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

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4-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]phenol (**8**) and 4-[3-(4-benzylpiperidin-1-yl)prop-1-ynyl]-phenol (**9**) are potent NR1A/2B receptor antagonists (IC_{50} values 0.17 and 0.10 μM, respectively). Administered intraperitoneally, they both potentiated the activity of L-DOPA in the unilaterally 6-hydroxydopamine-lesioned (6-OHDA) rat, a model of Parkinson's disease. However, compound **9** was not active orally, likely due to rapid first-pass metabolism of the phenol moiety. The phenol was replaced by several bicyclic heterocyclic systems containing an NH group to function as a H-bond donor in the hope that these would be less likely to undergo rapid metabolism. In general, indoles, indazoles, benzotriazoles, indolones, and isatins gave analogues with weaker NR1A/2B activity than the parent phenols, while benzimidazolones and benzimidazolinones gave equipotent or more potent analogues. The preference for a *para* arrangement between the H-bond donor and the linking acetylene moiety was confirmed, and a propyne link was preferred over a butyne link. Substitution on the benzyl group or a 4-hydroxyl group on the piperidine had little effect on NR1A/2B potency; however, 4-hydroxypiperidines demonstrated slightly improved selectivity for NR1A/2B receptors versus α-1 adrenergic and dopamine D2 receptor affinity. From this study, 5-[3-(4-benzylpiperidin-1-yl)prop-1-ynyl]-1,3-dihydrobenzoimidazol-2-one (**46b**) was identified as a very potent, selective NR1A/2B receptor antagonist (IC_{50} value 0.0053 μM). After oral administration at 10 and 30 mg/kg, **46b** potentiated the effects of L-DOPA in the 6-OHDA-lesioned rat and seemed to have improved oral bioavailability but lower brain penetration compared to phenol **9**.

Introduction

Parkinson's disease is characterized by motor dysfunction, in particular akinesia, bradykinesia, and tremor. There is a clear correlation between degeneration of substantia nigra dopaminergic neurons (the etiology of which is unclear) and the severity of the disease symptoms.[1] Degeneration of these neurons leads to dopamine depletion in the striatum, causing motor dysfunction. Administration of L-dihydroxyphenylalanine (L-DOPA), the precursor to dopamine, ameliorates the symptoms of the disease by replacing the shortage of endogenous dopamine. However, L-DOPA therapy causes unwanted side effects, such as dyskineasias and psychiatric disturbances, and does not halt the progression of the disease. Hence there is a need for therapies that reduce the side effects of L-DOPA use and slow the progression of the disease.

The excitatory neurotransmitter L-glutamic acid (glutamate) is known to be neurotoxic at high concentrations.[2] For example, excess glutamate released during ischemic events (such as stroke) overstimulates glutamate receptors, raising intraneuronal calcium ion concentrations to harmful levels.[3] It is speculated that glutamate toxicity may have a role in the neuronal death in Parkinson's disease and glutamate antagonists might arrest this. Glutamate is involved in neural signaling in the basal ganglia, which includes the striatum and the substantia nigra. It is thus involved in the changes that alter the normal functioning of the basal ganglia circuitry in Parkinson's disease.[4] Use of glutamate receptor antagonists might reverse these changes in basal ganglia glutamatergic neurotransmission. *N*-Methyl-D-aspartate (NMDA) receptors are the predominant form of glutamate receptor in the basal ganglia.[5] Hence, NMDA receptor antagonists in particular may be useful for treating the symptoms of Parkinson's disease and may slow the progression of the disease, although this is much more speculative.

