95% EtOH (100 mL). The resulting solution was refluxed for 10 min and cooled to 25 °C with an ice bath. The solution was concentrated on a rotoevaporator at 50−55 °C to give a suspension. The solid was collected and washed with H_2O (3 × 5 mL). The collected solid was dissolved with warming in MeOH:H_2O (1:1, 100 mL) and concentrated NH_4OH (10 mL) was added to give a suspension. The suspension was extracted with $CHCl_3$ (3 × 50 mL). The extract was washed with H_2O (3 × 50 mL) and filtered (cotton). The solvent was removed to give a pink solid. The solid was dissolved in warm EtOH (250 mL) and the solution was hydrogenated (Parr) over Pd/C (10%, 1.00 g) at 50 psig for 24 h. The catalyst was removed by filtration (Celite) and the solvent was removed from the filtrate to give a pale yellow solid. The solid was crystallized from MeCN/MeOH to yield **10** as a colorless solid (1.09 g, 46%): mp 217−219 °C (lit.[12] mp not reported); ^{1}H NMR (300 MHz, CD_3OD) δ 1.61 (qd, J = 12, 3.9 Hz, 2H), 1.78 (d, J = 12 Hz, 2H), 2.57 (tt, J = 12, 3.9 Hz, 1H), 2.72 (td, J = 12, 2.7 Hz, 2H), 3.14 (d, J = 12 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H).

4-Hydroxy-4-(4-hydroxyphenyl)piperidine (11). A mixture of **9** (837 mg, 2.24 mmol) and Pd/C (10% on carbon, 200 mg) in 95% EtOH (120 mL) was hydrogenated (Parr, 50 psig) for 62 h at 25 °C. The catalyst was removed by filtration (Celite) and the solvent was removed from the filtrate to give a yellow solid. The solid was crystallized from MeCN/MeOH to yield **11** as a pale beige solid (289 mg, 67%): mp 226−228 °C dec (lit.[14] mp 232−235 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.45 (d, J = 12 Hz, 2H), 1.62−1.78 (m, 2H), 2.59−2.72 (m, 2H), 2.87 (t, J = 12 Hz, 2H), 4.52 (s, 1H), 6.66 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 9.18 (b, 1H).

4-(4-Hydroxybenzyl)piperidine Hydrobromide (15). A solution of the HCl salt of 4-(4-methoxybenzyl)piperidine[15] (**14**; 2.00 g, 8.27 mmol) in 48% HBr (aqueous, 30 mL) was heated at reflux for 2 h. The solvent was removed to yield **15** as a solid (2.25 g, 100%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23 (q, J = 14 Hz, 2H), 1.65 (d, J = 12 Hz, 3H), 2.37 (d, J = 6.8 Hz, 2H), 2.78 (q, J = 11 Hz, 2H), 3.20 (d, J = 11 Hz, 2H), 6.60 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 8.3 Hz, 2H), 8.18 (b, 1H), 8.50 (b, 1H), 9.15 (b, 1H).

1-Butyl-4-(4-methoxyphenyl)piperidine (17). A mixture of the hydrochloride salt of 4-(4-methoxyphenyl)piperidine[13] (**16**; 250 mg, 1.10 mmol), 1-bromobutane (125 μL, 159 mg, 1.16 mmol) and K_2CO_3 (312 mg, 2.26 mmol) in MeCN (20 mL) was stirred at reflux for 48 h. The reaction was allowed to cool to 25 °C and added to 10% aqueous HCl (50 mL) to give a mixture. The mixture was extracted with $CHCl_3$ (3 × 40 mL). The extract was washed with 10% NH_4OH (80 mL) and filtered (cotton). The solvent was removed to give a yellow solid. The solid was purified by chromatography on silica gel with EtOH in $CHCl_3$ elution. Solvent removal yielded **17** as a solid (272 mg, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.39 (td, J = 15, 7.2 Hz, 2H), 1.70−1.82 (m, 2H), 1.86−1.98 (m, 2H), 2.17−2.38 (m, 2H), 2.38−2.68 (m, 3H), 2.68−2.82 (m, 2H), 3.33−3.46 (m, 2H), 3.79 (s, 3H), 6.84 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 9.0 Hz, 2H).

4-(4-Methoxyphenyl)-1-(4-phenylbutyl)piperidine Hydrochloride (18). Compound **18** was prepared as described for **17** from the hydrochloride salt of **16** (1.00 g, 4.39 mmol) and 4-phenyl-1-tosyloxybutane[27] (1.40 g, 4.61 mmol). The free base of **18** was obtained as a beige solid (979 mg, 69%): mp 48−50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52−1.86 (m, 8H), 2.01 (td, J = 11, 3.6 Hz, 2H), 2.34−2.50 (m, 3H), 2.65 (t, J = 7.2 Hz, 2H), 2.98−3.08 (m, 2H), 3.79 (s, 3H), 6.85 (d, J = 8.7 Hz, 2H), 7.12−7.32 (m, 7H).

Treatment of the free base of **18** with methanolic HCl followed by crystallization from MeCN gave **18** as a colorless crystalline solid: mp 211−213 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.67−2.15 (m, 8H), 2.66−2.92 (m, 3H), 3.00−3.24 (m, 4H), 3.61 (d, J = 11 Hz, 2H), 3.76 (s, 3H), 6.87 (d, J = 8.7 Hz, 2H), 7.13−7.33 (m, 7H). Anal. ($C_{22}H_{30}ClNO$) C, H, N.

