Subtype-Selective *N*-Methyl-D-aspartate Receptor Antagonists: Synthesis and Biological Evaluation of 1-(Arylalkynyl)-4-benzylpiperidines

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A search of our compound library for compounds with structural similarity to ifenprodil (**5**) and haloperidol (**7**) followed by in vitro screening revealed that 4-benzyl-1-(4-phenyl-3-butynyl)-piperidine (**8**) was a moderately potent and selective antagonist of the NR1A/2B subtype of NMDA receptors. Substitution on the benzyl group of **8** did not significantly affect NR1A/2B potency, while addition of hydrogen bond donors in the *para* position of the phenyl group enhanced NR1A/2B potency. Addition of a hydroxyl moiety to the 4-position of the piperidine group slightly reduced NR1A/2B potency while reducing α-1 adrenergic and dopamine D2 receptor binding affinities substantially, resulting in improved overall selectivity for NR1A/2B receptors. Finally, the butynyl linker was replaced with propynyl or pentynyl. When the phenyl was *para* substituted with amine or acetamide groups, the NR1A/2B potency order was butynyl > pentynyl ≫ propynyl. For the *para* methanesulfonamide or hydroxyl groups, the order was butynyl ≈ propynyl > pentynyl. The hydroxyl propyne (**48**) and butyne (**23**) were among the most potent NR1A/2B antagonists from this study. They both potentiated the effects of L-DOPA in the 6-hydroxydopamine-lesioned rat, a model of Parkinson's disease, dosed at 10 mg/kg ip, but **48** was not active at 30 mg/kg po.

Introduction

The excitatory neurotransmitter L-glutamic acid (glutamate) plays a key role in the neuronal death associated with stroke and head trauma.[1] High levels of glutamate released during such events hyperactivate glutamate receptors, allowing toxic increases in calcium ion flux into neurons. In addition, glutamate receptor overstimulation may also be involved in chronic neurodegenerative conditions, such as Alzheimer's disease[2] and Parkinson's disease.[3]

There is strong evidence that much of the toxicity associated with high levels of glutamate is mediated by *N*-methyl-D-aspartate (NMDA) receptors. For example, NMDA receptor antagonists have been shown to protect neurons in vitro, both in response to neurotoxic levels of L-glutamic acid or *N*-methyl-D-aspartic acid. In addition, NMDA receptor antagonists offer neuroprotection in models of focal ischemia in animals.[4]

First-generation NMDA receptor antagonists fall into three main classes: competitive antagonists at the glutamate binding site, such as CGS 19755 (selfotel)[5] (**1**) (see Chart 1); noncompetitive antagonists at a channel site, such as MK 801 (dizocilpine)[6] (**2**) and PCP (phencyclidine)[7] (**3**) ("ion-channel blockers"); and glycine site antagonists, such as ACEA 1021 (licostinel)[8] (**4**). Antagonists acting at these sites are neuroprotective; however, many of them cause psychotomimetic side effects. While these side effects may be tolerable in the acutely life-threatening situation of stroke, they are unacceptable in the treatment of neurodegenerative diseases where chronic drug administration is required.

Mammalian NMDA receptors are ligand-gated ion channels composed of hetero-oligomeric combinations of NR1 subunits (found in eight splice variants) and at least one of four NR2 subunits, designated NR2A−NR2D.[9] The existence of distinct NMDA receptor subtypes offers potential new classes of NMDA receptor modulators. Subtype-selective NMDA antagonists might retain therapeutic utility without the side effects associated with nonselective NMDA receptor antagonists.

The α-1 adrenergic antagonist ifenprodil (**5**) was discovered to be neuroprotective both in vitro and in animal models of stroke.[10] Ifenprodil was later shown to be an antagonist at native NMDA receptors and at the NR1A/2B combination of subunits expressed in *Xenopus* oocytes. Unfortunately, ifenprodil's activity at α-1 adrenergic receptors meant that its neuroprotective properties were compromised by hypotension, an undesirable side effect in stroke patients.

Using ifenprodil as a starting point, Pfizer developed CP-101,606 (**6**).[11] This compound is a potent NR1A/2B antagonist with weak α-1 adrenergic antagonist activity. CP-101,606 is neuroprotective in vitro, confirming that selective NR1A/2B antagonists can act as neuroprotectants. More significantly, **6** reduced neuronal damage in a cat model of stroke.[12] In addition, **6** does not appear to show PCP-like psychotomimetic behavioral effects.[13]

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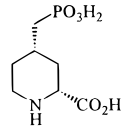
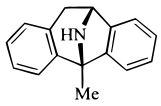
Chart 1



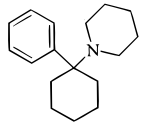
CGS 19755

1



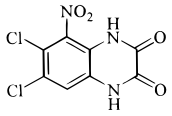
MK 801

2



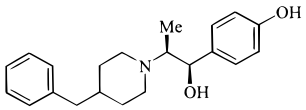
PCP

3



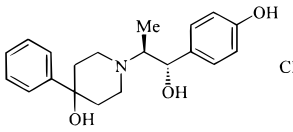
ACEA 1021

4



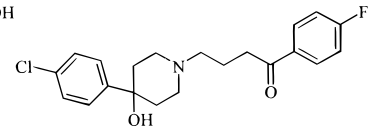
Ifenprodil

5



CP-101,606

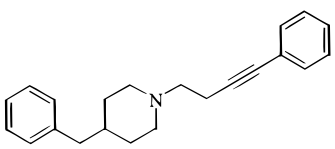
6



Haloperidol

7

The dopamine antagonist haloperidol (**7**) is also a NR1A/2B receptor antagonist.[14] To find novel NR1A/2B-selective ligands, we conducted similarity structure searches of our compound library based on the structures of ifenprodil and haloperidol. We identified compounds with varying levels of structural overlap and tested them in oocytes expressing the various NMDA receptor subtype combinations. Among others, compound **8** was found to be a moderately potent, selective NR1A/2B antagonist. In this paper we report the results of our structure−activity (SAR) studies around **8** designed to optimize NR1A/2B potency and monitor selectivity versus other receptors. We studied the effects of substitution on the benzyl and phenyl groups, altering the alkyne chain length, and substituting a hydroxyl group at the 4-position of the piperidine.

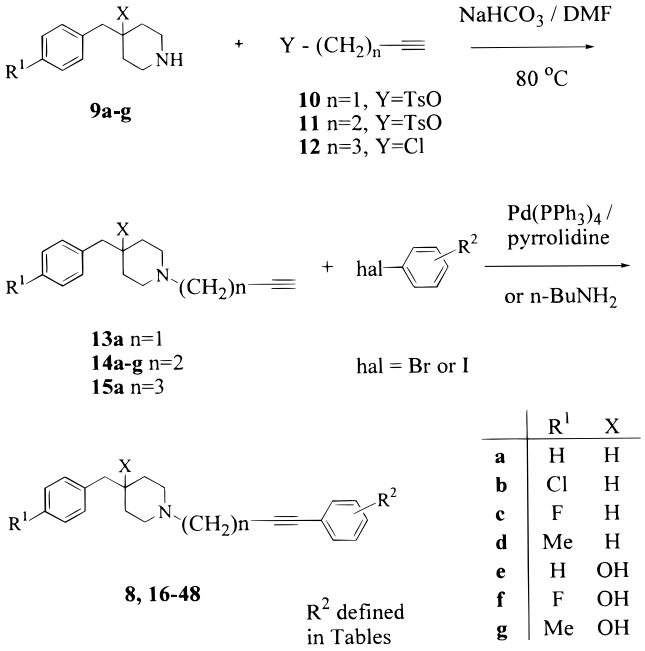


8

Chemistry

The compounds in Tables 1−3 were most conveniently prepared via the general synthesis outlined in Scheme 1. The benzylpiperidines **9a**−**g** were reacted with commercially available alkynyl tosylates or chlorides. The palladium-assisted coupling of aryl halides to benzylpiperidine alkynes **13a**, **14a**−**g**, and **15a** was most reliably accomplished using $Pd(PPh_3)_4$ as catalyst with pyrrolidine as solvent. The use of pyrrolidine accelerated the rate of the couplings compared to alternate conditions, such as $Pd(PPh_3)_4$/*n*-$BuNH_2$. In most cases, the aryl iodide was used; coupling proceeded at room temperature and was complete in a few hours. Yields were variable, and often several purification steps were necessary to produce pure product. In most cases, a crystallization was performed as the last step; this usually ensured that the material would pass elemental analysis, but decreased yields. Optimization of the reaction conditions and purification schemes was not attempted and would likely increase many of the yields reported.

Scheme 1



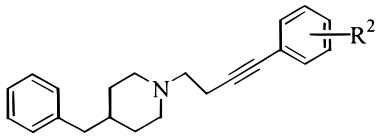
	R^1	X
a	H	H
b	Cl	H
c	F	H
d	Me	H
e	H	OH
f	F	OH
g	Me	OH

The $Pd(PPh_3)_4$/pyrrolidine conditions also worked with aryl bromides, although elevated temperatures were needed for coupling to proceed. Stirring at 50 °C overnight was sufficient in most cases for complete consumption of starting materials. In some cases, the nucleophilicity of the pyrrolidine solvent was an issue. If the halide was activated toward displacement, such as in 4-bromonitrobenzene, or the aryl group contained displaceable functional groups, such as esters, then the $Pd(PPh_3)_4$/pyrrolidine conditions could not be used. Instead, the less reactive $Pd(PPh_3)_4$/*n*-$BuNH_2$ conditions were employed. The temperatures had to be further elevated to reflux (80 °C) for coupling to occur.