Early NMDA receptor antagonists fell into three main classes: competitive antagonists at the glutamate binding site, such as CGS 19755 (Selfotel)[6] (**1**); noncompetitive antagonists at the channel site, such as MK-801[7] (**2**) and PCP[8] (**3**) ("ion-channel blockers"); and glycine site antagonists, such as ACEA 1021[9] (**4**). Competitive NMDA receptor antagonists have been shown to potentiate the effects of L-DOPA in animal models of Parkinson's disease.[10] In addition, MK-801 reverses L-DOPA-induced motor fluctuations in rats with nigrostriatal lesions.[11] Unfortunately, many of these agents cause

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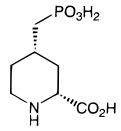
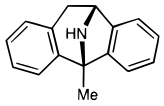
psychotomimetic, neurotoxic, and cardiovascular side effects, which have limited their utility as drugs.[12]



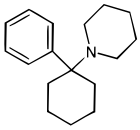
CGS 19755

1



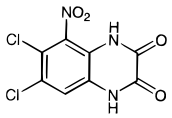
MK 801

2



PCP

3

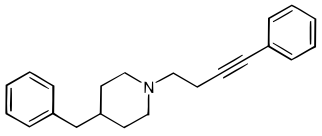


ACEA 1021

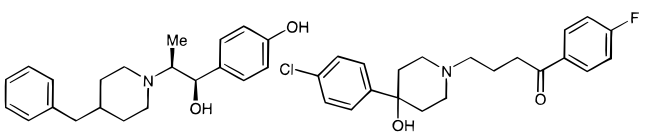
4

Mammalian NMDA receptors are ligand-gated ion channels composed of hetero-oligomeric combinations of an NR1 subunit (found in eight splice variants) and at least one of four NR2 subunits designated NR2A−NR2D.[13] The existence of distinct NMDA receptor subtypes raises the possibility of finding subtype-selective NMDA receptor modulators. Subtype-selective NMDA antagonists might be useful in the treatment of Parkinson's disease (especially as an adjunct to L-DOPA) without the side effects associated with many nonselective NMDA receptor antagonists. If a lower dose of L-DOPA could be used, this may delay the onset of side effects associated with its long-term use. Subtype-selective NMDA antagonists have already been demonstrated clinically to have reduced propensity for psychotomimetic side effects compared to nonselective NMDA receptor antagonists.[14]

In our previous paper,[15] we had studied the SAR of a novel NR1A/2B-selective antagonist **5** found via structure similarity searching of our compound library for structural overlap with the NR2B-selective antagonists ifenprodil (**6**) and haloperidol (**7**).



5



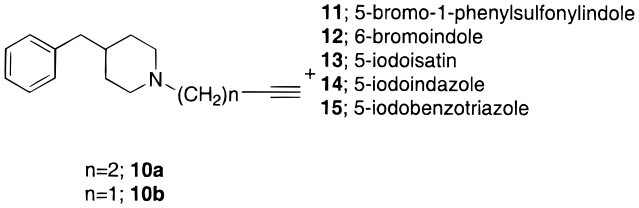
Ifenprodil

Haloperidol

6 **7**

From this hit, the more potent phenols **8** and **9** were developed. These compounds potentiated the effects of L-DOPA in the 6-hydroxydopamine-lesioned rat, a model of Parkinson's disease, administered intraperitoneally (ip), but had little effect by themselves. These data support the hypothesis that NR1A/2B subtype-selective antagonists could have utility for the treatment of Parkinson's disease as an add-on to L-DOPA. However, compound **9** was not active after oral dosing, suggesting low oral bioavailability. Preliminary pharmacokinetic and metabolic studies indicated that these compounds had good permeability across membranes but had short half-lives in vivo. Further investigation revealed that the phenol moiety was subject to rapid secondary hydroxylation and conjugation. In this paper we discuss the replacement of the phenol by heterocyclic NH-containing rings that were expected to slow metabolism and hence improve oral bioavailability.

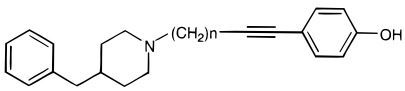
Scheme 1[a]



	n	Ar
16a	2	5-indole
16b	1	5-indole
17a	2	6-indole
18a	2	5-indazole
18b	1	5-indazole
19a	2	5-benzotriazole
19b	1	5-benzotriazole
20a	2	5-isatin
20b	1	5-isatin
21a	2	5-indolone
21b	1	5-indolone

b b

[a] (a) $Pd(PPh_3)_4$/pyrrolidine/50−80 °C; (b) $NH_2NH_2 \cdot xH_2O$/reflux.