1-Butyl-4-(4-hydroxyphenyl)piperidine Hydrobromide (19). BBr_3 (1.0 M in CH_2Cl_2, 3.0 mL, 3.0 mmol) was added in one portion to a stirred solution of **17** (220 mg, 890 μmol) in CH_2Cl_2 (20 mL) at 0 °C. The ice bath was removed and the solution was stirred for 1 h. The reaction was added to a saturated aqueous $NaHCO_3$ solution (50 mL) to give a mixture. The mixture was stirred at 25 °C for 5 min. The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic portion was washed with H_2O (50 mL) and filtered (cotton). The solvent was removed to give a solid. The solid was crystallized from methyl ethyl ketone/MeOH to yield **19** as a beige solid (80 mg, 30%): mp 263−265 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (t, J = 7.5 Hz, 3H), 1.24−1.40 (m, 2H) 1.60−2.00 (m, 6H), 2.62−2.77 (m, 1H), 2.90−3.26 (m, 4H), 3.54 (d, J = 12 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.1 Hz, 2H), 9.25 (s, 1H), 9.32 (b, 1H). Anal. ($C_{15}H_{24}BrNO$) C, H, N.

4-(4-Hydroxyphenyl)-1-(3-phenylpropyl)piperidine Hydrochloride (20). A mixture of **10** (400 mg, 2.26 mmol), 1-bromo-3-phenylpropane (472 mg, 2.37 mmol) and $NaHCO_3$ (199 mg, 2.37 mmol) in DMF (5 mL) was stirred at 80 °C for 18 h. The reaction was allowed to cool to 25 °C and was added to H_2O (50 mL). The mixture was extracted with $CHCl_3$ (3 × 50 mL). The extract was washed with H_2O (2 × 50 mL) and filtered (cotton). The solvent was removed to give a yellow liquid. The product was purified by chromatography on silica gel with EtOH/$CHCl_3$ elution to give an oil. Treatment of the oil with methanolic HCl followed by crystallization from

methyl ethyl ketone/MeOH yielded **20** as a colorless, crystalline solid (388 mg, 52%): mp 181−182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.79−2.13 (m, 6H), 2.58−2.73 (m, 3H), 2.87−3.25 (m, 4H), 3.50 (d, J = 12 Hz, 2H), 6.70 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 7.07−7.34 (m, 5H), 9.30 (s, 1H), 10.66 (b, 1H). Anal. ($C_{20}H_{26}ClNO$) C, H, N.

4-(4-Hydroxyphenyl)-1-(4-phenylbutyl)piperidine Hydrobromide (21). Compound **21** was prepared as described for **20** from **10** (1.70 g, 9.59 mmol) and 1-phenyl-4-tosyloxybutane (3.07 g, 10.1 mmol). The reaction was allowed to proceed for 3 h. The free base was converted to the HBr salt by treatment with 48% aqueous HBr in MeOH/ $CHCl_3$ (1:1). Crystallization from MeOH yielded **21** as a colorless, crystalline solid (1.60 g, 43%): mp 217−218 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.66−2.12 (m, 8H), 2.66−2.87 (m, 3H), 3.00−3.20 (m, 4H), 3.54−3.68 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.14−7.32 (m, 5H). Anal. ($C_{21}H_{28}BrNO$) C, H, N.

1-(2-Benzyloxyethyl)-4-(4-hydroxyphenyl)piperidine Citrate (22). Methanesulfonyl chloride (650 μL, 962 mg, 8.40 mmol) in CH_2Cl_2 (15 mL) was added to a stirred solution of 2-benzyloxyethanol (1.00 mL, 1.07 g, 7.03 mmol) in TEA (2 mL). The resulting mixture was stirred overnight at room temperature, and washed with dilute aqueous HCl, saturated $NaHCO_3$ and H_2O. The organic layer was dried ($MgSO_4$) and the crude product which was purified by chromatography on silica gel with EtOAc/hexanes elution to yield 2-(benzyloxy)-ethyl mesylate as a colorless liquid (679 mg, 42%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03 (s, 3H), 3.73−3.75 (m, 2H), 4.40 (t, J = 2.2 Hz, 2H), 4.58 (s, 2H), 7.31−7.37 (m, 5H).

Compound **22** was prepared as described for **20** from **10** (189 mg, 1.07 mmol) and 2-(benzyloxy)ethyl mesylate (234 mg, 1.02 mmol). The reaction was allowed to proceed for 18 h. The free base was treated with citric acid in MeOH. Solvent removal and trituration with ether yielded **22** as a colorless, hygroscopic solid (133 mg, 26%): ^{1}H NMR (300 MHz, CD_3OD) δ 1.98 (s, 4H), 2.70−2.85 (m, 6H), 3.09 (b, 1H), 3.37 (s, 2H), 3.62 (d, J = 11 Hz, 2H), 3.82 (s, 2H), 4.58 (s, 2H), 6.73 (d, J = 7.6 Hz, 2H), 7.07 (d, J = 7.6 Hz, 2H), 7.37 (s, 5H). Anal. ($C_{26}H_{33}NO_9\cdot 0.25H_2O$) C, H, N.

4-(4-Hydroxyphenyl)-1-(5-phenylpentyl)piperidine Hydrochloride (23). Compound **23** was prepared as described for **20** from the hydrochloride salt of **10** (350 mg, 1.64 mmol) and 1-phenyl-5-tosyloxypentane[28] (548 mg, 1.72 mmol). The reaction was allowed to proceed for 20 h. Treatment of the free base with methanolic HCl followed by crystallization from MeCN yielded **23** as a colorless, crystalline solid (327 mg, 55%): mp 169−171 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.24−1.37 (m, 2H), 1.52−2.08 (m, 8H), 2.54−2.73 (m, 3H), 2.84−3.04 (m, 4H), 3.48 (d, J = 16 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 7.12−7.31 (m, 5H), 9.29 (s, 1H), 10.45 (b, 1H). Anal. ($C_{22}H_{30}ClNO$) C, H, N.

