Subtype-Selective *N*-Methyl-D-aspartate Receptor Antagonists: Benzimidazalone and Hydantoin as Phenol Replacements

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Previous work in our laboratories investigating compounds with structural similarity to ifenprodil (**5**) and **6** (CP101,606) resulted in compound **7** as a potent and selective antagonist of the NR1/2B subtype of the NMDA receptors. Replacement of the phenol group of **7** with a benzimidazalone group tethered by a three-carbon chain to 4-benzylpiperidine resulted in a slightly less active, but selective, compound. Lengthening the carbon tether resulted in a decrease in NR1/2B potency. Replacement of the phenol ring with a hydantoin resulted in weak antagonists. Compound **11a** was one of the most potent NR1/2B antagonists from this study. Compound **11a** also potentiated the effects of L-DOPA in a rat model of Parkinson's disease (the 6-hydroxydopamine-lesioned rat), dosed at 30 mg/kg orally.

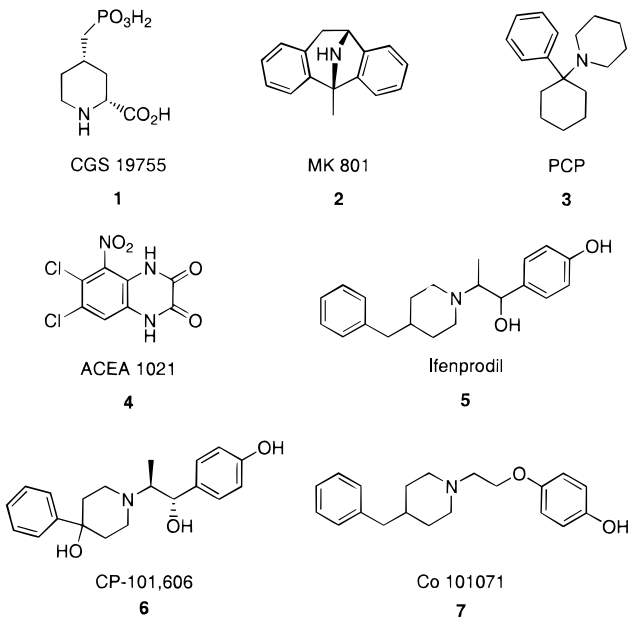
Introduction

The excitatory neurotransmitter L-glutamic acid (glutamate) has been shown to cause neuronal death in instances of stroke and head trauma.[1] Large amounts of glutamate released during such events overstimulate glutamate receptors, causing excessive amounts of calcium ion to enter into the neurons. These sustained elevations of calcium concentrations in neurons trigger a number of biochemical events such as formation of free radicals, activation of proteases, and breakdown of neuronal membranes, which can ultimately lead to cell death. Also, glutamate receptor overstimulation may play a role in chronic neurodegenerative conditions, such as Alzheimer's disease[2] and Parkinson's disease.[3]

A number of reports in the literature strongly suggest that the toxicity of high levels of glutamate is mediated primarily by *N*-methyl-D-aspartate (NMDA) receptors. Antagonists of NMDA receptor have shown in vitro neuronal protection in response to toxic levels of L-glutamic acid or *N*-methyl-D-aspartic acid. Also, these antagonists have demonstrated neuroprotection in animal models of focal ischemia.[4]

A number of NMDA receptor antagonists have been reported in the literature. Some examples are CGS 19755 (selfotel)[5] (**1**) (see Chart 1), a competitive glutamate antagonist; MK 801 (dizocilpine)[6] (**2**) and PCP (phencyclidine)[7] (**3**), noncompetitive antagonists at a channel site; and ACEA 1021 (licostinel)[8] (**4**), a glycine site antagonist. While these types of antagonists demonstrate neuroprotection in animal models, development of clinically useful NMDA antagonists as drugs has been hindered by a number of dose-limiting side effects. These side effects include memory deficits, neurotoxicity, psychotomimetic behaviors, and sedation.[9]

Chart 1



Investigations into the structure of mammalian NMDA receptors have shown them to be ligand-gated ion channels that are heterooligomeric combinations of NR1 subunits, found in eight isoforms, and at least one of four NR2 subunits (NR2A−NR2D).[10] These distinct forms of the NMDA receptor could be utilized in designing new classes of subtype-selective NMDA receptor antagonists that might retain therapeutic activity without the side effects observed previously in nonselective NMDA receptor antagonists.