Pharmacology

All compounds were tested for inhibitory activity at NR1A/2A, NR1A/2B, and NR1A/2C receptors expressed in *Xenopus* oocytes using electrophysiological techniques.[15] Compounds that possessed good activity and selectivity for the NR1A/2B receptor were further profiled in α-1 adrenergic (displacement of [^{3}H]prazosin from rat brain cortical membranes)[16] and dopamine D2 (displacement of [^{3}H]raclopride from rat brain striatal membranes)[17] receptor binding assays. Compounds with potency and selectivity for NR1A/2B receptors were tested in the 6-hydroxydopamine-lesioned rat, a model of Parkinson's disease, for increases in the number of

Table 1. NMDA Receptor Activity for Phenyl Analogues of Compound **8**



		IC$_{50}$ (μM)				
compd	R^2	NR1A/2A[a]	NR1A/2B	NR1A/2C	α-1[b]	DA D2[c]
8	H	>100 (1)[d]	4.7 ± 1.5 (3)	>100 (1)	–[e]	–
16	4-NO_2	>100 (1)	5.0 ± 0.7 (3)	>100 (1)	–	–
17	4-Cl	47 (1)	4.0 (2)	>100 (1)	–	–
18	3-Cl	>100 (1)	3.8 ± 1.0 (4)	>100 (2)	–	–
19	2-Cl	85 (1)	1.2 ± 0.1 (3)	>100 (1)	–	–
20	4-F	>100 (1)	2.7 ± 1.0 (3)	>100 (1)	–	–
21	4-Me	42 (1)	4.2 ± 1.8 (3)	>100 (1)	–	–
22	4-MeO	>100 (1)	2.6 ± 0.4 (3)	>100 (1)	–	–
23	4-OH	>100 (2)	0.17 ± 0.03 (3)	>100 (2)	0.58 ± 0.07	0.29 ± 0.03
24	4-NH_2	>100 (3)	0.43 ± 0.1 (6)	>100 (4)	1.0	0.8
25	4-NHMe	84 (1)	0.46 ± 0.08 (3)	>100 (2)	1.0	0.3
26	4-NMe_2	>100 (1)	15 (2)	>100 (1)	–	–
27	4-NHAc	>100 (1)	0.26 ± 0.05 (3)	>100 (1)	1.1	0.1
28	4-$NHSO_2Me$	>100 (1)	0.24 ± 0.04 (4)	>100 (2)	1.2	0.2
29	3-NH_2	>100 (1)	1.1 (2)	>100 (1)	–	–
30	2-NH_2	70 (1)	1.1 (2)	>100 (1)	–	–
31	4-$CONH_2$	>100 (1)	2.0 (2)	>100 (1)	–	–
32	4-SO_2NH_2	22 (1)	0.31 ± 0.08 (3)	>100 (1)	1.4	0.1
33	3-CH_2NH_2	15 (1)	0.52 ± 0.1 (5)	>100 (2)	0.8	0.3
35	3,4-$(NH_2)_2$	>100 (2)	0.19 ± 0.03 (3)	>100 (1)	1.0	1.1

[a] IC50 values for inhibition of NMDA reponses at cloned NMDA receptors expressed in *Xenopus* oocytes. Number of determinations (n) shown in parentheses. Data are presented as mean ± SEM. [b] Compounds were evaluated at nine concentrations for the displacement of [^{3}H]prazosin from rat brain cortices and an IC$_{50}$ was calculated; $n = 1$ for screening data, $n = 3$ for key compounds (±95% confidence limits). [c] Compounds were evaluated at nine concentrations for the displacement of [^{3}H]raclopride from rat brain striata, and an IC$_{50}$ was calculated; $n = 1$ for screening data, $n = 3$ for key compounds (±95% confidence limits). [d] Less than 50% inhibition at 100 μM. [e] Not tested.

contraversive (to the side of lesion) rotations produced by L-DOPA over a 6-h period.[18]

Results and Discussion

Our goals were to identify analogues of **8** with potent activity at NR1A/2B receptors (IC$_{50}$ < 1 μM) and weak activity at NR1A/2A and NR1A/2C receptors (IC$_{50}$'s > 10 μM). This requirement would increase confidence that these compounds were acting at the NR1A/2B site in vivo. As these structures were related to ifenprodil (α-1 adrenergic receptor antagonist) and haloperidol (dopamine D2 antagonist), we determined α-1 adrenergic and dopamine D2 receptor affinity for key analogues. To reduce the chances that we would see α-1 adrenergic or dopaminergic effects in vivo, the goal was to attain IC$_{50}$'s in these assays greater than 1 μM.

Our initial studies explored the effects of changing electron density of the acetylenic phenyl group of **8**. Compounds **16**, **17**, and **20** contain a *para*-electron-withdrawing substituent. These compounds had NR1A/2B potencies similar to that of the phenyl parent **8**. Moving the chloro substituent to the *meta* or *ortho* positions (compounds **18** and **19**) also did not produce a significant change in potency.

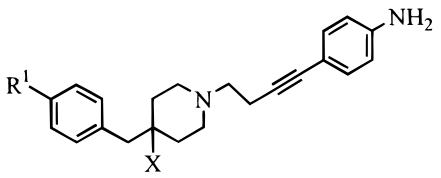
The 4-methyl analogue **21** and the 4-methoxy analogue **22** were synthesized to explore the effects of electron-donating groups. Again neither analogue showed significant differences from **8**, and we concluded that NR1A/2B potency of **8** was not sensitive to the relative electron density of the phenyl group.

The first analogues synthesized that had submicromolar NR1A/2B IC$_{50}$ values were the *para*-phenol **23** and *para*-aniline **24**. Comparing the phenol **23** with the less active methoxy analogue **22** suggested that the hydrogen bond-donating ability of **23** was responsible for the improved NR1A/2B potency. This was confirmed by comparison of the *N*-methylaniline **25** and dimethylaniline **26**. Monomethyl compound **25** was equipotent with aniline **24**, while the dimethyl aniline **26**, which does not contain a hydrogen bond donor, was 100-fold less potent as a NR1A/2B antagonist. While the phenol **23** might be slightly more potent than the aniline **24** at the NR1A/2B receptor, we studied the aniline **24** in more detail as we could not derivatize the phenol **23** while maintaining a hydrogen bond donor. Initially we prepared the acetamide (compound **27**) and sulfonamide (compound **28**) derivatives of **24**; the increased NH hydrogen bond-donating ability of **27** and **28** versus **24** is reflected by their increased NR1A/2B potency.

The location of this hydrogen bond donor was important; moving the amino group of **24** to the *meta* (compound **29**) or *ortho* (compound **30**) positions reduced NR1A/2B potency. Extending the hydrogen bond donor away from the phenyl as in carboxamide **31** reduced potency. However, the sulfonamide **32** and *meta*-benzylamine **33** were similar or better in potency to aniline **24**; the *meta* attachment of the aminomethyl group of **33** may allow the amine to occupy the same space as the aniline at the NR1A/2B receptor. Addition of a second hydrogen bond donor (the diamino analogue **35**) did enhance activity slightly; the potency was similar to that of phenol **23**.

Key compounds in Table 1 were tested for their α-1 adrenergic and dopamine D2 receptor affinities. The α-1 IC$_{50}$'s were clustered around 1 μM, and D2 IC$_{50}$'s were

Table 2. NMDA Receptor Activity for Benzyl and Piperidinyl Analogues of **24**



			IC$_{50}$ (μM)				
compd	R^1	X	NR1A/2A[a]	NR1A/2B	NR1A/2C	α-1[b]	DA D2[c]
24	H	H	>100 (3)[d]	0.43 ± 0.1 (6)	>100 (4)	1.0	0.8
36	Cl	H	>100 (1)	1.2 (2)	>100 (1)	—[e]	—
37	F	H	70 (1)	0.26 ± 0.03 (3)	>100 (1)	0.7	0.4
38	Me	H	75 (1)	0.31 ± 0.03 (3)	27 (2)	1.2	0.8
39	H	OH	>100 (1)	0.83 ± 0.12 (9)	>100 (1)	63	15
40	F	OH	29 (1)	0.65 (2)	>100 (1)	31	7.9
41	Me	OH	68 (1)	0.37 ± 0.06 (3)	>100 (2)	85	10

[a–e] For notes, see Table 1.

in the 0.1−0.3 μM range. While weaker than ifenprodil or haloperidol, it was expected that reducing these binding affinities would minimize the possibility of seeing dopamine D2 or α-1 adrenergic side effects in vivo. Hence compound **24**, containing a 4-amino substituent on the phenyl group, was chosen as a template for study of structure changes elsewhere in the molecule.