4-Hydroxy-4-(4-hydroxyphenyl)-1-(4-phenylbutyl)piperidine (24). Compound **24** was prepared as described for **20** from **11** (280 mg, 1.45 mmol) and 1-phenyl-4-tosyloxybutane (463 mg, 1.52 mmol). The reaction was allowed to proceed for 3 h. After chromatography, the free base was crystallized from MeCN to yield **24** as a colorless, crystalline solid (287 mg, 61%): mp 157−159 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38−1.65 (m, 6H), 1.77−1.94 (m, 2H), 2.23−2.75 (m, 8H), 4.58 (b, 1H), 6.67 (d, J = 8.4 Hz, 2H), 7.10−7.32 (m, 7H), 9.19 (s, 1H). Anal. ($C_{21}H_{27}NO_2\cdot 0.2H_2O$) C, H, N.

1,2,5,6-Tetrahydro-4-(4-hydroxyphenyl)-1-(4-phenylbutyl)pyridine Hydrochloride (25). Aqueous, concentrated HCl (4 mL) was added dropwise over 30 s to a stirred boiling solution of **24** (150 mg, 461 μmol) in absolute EtOH (4 mL). The resulting solution was stirred at reflux for 6 min to give a suspension. The suspension was allowed to cool to 25 °C. The suspended solid was collected, washed with H_2O (3 × 1 mL) and dried to yield **25** as a pale yellow crystalline solid (145 mg, 91%): mp 230−231 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.53−1.85 (m, 4H), 2.54−2.88 (m, 4H), 3.04−3.24 (m, 3H), 3.49−3.75 (m, 2H), 3.82−3.99 (m, 1H), 5.98 (s, 1H), 6.76 (d, J = 8.7 Hz, 2H), 7.14−7.36 (m, 7H), 9.65 (s, 1H), 10.56 (b, 1H). Anal. ($C_{21}H_{26}ClNO$) C, H, N.

(±)-1-(2-Hydroxy-4-phenylbutyl)-4-(4-hydroxyphenyl)-piperidine (26). A mixture of the HCl salt of **10** (350 mg, 1.64 mmol) and $NaHCO_3$ (138 mg, 1.64 mmol) in DMF (4 mL) was stirred at 85 °C for 10 min to give a near homogeneous solution. Neat 4-phenylbutane 1,2-oxide[16] (510 mg, 3.44 mmol) was added and the reaction mixture was stirred overnight at 85 °C. The reaction was allowed to cool to 25 °C. The DMF was removed in vacuo. The crude reaction product was purified by chromatography on silica gel with EtOH in $CHCl_3$ elution followed by crystallization from ether/hexanes to yield **26** as a colorless solid (225 mg, 42%): mp 154−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68−1.84 (m, 6H), 2.00 (td, J = 16, 2.4 Hz, 1H), 2.26−2.51 (m, 4H), 2.64−2.77 (m, 1H), 2.80−2.93 (m, 2H), 3.08 (d, J = 16 Hz, 1H), 3.67−3.78 (m, 1H), 6.77 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.14−7.32 (m, 5H). Anal. ($C_{21}H_{27}NO_2$) C, H, N.

(±)-4-Hydroxy-1-(2-hydroxy-4-phenylbutyl)-4-(4-hydroxyphenyl)piperidine (27). A mixture of **11** (300 mg, 1.55 mmol) and 4-phenylbutane 1,2-oxide (484 mg, 3.26 mmol) in DMF (5 mL) was stirred at 80 °C for 6 h. The DMF was removed in vacuo. The crude reaction product was purified by chromatography on silica gel with EtOH in $CHCl_3$ elution followed by crystallization from $CHCl_3$/hexanes to yield **27** as a colorless solid (170 mg, 32%): ^{1}H NMR ($CDCl_3$) δ 1.63−1.84 (m, 4H), 2.06 (pd, J = 13, 4.2 Hz, 2H), 2.30−2.48 (m, 3H), 2.62−2.93 (m, 5H), 3.76 (m, 1H), 6.82 (d, J = 8.4 Hz, 2H), 7.14−7.38 (m, 7H). Anal. ($C_{21}H_{27}NO_3$) C, H, N.

1-(4-(4-Hydroxyphenyl)butyl)-4-phenylpiperidine Hydrochloride (29). The demethylation of 1-bromo-4-(4-methoxyphenyl)butane[17] (**28**; 1.21 g, 5.00 mmol) was performed as described for **19** to yield 1-bromo-4-(4-hydroxyphenyl)butane as a pale yellow oil (767 mg, 67%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.62 (m, 2H), 1.76 (m, 2H), 2.48 (m, 2H), 3.54 (d, J = 6.6 Hz, 2H), 6.65 (d, J = 7.4 Hz, 2H), 6.96 (d, J = 7.4 Hz, 2H), 9.13 (s, 1H).

A mixture of 4-phenylpiperidine (241 mg, 1.50 mmol), 1-bromo-4-(4-hydroxyphenyl)butane (366 mg, 1.60 mmol) and $NaHCO_3$ (315 mg, 3.75 mmol) in MeCN (50 mL) was refluxed for 24 h. The inorganic salts were removed by passing the reaction mixture through a short column of silica gel. The crude reaction product was purified by chromatography on silica gel with MeOH/EtOAc elution. The free base was treated with methanolic HCl to yield **29** as a colorless solid (250 mg, 48%): mp 315 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 1.69 (m, 4H), 1.94 (m, 4H), 2.80 (m, 1H), 3.06 (m, 4H), 3.26 (m, 2H), 3.56 (m, 2H), 6.65 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 8.2 Hz, 2H), 7.25 (m, 5H). Anal. ($C_{21}H_{28}ClNO\cdot 1.0H_2O$) C, H, N.