Research in this area has produced a number of NR1/2B subtype-selective antagonists. Ifenprodil (**5**) was the first reported NR1/2B subtype-selective antagonist that was neuroprotective in both in vitro and animal models

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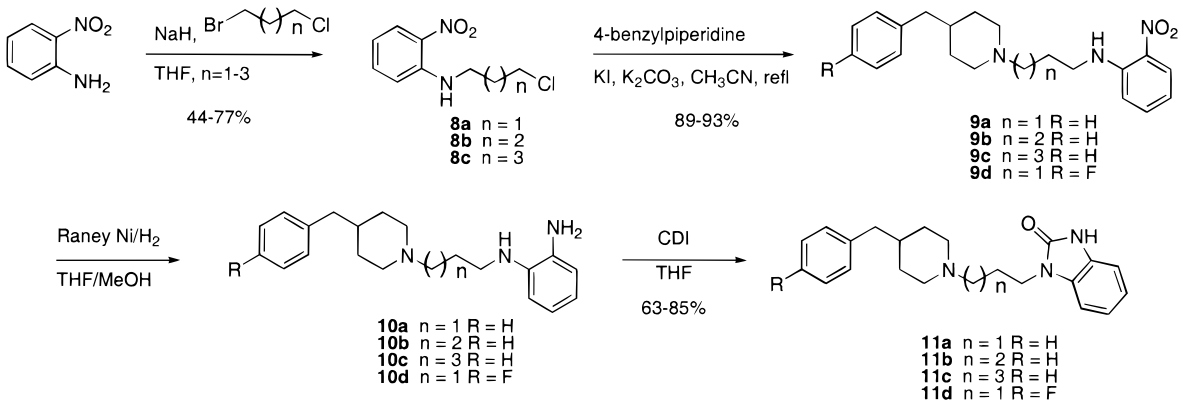
Scheme 1



Scheme 2

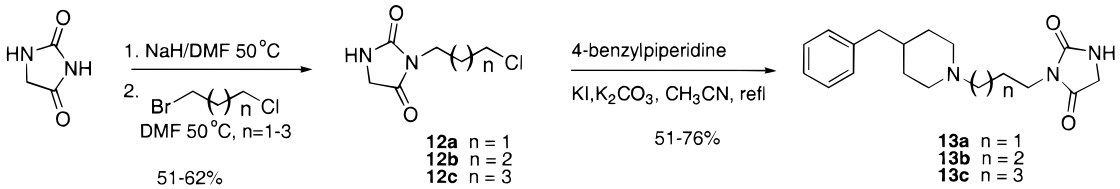
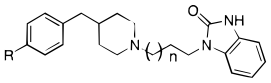


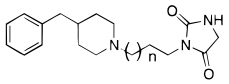
Table 1. Functional Antagonism of Benzimidazalone Compounds at NMDA Receptor Subtypes



			IC_{50} (μM)		
compd	n	R	NR1A/2A[a]	NR1A/2B	NR1A/2C
7			> 100 (1)	0.025 ± 0.009 (3)	> 100 (1)
11a	1	H	> 100 (1)	0.095 ± 0.02 (4)	> 100 (1)
11b	2	H	> 100 (1)	3.4 ± 0.3 (3)	> 100 (1)
11c	3	H	> 100 (1)	11 ± 0.8 (3)	> 100 (1)
11d	1	F	> 100 (1)	0.11 ± 0.02 (4)	> 100 (1)

[a] IC_{50} values for inhibition of NMDA responses at cloned NMDA receptors expressed in *Xenopus* oocytes. Number of individual experiments (*n*) shown in parentheses. Data are represented as mean ± SEM.

Table 2. Functional Antagonism of Hydantoin Compounds at NMDA Receptor Subtypes



		IC_{50} (μM)		
compd	n	NR1A/2A[a]	NR1A/2B	NR1A/2C
13a	1	> 100 (1)	27 ± 5 (3)	> 100 (1)
13b	2	> 100 (1)	10 ± 0.7 (3)	> 100 (1)
13c	3	88 (1)	49 ± 4 (3)	> 100 (1)

[a] See corresponding footnote in Table 1.

of stroke.[11] Using ifenprodil as a starting point, compounds such as **6** have been designed.[12] This compound is a potent and selective antagonist for NR1/2B receptors and is neuroprotective in vitro. Previous work in our own laboratories produced a series of compounds based on the selective NR1/2B antagonist **7**.[13] One common feature found in compounds **5**−**7** is the presence of a phenol ring. This group acts as a hydrogen-bond donor in the NMDA receptor site and is important for NR1/2B potency.[13b,14−16] We were interested in expanding our work around **7** to find other functional groups besides phenol that would act as hydrogen-bond donors and retain selectivity for NR1/2B receptors as well as possess oral activity in the 6-hydroxydopamine-lesioned rat model for Parkinson's disease.

Chemistry

The compounds in Tables 1 and 2 were most easily synthesized via the general routes outlined in Schemes 1 and 2. 2-Nitroaniline was treated with commercially available bromochloroalkanes to give the mono-N-alkylated products **8a**−**c**. In the case of **8b**, (2-nitrophenyl)-pyrrolidine was also isolated as a byproduct from the reaction. Its formation can be attributed to the ease of formation of five-membered rings under an *exo-tet* classification.[17] The analogous (2-nitrophenyl)piperidine byproduct for **8c** was not observed. These nitroanilines were coupled with either 4-benzylpiperidine or 4-(4-fluorobenzyl)piperidine[6] by in situ conversion of the chloride to the iodide. The phenyldiamines **10a**−**d** were formed by catalytic reduction of the nitroanilines **9a**−**d** with Raney nickel. These were used immediately without purification for conversion to the final benzimidazalones **11a**−**d**. This was due to the instability of the diamines **10a**−**d**. In most cases, a recrystallization was performed on the piperidine benzimidazalone free base as the last step; this usually ensured that the material would pass elemental analysis. However, in the case of **11a**, conversion to the oxalate salt and recrystallization were necessary in order to isolate solid material.