The compounds in Table 2 are examples of anilines that have substituents on the benzyl group and/or a 4-hydroxy substituent on the piperidine group. Placing a chloro group *para* on the benzyl (compound **36**) reduced NR1A/2B potency, while a fluoro or methyl group (compounds **37** and **38**, respectively) did not significantly change the NR1A/2B potency. Addition of a hydroxyl group to the 4-position of the piperidine of compounds **24** and **37** gave compounds **39** and **40**. While they showed a modest 2−3-fold drop in NR1A/2B potency, the affinities at α-1 and D2 receptors for **40** versus **37** have dropped over 10-fold. Comparison of 4-methylbenzyl pair **38** and **41** revealed that addition of the 4-hydroxy group does not effect NR1A/2B potency while again reducing the α-1 and D2 affinities over 10-fold. Thus substitution on the benzyl group did not improve NR1A/2B potency significantly while addition of a 4-hydroxyl group onto the piperidine ring appeared to increase selectivity for NR1A/2B receptors over α-1 adrenergic and dopamine D2 receptors.

The final study optimized the length of the alkynyl chain connecting the piperidine to the aromatic ring. Again we used aniline **24** as a standard template. As several other compounds from Table 1 showed similar NR1A/2B potency, we also studied the chain length effect on the potency of acetamide **27**, sulfonamide **28**, and phenol **23**. This would include compounds that may orient the hydrogen bond donor slightly differently at NR1A/2B receptors and may therefore behave differently as the chain length was altered. As the butyne moiety of aniline **24** was shortened to propyne (compound **42**, Table 3), the NR1A/2B potency reduced sharply. However, when it was lengthened to pentyne (compound **43**), the NR1A/2B potency was essentially the same. A similar trend was seen with the acetamide **27**; the shorter analogue **44** lost NR1A/2B potency sharply. In this case, however, the longer analogue **45** was significantly weaker. The sulfonamide series, **46**, **28**, and **47**, showed no sensitivity to chain length; the NR1A/2B potency remained below 1 μM for all three compounds. Finally, the phenol propynyl and butynyl analogues **48** and **23** had similar potency at NR1A/2B receptors.

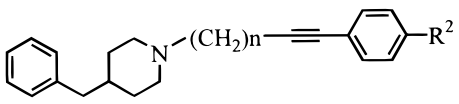
The two phenolic compounds **48** and **23** were among the most potent NR1A/2B antagonists tested from this series. The propynylphenol **48** had moderately weak α-1 and dopamine D2 binding activity. These two compounds were tested in the 6-hydroxydopamine-lesioned rat, a model of Parkinson's disease (see Figure 1). After intraperitoneal administration at 10 mg/kg, they both caused significant potentiation of the contraversive rotations produced by L-DOPA at 10 mg/kg sc, but **48** did not show significant potentiation at 30 mg /kg orally.

In summary, we have developed a new series of NMDA subtype-selective antagonists derived from ifenprodil and haloperidol. Substitution on the benzyl group of **8** had little effect on NR1A/2B potency; however addition of hydrogen bond donors to the 4-position of the phenyl group caused large increases in potency. Two of the most potent NR1A/2B antagonists showed significant activity in a rat model of Parkinson's disease after intraperitoneal administration.

Experimental Section

Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were determined on Varian Unity 400 spectrometers. Mass

Table 3. NMDA Receptor Activity for Chain Length Analogues



			IC$_{50}$ (μM)				
compd	R^2	*n*	NR1A/2A[a]	NR1A/2B	NR1A/2C	α-1[b]	DA D2[c]
42	NH_2	1	>100 (1)[d]	12 ± 2 (4)	>100 (1)	—[e]	—
24	NH_2	2	>100 (3)	0.43 ± 0.1 (6)	>100 (4)	1.0	0.8
43	NH_2	3	12 (1)	0.38 (2)	>100 (1)	—	—
44	NHAc	1	56 (1)	13 (2)	>100 (1)	—	—
27	NHAc	2	>100 (1)	0.26 ± 0.05 (3)	>100 (1)	1.1	0.1
45	NHAc	3	>100 (1)	1.4 ± 0.2 (3)	>100 (1)	—	—
46	$NHSO_2Me$	1	>100 (1)	0.15 ± 0.03 (7)	>100 (1)	2.2	12
28	$NHSO_2Me$	2	>100 (1)	0.24 ± 0.04 (4)	>100 (2)	1.1	0.2
47	$NHSO_2Me$	3	>100 (2)	0.28 ± 0.05 (3)	>100 (1)	1.1	2.3
48	OH	1	>100 (2)	0.10 ± 0.01 (5)	>100 (2)	1.5 ± 0.5	1.7 ± 0.1
23	OH	2	>100 (2)	0.17 ± 0.03 (4)	>100 (2)	0.58 ± 0.07	0.29 ± 0.03

[a–e] For notes, see Table 1.

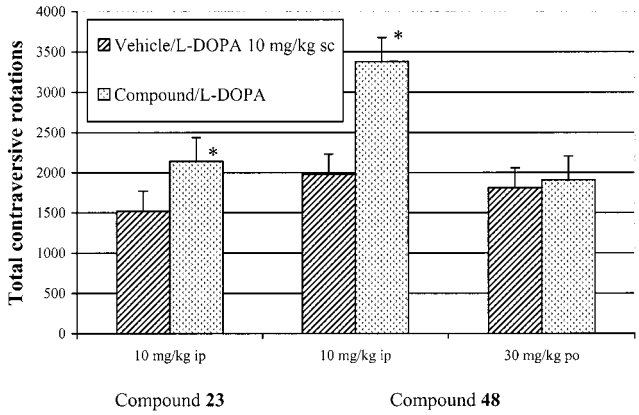


Figure 1. Interaction of compounds **23** and **48** on L-DOPA-induced rotations in 6-hydroxydopamine-lesioned rats. A baseline response to L-DOPA (10 mg/kg sc) alone was established for groups of rats ($n = 8$). The compounds were administered at the same time as L-DOPA (10 mg/kg sc), and the total number of full contraversive rotations over 6 h was compared to the L-DOPA baseline for that group. *$P < 0.05$ (paired t-test).

spectra were obtained on Finnigan 4500 or VG Analytical 7070E/HF mass spectrometers. IR spectra were recorded as KBr disks on a Nicolet MX-1 FT spectrophotometer. Elemental analyses were performed by Robertson Laboratories. TLC was performed on 0.25-mm silica gel F254 (E. Merck) glass plates. Medium-pressure liquid chromatography (MPLC) was performed on self-packed Michel-Miller 40-mm i.d. × 350-mm (~200 g of silica gel) or 51-mm i.d. × 450 mm (~400 g of silica gel) glass columns using 32−63-μm, 60-A pore silica gel. HPLC was performed on Beckman Ultrasphere 5-μm 4.6-mm × 25-cm C-18 columns eluting with pH 3 buffer:acetonitrile mixtures (unless otherwise noted) at 1.5 mL/min, and compounds were detected using UV absorption at 214 nm. pH 3 buffer was prepared by adjusting a 0.05 M solution of Et_3N in water to pH 3 with phosphoric acid. Ether refers to diethyl ether. Compounds **36**, **38**, and **41** were not submitted for microanalysis but had ^{1}H NMR and mass spectra that were consistent with the assigned structure.

4-Benzyl-1-(4-phenyl-3-butynyl)piperidine Oxalate (8). A mixture of 4-benzyl-1-(3-butynyl)piperidine (**14a**; 454 mg, 2 mmol), iodobenzene (408 mg, 2 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) was stirred in pyrrolidine (5 mL) at room temperature under N_2 overnight. The solvent was evaporated and the residue purified by MPLC (120 g silica gel) eluting with CH_2Cl_2 → 200:8:1 CH_2Cl_2:EtOH:0.880 NH_4OH to give a brown oil (540 mg). This was further purified by MPLC (90 g silica gel) eluting with 20% → 50% EtOAc/hexanes to give a pale-brown oil (313 mg). This oil was stirred in EtOH (10 mL), and oxalic acid·$2H_2O$ in EtOH (3 mL) added. The oxalate salt precipitated on standing overnight in the freezer as a white solid (268 mg): mp 157−158 °C; IR 1721, 1626, 1604, 1491, 1454, 1405, 1189, 760, 701 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.30−7.36 (m, 5H), 7.24 (t, $J = 7.4$ Hz, 2H), 7.14 (m, 3H), 3.34 (d, $J = 11.4$ Hz, 2H), 3.13 (t, $J = 7.4$ Hz, 2H), 2.80 (t, $J = 7.6$ Hz, 2H), 2.74 (t, $J = 11.2$ Hz, 2H), 2.49 (d, $J = 6.6$ Hz, 2H), 1.66 (d, $J = 12.0$ Hz, 3H), 1.37 (m, 2H); APCI MS m/z 304.2 (100%, MH^+); HPLC (50% 0.1% aqueous CF_3CO_2H:50% MeCN) 3.75 min (100%). Anal. ($C_{22}H_{25}N·C_2H_2O_4$) C, H, N, water.