4-(4-Hydroxybenzyl)-1-(4-phenylbutyl)piperidine Hydrobromide (30). A mixture of 4-(4-methoxybenzyl)piperidine[15] (**14**; 600 mg, 2.92 mmol), 4-phenyl-1-tosyloxybutane (934 mg, 3.07 mmol) and K_2CO_3 (827 mg, 5.99 mmol) in MeCN (25 mL) was stirred at reflux for 27 h. The work up and purification were as described for **17** to yield 4-(4-methoxybenzyl)-1-(4-phenylbutyl)piperidine as a yellow solid (920 mg, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50−1.85 (m, 9H), 2.17−2.35 (m, 2H), 2.48−2.55 (d, J = 6.9 Hz, 2H), 2.58−2.70 (t, J = 7.2 Hz, 4H), 3.16−3.30 (m, 2H), 3.78 (s, 3H), 6.77−6.85 (d, J = 8.4 Hz, 2H), 6.98−7.07 (d, J = 8.7 Hz, 2H), 7.08−7.21 (m, 3H), 7.21−7.31 (m, 2H).

Demethylation of the intermediate methoxy compound (905 mg, 2.68 mmol) was performed as described for **19**. Crystallization of the reaction product from methyl ethyl ketone/MeOH yielded **30** as a light brown solid (97 mg, 9%): mp 163−164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26−1.82 (m, 9H), 2.34−2.46 (m, 2H), 2.58 (t, J = 6.9 Hz, 2H), 2.72−3.20 (m, 4H), 3.40 (d, J = 13 Hz, 2H), 6.66 (d, J = 7.8 Hz, 2H), 6.94 (d, J = 8.1 Hz, 2H), 7.12−7.35 (m, 5H), 9.02 (b, 1H), 9.18 (s, 1H). Anal. ($C_{22}H_{30}BrNO$) C, H, N.

4-(4-Hydroxybenzyl)-1-(4-phenyl-3-butynyl)piperidine (32). A mixture of 4-(4-hydroxybenzyl)piperidine (**15**; 2.25 g, 8.27 mmol), 1-tosyloxy-3-butyne[18] (1.85 g, 8.27 mmol) and $NaHCO_3$ (2.10 g, 25.0 mmol) in DMF (50 mL) was stirred at

80 °C for 18 h. The DMF was removed and the residue was partitioned between ether and water. The ether portion was washed with brine and dried ($MgSO_4$). The ether was removed and the residue was purified by chromatography on silica gel with EtOAc elution to yield 1-(3-butynyl)-4-(4-hydroxybenzyl)-piperidine as a solid (800 mg, 40%): mp 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (qq, J = 14.2, 7.1 Hz, 2H), 1.40 (m, 1H), 1.60 (d, J = 12.2 Hz, 2H), 1.90 (m, 2H), 1.95 (s, 1H), 2.35 (m, 1H), 2.42 (d, J = 6.8 Hz, 1H), 2.57 (t, J = 7.3 Hz, 2H), 2.90 (d, J = 12.5 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 6.97 (d, J = 8.3 Hz, 2H).

A mixture of 1-(3-butynyl)-4-(4-hydroxybenzyl)piperidine (730 mg, 3.00 mmol), iodobenzene (630 mg, 3.09 mmol) and $Pd(Ph_3P)_4$ (176 mg, 152 μmol) in pyrrolidine (20 mL) was stirred for 3 days at 25 °C. The pyrrolidine was removed and the residue was purified by chromatography on silica gel with EtOAc elution. Crystallization from EtOAc yielded **32** as a solid (600 mg, 62%): mp 136−138 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05−1.23 (m, 2H), 1.27−1.45 (m, 1H), 1.52 (d, J = 12 Hz, 2H), 1.82−2.04 (m, 2H), 2.36 (d, J = 6.6 Hz, 2H), 2.50−2.62 (m, 4H), 2.87 (d, J = 8.4 Hz 2H), 6.63 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 7.28−7.44 (m, 5H), 9.09 (s, 1H). Anal. ($C_{22}H_{25}NO\cdot0.50H_2O$) C, H, N.

4-(4-Hydroxybenzyl)-1-(3-phenyl-2-propynyl)piperidine (31). Compound **31** was prepared as described for **32** using 3-tosyloxy-1-propyne to yield **31** as a solid: mp 154−155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.07−1.24 (m, 2H), 1.28−1.44 (m, 1H), 1.54 (d, J = 12 Hz, 2H), 2.09 (t, J = 11 Hz, 2H), 2.35 (d, J = 6.9 Hz, 2H), 2.80 (d, J = 11 Hz, 2H), 3.44 (s, 2H), 6.63 (d, J = 8.1 Hz, 2H), 6.91 (d, J = 8.1 Hz, 2H), 7.27−7.45 (m, 5H), 9.10 (s, 1H). Anal. ($C_{21}H_{23}NO$) C, H, N.

4-(4-Hydroxybenzyl)-1-(3-phenylpropyl)piperidine (33). A mixture of **31** (420 mg, 1.38 mmol) and Pd/C (20%, 100 mg) in MeOH/THF (1:1, 75 mL) was hydrogenated (Parr, 50 psig) until H_2 uptake ceased. The catalyst was removed by filtration and the solvent was removed from the filtrate. The residue was triturated with ether to yield **33** as a solid (350 mg, 82%): mp 133−135 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03−1.20 (m, 2H), 1.24−1.42 (m, 1H), 1.49 (d, J = 12 Hz, 2H), 1.60−1.82 (m, 4H), 2.19 (t, J = 6.9 Hz, 2H), 2.34 (d, J = 6.6 Hz, 2H), 2.53 (t, J = 7.5 Hz, 2H), 2.76 (d, J = 11 Hz, 2H), 6.63 (d, J = 7.2 Hz, 2H), 6.90 (d, J = 6.9 Hz, 2H), 7.20−7.65 (m, 5H), 9.11 (b, 1H). Anal. ($C_{21}H_{27}NO\cdot0.30H_2O$) C, H, N.