The hydantoin compounds **13a**−**c** were synthesized using the steps in Scheme 2. Alkylation on the imide nitrogen occurred exclusively as evidenced by the loss of the imide proton signal in the ^{1}H NMR. Treatment of the alkylated hydantoins **12a**−**c** with 4-benzylpiperidine was carried out as described previously. A recrystallization was performed as the last step in order to obtain analytically pure material. Optimization of the

reaction conditions and purification schemes was not attempted and would likely increase many of the yields reported.

Pharmacology

The compounds **11a**−**d** and **13a**−**c** were tested for antagonism at the three binary NMDA receptor subunit combinations expressed in *Xenopus* oocytes using electrophysiological techniques.[15] IC_{50} values were determined by curve fitting to concentration−inhibition data pooled from 1−4 separate experiments. Compounds that possessed good activity and selectivity for the NR1/2B receptor were tested in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease looking for increases in the number of contraversive (to the side of lesion) rotations produced by L-DOPA over a 6-h period.[18]

Results and Discussion

Our goal was to identify analogues of **7** with potent activity at NR1/2B receptors (IC_{50} < 1 μM) and weak activity at NR1/2A and NR1/2C receptors (IC_{50} > 10 μM). These criteria would help ensure that the compounds were acting at NR1/2B receptors in vivo. Those compounds that possessed good potency and selectivity would then be tested for oral activity in a rat model of Parkinson's disease.

Our first efforts looked at replacing the phenol ring of **7** with a benzimidazalone ring. We then varied the carbon tether length between the benzimidazalone and the 4-benzylpiperidine in order to optimize the spacing between the two halves of the molecule. Compound **11a** with a three-carbon tether showed good activity and selectivity. When the carbon tether was lengthened, as in compounds **11b**,**c**, there was a marked decrease in potency. This drop off in potency can be attributed to either an improper positioning of the NH bond of the benzimidazalone within the NR1/2B receptor or the chain extension exceeding the limits of the binding pocket. The 4-fluoro analogue **11d** was equipotent with analogue **11a** in the binding assays.

The hydantoin compounds were synthesized to determine the need of an aromatic ring in that part of the molecule for potent binding at the NR1/2B receptor. The hydantoins would still retain hydrogen-bond-donating ability with the amide NH. Compounds **13a**−**c** were all less active as NR1/2B antagonists. This demonstrates the need of both an aromatic ring and a hydrogen-bond donor for potency at the NR1/2B receptor.

The two benzimidazalone compounds **11a**,**d** were the most potent NR1a/2B antagonists tested from these two series. Compounds **11a** and **6** were tested in the 6-hydroxydopamine-lesioned rat, a model of Parkinson's disease (see Figures 1 and 2). After oral administration at 30 mg/kg, compound **11a** caused significant potentiation of the contraversive rotations produced by L-DOPA at 10 mg/kg sc. This is an improvement over **6** which did not show significant potentiation given orally at 30 mg/kg. Compound **7** was also tested in this Parkinson's disease model and, like **6**, did not show significant potentiation given orally at 30 mg/kg.

In summary, we have designed an NMDA subtype-selective antagonist that utilizes a benzimidazalone to mimic the phenol group found in previously reported NR1/2B-selective antagonists. Whereas the benzimidazalone served as a phenol replacement, use of a hydantoin ring resulted in a large decrease in activity. Compound **11a** was one of the most potent NR1/2B antagonists in this series and showed significant activity in a rat model of Parkinson's disease when administered orally. This is an improvement over previous phenol-based NR1/2B antagonists which did not possess oral activity in the Parkinson's disease rat model despite potent activity for the NR1/2B receptor.