4-(4-Methylbenzyl)piperidine (9d). n-Butyllithium (1.6 M in hexanes, 49.3 mL, 79 mmol) was added to 4-bromotoluene (9.3 mL, 75 mmol) in THF (250 mL) at −78 °C under N_2 and stirred at −78 °C for 75 min. 4-Pyridinecarboxaldehyde (7.16 mL, 75 mmol) was added and the mixture allowed to warm to −20 °C over 2 h with stirring. The mixture was quenched with saturated aqueous NH_4Cl (300 mL) and stirred for 30 min and the THF evaporated. The aqueous layer was diluted with 0.1% aqueous $NaHCO_3$ (300 mL) and extracted with $CHCl_3$ (600 mL). The extract was dried over K_2CO_3, filtered, and evaporated to a solid. This solid was triturated with ether to give 11.9 g of a solid: ^{1}H NMR (DMSO-d_6) δ 8.47 (d, $J = 4.6$ Hz, 2H), 7.36 (d, $J = 6.0$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 6.08 (d, $J = 3.6$ Hz, 2H), 5.68 (d, $J = 3.6$ Hz, 1H), 2.25 (s, 3H).

This solid (11 g) was hydrogenated (50 psi H_2) in MeOH (200 mL) with concentrated HCl (5 mL) and 20% Pd/C (2 g) for 16 h. The mixture was filtered and evaporated to leave a white solid (11.2 g): ^{1}H NMR ($CDCl_3$) δ 7.02 (ABq, $J = 8.1$ Hz, $\delta\nu = 20.7$ Hz, 4H), 3.01 (d, $J = 12.5$ Hz, 2H), 2.49 (dt, $J = 1.7$, 12.0 Hz, 2H), 2.44 (d, $J = 6.6$ Hz, 2H), 2.28 (s, 3H), 1.51−1.60 (m, 3H), 1.12 (m, 2H).

4-(4-Fluorobenzyl)-4-hydroxypiperidine (9f). A stirred slurry of Mg turnings (12 g, 0.49 mol) in 1,2-dibromoethane (2 mL, 23.2 mmol) and THF (150 mL) was warmed slightly and 4-fluorobenzyl chloride (Aldrich; 57.4 mL, 0.48 mol) in THF (75 mL) added slowly. Occasional gentle heating was required to keep the reaction going. After addition was complete, the mixture was allowed to cool to room temperature and stirred for 30 min. The mixture was diluted with THF (150 mL) and cooled to −40 °C. *N*-Benzyl-4-piperidone (Aldrich; 25.3 mL, 0.14 mol) in THF (75 mL) was added dropwise and the mixture allowed to warm to room temperature with stirring overnight. The mixture was cooled in an ice bath and saturated aqueous NH_4Cl (250 mL) added. Once the mixture had warmed to room temperature with stirring, water (500 mL) was added and the mixture extracted with EtOAc (3 × 200 mL). The extracts were washed with brine (300 mL), dried over $MgSO_4$, filtered, and evaporated to leave a yellow solid. This solid was purified by MPLC (400 g silica gel) loading in CH_2Cl_2 and eluting with 100:8:1 CH_2Cl_2:EtOH:0.880 NH_4OH to give a yellow oil (29.5 g, 72%): ^{1}H NMR ($CDCl_3$) δ 7.19−7.32 (m, 5H), 7.11 (m, 2H), 6.95 (t, $J = 8.7$ Hz, 2H), 3.48 (s, 2H), 2.69 (s, 2H), 2.61 (m, 2H), 2.26 (t, $J = 10.6$ Hz, 2H), 1.68 (dt, $J = 4.4$, 12.6 Hz, 2H), 1.45 (d, $J = 12.0$ Hz, 2H); HPLC (70% pH 3 buffer:30% MeCN) 5.13 min (100%).

A portion of the oil (6.5 g, 21.7 mmol) was stirred in EtOH (100 mL) and AcOH (1 mL) with 10% Pd/C (1 g) under H_2 overnight. The mixture was filtered and evaporated. The residue was purified by MPLC (200 g silica gel) eluting with 100:8:1 → 50:8:1 CH_2Cl_2:EtOH:0.880 NH_4OH to give **9f** as a pale-yellow oil (3.48 g, 77%): ^{1}H NMR ($CDCl_3$) δ 7.12 (t, $J = 8.3$ Hz, 2H), 6.96 (t, $J = 8.7$ Hz, 2H), 2.78−2.90 (m, 4H), 2.69 (s, 2H), 1.52−1.59 (m, 4H), 1.43 (d, $J = 12.5$ Hz, 2H); HPLC (80% 0.1% aqueous CF_3CO_2H:20% MeCN) 3.72 min (100%).

4-(4-Methylbenzyl)-4-hydroxypiperidine (9g). A procedure identical to that described for the preparation of **9f** using 4-methylbenzyl chloride gave **9g**, which was isolated as the HCl salt: ^{1}H NMR (DMSO-d_6) δ 9.02 (br s, 1H), 8.56 (br s, 1H), 7.03 (AA′BB′, 4H), 4.71 (br s, 1H), 2.86−2.99 (m, 4H), 2.61 (s, 2H), 2.21 (s, 3H), 1.59 (dt, $J = 4.6$, 13.9 Hz, 2H), 1.45 (d, $J = 13.4$ Hz, 2H).

4-Benzyl-1-but-3-ynylpiperidine (14a). A mixture of 3-butyn-1-yl *p*-toluenesulfonate (**11**) (Lancaster; 29.9 g, 0.13 mol), 4-benzylpiperidine (**9a**) (Aldrich; 21.2 mL, 0.12 mol), and $NaHCO_3$ (12.2 g, 0.15 mol) in DMF (300 mL) was stirred at 80 °C under N_2 overnight. The DMF was evaporated under high vacuum on a rotary evaporator and the residue treated with water (500 mL) and extracted with ether (2 × 300 mL). The combined extracts were washed with saturated brine (500 mL), dried over $MgSO_4$, filtered, and evaporated to leave **14a** as a brown oil (24.8 g, 90%): ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 2H), 7.11 (m, 3H), 2.85 (d, $J = 11.5$ Hz, 2H), 2.50 (m, 4H), 2.33 (m, 2H), 1.85−1.95 (m, 3H), 1.60 (d, $J = 12.9$ Hz, 2H), 1.47 (m, 1H), 1.28 (m, 2H).

4-(4-Chlorobenzyl)-1-but-3-ynylpiperidine (14b). A procedure identical to that described for the preparation of **14a** using 4-(4-chlorobenzyl)piperidine[19] (**9b**) gave **14b**: ^{1}H NMR ($CDCl_3$) δ 7.26 (d, $J = 8.1$ Hz, 2H), 7.04 (d, $J = 8.1$ Hz, 2H), 2.88 (d, $J = 11.1$ Hz, 2H), 2.55 (m, 2H), 2.48 (m, 2H), 2.38 (m, 2H), 1.96 (m, 3H), 1.59 (m, 2H), 1.50 (m, 1H), 1.31 (m, 2H); EI MS m/z 261 (M^+, ^{35}Cl, 2%), 222 (100%), 194 (50%), 188 (82%), 125 (30%), 91 (25%).

4-(4-Fluorobenzyl)-1-but-3-ynylpiperidine (14c). A procedure identical to that described for the preparation of **14a** using 4-(4-fluorobenzyl)piperidine[20] (**9c**) gave **14c**: ^{1}H NMR

($CDCl_3$) δ 7.03 (m, 2H), 6.91 (t, J = 8.7 Hz, 2H), 2.85 (m, 2H), 2.53 (t, J = 7.7 Hz, 2H), 2.45 (d, J = 7.1 Hz, 2H), 2.33 (dt, J = 2.7, 7.7 Hz, 2H), 1.92 (m, 3H), 1.57 (d, J = 12.9 Hz, 2H), 1.41 (m, 1H), 1.26 (dq, J = 3.7, 12.5 Hz, 2H).

4-(4-Methylbenzyl)-1-but-3-ynylpiperidine (14d). A procedure identical to that described for the preparation of **14a** using **9d** gave **14d**: ^{1}H NMR ($CDCl_3$) δ 7.02 (ABq, J = 8.1 Hz, $\delta\nu$ = 22.8 Hz, 4H), 2.84 (d, J = 11.5 Hz, 2H), 2.53 (t, J = 7.3 Hz, 2H), 2.45 (d, J = 7.1 Hz, 2H), 2.33 (dt, J = 2.7, 8.5 Hz, 2H), 2.28 (s, 3H), 1.86−1.93 (m, 3H), 1.59 (d, J = 12.9 Hz, 2H), 1.44 (m, 1H), 1.24 (dq, J = 3.7, 12.2 Hz, 2H).

4-Benzyl-4-hydroxy-1-but-3-ynylpiperidine (14e). A procedure identical to that described for the preparation of **14a** using commercially available 4-benzyl-4-hydroxypiperidine (**9e**) gave **14e** as a brown oil (81% yield): ^{1}H NMR ($CDCl_3$) δ 7.15−7.30 (m, 5H), 2.71 (s, 2H), 2.56−2.65 (m, 4H), 2.28−2.36 (m, 4H), 1.93 (t, J = 1.3 Hz, 1H), 1.70 (dt, J = 3.9, 13.4 Hz, 2H), 1.50 (m, 2H).