2-(4-Methoxyphenyl)maleic acid Diethyl Ester (35). The general procedure of Dean and Blum[19] was employed. A mixture of 4-methoxybenzyl cyanide (**34**; 10.0 g, 68.0 mmol), glyoxylic acid monohydrate (12.5 g, 136 mmol), and K_2CO_3 (37.0 g, 268 mmol) in MeOH (100 mL) was stirred at reflux for 24 h to give a thick suspension. The solid was collected by filtration and washed with CH_2Cl_2. The collected solid was suspended in H_2O (500 mL) and the suspension was stirred overnight. The solid was collected and air-dried to yield (*Z*)-3-(4-methoxyphenyl)-3-cyano-2-propenoic acid potassium salt as a colorless solid (8.00 g, 52%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H), 6.92 (s, 1H), 6.98 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 7.5 Hz, 2H).

A solution of the above solid (5.00 g, 22.2 mmol) and concentrated H_2SO_4 (20 mL) in EtOH (50 mL) was stirred at reflux for 5 h. The solvent was removed to give an oil. The oil was mixed with aqueous $NaHCO_3$ (100 mL) and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic portion was washed with brine (100 mL) and dried (Na_2SO_4). The solvent was removed to give an oil. The crude product was purified by chromatography on silica gel with CH_2Cl_2 elution to yield **35** as an oil (4.40 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, J = 6.9 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H), 3.84 (s, 3H), 4.23 (q, J = 7.2 Hz, 2H), 4.42 (q, J = 7.2 Hz, 2H), 6.22 (s, 1H), 6.93 (d, J = 9.0 Hz, 2H), 7.42 (d, J = 9.0 Hz, 2H).

2-(4-Methoxyphenyl)butane 1,4-Dimesylate (36). A mixture of **35** (2.90 g, 10.4 mmol) and Pd/C (10% on carbon, 100 mg) in EtOH (30 mL) was stirred under H_2 (ambient pressure) for 24 h. The catalyst was removed by filtration and the solvent was removed to give 2-(4-methoxyphenyl)succinic acid diethyl ester as an oil (2.92 g, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (m, 6H), 2.61 (dd, J = 16, 5.4 Hz, 1H), 3.14 (dd, J = 17, 10 Hz, 1H), 3.71 (s, 1H), 3.80 (s, 3H), 4.10−4.30 (m, 4H), 6.87 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H).

A mixture of the above diethyl ester (2.50 g 8.93 mmol) and $LiAlH_4$ (1.40 g, 37.0 mmol) in THF (50 mL) was stirred at reflux for 3 h. Water (10 mL) was added. The solid was removed by filtration and washed with CH_2Cl_2 (2 × 10 mL). The organic solution was diluted with ether (100 mL) and washed with brine (2 × 100 mL). The organic portion was dried (Na_2SO_4) and the solvent was removed. The crude product was purified by chromatography on silica gel with EtOAc/hexanes elution to give 2-(4-methoxyphenyl)butane-1,4-diol as an oil (1.20 g, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (m, 1H), 1.98 (m, 1H), 2.92 (p, J = 6.9 Hz, 1H), 3.5−3.7 (m, 4H), 3.80 (s, 3H), 6.86 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H).

A solution of the above diol (1.00 g, 5.10 mmol), TEA (2.13 mL, 1.55 g, 15.3 mmol), methanesulfonyl chloride (1.20 mL, 1.78 g, 15.5 mmol) and DMAP (150 mg, 1.22 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 6 h. The reaction solution was diluted with CH_2Cl_2 (20 mL) and washed with NH_4Cl solution (20 mL) and brine (20 mL). The organic portion was dried (Na_2SO_4) and the solvent was removed. The crude product was purified by chromatography on silica gel with EtOAc/hexanes elution to yield **36** as a colorless oil (1.70 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (m, 1H), 2.33 (m, 1H), 2.88 (s, 3H), 2.93 (s, 3H), 3.19 (m, 1H), 3.80 (s, 3H), 4.00−4.40 (m, 4H), 6.78 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H).

(±)-3-(4-Methoxyphenyl)-1-(4-phenylbutyl)pyrrolidine (37). A mixture of **36** (750 mg, 2.12 mmol) and 4-phenylbutylamine (3.30 mL, 3.11 g, 465 mmol) was stirred at 100 °C for 12 h. The excess amine was removed in vacuo. The crude product was purified by chromatography on silica gel with MeOH/CH_2Cl_2 elution to give **37** as a colorless oil (420 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50−1.90 (m, 6H), 2.20−2.60 (m, 6H), 2.83 (m, 1H), 3.03 (t, J = 8.1, 1H), 3.30 (m, 1H), 3.79 (s, 3H), 6.86 (d, J = 8.4 Hz, 2H), 7.00−7.30 (m, 7H).

(±)-3-(4-Methoxyphenyl)-1-(5-phenylpentyl)pyrrolidine (38). Compound **38** was prepared as described for **37** from **36** (420 mg, 1.19 mmol) and 5-phenylpentylamine[20] (430 mg, 2.67 mmol) to yield **38** as a colorless oil (110 mg, 29%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (p, J = 8.1 Hz, 2H), 1.64 (m, 4H), 1.89 (m, 1H), 2.31 (m, 1H), 2.40−2.80 (m, 6H), 2.96 (m, 1H), 3.14 (m, 1H), 3.36 (p, J = 8.7 Hz, 1H), 3.80 (s, 3H), 6.86 (d, J = 8.4 Hz, 2H), 7.00−7.30 (m, 7H).