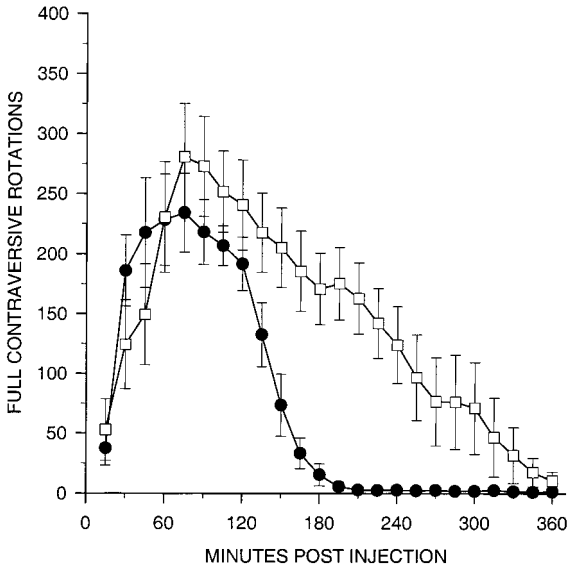


Figure 1. Interaction of compound **11a** on L-DOPA-induced rotations in 6-hydroxydopamine-lesioned rats. The compound or vehicle was administered at the same time as L-DOPA (10 mg/kg sc) in a randomized crossover paradigm, and the number of full contraversive rotations counted in 15-min intervals over 6 h following compound **11a** and L-DOPA was compared to the number of rotations following vehicle and L-DOPA; $N = 8$. Mean total number of rotations for the full 6 h ± SEM: (●) vehicle + L-DOPA (10 mg/kg sc) 1810 ± 130; (□) compound **11a** (30 mg/kg po) + L-DOPA (10 mg/kg sc) 3420 ± 580; $P < 0.05$, paired *t*-test.

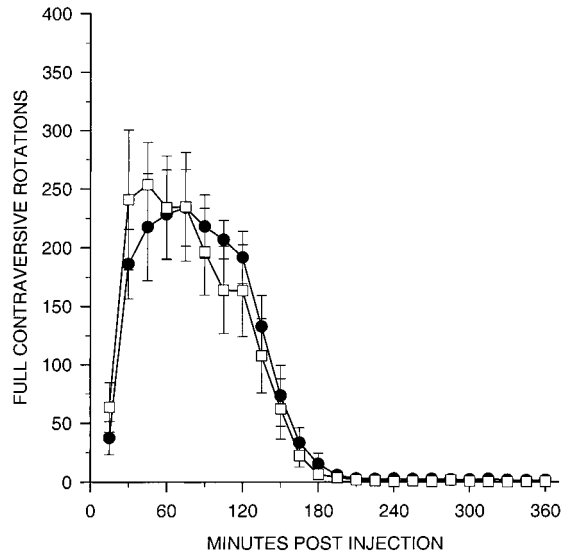


Figure 2. Interaction of compound **6** on L-DOPA-induced rotations in 6-hydroxydopamine-lesioned rats. See Figure 1 for details. Mean total number of rotations for the full 6 h ± SEM: (●) vehicle + L-DOPA (10 mg/kg sc) 1810 ± 130; (□) compound **6** (30 mg/kg po) + L-DOPA (10 mg/kg sc) 1760 ± 330.

Experimental Section

General. Reagents and solvents were purchased from commercial sources and used as received. All starting materials were commercially available unless otherwise indicated. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from blue sodium benzophenone ketyl solution. Yields are of purified product and are not optimized. ^{1}H NMR spectra were recorded on Varian Unity 400 spectrometers. Mass 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 silica gel) or 51-mm i.d. × 450-mm (∼400 g silica gel) glass columns using 32−63-μm, 60 A pore silica gel.

1-(3-Chloropropyl)-2-nitroaniline (8a). A mixture of 2-nitroaniline (2.00 g, 14.5 mmol) and 1-bromo-3-chloropropane (7.2 mL, 72.4 mmol) in THF (50 mL) was treated with NaH (0.64 g, 60% w/w, 15.9 mmol) added in small portions. The deep orange colored suspension was refluxed for 4 h and 1-bromo-3-chloropropane (3 mL, 30.3 mmol) added again. The reaction was refluxed for 3 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (2 × 30 mL). The extracts were dried over $MgSO_4$, filtered, and evaporated to give an orange oil. The oil was purified by MPLC loading in benzene and eluting with 10% EtOAc/hexanes to give an orange oil (1.87 g, 50%): ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 8.68 Hz, 1H), 8.09 (br s, 1H), 7.46 (tr, J = 7.72 Hz, 1H), 6.90 (d, J = 8.44 Hz, 1H), 6.68 (dd, J = 8.32, 7.35 Hz, 1H), 3.54 (q, J = 6.35 Hz, 2H), 2.19 (quin, J = 6.21 Hz, 2H); APCI MS m/z 215 (100%), 217 (30%); IR 3376, 1618, 1573, 1510, 742 cm^{-1}. Anal. ($C_9H_{11}ClN_2O_2$) C, H, N, Cl.

1-(4-Chlorobutyl)-2-nitroaniline (8b). A procedure identical to that described for the preparation of **1a** using 1-bromo-4-chlorobutane gave **8b** as an orange oil that solidified upon standing (1.45 g, 44%): mp = 40−41 °C; ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, J = 8.67, 1.59 Hz, 1H), 8.02 (br s, 1H), 7.41 (m, 1H), 6.81 (d, J = 8.06 Hz, 1H), 6.62 (m, 1H), 3.57 (q, J = 6.10 Hz, 2H), 3.32 (q, J = 6.19 Hz, 2H), 1.94−1.84 (m, 4H); APCI MS m/z 229 (100%), 231 (76%); IR 3379, 1619, 1571, 1513, 1266, 1151, 741 cm^{-1}. Anal. ($C_{10}H_{13}ClN_2O_2$) C, H, N; Cl: calcd, 15.50; found, 14.83.