4-(4-Fluorobenzyl)-1-but-3-ynyl-4-hydroxypiperidine (14f). A procedure identical to that described for the preparation of **14a** using 4-hydroxy-4-(4-fluorobenzyl)piperidine (**9f**) gave **14f** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.11 (m, 2H), 6.95 (t, J = 8.5 Hz, 2H), 2.68 (s, 2H), 2.55−2.64 (m, 4H), 2.27−2.36 (m, 4H), 1.93 (m, 1H), 1.66 (dt, J = 4.4, 13.4 Hz, 2H), 1.46 (d, J = 12.0 Hz, 2H).

4-(4-Methylbenzyl)-1-but-3-ynyl-4-hydroxypiperidine (14g). A procedure identical to that described for the preparation of **14a** using 4-hydroxy-4-(4-methylbenzyl)piperidine (**9g**) gave **14g** as a brown oil: ^{1}H NMR ($CDCl_3$) δ 7.06 (ABq, J = 7.5 Hz, $\delta\nu$ = 15.8 Hz, 4H), 2.67 (s, 2H), 2.55−2.65 (m, 4H), 2.25−2.38 (m, 7H including s at 2.29), 1.93 (m, 2H), 1.68 (dt, J = 3.9, 12.5 Hz, 2H), 1.48 (d, J = 13.2 Hz, 2H).

4-Benzyl-1-prop-2-ynylpiperidine (13a). A procedure identical to that described for the preparation of **14a** using 4-benzylpiperidine (**9a**) (Aldrich) and propargyl *p*-toluenesulfonate (Lancaster) (**10**) gave **13a**: ^{1}H NMR ($CDCl_3$) δ 7.23 (d, J = 5.9 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H), 7.11 (d, J = 7.3 Hz, 2H), 3.24 (d, J = 2.4 Hz, 2H), 2.83 (d, J = 11.5 Hz, 2H), 2.50 (d, J = 7.1 Hz, 2H), 2.18 (t, J = 2.4 Hz, 1H), 2.10 (dt, J = 1.7, 11.5 Hz, 2H), 1.63 (d, J = 12.9 Hz, 2H), 1.29 (dq, J = 3.7, 12.7 Hz, 2H).

4-Benzyl-1-pent-4-ynylpiperidine (15a). A mixture of 5-chloropentyne (5.4 mL, 33 mmol), 4-benzylpiperidine (**9a**) (5.3 mL, 30 mmol), and $NaHCO_3$ (3.0 g, 36 mmol) in DMF (100 mL) was stirred at 80 °C under N_2 overnight. Water (500 mL) was added and the mixture extracted with ether (3 × 150 mL). The extracts were washed with saturated brine (300 mL), dried over $MgSO_4$, filtered, and evaporated to leave a brown oil. This oil was purified by MPLC (400 g of silica gel) eluting with 25% → 50% EtOAc/hexanes to give a brown oil (6.3 g, 87%): ^{1}H NMR ($CDCl_3$) δ 7.22−7.25 (m, 2H), 7.09−7.16 (m, 3H), 2.84 (d, J = 10.7 Hz, 2H), 2.49 (d, J = 6.8 Hz, 4H), 2.34 (dt, J = 1.2, 7.3 Hz, 2H), 2.17 (tt, J = 2.4, 7.1 Hz), 1.90 (m, 1H), 1.82 (t, J = 11.7 Hz, 2H), 1,67 (dquin, J = 1.2, 7.3 Hz, 2H), 1.59 (d, J = 12.0 Hz, 2H), 1.47 (m, 1H), 1.25 (dq, J = 3.2, 11.5 Hz, 2H).

4-Benzyl-1-[4-(4-nitrophenyl)but-3-ynyl]piperidine (16). A mixture of 4-benzyl-1-(3-butynyl)piperidine (**14a**; 909 mg, 4 mmol), 4-iodonitrobenzene (1.49 g, 6 mmol), and $Pd(PPh_3)_4$ (347 mg, 0.3 mmol) was stirred in *n*-$BuNH_2$ (10 mL) and deoxygenated by bubbling N_2 through the mixture for 10 min. The mixture was stirred at room temperature under N_2 overnight. The solvent was evaporated and the residue purified by MPLC (200 g of silica gel) eluting with 30% → 75% EtOAc/hexanes to give a red oil (918 mg). This oil was repurified by MPLC (200 g of silica gel) eluting with 25% → 50% EtOAc/hexanes to give a red oil (504 mg). This oil was stirred in EtOH (10 mL) and oxalic acid·$2H_2O$ (182 mg) in EtOH (2 mL) added. The salt precipitated on standing in the freezer overnight; it was collected, washed with cold EtOH, and dried at 50 °C under high vacuum overnight to give **16** as a pink solid (379 mg, 22%): mp 112−115 °C; IR 1594, 1516, 1342 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.16 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.24 (m, 2H), 7.14 (m, 3H), 3.32 (m, 2H), 3.13 (m, 2H), 2.87 (m, 2H), 2.70 (m, 2H), 2.48 (d, J = 6.3 Hz, 2H), 1.66 (d, J = 11.7 Hz, 3H), 1.38 (m, 2H); APCI MS m/z 349.5 (100%, MH^+); HPLC (60% pH 3 buffer:40% MeCN) 6.53 min (99.45%). Anal. ($C_{22}H_{24}N_2O_2 \cdot C_2H_2O_4 \cdot 0.1H_2O$) C, H, N, water.

4-Benzyl-1-[4-(4-chlorophenyl)but-3-ynyl]piperidine (17). A mixture of 4-benzyl-1-(3-butynyl)piperidine (**14a**; 454 mg, 2 mmol), 4-chloroiodobenzene (715 mg, 3 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) was stirred in pyrrolidine (5 mL) at room temperature under N_2 for 3 days. The solvent was evaporated and the residue purified by MPLC (200 g silica gel) eluting with 25% → 50% EtOAc/hexanes to give a pale-yellow oil (577 mg). This oil was stirred in EtOH (15 mL) and oxalic acid·$2H_2O$ (215 mg) in EtOH (2 mL) added. The salt precipitated on standing; it was collected, washed with cold EtOH, and dried at 50 °C under high vacuum overnight to give **17** as an off-white solid (449 mg, 52%): mp 155−158 °C; IR 1489, 1404, 1198, 1090, 721 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.38 (s, 4H), 7.24 (m, 2H), 7.13 (m, 3H), 3.33 (d, J = 12.0 Hz, 2H), 3.12 (t, J = 7.4 Hz, 2H), 2.81 (t, J = 7.6 Hz, 2H), 2.72 (br t, J = 11.2 Hz, 2H), 2.48 (d, J = 6.8 Hz, 2H), 1.65 (d, J = 12.2 Hz, 3H), 1.36 (m, 2H); APCI MS m/z 338.5 (100%, ^{35}Cl MH^+), 340.5 (35%, ^{37}Cl MH^+); HPLC (60% pH 3 buffer:40% MeCN) 11.12 min (100%). Anal. ($C_{22}H_{24}ClN \cdot C_2H_2O_4 \cdot 0.15H_2O$) C, H, N, Cl, water.

The following analogues were prepared using the procedure outlined for **17** above.

4-Benzyl-1-[4-(3-chlorophenyl)but-3-ynyl]piperidine oxalate (18): mp 171−172 °C; IR 1721, 1641, 1591, 1474, 1454, 1405, 1078, 788, 709 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.18−7.30 (m, 7H), 7.08 (d, J = 7.1 Hz, 2H), 3.74 (d, J = 12.2 Hz, 2H), 3.22 (t, J = 7.3 Hz, 2H), 2.89 (t, J = 7.1 Hz, 2H), 2.56 (m, 4H), 1.71−1.84 (m, 5H); APCI MS m/z 338.6 (100%, ^{35}Cl MH^+), 340.6 (39%, ^{37}Cl MH^+); HPLC (70% pH 3 buffer:30% MeCN) 11.33 min (99.77%). Anal. ($C_{22}H_{24}ClN \cdot 1.07C_2H_2O_4$) C, H, N.

4-Benzyl-1-[4-(2-chlorophenyl)but-3-ynyl]piperidine oxalate (19): mp 165 °C; IR 1717, 1703, 1635, 1498, 1474, 1430, 1068, 953, 760, 722, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.16−7.37 (m, 7H), 7.08 (d, J = 7.1 Hz, 2H), 3.77 (d, J = 11.0 Hz, 2H), 3.26 (m, 2H), 2.94 (t, J = 6.3 Hz, 2H), 2.54−2.67 (m, 4H), 1.70−1.80 (m, 5H); APCI MS m/z 338.3 (100%, ^{35}Cl MH^+), 340.3 (32%, ^{37}Cl MH^+); HPLC (60% pH 3 buffer:40% MeCN) 8.50 min (99.22%). Anal. ($C_{22}H_{24}ClN \cdot C_2H_2O_4$) C, H, N, Cl.