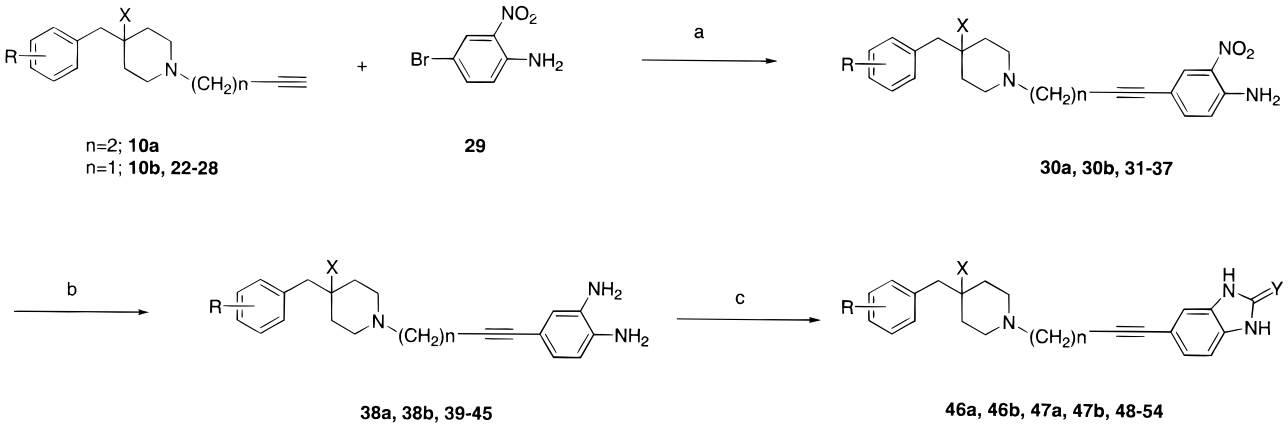


n = 2; **8** NR1A/2B IC_{50} 0.17 μM
n = 1; **9** NR1A/2B IC_{50} 0.10 μM

Chemistry

Compounds **16a**−**20a**, **16b**, **18b**, and **19b** in Table 1 and **20b** were prepared via the general synthesis outlined in Scheme 1. The palladium-mediated coupling of aryl halides to acetylenes **10a** and **10b**[15] was most reliably accomplished using $Pd(PPh_3)_4$ as catalyst with

Scheme 2[a]



10a, 30a, 38a, 46a; R = H; X = H; n = 2; Y = O
10b, 30b, 38b, 46b; R = H, X = H; n = 1; Y = O
22, 31, 39, 48; R = 4-F; X = H; n = 1; Y = O
23, 32, 40, 49; R = 4-Cl; X = H; n = 1; Y = O
24, 33, 41, 50; R = 4-M; X = H; n = 1; Y = O
25, 34, 42, 51; R = 4-MeO; X = H; n = 1; Y = O
26, 35, 43, 52; R = 3-F; X = H; n = 1; Y = O
27, 36, 44, 53; R = H; X = OH; n = 1; Y = O
28, 37, 45, 54; R = 4-F; X = OH; n = 1; Y = O
47a; R = H; X = H; n = 2; Y = S
47b; R = H; X = H; n = 1; Y = S

[a] (a) $Pd(PPh_3)_4$/pyrrolidine; (b) Fe/H_3O^+/EtOH/reflux; (c) carbonyldiimiazole or thiocarbonyldiimidazole/THF.