1-(5-Chloropentyl)-2-nitroaniline (8c). A procedure identical to that described for the preparation of **8a** using 1-bromo-4-chloropentane gave **8b** as an orange oil (6.80 g, 77%): ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, J = 8.55, 1.71 Hz, 1H), 8.02 (br s, 1H), 7.40 (m, 1H), 6.80 (d, J = 8.79 Hz, 1H), 6.61 (m, 1H), 3.53 (t, J = 6.59 Hz, 2H), 3.29 (q, J = 6.43 Hz, 2H), 1.85−1.77 (m, 2H), 1.73 (q, J = 7.32 Hz, 2H), 1.61−1.54 (m, 2H); APCI MS m/z 242 (100%), 244 (32%); IR 3379, 1618, 1572, 1511, 1418, 1353, 1037, 742 cm^{-1}. Anal. ($C_{11}H_{15}ClN_2O_2$) C, H, N.

[3-(4-Benzylpiperidin-1-yl)propyl](2-nitrophenyl)-amine (9a). A mixture of 1-(3-chloropropyl)-2-nitroaniline (**8a**) (0.60 g, 2.84 mmol), 4-benzylpiperidine (0.624 mL, 3.55 mmol), NaI (0.43 g, 2.87 mmol), and K_2CO_3 (0.74 g, 5.68 mmol) in acetonitrile (20 mL) was heated to reflux for 18 h. The solids were filtered and washed with EtOAc. The filtrate was evaporated, and the orange oil chromatographed on MPLC eluting with EtOAc to give **9a** as an orange oil (0.93 g, 93%): ^{1}H NMR ($CDCl_3$) δ 8.20 (br s, 1H), 8.13 (dd, J = 8.67, 1.59 Hz, 1H), 7.38 (m, 1H), 7.26 (m, 2H), 7.17−7.10 (m, 3H), 6.84 (dd, J = 8.67, 0.85 Hz, 1H), 6.59 (m, 1H), 3.33 (q, J = 6.27 Hz, 2H), 2.86 (d, J = 11.23 Hz, 2H), 2.51 (d, J = 7.08 Hz, 2H), 2.39 (t, J = 6.84 Hz, 2 Hz), 1.88−1.81 (m, 4H), 1.60 (d, J = 14.2 Hz, 2H), 1.55 (m, 1H) 1.36−1.22 (m, 2H); APCI MS m/z 354 (M^+ + 1, 100%); IR 2922, 1618, 1571, 1512, 1418, 1350, 1155, 1037, 742, 699 cm^{-1}. Anal. ($C_{21}H_{27}N_3O_2$) C, H, N.

[4-(4-Benzylpiperidin-1-yl)butyl](2-nitrophenyl)-amine (9b). A procedure identical to that described for the preparation of **9a** using 1-(4-chlorobutyl)-2-nitroaniline (**8b**) gave **9b** as an orange oil (0.53 g, 83%): ^{1}H NMR ($CDCl_3$) δ 8.16 (dd, J = 8.56, 1.57 Hz, 1H), 8.06 (br, 1H),7.41 (m, 1H), 7.29−7.25 (m, 2H), 7.20−7.13 (m, 3H), 6.85 (d, J = 8.68 Hz, 1 H), 6.23 (m, 1H), 3.32 (m, 2H), 2.89 (d, J = 11.6 Hz, 2H), 2.53 (d, J = 6.99 Hz, 2H), 2.53 (m, 2H), 2.35 (m, 2H), 1.86 (m, 2H), 1.76−1.71 (m, 2H), 1.67−1.62 (m, 4H), 1.53−1.50 (m, 1H), 1.36−1.25 (m, 2H); APCI MS m/z 368 (M^+ + 1, 100%); IR 3381, 2924,1618, 1572, 1512, 1418, 1354, 1264, 742, 699 cm^{-1}. Anal. ($C_{22}H_{29}N_3O_2$) C, H, N.

[5-(4-Benzylpiperidin-1-yl)pentyl](2-nitrophenyl)-amine (9c). A procedure identical to that described for the preparation of **9a** using 1-(5-chloropentyl)-2-nitroaniline (**8c**) gave **9c** as an orange oil (1.40 g, 89%): ^{1}H NMR ($CDCl_3$) δ 8.16 (dd, J = 8.68, 1.45 Hz, 1H), 8.04 (br, 1H), 7.42 (m, 1H), 7.29−7.25 (m, 2H), 7.20−7.13 (m, 3H), 6.83 (d, J = 8.68 Hz, 1H), 6.63 (m, 1H), 3.29 (dd, J = 12.3, 6.99 Hz, 2H), 2.89 (d, J = 11.3 Hz, 2H), 2.53 (d, J = 6.99 Hz, 2H), 2.33−2.30 (m, 2H), 1.88−1.83 (m, 2H), 1.78−1.71 (m, 2H), 1.65−1.41 (m, 5H), 1.36−1.24 (m, 2H); APCI MS m/z 381 (M^+, 100%); IR 3381, 2928, 1618, 1572, 1512, 1264, 1153, 742, 699 cm^{-1}. Anal. ($C_{23}H_{31}N_3O_2$) C, H, N.