(±)-3-(4-Hydroxyphenyl)-1-(4-phenylbutyl)pyrrolidine (39). Boron tribromide (1 M in CH_2Cl_2, 400 μL) was added to a stirred solution of **37** (400 mg, 1.29 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was stirred at room temperature for 3 h. Water (3 mL) was added followed by NH_4OH (10 mL). The mixture was stirred for 10 min and diluted with H_2O (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the extract was washed with brine (50 mL). The extract was dried (Na_2SO_4) and the solvent was removed. The crude product was purified by chromatography on silica gel with MeOH/CH_2Cl_2 elution followed by crystallization from MeOH/ CH_2Cl_2 to give **39** as a colorless solid (120 mg, 31%): mp 109−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (m, 4H), 1.84 (m, 1H), 2.28 (m, 1H), 2.40−2.60 (m, 6H), 2.87 (m, 1H), 3.07 (t, J = 8.1 Hz, 1H), 3.31 (p, J = 8.4 Hz, 1H), 6.72 (d, J = 8.7 Hz, 2H), 7.00−7.40 (m, 7H). Anal. ($C_{20}H_{25}NO$) C, H, N.

(±)-3-(4-Hydroxyphenyl)-1-(5-phenylpentyl)pyrrolidine (40). Compound **40** was prepared as described for **39** from **38** (100 mg, 309 μmol) to yield **40** as a colorless solid (13 mg, 14%): mp 107−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (m, 2H), 1.65 (m, 4H), 1.88 (m, 1H), 2.29 (m, 1H), 2.40−2.80 (m, 6H), 2.94 (m, 1H), 3.13 (m, 1H), 3.45 (m, 1H), 6.74 (d, J = 8.4 Hz, 2H), 7.00−7.40 (m, 7H). Anal. ($C_{21}H_{27}NO$) C, H, N.

Electrophysiology Data Analysis. The methods employed were described previously.[9a]

Molecular Modeling. The methods employed were described previously.[9b]

[^{3}H]Prazosin Binding Assay. This assay was modified from previously described methods.[21] 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 μg 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 μM phentolamine.

[^{3}H]Raclopride Binding Assay. This assay was modified from previously described methods.[22] Frozen Sprague−Dawley rat striata obtained from ABS (Wilmington, DE) were thawed, homogenized in ice-cold 50 mM Tris-HCl, pH 7.4 buffer (8−9 pairs of striata/10 mL), and centrifuged at 20000*g* for 10 min at 4 °C. The pellet was resuspended in 10 mL of ice-cold 50 mM Tris-HCl, pH 7.4 buffer, and centrifuged at 20000*g* for 10 min. The pellet was resuspended in 120 mM NaCl/5 mM KCl/50 mM Tris-HCl, pH 7.4 buffer (raclopride binding buffer) (1 mL/pair of striata) and was stored at −80 °C. On the day of the binding assay, the membrane suspensions were thawed and diluted in raclopride binding buffer, and 200 μg of membrane protein was incubated with 3 nM [^{3}H]raclopride (~80 Ci/mmol; NEN). Nonspecific binding was determined in the presence of 300 μM sulpiride.

Mouse MES Studies. General methods for MES studies were performed as previously reported.[23] Briefly, seizures were induced in male Swiss Webster mice (body weight 23−27 g, housed with ad libitum food and water) via corneal electrodes (ECT 7801, Ugo Basile). Rectagular pulses (50 mA, 60−75 Hz, 0.8 ms width, 0.2 s train length) were employed. Seizure occurrence was recorded as a tonic hind-limb extension after electroshock stimulus. Test compounds were formulated for iv administration as 5 mg/mL solutions in 0.2 M tris(hydroxymethyl)aminomethane. The vehicle alone induced no detectable levels of protection. ED_{50} and 95% confidence limits were calculated by Litchfield and Wilcoxon analysis (Micro-Computer Specialists, Philadelphia, PA).

Acknowledgment. Financial support was provided by CoCensys, Inc. and Parke-Davis Pharmaceutical Research. We thank Dr. L. Zhang (CoCensys) for the preparation of NMDA receptor (NR1A/2A, NR1A/2B, and NR1A/2C) cRNA and Dr. Peter H. Seeburg (University of Heidelberg, Heidelberg, Germany) for the NMDA receptor clones.

References

(1) (a) McCulloch, J. Excitatory Amino Acid Antagonists and their Potential for the Treatment of Ischeamic Brain Damage in Man. *Br. J. Clin. Pharmacol.* **1992**, *34*, 106−114. (b) Rogawski, M. A. The NMDA Receptor, NMDA Antagonists and Epilepsy Therapy. A Status Report. *Drugs* **1992**, *44*, 279−292. (c) Starr, M. S. Antiparkinsonian Actions of Glutamate Antagonists − Alone and with L-Dopa: A Review of Evidence and Suggestions for Possible Mechanisms. *J. Neural. Transm. Parkinson's Dis. Dementia Sect.* **1995**, *10*, 141−185.

(2) (a) Olney, J. W.; Labruyere, J.; Price, M. T. Pathological Changes Induced in Cerebrocortical Neurons by Phencyclidine and Related Drugs. *Science (Washington, DC)* **1989**, *244*, 1360−1362. (b) Willetts, J.; Balster, R. L. The Discriminative Stimulus Effects of *N*-Methyl-D-aspartate Antagonists in Phencyclidine-trained Rats. *Neuropharmacology* **1988**, *27*, 1249−1256. (c) Tricklebank, M. D.; Singh, L.; Oles, R. J.; Preston, C.; Iversen, S. D. The Behavioral Effects of MK-801: A Comparison with Antagonists Acting Noncompetitively and Competitively at the NMDA Receptor. *Eur. J. Pharmacol.* **1989**, *167*, 127−135.