pyrrolidine as base/solvent. 5-Bromoindole, 6-bromoindole (**12**), and 5-iodoisatin (**13**) were commercially available, although 5-bromoindole coupled in very poor yield. It was found that the 1-phenylsulfonyl derivative **11**[16] coupled in much higher yield with **10a** and **10b**, and the phenylsulfonyl protecting group was removed with ethanolic sodium hydroxide to give the free indole analogues **16a** and **16b**. 6-Bromoindole (**12**) coupled with **10a** (without protection) to give **17a**, albeit in poor yield. 5-Iodoindazole (**14**)[17] and 5-iodobenzotriazole (**15**), the coupling partners for analogues **18a**, **18b**, **19a**, and **19b**, were both made via diazotization/iodination of 5-aminoindazole or 5-aminobenzotriazole, respectively. Indolone analogues **21a** and **21b** were obtained by hydrazine reduction[18] of isatin derivatives **20a** and **20b**. Benzimidazolones and benzimidazothiolones **46a**, **46b**, **47a**, and **47b** in Table 1 and **48**−**54** in Table 2 were prepared as described in Scheme 2. The acetylenes **22**−**28** were synthesized as reported previously[15] and coupled, along with **10a** and **10b**, with commercially available 2-nitro-4-bromoaniline (**29**) to give **30a**, **30b**, and **31**−**37**. Iron/HCl reduction allowed isolation of the stable diamines **38a**, **38b**, and **39**−**45** that were transformed to final products with carbonyl diimidazole (**46a**, **46b**, **48**−**54**) or thiocarbonyl diimidazole (**47a**, **47b**) at room temperature in THF.

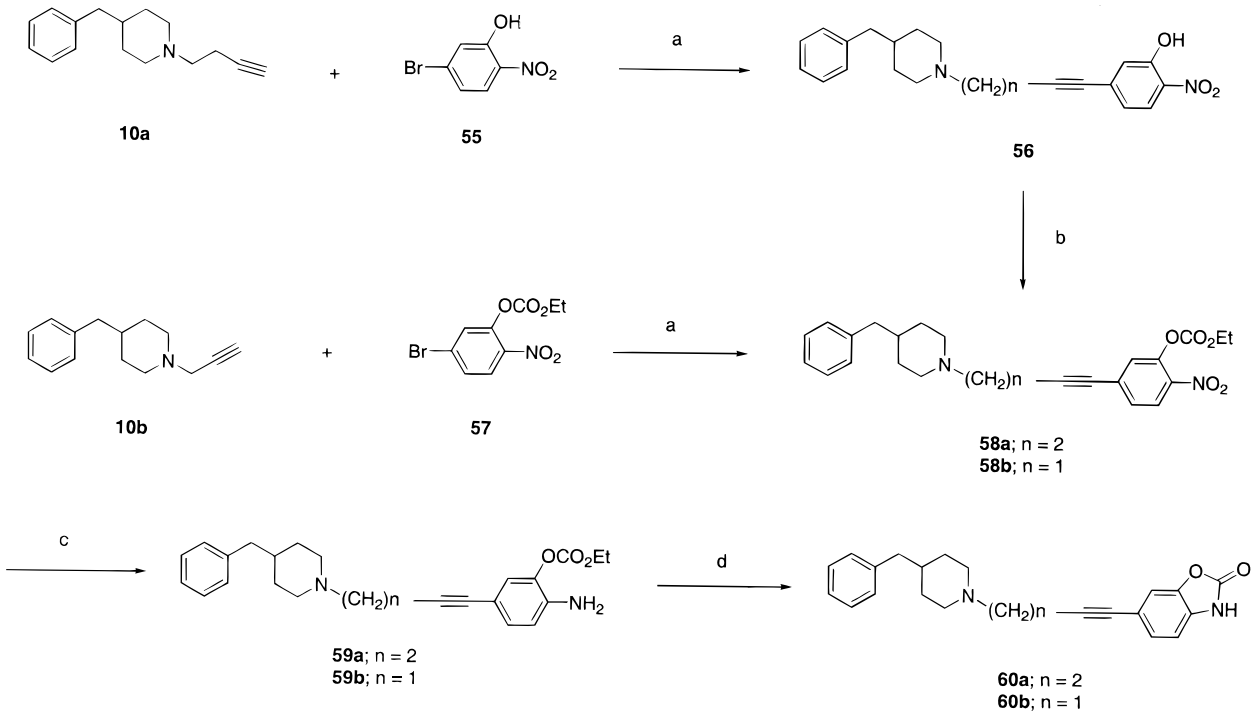
The benzimidazolinones **60a** and **60b** in Table 1 were prepared as shown in Scheme 3. Acetylene **10a** was coupled with 5-bromo-2-nitrophenol (**55**)[19] in moderate yield and the product phenol **56** formylated to give **58a**. The $Pd(PPh_3)_4$/pyrrolidine conditions could not be used here due to displacement of the activated bromine substituent by pyrrolidine; $Pd(PPh_3)_2Cl_2/Et_3N/CH_2Cl_2$/CuI conditions were employed instead. Iron/HCl conditions were used to reduce the nitro group of **58a**, and the resulting amine **59a** cyclized under basic conditions to give product **60a**. Acetylene **10b** was coupled with 5-bromo-2-nitrophenyl methyl carbonate (**57**) to give an improved yield of coupled product **58b**. This was reduced and cyclized as above to give **60b**. Some deformylation occurred during the reduction step for both series; mixtures of formyl product, cyclized product, and aminophenol were obtained that were separated by chromatography.