4-Benzyl-1-[4-(4-fluorophenyl)but-3-ynyl]piperidine oxalate (20): mp 148−149 °C; IR 3426, 2924, 2551, 1718, 1600, 1506, 1455, 1403, 1221, 839, 720, 497 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.45−7.48 (m, 2H), 7.28−7.31 (m, 2H), 7.17−7.23 (m, 5H), 3.37 (d, J = 12.0 Hz, 2H), 3.17 (t, J = 7.5 Hz, 2H), 2.75−2.87 (m, 4H), 2.53 (d, J = 6.7 Hz, 2H), 1.70 (br d, J = 12.5 Hz, 3H), 1.40−1.46 (m, 2H); CI MS m/z 322 (70%). Anal. ($C_{22}H_{24}FN \cdot C_2H_2O_4 \cdot 0.27H_2O$) C, H, N, F, water.

4-Benzyl-1-[4-(4-methylphenyl)but-3-ynyl]piperidine oxalate (21): mp 163−164 °C; IR 1717, 1703, 1640, 1509, 1497, 1454, 1404, 954, 815, 722, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.18−7.27 (m, 5H), 7.07 (t, J = 8.3 Hz, 4H), 3.73 (d, J = 12.2 Hz, 2H), 3.22 (t, J = 7.2 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 2.55 (m, 4H), 2.29 (s, 3H), 1.70−1.83 (m, 5H); APCI MS m/z 318.6 (100%, MH^+); HPLC (70% pH 3 buffer:30% MeCN) 10.87 min (100%). Anal. ($C_{23}H_{27}N \cdot C_2H_2O_4$) C, H, N.

4-Benzyl-1-[4-(4-methoxyphenyl)but-3-ynyl]piperidine oxalate (22): mp 158−161 °C; IR 1715, 1704, 1606, 1289, 1246, 1170, 1033, 954, 826, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.22−7.30 (m, 4H), 7.14 (m, 3H), 6.86 (d, J = 8.8 Hz, 2H), 3.70 (s, 3H), 3.34 (d, J = 11.7 Hz, 2H), 3.11 (t, J = 7.6 Hz, 2H), 2.75 (m, 4H), 2.48 (d, J = 6.8 Hz, 2H), 1.67 (m, 3H), 1.36 (m, 2H); APCI MS m/z 334.6 (100%, MH^+); HPLC (60% pH 3 buffer:40% MeCN) 8.35 min (98.94%). Anal. ($C_{23}H_{27}NO \cdot C_2H_2O_4 \cdot 0.1H_2O$) C, H, N, water.

4-Benzyl-1-[4-(4-hydroxyphenyl)but-3-ynyl]piperidine (23): mp 124−128 °C; IR 1606, 1511, 1274, 829 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.21 (m, 2H), 7.10 (m, 5H), 6.63 (d, J = 8.8 Hz, 2H), 2.78 (d, J = 11.5 Hz, 2H), 2.42 (m, 6H), 1.83 (t, J = 10.5 Hz, 2H), 1.35−1.50 (m, 3H), 1.12 (m, 2H); APCI MS m/z 320.6 (100%, MH^+); HPLC (60% pH 3 buffer:40% MeCN) 3.85 min (99.44%). Anal. ($C_{22}H_{25}NO$) C, H, N.

4-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]phenylamine oxalate (24): mp 120−121 °C; ^{1}H NMR (DMSO-d_6) δ 7.24 (t, J = 7.2 Hz, 2H), 7.14 (m, 3H), 6.99 (d, J = 8.5 Hz, 2H), 6.43 (d, J = 8.5 Hz, 2H), 3.40 (m, 2H), 3.17 (m, 2H), 2.83 (m, 2H), 2.76 (t, J = 7.6 Hz, 2H), 2.49 (d, J = 6.3 Hz, 2H), 1.50−1.80 (m, 3H), 1.38 (m, 2H); APCI MS m/z 319.2 (100%, MH$^+$); HPLC (70% 0.1% aqueous CF_3CO_2H:30% MeCN) 4.33 min (93.84%). Anal. ($C_{22}H_{26}N_2 \cdot 1.72C_2H_2O_4 \cdot 0.37H_2O$) C, H, N, water.

{4-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]phenyl}methylamine oxalate (25): mp foams at 151 °C; IR 3403, 1610, 1523, 1178, 819 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.24 (m, 2H), 7.14 (m, 3H), 7.05 (d, J = 8.5 Hz, 2H), 6.41 (d, J = 8.8 Hz, 2H), 3.34 (m, 2H), 3.09 (m, 2H), 2.73 (m, 4H), 2.60 (s, 3H), 2.48 (d, J = 6.8 Hz, 2H), 1.66 (m, 3H), 1.36 (m, 2H); APCI MS m/z 333.6 (100%, MH$^+$); HPLC (60% pH 3 buffer:40% MeCN) 5.18 min (96.15%). Anal. ($C_{23}H_{28}N_2 \cdot C_2H_2O_4$) C, H, N, water.

{4-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]phenyl}dimethylamine oxalate (26): mp 163−164 °C; IR 1608, 1523, 1191, 819 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.24 (m, 2H), 7.13 (m, 5H), 6.59 (d, J = 9.0 Hz, 2H), 3.34 (m, 2H), 3.08 (m, 2H), 2.85 (s, 6H), 2.74 (m, 4H), 2.49 (d, J = 6.8 Hz, 2H), 1.66 (m, 3H), 1.35 (m, 2H); APCI MS m/z 347.6 (100%, MH$^+$); HPLC (60% pH 3 buffer:40% MeCN) 7.88 min (100%). Anal. ($C_{24}H_{30}N_2 \cdot C_2H_2O_4$) C, H, N, water.

***N*-{4-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]phenyl}acetamide (27):** mp 161−163 °C; IR 1663, 1598, 1535, 1509, 1320, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 8.5 Hz, 2H), 7.29 (m, 2H), 7.15−7.30 (m, 3H), 7.10 (d, J = 6.8 Hz, 2H), 2.89 (d, J = 11.5 Hz, 2H), 2.50−2.65 (series of m, 6H), 2.13 (s, 3H), 1.95 (dt, J = 2.0, 11.5 Hz, 2H), 1.61 (d, J = 14.2 Hz, 2H), 1.49 (m, 1H), 1.28 (m, 2H); APCI MS m/z 361.7 (100%, MH$^+$); HPLC (70% pH 3 buffer:30% MeCN) 6.97 min (98.87%). Anal. ($C_{24}H_{28}N_2O$) C, H, N.

***N*-{4-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]phenyl}methanesulfonamide (28):** mp 125−127 °C; IR 1506, 1326, 1152, 980, 755 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.88 (br s, 1H), 7.20−7.30 (m, 4H), 7.06−7.15 (m, 5H), 3.28 (s, 3H), 2.80 (d, J = 11.5 Hz, 2H), 2.45 (m, 6H), 1.85 (t, J = 10.7 Hz, 2H), 1.35−1.50 (m, 3H), 1.13 (m, 2H); APCI MS m/z 397.6 (100%, MH$^+$); HPLC (60% pH 3 buffer:40% MeCN) 10.73 min (99.40%). Anal. ($C_{23}H_{28}N_2O_2S$) C, H, N.

3-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]phenylamine (29): mp 96 °C; IR (KBr) 3452, 3324, 3201, 2917, 2805, 1638, 1599, 1492, 1120, 858, 786, 747, 702, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.22−7.25 (m, 2H), 7.14 (d, J = 7.3 Hz, 1H), 7.09 (d, J = 6.8 Hz, 2H), 7.02 (t, J = 7.8 Hz, 2H), 6.73 (d, 1H, J = 7.5 Hz, 1H), 6.67 (s, 1H), 6.54 (d, J = 8.0 Hz, 1H), 3.58 (br s, 2H), 2.89 (d, J = 11.4 Hz, 2H), 2.48 (m, 7H), 1.97 (t, J = 9.8 Hz, 2H), 1.44−1.62 (m, 8H), 1.23−1.33 (m, 2H); CI MS m/z 319 (62%); HPLC (80% pH 3.0 buffer:20% MeCN) 3.02 min (100%). Anal. ($C_{22}H_{26}N_2 \cdot 0.25H_2O$) C, H, N, water.

2-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]phenylamine oxalate (30): mp 112−113 °C; IR (KBr) 3444, 3376, 3026, 2923, 2853, 1723, 1617, 1493, 1454, 749, 702, 487 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.28 (d, J = 7.5 Hz, 2H), 7.17−7.22 (m, 3H), 7.07 (d, J = 7.7 Hz, 1H), 7.00 (t, J = 8.4 Hz, 1H), 6.66 (d, J = 7.7 Hz, 1H), 6.44 (t, J = 8.4 Hz, 1H), 3.36−3.40 (m, 2H), 3.16−3.18 (m, 2H), 2.87 (t, J = 7.5 Hz, 2H), 2.63−2.77 (m, 2H), 2.54 (d, J = 6.8 Hz, 2H), 1.69−1.73 (m, 3H), 1.40−1.46 (m, 2H); CI MS m/z 319 (100%). Anal. ($C_{22}H_{26}N_2 \cdot 1.1C_2H_2O_4 \cdot 0.05H_2O$) C, H, N, water.