(3) For a review see: Chenard, B. L.; Menniti, F. S. Antagonists Selective for NMDA Receptors Containing the NR2B Subunit. *Curr. Pharm. Des.* **1999**, *5*, 381−404.

(4) (a) Moriyoshi, K. M.; Masu, M.; Ishii, T.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. Molecular Cloning and Characterization of the Rat NMDA Receptor. *Nature (London)* **1991**, *354*, 31−37. (b) Sugihara, H.; Moriyoshi, K.; Ishii, T.; Masayuki, M.; Nakanishi, S. Structures and Properties of Seven Isoforms of the NMDA Receptor Generated by Alternative Splicing. *Biochem. Biophys. Res. Commun.* **1992**, *185*, 826−832. (c) Monyer, H.; Sprengel, R.; Schoeper, R.; Herb, A.; Higuchi, M.; Lomeli, H.; Burnashev, N.; Sakmann, B.; Seeburg, P. H. Heteromeric NMDA Receptors: Molecular and Functional Distinction of Subtypes. *Science* **1992**, *256*, 1217−1221. (d) Monyer, H.; Burnashev, N.; Laurie, D. J.; Sakmann, B.; Seeburg, P. H. Developmental and Regional Expression in the Rat Brain and Functional Properties of Four NMDA Receptors. *Neuron* **1994**, *12*, 529−540.

(5) (a) Williams, K. Ifenprodil Discriminates Subtypes of the *N*-Methyl-D-aspartate Receptor: Selectivity and Mechanism at Recombinant Heteromeric Receptors. *Mol. Pharmacol.* **1993**, *44*, 851−859. (b) Chenard, B. L.; Shalaby, I. A.; Koe, B. K.; Ronau, R. T.; Butler, T. W.; Prochniak M. A.; Schmidt, A. W.; Fox C. B. Separation of α_1 Adrenergic and *N*-Methyl-D-aspartate Antagonist Activity in a Series of Ifenprodil Compounds. *J. Med. Chem.* **1991**, *34*, 3085−3090.

(6) Fischer, G.; Mutel, V.; Trube, G.; Malherbe, P.; Kew, J. N. C.; Mohacsi, E.; Heitz, M. P.; Kemp, J. A. Ro25-6981, a Highly Potent and Selective Blocker of *N*-Methyl-D-aspartate Receptors Containing the NR2B subunit. Characterization in vitro. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 1285−1292.

(7) Chenard, B. L.; Bordner, J.; Butler, T. W.; Chembers, L. K.; Collins, M. A.; De Costa, D. L.; Ducat, M. F.; Dumont, M. L.; Fox, C. B.; Mena, E. E.; Menniti, F. S.; Nielsen, J.; Pagnozzi, M. J.; Richter, K. E. G.; Ronau, R. T.; Shalaby, I. A.; Stemple, J. Z.; White, W. F. (1*S*,2*S*)-1-(4-Hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol: A Potent New Neuroprotectant which Blocks *N*-Methyl-D-aspartate Responses. *J. Med. Chem.* **1995**, *38*, 3138−3145.

(8) Zhou, Z. L.; Cai, S. X.; Whittemore, E. R.; Konkoy, C. S.; Espitia, S. A.; Tran, M.; Rock, D. M.; Coughenour, L. L.; Hawkinson, J. E.; Boxer, P. A.; Bigge, C. F.; Wise, L. D.; Weber, E.; Woodward, R. M.; Keana, J. F. W. 4-Hydroxy-1-[2-(4-hydoxyphenyl)ethyl]−(4-methylbenzyl)piperidine: A Novel, Potent and Selective 1A/2B NMDA Receptor Antagaonist. *J. Med. Chem.* **1999**, *42*, 2993−3000.

(9) (a) Whittemore, E. R.; Ilyin, V. I.; Konkoy, C. S.; Woodward, R. M. Subtype-selective Antagonism of NMDA Receptors by Nylidrin. *Eur. J. Pharmacol.* **1997**, *337*, 197−208. (b) Tamiz, A. P.; Whittemore, E. R.; Zhou, Z. L.; Huang, J. C.; Drewe, J. A.; Chen, J. C.; Cai, S. X.; Weber, E.; Woodward, R. M.; Keana, J. F. W. Structure−Activity Relationships for a Series of Bis(phenylalkyl)amines: Potent Subtype-Selective Inhibitors of *N*-Methyl-D-aspartate Receptors. *J. Med. Chem.* **1998**, *41*, 3499−3506.

(10) (a) Tamiz, A. P.; Whittemore, E. R.; Schelkun, R. M.; Yuen, P. W.; Woodward, R. M.; Cai, S. X.; Weber, E.; Keana, J. F. W. *N*-(2-(4-Hydroxyphenyl)ethyl)-4-chlorocinnamide: A Novel Antagonist at the 1A/2B NMDA Receptor Site. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 199−200. (b) Tamiz, A. P.; Cai, S. X.; Zhou, Z. L.; Yuen, P. W.; Schelkun, R. M.; Whittemore, E. R.; Weber, E.; Woodward, R. M.; Keana, J. F. W. Structure Activity Relationship of *N*-(Phenylalkyl)cinnamides as Novel NR2B Subtype Selective NMDA Receptor Antagonists. *J. Med. Chem.* **1999**, *17*, 3412−3420.

(11) Replacing the *p*-hydroxy group of **6** and **7** with a chloro group results in a substantial loss of potency at the NR1A/2B subtype (see ref 10).

(12) Jacobs, R. T.; Shenvi, A. B. 4-(Aryl-substituted)-piperidines as Neurokinin Receptor Antagonists. Eur. Patent Appl. 630887A1, Dec 28, 1994.