{**3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl**}**(2-nitrophenyl)amine (9d).** A procedure identical to that described for the preparation of **9a** using 1-(3-chloropropyl)-2-nitroaniline (**8a**) and 4-(fluorobenzyl)piperidine[19] gave **9d** as an orange oil (1.79 g, 88%): ^{1}H NMR ($CDCl_3$) δ 8.24 (br s, 1H), 8.16 (dd, J = 8.56, 1.57 Hz, 1H), 2.42 (m, 2H), 7.11−7.07 (m, 2H), 6.99−6.93 (m, 2H), 6.87 (d, J = 8.72 Hz, 1H), 6.62 (m, 2H), 3.49−3.34 (m, 2H), 2.91 (d, J = 11.56 Hz, 2H), 2.52 (d, J = 6.99 Hz, 2H), 2.44 (t, J = 6.87 Hz, 2H), 1.92−1.85 (m, 4H), 1.61 (d, J = 13.7 Hz, 2H), 1.53−1.44 (m, 1H), 1.38−1.29 (m, 2H); APCI MS m/z 371 (M^+, 100%); IR 2922, 1618, 1571, 1509, 1418, 1350, 1155, 1038, 742 cm^{-1}. Anal. ($C_{21}H_{26}FN_3O_2$) C, H, N.

1-[3-(4-Benzylpiperidin-1-yl)propyl]-1,3-dihydrobenzimidazol-2-one (11a). To a solution of [3-(4-benzylpiperidin-1-yl)propyl](2-nitrophenyl)amine **(9a)** (0.91 g, 2.57 mmol) in THF/MeOH (20 mL/20 mL) was added Raney nickel that had been washed with water until the washings were pH ∼ 7. The yellow solution was purged with H_2 and stirred at room temperature under 1 atm for 1 h. The colorless solution was filtered and the catalyst washed generously with THF. The filtrate was evaporated to give an **10a** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.26−7.10 (m, 5H), 6.78−6.74 (m, 1H), 6.67−6.57 (m, 3H), 3.26 (br s, 1H), 3.12 (t, J = 6.35 Hz, 2H), 2.93 (d, J = 11.5 Hz, 2H), 2.51 (d, J = 6.84 Hz, 2H), 2.43 (t, J = 6.59 Hz, 2H), 1.85−1.79 (m, 4H), 1.61 (d, J = 13.4 Hz, 2H), 1.57−1.47 (m, 1H), 1.35−1.25 (m, 2H).

The oil from **10a** was used immediately after isolation and combined with 1,1′-carbonyldiimidazole (0.87 g, 5.36 mmol) in THF (25 mL). The reaction was stirred at room temperature for 18 h, after which the solvent was evaporated to give an oil. The oil was taken up in EtOAc (75 mL), washed with water (5 × 25 mL), dried over Na_2SO_4, filtered, and evaporated. The crude material was chromatographed on MPLC loading with EtOAc and eluting with 10% MeOH/EtOAc to give an oil (0.57 g). This oil was stirred in EtOAc (5 mL) with oxalic acid·$2H_2O$ in EtOH (0.21 g/5 mL) for 15 min. The solvent was evaporated, and the oil recrystallized from acetonitrile to give a solid (0.35 g). A second crop of crystals (0.27 g) was also isolated: ^{1}H NMR ($CDCl_3$) δ 10.86 (s, 1H), 7.23 (m, 2H), 7.15−7.09 (m, 4H), 6.98−6.93 (m, 3H), 3.78 (m, 2H), 3.27 (d, J = 11.5 Hz, 2H), 2.93 (br, 2H), 2.69 (br, 2H), 2.47−2.44 (m, 2H), 1.98−1.92 (m, 2H), 1.65−1.62 (m, 3H), 1.35−1.30 (m, 2H); APCI MS m/z 351 (M^+ + 2, 100%); IR 1710, 1689, 1486, 1404, 1200, 751, 703 cm^{-1}. Anal. ($C_{22}H_{27}N_3O{\cdot}C_2H_2O_4$) C, H, N.

1-[4-(4-Benzylpiperidin-1-yl)butyl]-1,3-dihydrobenzimidazol-2-one (11b). A procedure identical to that described for the preparation of **11a** using [4-(4-benzylpiperidin-1-yl)-butyl](2-nitrophenyl)amine (**9b**) gave **10b** as an oil (0.48 g, 100%). The oil from **10b** was then converted to the benzimidazalone **11b** using the procedure previously described for preparation of **11a**. Crystallization of the free base from acetonitrile yielded **11b** (0.22 g, 43%): mp = 118−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.22−6.92 (m, 9H), 3.82 (t, J = 7.32 Hz, 2H), 2.81 (d, J = 10.99 Hz, 2H), 2.44 (d, J =

7.08 Hz, 2H), 2.28 (t, J = 7.57 Hz, 2H), 1.81−1.40 (m, 9H), 1.26−1.17 (m, 2H); APCI MS m/z 364 ($M^+ + 1$, 100%); IR 1711, 1694, 1487, 1402, 1142, 748, 697 cm^{-1}. Anal. ($C_{23}H_{29}N_3O$) C, H, N.