4-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]benzamide (31): prepared using 4-iodobenzamide;[21] mp 179−182 °C; IR 3412, 1648, 1614, 1410, 1395, 1132, 856 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.20 (m, 2H), 7.08 (m, 3H), 6.00 (br s, 1H), 5.64 (br s, 1H), 2.87 (d, J = 11.7 Hz, 2H), 2.57 (m, 4H), 2.47 (d, J = 7.1 Hz, 2H), 1.94 (dt, J = 2.3, 11.7 Hz, 2H), 1.58 (d, J = 12.9 Hz, 2H), 1.46 (m, 1H), 1.24 (m, 2H); APCI MS m/z 347.6 (100%, MH$^+$); HPLC (65% pH 3 buffer:35% MeCN) 3.48 min (98.34%). Anal. ($C_{23}H_{26}N_2O$) C, H, N.

4-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]benzenesulfonamide (32): mp 171−172 °C; IR 3359, 2937, 2829, 1594, 1327, 1152, 1096, 839, 749, 700, 644, 614, 555 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.27 (m, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 6.8 Hz, 2H), 4.82 (br s, 2H), 2.92 (d, J = 11.3 Hz, 2H), 2.59−2.67 (m, 4H), 2.53 (d, J = 7.2 Hz, 2H), 2.00 (t, J = 11.8 Hz, 2H), 1.49−1.67 (m, 3H), 1.23−1.36 (m, 2H); APCI MS m/z 383 (49%). Anal. ($C_{22}H_{26}N_2O_2S \cdot 0.10H_2O$) C, H, N, S, water.

3-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]benzylamine oxalate (33): mp 99−100 °C; IR 3450, 3058, 3026, 2924, 1723, 1624, 1453, 1207, 703, cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.52 (s, 1H), 7.39−7.45 (m, 3H), 7.29 (t, J = 7.5 Hz, 2H), 7.17−7.21 (m, 3H), 4.02 (s, 2H), 3.27 (d, J = 12.0 Hz, 2H), 3.01 (t, J = 7.2 Hz, 2H), 2.52−2.86 (m, 4H), 1.66 (d, J = 11.3 Hz, 3H), 1.33 (q, J = 12.5 Hz, 2H); CI MS m/z 333 (100%). Anal. ($C_{23}H_{28}N_2 \cdot 1.96C_2H_2O_4 \cdot 0.82H_2O$) C, H, N, water.

4-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-2-nitrobenzeneamine Oxalate (34). A procedure similar to that described for **17** on a 10-mmol scale starting with 4-bromo-2-nitroaniline (Trans World Chemicals) stirring overnight at 50 °C gave **34** as a red oil (3.14 g, 86%). A portion of the oil (340 mg) was converted to the oxalate salt for characterization: orange solid (200 mg); mp 150−153 °C; IR 1631, 1515, 1253 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.91 (d, J = 2.0 Hz, 1H), 7.63 (br s, 2H), 7.31 (dd, J = 2.0, 8.8 Hz, 1H), 7.24 (m, 2H), 7.13 (m, 3H), 6.92 (d, J = 9.0 Hz, 1H), 3.32 (d, J = 11.5 Hz, 2H), 3.10 (m, 2H), 2.78 (m, 4H), 2.48 (d, J = 6.8 Hz, 2H), 1.67 (m, 3H), 1.35 (m, 2H); APCI MS m/z 364.5 (100%, MH$^+$); HPLC (60% pH 3 buffer:40% MeCN) 4.88 min (98.96%). Anal. ($C_{22}H_{25}N_3O_2 \cdot C_2H_2O_4 \cdot 0.3H_2O$) C, H, N, water.

4-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]benzene-1,2-diamine (35). A mixture of **34** (2.56 g, 7.0 mmol), iron powder (3.75 g), and concentrated HCl (5 drops) in EtOH (52 mL) and water (8 mL) was stirred at reflux for 2 h. The mixture was filtered and evaporated. The residue was purified by MPLC (400 g of silica gel) eluting with 200:8:1 → 100:8:1 CH_2Cl_2:EtOH:0.880 NH_4OH to give, after drying at 40 °C under high vacuum overnight, **35** as a beige solid (1.82 g, 77%): mp 141−142 °C; IR 1517, 1282, 1131 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 2H), 7.11−7.16 (m, 3H), 6.74 (dd, J = 1.7, 8.1 Hz, 1H), 6.70 (d, J = 1.5 Hz, 1H), 6.54 (d, J = 7.8 Hz, 1H), 3.42 (br s, 2H), 3.27 (br s, 2H), 2.89 (d, J = 11.7 Hz, 2H), 2.59 (m, 2H), 2.50 (m, 4H), 1.94 (dt, J = 1.7, 11.7 Hz, 2H), 1.60 (m, 2H), 1.48 (m, 1H), 1.28 (m, 2H); APCI MS m/z 334.6 (100%, MH$^+$); HPLC (70% pH 3 buffer:30% MeCN) 3.02 min (99.05%). Anal. ($C_{22}H_{27}N_3 \cdot 0.07H_2O$) C, H, N, water.

4-{4-[4-(4-Chlorobenzyl)piperidin-1-yl]but-1-ynyl}phenylamine (36): ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 4H), 7.05 (m, 2H), 6.53 (d, J = 6.0 Hz, 2H), 3.75 (br. s, 2H), 2.89 (m, 2H), 2.55 (m, 4H), 2.15 (m, 2H), 1.96 (m, 3H), 1.58 (m, 2H), 1.44 (m, 1H), 1.24 (m, 2H); EI MS m/z 354 (^{37}Cl M$^+$, 3%), 353 (^{35}Cl, M$^+$, 9%), 222 (100%), 188 (15%), 125 (20%); HRMS calcd for $C_{22}H_{25}{}^{35}ClN_2$ 352.1714, found 352.1710.

4-{4-[4-(4-Fluorobenzyl)piperidin-1-yl]but-1-ynyl}phenylamine (37): mp 83−84 °C; IR 3406, 3345, 3225, 2943, 2916, 2834, 1639, 1606, 1511, 1217, 828 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.17 (d, J = 8.7 Hz, 2H), 7.08 (m, 2H), 6.96 (t, J = 8.7 Hz, 2H), 6.58 (d, J = 8.7 Hz, 2H), 3.72 (s, 2H), 2.93 (m, 2H), 2.50−2.65 (m, 6H), 2.00 (m, 2H), 1.39−1.72 (m, 3H), 1.19−1.31 (m, 2H); CI MS m/z 337 (M$^+$, 100); HPLC (80% pH 3.0 buffer:20% MeCN) 3.52 min (95.02%). Anal. ($C_{22}H_{25}FN_2 \cdot 0.59H_2O$) C, H, N, F, water.

4-{4-[4-(4-Methylbenzyl)piperidin-1-yl]but-1-ynyl}phenylamine (38): ^{1}H NMR ($CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 2H), 7.04 (q, J = 7.8 Hz, 4H), 6.54 (d, J = 8.4 Hz, 2H), 3.73 (br s, 2H), 2.91 (d, J = 11.1 Hz, 2H), 2.48−2.64 (m, 6H), 2.32 (s, 3H), 1.99 (t, J = 12.0 Hz, 2H), 1.62 (d, J = 12.0 Hz, 2H), 1.50 (m, 1H), 1.31 (m, 2H); EI MS m/z 332 (M$^+$, 10%), 202 (100%), 189 (30%), 105 (32%); HRMS calcd for $C_{23}H_{28}N_2$ 332.2252, found, 332.2260.

1-[4-(4-Aminophenyl)but-3-ynyl]-4-benzylpiperidin-4-ol (39): mp 89−92 °C; IR 1620, 1606, 1513, 1118, 828, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.10−7.21 (m, 5H), 6.94 (d, J = 8.3 Hz, 2H), 6.41 (d, J = 8.5 Hz, 2H), 2.59 (s, 2H), 2.44 (m, 4H), 2.24 (t, J = 10.7 Hz, 2H), 1.41 (m, 2H), 1.29 (m, 2H); APCI

MS *m/z* 335.0 (100%, MH^+); HPLC (80% pH 3 buffer:20% MeCN) 4.65 min (100%). Anal. ($C_{22}H_{26}N_2O$) C, H, N.

1-[4-(4-Aminophenyl)but-3-ynyl]-4-(4-fluorobenzyl)piperidin-4-ol (40): mp 113.5 °C; IR 1621, 1607, 1511, 1218, 829 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10−7.17 (m, 4H), 6.96 (t, J = 8.5 Hz, 2H), 6.53 (d, J = 8.5 Hz, 2H), 3.69 (br s, 2H), 2.69 (s, 2H), 2.50−2.70 (m, 6H), 2.35 (m, 2H), 1.69 (m, 2H), 1.48 (m, 2H); APCI MS *m/z* 353.1 (100%, MH^+); HPLC (80% pH 3 buffer:20% MeCN) 5.85 min (92.4%). Anal. ($C_{22}H_{25}FN_2O$) C, H, N, water.

1-[4-(4-Aminophenyl)but-3-ynyl]-4-(4-methylbenzyl)piperidin-4-ol (41): ^1H NMR ($CDCl_3$) δ 7.11−7.19 (m, 6H), 6.58 (m, 2H), 3.73 (s, 2H), 3.45 (m, 4H), 2.71 (m, 4H), 2.59 (m, 2H), 2.33 (s, 3H), 2.05 (m, 2H), 1.88 (m, 2H), 1.65 (m, 3H); HRMS calcd for $C_{23}H_{28}N_2O$ + H 349.2279, found 348.2280.