(13) Allen & Hansbury Ltd. Neth. Appl. 6,510,107, Feb 7, 1966; *Chem. Abstr.* **1966,** *65*, 7155a.

(14) Emonds-Alt, X.; Goulaouic, P.; Proietto, V.; van Broeck, D. Arylalkylamines, Process for Their Preparation and Pharmaceutical Compositions Containing Them. Eur. Patent Appl. 474561A1, Mar 11, 1992.

(15) Gray, A. P.; Heitmeir, D. E.; Godberg, M. E. Treatment of Depression with 4-Substituted Piperidines. U.S. Patent 3632767, Jan 4, 1972.

(16) Schwan, A. L.; Roche, M. R.; Gallagher, J. F.; Ferguson, G. On the Conformational Preferences of the Dehydrochlorination of α-chlorosulfoxides. *Can. J. Chem.* **1994**, *72*, 312−324.

(17) Henely-Smith, P.; Whiting, D. A.; Wood, A. F. Methods for the Construction of Linear 1,7-Diarylheptanoids; Synthesis of Di-*O*-methylcentrolobol and Precursors (Synthetic and Biosynthetic) to the *meta,meta*-Bridged Biphenyls Myricanol and Myricanone. *J. Chem. Soc., Perkin Trans. 1* **1980**, 614−622.

(18) Glase, S. A.; Akunne, H. C.; Heffner, T. G.; Jaen, J. C.; MacKenzie, R. G.; Meltzer, L. T.; Pugsley, T. A.; Smith, S. J.; Wise, L. D. Aryl 1-But-3-ynyl-4-phenyl-1,2,3,6-tetrahydropyridines as Potential Antipsychotic Agents: Synthesis and Structure Activity Relationships. *J. Med. Chem.* **1996**, *39*, 3179−3187.

(19) Dean, W. D.; Blum, D. M. Condensation of Arylacetonitriles with Glyoxylic Acid. Facile Synthesis of Arylmaleic Acid Derivatives. *J. Org. Chem.* **1993**, *58*, 7916−7917.

(20) Lever, O. W.; Bell, L. N.; McGuire, H. M.; Ferone, R. Monocyclic Pteridine Analogues. Inhibition of Escherichia Coli Dihydropteroate Synthase by 6-Amino-5-nitrosoiso-cytosines. *J. Med. Chem.* **1985**, *28*, 1870−1874.

(21) (a) Tsuchihashi, H.; Maruyama, K.; Baba, S.; Mano, F.; Kinami, J.; Nagatomo, T. Comparison of α_1 Adrenoreceptors Between Rat Brain and Spleen. *Jpn. J. Pharmacol.* **1991**, *56*, 523−530. (b) Veenstra, D. M.; van Buuren, K. J.; Krielaart, M. J.; Nijkamp, F. P. Errors Introduced in Radioligand Binding Studies Due to Displaceable, Cation Dependent, [^{3}H]Prazosin Binding to Glass-Fibre Filters and Glass Surfaces. *J. Receptor Res.* **1993**, *13*, 801−814.

(22) Dewar, K. M.; Montreuil, B.; Grondin, L.; Reader, T. A. Dopamine D2 Receptors Labeled with [^{3}H]Raclopride in Rat and Rabbit Brains. Equilibrium Binding, Kinetics, Distribution and Selectivity. *J. Pharmacol. Exp. Ther.* **1989**, *250*, 696−706.

(23) Swinyard, E. A. Assay of Antiepileptic Drug Activity in Experimental Animals: Standard Tests. In *Anticonvulsant* Drugs. *International Encyclopedia of Pharmacology and Therapeutics*; Mercier, J., Ed.; Pergamon Press: Oxford, 1972; pp 47−65.

(24) (a) Hashimoto, K.; London, E. D. Further Characterization of [^{3}H]infenprodil Binding to Sigma Receptors in Rat Brain. *Eur. J. Pharmacol.* **1993**, *236*, 159−163. (b) Takahashi, H.; Kirsch, J. R.; Hashimoto, K.; London, E. D.; Koehler, R. C.; Traystman, R. PPBP (4-Phenyl-1-(4-phenylbutyl) piperidine), a Potent Sigma Receptor Ligand, Decreases Brain Injury After Transient Focal Ischemia in Cats. *Stroke* **1995**, *26*, 1676−1682.

(25) (a) Whittemore, E. R.; Ilyin, V. I.; Woodward, R. M. Antagonism of *N*-Methyl-D-aspartate Receptors by Sigma Site Ligands: Potency, Subtype-selectivity, and Mechanisms of Inhibition. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 326−338. (b) Ilyin, V. I.; Whittemore, E. R.; Guastella, J.; Weber, E.; Woodward, R. M. Subtype Selective Inhibition of *N*-Methyl-D-aspartate Receptors by Haloperidol. *Mol. Pharmacol.* **1996**, *50*, 1541−1550.

(26) Novascreen is a division of Oceanix Biosciences Corp., 7170 Standard Dr., Hanover, MD 21076-1334.

(27) Subbarao, K. V.; Damodaran, N. P.; Dev, S. Photochemical Transformations V Organic Iodides (Part 4): Solution Photochemistry of 4-Phenyl-1-iodobutane and 4-Phenyl-1-bromobutane. *Tetrahedron* **1987**, *43*, 2543−2548.

(28) Pang, Y. P.; Hong, F.; Quiram, P.; Jelacic, T.; Brimijoin, S. Synthesis of Alkylene Linked Bis-THA as Highly Potent and Selective Inhibitors and Molecular Probes of Acetylcholinesterase. *J. Chem. Soc., Perkin Trans. 1* **1997**, 171−176.

JM990428C