1-[5-(4-Benzylpiperidin-1-yl)pentyl]-1,3-dihydrobenzimidazol-2-one (11c). A procedure identical to that described for the preparation of **11a** using [5-(4-benzylpiperidin-1-yl)-pentyl](2-nitrophenyl)amine (**9c**) gave **10c** as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.22 (m, 2H), 7.16−7.10 (m, 3H), 6.78 (td, J = 7.57, 1.71 Hz, 1H), 6.69−6.59 (m, 3H), 3.26 (br, 3H), 3.06 (m, 2H), 2.86 (d, J = 11.7 Hz, 2H), 2.49 (d, J = 7.08 Hz, 2H), 2.28−2.24 (m, 2H), 1.79 (td, J = 11.6, 2.1 Hz, 2H), 1.68−1.58 (m, 4H), 1.53−1.45 (m, 3H), 1.42−1.37 (m, 2H), 1.32−1.27 (m, 2H).

The oil from **10c** was then converted to the benzimidazalone **11c** using the procedure previously described for preparation of **11a** (1.03 g, 76%): mp = 107−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (br, 1H), 7.30−6.96 (m, 9H), 3.87 (t, J = 7.32 Hz, 2H), 2.87 (d, J = 11.7 Hz, 2H), 2.51 (d, J = 6.96 Hz, 2H), 2.29−2.24 (m, 2H), 1.86−1.73 (m, 4H), 1.63−1.42 (m, 5H), 1.42−1.22 (m, 4H); APCI MS m/z 378 ($M^+ + 1$, 100%); IR 2927, 1704, 1487, 1446, 1397, 753, 735, 702, 681 cm^{-1}. Anal. ($C_{23}H_{29}N_3O \cdot 0.14H_2O$) C, H, N.

1-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]propyl}-1,3-dihydrobenzimidazol-2-one (11d). A procedure identical to that described for the preparation of **11a** using {3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}(2-nitrophenyl)amine (**9d**) gave **10d** (1.61 g, 100%) as an oil: APCI MS m/z 342 ($M^+ + 1$, 100%).

The oil from **10d** was then converted to the benzimidazalone **11d** (1.09 g, 63%) using the procedure previously described for preparation of **11a**: mp = 125−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (br s, 1H), 7.05−7.00 (m, 6H), 6.91 (t, J = 8.7 Hz, 2H), 3.89 (t, J = 6.96 Hz, 2H), 2.81 (d, J = 11.48 Hz, 2H), 2.45 (d, J = 7.08 Hz, 2H), 2.33 (t, J = 7.2 Hz, 2H), 1.91 (quin, J = 7.08 Hz, 2H), 1.55 (d, J = 12.7 Hz, 2H), 1.46−1.37 (m, 1H), 1.26−1.16 (m, 2H); APCI MS m/z 368 ($M^+ + 1$, 100%); IR 2943, 2924, 1690, 1509, 1488, 1393, 1217, 1154, 753, 735, 686 cm^{-1}. Anal. ($C_{22}H_{26}FN_3O \cdot 0.16H_2O$) C, H, N, F.

3-(3-Chloropropyl)imidazolidine-2,4-dione (12a). Hydantoin (0.53 g, 5.24 mmol) was dissolve in anhydrous DMF (20 mL) and warmed to 50 °C. NaH (0.21 g, 5.25 mmol) was added, and the mixture stirred for 30 min at 50 °C. 1-Bromo-3-chloropropane (1.30 mL, 13.13 mmol) was added, and the suspension stirred for 18 h at 50 °C. The clear solution was quenched with 1 N HCl (10 mL), and the solvent evaporated. The solids were washed with EtOAc and filtered. The filtrate was chromatographed on MPLC eluting with EtOAc gave **12a** (0.60 g, 65%) as a solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (br s, 1H), 3.83 (d, J = 0.98 Hz, 2H), 3.57 (t, J = 6.47 Hz, 2H), 3.41 (t, J = 6.84 Hz, 2H), 1.89 (quin, J = 6.60 Hz, 2H); APCI MS m/z 177 ($M^+ + 1$, 100%); IR 3286, 1775, 1698, 1461, 1130, 766, 716, 637 cm^{-1}.

3-(4-Chlorobutyl)imidazolidine-2,4-dione (12b). A procedure identical to that described for **12a** using 1-bromo-4-chlorobutane gave **12b** (0.88 g, 62%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (br s, 1H), 3.83 (d, J = 0.73 Hz, 2H), 3.57 (t, J = 6.47 Hz, 2H), 3.41 (t, J = 6.84 Hz, 2H), 1.74−1.52 (m, 4H); APCI MS m/z 191 ($M^+ + 1$, 100%); IR 3248, 1777, 1758, 1694, 1456, 1423, 1207, 1137, 758, 696 cm^{-1}.