4-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]phenylamine (42): mp 99−101 °C; IR 3445, 3325, 2936, 2922, 1634, 1607, 1515, 1302, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13−7.52 (m, 7H), 6.57 (d, J = 10.8 Hz, 2H), 3.76 (s, 2H), 3.47 (s, 2H), 2.94 (d, J = 11.3 Hz, 2H), 2.53 (d, J = 7.0 Hz, 2H), 2.2 (m, 2H), 1.2−1.7 (m, 5H); APCI MS *m/z* 305 (99%, MH^+). Anal. ($C_{21}H_{24}N_2 \cdot 0.15H_2O$) C, H, N, water.

4-[5-(4-Benzylpiperidin-1-yl)pent-1-ynyl]phenylamine oxalate (43): mp 148−150 °C; IR 1720, 1609, 1515, 1202, 1177, 703 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.24 (m, 2H), 7.13 (m, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.42 (d, J = 8.3 Hz, 2H), 3.35 (m, 2H), 2.98 (m, 2H), 2.77 (m, 2H), 2.48 (d, J = 6.3 Hz, 2H), 2.37 (t, J = 6.8 Hz, 2H), 1.60−1.90 (m, 5H), 1.36 (m, 2H); APCI MS *m/z* 333.4 (100%, MH^+); HPLC (70% pH 3 buffer: 30% MeCN) 6.33 min (100%). Anal. ($C_{23}H_{28}N_2 \cdot C_2H_2O_4 \cdot 0.10H_2O$) C, H, N, water.

***N*-{4-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]phenyl}acetamide (44):** mp 185−188 °C; IR 1670, 1599, 1526, 1513, 1320, 839 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.01 (s, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.27 (dd, J = 1.7, 6.8 Hz, 2H), 7.21 (t, J = 7.4 Hz, 2H), 7.11 (m, 3H), 3.37 (s, 2H), 2.75 (d, J = 11.5 Hz, 2H), 2.44 (m, 2H), 2.03 (t, J = 9.8 Hz, 2H), 1.98 (s, 3H), 1.50 (d, J = 12.5 Hz, 2H), 1.40 (m, 1H), 1.14 (m, 2H); APCI MS *m/z* 347.1 (100%, MH^+); HPLC (70% pH 3 buffer:30% MeCN) 6.15 min (98.55%). Anal. ($C_{23}H_{26}N_2O$) C, H, N.

***N*-{4-[5-(4-Benzylpiperidin-1-yl)pent-1-ynyl]phenyl}acetamide (45).** A procedure similar to that described for **17** on a 2-mmol scale starting with 4-iodoacetanilide and **15a** gave a yellow oil (588 mg). The material was triturated with EtOH to give a brown solid (139 mg, 18%): mp 142−143 °C; IR 1669, 1600, 1526, 1513, 1320, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.23 (m, 1H), 7.09−7.22 (m, 4H), 2.87 (d, J = 11.5 Hz, 2H), 2.49 (d, J = 7.1 Hz, 2H), 2.38 (m, 4H), 2.13 (s, 3H), 1.79 (dt, J = 1.7, 11.7 Hz, 2H), 1.73 (quin, J = 7.3 Hz, 2H), 1.59 (d, J = 12.2 Hz, 2H), 1.48 (m, 1H), 1.20−1.31 (m, 2H); APCI MS *m/z* 375.4 (100%, MH^+); HPLC (70% pH 3 buffer:30% MeCN) 9.20 min (100%). Anal. ($C_{25}H_{30}N_2O \cdot 0.10H_2O$) C, H, N, water.

***N*-{4-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]phenyl}methanesulfonamide (46):** mp 141−142 °C; IR 3448, 3023, 2933, 2918, 2814, 1605, 1508, 1331, 1149 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (d, J = 6.8 Hz, 2H), 7.26 (m, 2H), 7.13−7.20 (m, 5H), 3.47(s, 2H), 2.96−3.01 (m, 5H), 2.54 (d, J = 7.0 Hz, 2H), 2.17 (t, J = 11.3 Hz, 2H), 1.68 (d, J = 13.0 Hz, 2H), 1.50−1.57 (m, 1H), 1.32−1.41 (m, 2H); APCI MS *m/z* 383 (100%); HPLC (80% pH 3.0 buffer:20% MeCN) 3.22 min (100%). Anal. ($C_{22}H_{26}N_2O_2S$) C, H, N, S.

***N*-{4-[5-(4-Benzylpiperidin-1-yl)pent-1-ynyl]phenyl}methanesulfonamide oxalate (47):** mp 207−208 °C; IR 1608, 1595, 1509, 1329, 1150 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.29 (d, J = 6.8 Hz, 2H), 7.22 (d, J = 7.6 Hz, 2H), 7.11 (m, 5H), 3.13 (m, 2H), 2.95 (s, 3H), 2.72 (m, 2H), 2.48 (m, 4H), 2.40 (t, J = 6.8 Hz, 2H), 1.73 (m, 2H), 1.59 (m, 3H), 1.25 (m, 2H); APCI MS *m/z* 411.6 (100%, MH^+); HPLC (60% pH 3 buffer:40% MeCN) 4.05 min (100%). Anal. ($C_{24}H_{30}N_2O_2S \cdot 0.61C_2H_2O_4 \cdot 0.04H_2O$) C, H, N, water.

4-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]phenol (48): mp 139−140 °C; IR 1606, 1511, 1284, 1238, 836 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.76 (br s, 1H), 7.09−7.23 (m, 7H), 6.66 (d, J = 8.8 Hz, 2H), 3.34 (s, 2H), 2.74 (d, J = 11.2 Hz, 2H), 2.44 (m, 2H), 2.02 (t, J = 10.5 Hz, 2H), 1.32−1.55 (m, 3H), 1.15 (m, 2H); APCI MS *m/z* 306.0 (100%, MH^+); HPLC (70% pH 3 buffer:30% MeCN) 7.75 min (100%). Anal. ($C_{21}H_{23}NO$) C, H, N.

Pharmacological Methods. Electrophysiology. Oocytes were obtained from mature female *Xenopus* laevis and were prepared and maintained as described previously.[22] Individual oocytes were microinjected with a mixture of NMDA receptor-encoding cRNAs, provided by Dr. P. H. Seeburg (Heidelberg University, Heidelberg, Germany).[23] 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 two electrode voltage-clamp recordings were made at −70 mV in nominally Ca^{2+}-free Ringer (in mM): NaCl, 115; KCl, 2; $BaCl_2$, 1.8; HEPES, 5; pH 7.4.[15] All drugs were diluted in Ringer and applied via bath perfusion (7−10 mL/min) in a conventional flow-through chamber (volume ∼ 0.2 mL). Test drugs were initially dissolved in DMSO and diluted into Ringer just prior to application (final [DMSO] = 0.1−1%). IC_{50} values were obtained by fitting the partial (3−5 point) concentration−inhibition curves to the following equation using Origin (Microcal):

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

where $I_{control}$ is the current in the absence of antagonist, min (minimum) is the residual fractional response at saturating concentration of antagonist, and IC_{50} is the concentration of drug that causes one-half this level of inhibition. To fit the curves for NR1A/2B, 'min' was fixed at 0.15.[24] Data in the text are mean ± standard error (SE).

Radioligand Binding Assays. Test compounds were evaluated at nine concentrations in duplicate added in 5-μL aliquots (1% DMSO final) to 96-well, 1.0-mL volume assay plates and incubated in a total volume of 500 μL 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 μL/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, SanDiego, CA).

α-1 Adrenergic Receptor Binding. The [^{3}H]prazosin binding assay was modified from previously described methods.[16] 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 40,000*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.

Dopamine D2 Receptor Binding. The [^{3}H]raclopride binding assay was modified from previously described methods.[17] 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.

6-Hydroxydopamine-Lesioned Rat.[18] Adult male Sprague−Dawley rats were anesthetized with chloral hydrate, and unilateral lesions of the nigrostriatal dopamine system were accomplished by infusion of 8 μg of 6-hydroxydopamine HBr (6-OHDA) into the right medial forebrain bundle. Rats were pretreated 30 min before surgery with desipramine HCl (25 mg/kg ip) to protect noradrenergic neurons and pargyline (25 mg/kg ip) to potentiate the effects of 6-OHDA. A minimum of 3 weeks after surgery, the rotational behavior induced by apomorphine HCl (50 μg/kg sc) was assessed. Only rats demonstrating more than 100 contraversive turns/hour to apomorphine were used for the present experiments. Rotational behavior was measured using an automated rotometer system (Rotorat Rotational Activity System, MED Associates, Georgia, VT). Anti-parkinsonian activity was assessed as the ability of the compound to potentiate the contraversive rotation induced by L-DOPA methyl ester (10 mg/kg sc) over a 6-h period. Experiments were conducted using a crossover paradigm where each rat received either a vehicle plus L-DOPA, or the test compound plus L-DOPA in randomized order. Rats were tested at 7-day intervals. In experiments in which the compound was tested orally, rats were food deprived for 16 h. Statistical analysis between treatment groups was performed using a paired *t*-test.

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