Benzoxazinone analogue **63** (Table 1) was prepared according to Scheme 4. 6-Hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**61**)[20] was triflated and coupled with butyne **10a** using the $Pd(PPh_3)_4$/pyrrolidine conditions to give coupled product **63**. *N*-Monomethylbenzimidazolones **67** and **71** were prepared as outlined in Scheme 5. 5-Bromo-*N*-methyl-2-nitroaniline (**64**), obtained by stirring 1,3-dibromo-4-nitrobenzene[21] with methylamine, was coupled with propyne **10b** under $Pd(PPh_3)_2Cl_2/Et_3N$/DMF/CuI conditions (again use of pyrrolidine resulted in displacement of the bromide). Iron/HCl reduction of the product (**65**) followed by treatment with carbonyldiimidazole gave benzimidazolone **67**. Coupling of bromide **68**, obtained by methylation and formylation of commercially available 2-nitro-4-bromoaniline, with propyne **10b** under $Pd(PPh_3)_4$/pyrrolidine conditions gave **69**, which could be reduced and cyclized to product **71** as above.

Pharmacology

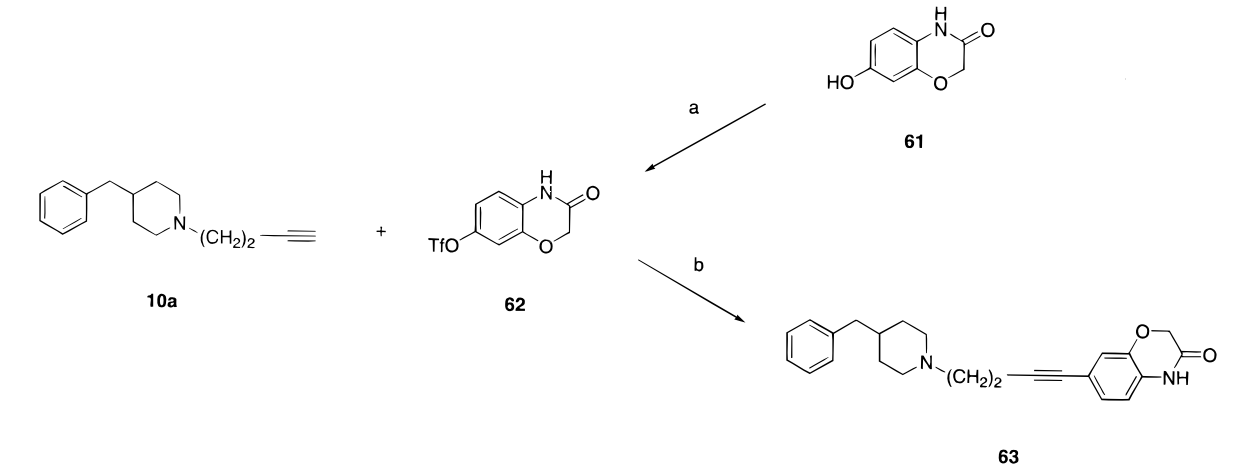
All compounds were tested for inhibitory activity at NR1A/2A, NR1A/2B, and NR1A/2C receptors expressed in *Xenopus* oocytes using electrophysiological techniques.[22] Compounds that possessed high antagonist potency and selectivity for the NR1A/2B receptor were further profiled in α-1 adrenergic (displacement of [^{3}H]-