3-(5-Chloropentyl)imidazolidine-2,4-dione (12c). A procedure identical to that described for **12a** using 1-bromo-5-chloropentane gave **12c** (0.81 g, 51%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H), 3.84 (s, 2H), 3.56 (t, J = 6.71 Hz, 2H), 3.29 (m, 2H), 1.66 (m, 2H), 1.46 (m, 2H), 1.29 (m, 2H); APCI MS m/z 205 ($M^+ + 1$, 60%), 246 ($M^+ +$ MeCN, 100%); IR 3265, 2941, 1765, 1702, 1465, 1349, 1314, 1125 cm^{-1}.

3-[3-(4-Benzylpiperidin-1-yl)propyl]imidazolidine-2,4-dione (13a). A procedure identical to that described in **9a** using 3-(3-chloropropyl)imidazolidine-2,4-dione (**12a**) yielded a solid that was crystallized from EtOAc/hexanes to give **13a** (0.44 g, 50%): mp = 128−129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.23−7.19 (m, 2H), 7.13−7.08 (m, 3H), 3.81 (s, 2H), 3.29 (m, 2H), 2.71 (d, J = 11.2 Hz, 2H), 2.44 (m, 2H), 2.15 (t, J = 6.96 Hz, 2H), 1.67 (t, J = 10.9 Hz, 2H), 1.55 (quin, J = 6.96 Hz, 2H), 1.44 (d, J = 12.9 Hz, 2H), 1.41−1.35 (m, 1H), 1.13−1.05 (m, 2H); IR 2926, 2774, 1762, 1703, 1462, 1351, 751, 701 cm^{-1}. Anal. ($C_{18}H_{25}N_3O_2$) C, H, N.

3-[4-(4-Benzylpiperidin-1-yl)butyl]imidazolidine-2,4-dione (13b). A procedure identical to that described in **9a** using 3-(4-chlorobutyl)imidazolidine-2,4-dione (**12b**) yielded a solid that was crystallized from EtOAc/hexanes to give **13b** (0.51 g, 74%): mp = 119−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.21 (m, 2H), 7.16−7.08 (m, 3H), 5.51 (s, 1H), 3.91 (s, 2H), 3.49 (t, J = 7.2 Hz, 2H), 2.83 (d, J = 11.5 Hz, 2H), 2.48 (d, J = 7.08 Hz, 2H), 2.26 (m, 2H), 1.79 (t, J = 11.6 Hz, 2H), 1.63−1.57 (m, 4H), 1.50−1.42 (m, 3H), 1.29−1.19 (m, 2H); APCI MS m/z 330 ($M^+ + 1$, 100%); IR 2930, 1763, 1702, 1451, 1132, 1082, 748, 701 cm^{-1}. Anal. ($C_{19}H_{27}N_3O_2$) C, H, N.

3-[5-(4-Benzylpiperidin-1-yl)pentyl]imidazolidine-2,4-dione (13c). A procedure identical to that described in **9a** 3-(5-chloropentyl)imidazolidine-2,4-dione (**12c**) yielded a solid that was crystallized from EtOAc/hexanes to give **13c** (0.51 g, 76%): mp = 113−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.21 (m, 2H), 7.16−7.09 (m, 3H), 5.68 (s, 1H), 3.91 (s, 2H), 3.46 (t, J = 7.32 Hz, 2H), 2.84 (d, J = 11.48 Hz, 2H), 2.48 (d, J = 7.08 Hz, 2H), 2.25−2.21 (m, 2H), 1.78 (t, J = 11.48 Hz, 2H), 1.63−1.57 (m, 4H), 1.51−1.43 (m, 3H), 1.30−1.22 (m, 4H); APCI MS m/z 344 ($M^+ + 1$, 100%); IR 2932, 1761, 1701, 1458, 1427, 1117, 751, 701 cm^{-1}. Anal. ($C_{20}H_{29}N_3O_2$) C, H, N.

Pharmacological Methods. Electrophysiology: Oocytes were obtained from mature female *Xenopus* laevis and were prepared and maintained as described previously.[20] Individual oocytes were microinjected with a mixture of NMDA receptor-encoding cRNAs, provided by Dr. P. H. Seeburg (Heidelberg University, Heidelberg, Germany).[21] 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 (2−5 point) concentration−inhibition curves to the following equation using Origin (Microcal):

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

where $I_{control}$ is the current in the absence of antagonist, min (minimum) is the residual fractional response at saturating concentration of antagonist, n is the slope factor, and IC_{50} is the concentration of drug that causes half this level of inhibition. To fit the curves for NR1A/2B, 'min' was fixed at 0.15.[22] Data in the text are mean ± SEM.

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 intraperitoneally (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 subcutaneously (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 3-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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