Scheme 3[a]



[a] (a) $Pd(PPh_3)_2Cl_2/Et_3N/CH_2Cl_2/CuI$/reflux; (b) Et_2OCCl/K_2CO_3/MeCN; (c) Fe/HCl/H_2O/EtOH/reflux; (d) K_2CO_3/MeCN/reflux.

Scheme 4[a]



[a] (a) Tf_2NPh/Et_3N/THF; (b) $Pd(PPh_3)_4$/pyrrolidine/50 °C.

prazosin from rat brain cortical membranes)[23] and dopamine D2 (displacement of [^{3}H]raclopride from rat brain striatal membranes)[24] receptor binding assays. Compounds with potency and selectivity for NR1A/2B receptors were tested orally in the 6-hydroxydopamine-lesioned rat, a model of Parkinson's disease, for increases in the number of contraversive (away from the side of lesion) rotations produced by L-DOPA (10 mg/kg sc) over a 6-h period.[25]

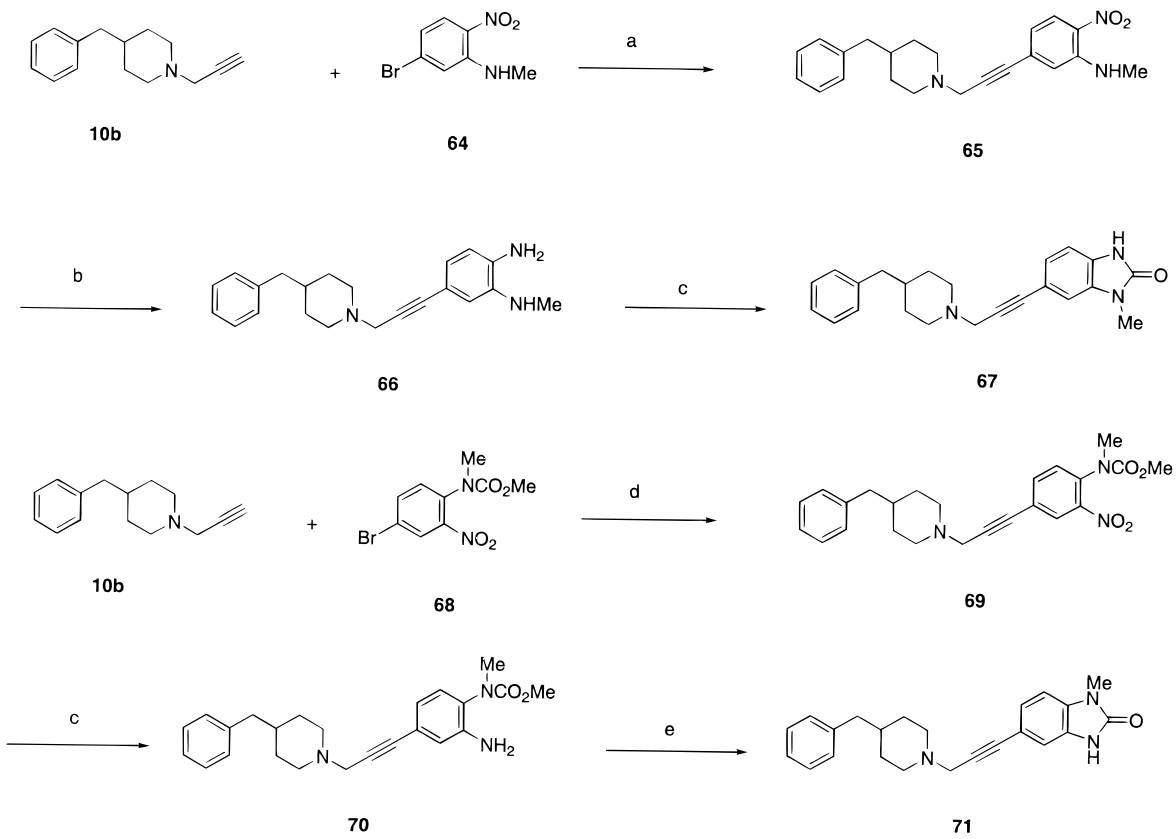
Results and Discussion

Our goals were to identify analogues of **8** and **9** with potent activity at NR1A/2B and weak activity at NR1A/2A and NR1A/2C receptors. Selectivity would demonstrate a unique interaction at NR1A/2B receptors; channel blockers, for example, generally have similar activity at all three receptor subtypes. As these structures were derived from ifenprodil (α-1 adrenergic receptor antagonist) and haloperidol (dopamine D2 antagonist), α-1 adrenergic and dopamine D2 receptor affinities were determined for key analogues.

Our previous studies concluded that a hydrogen-bond donor was required on the right-hand phenyl ring for potent activity at NR1A/2B receptors. In addition, a *para* arrangement between the hydrogen-bond donor and the linking acetylene moiety was preferred. Hence these requirements were considered when choosing potential phenol replacements. These previous studies had also indicated that the acetylene-containing link should be propyne or butyne; pentyne reduced NR1A/2B potency.

Compounds **16a** and **17a** in Table 1 explored the use of indole as a phenol replacement. When attached to

Scheme 5[a]



[a] (a) $Pd(PPh_3)_2Cl_2/Et_3N/DMF/CuI/50$ °C; (b) Fe/H_3O^+/EtOH/reflux; (c) CDI/THF; (d) $Pd(PPh_3)_4$/pyrrolidine; (e) NaH/THF/reflux.

the butyne via the 5-position (**16a**) or 6-position (**17a**), the compounds had relatively weak NR1A/2B activity, with a preference for the 5-connected indole **16a**. In this case the propyne-linked analogue of 5-indole **16b** was very weak, with an NR1A/2B IC_{50} value of 15 μM. The indole NH may not be acidic enough to form strong H-bonds; hence the butynyl indazole analogue **18a** and benzotriazole analogue **19a** were prepared. Both compounds were significantly more potent at NR1A/2B receptors, suggesting again that strong H-bond donor ability is beneficial to NR1A/2B activity. As before, the propyne analogues **18b** and **19b** were slightly weaker at NR1A/2B receptors. All these compounds were highly selective for NR1A/2B receptors versus NR1A/2A and NR1A/2C receptors − in most cases the selectivity exceeded 100-fold. This selectivity clearly separated these compounds from traditional, nonselective NMDA receptor antagonists such as channel blockers.

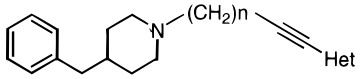
With the knowledge that a relatively acidic NH was preferred for potent NR1A/2B activity, the isatin analogue **20a** and indolone analogue **21a** were prepared. Isatin **20a** had fairly weak activity at NR1A/2B receptors, while indolone **21a** had similar potency to indazole **18a** and benzotriazole **19a**. However, in this case the propynyl indolone analogue **21b** was significantly more potent with an IC_{50} value of 0.11 μM, equipotent with the starting phenol analogue **9**. This trend was repeated with benzimidazolones **46a** and **46b**. Butynylbenzimidazolone **46a** was a potent antagonist with an NR1A/2B IC_{50} value of 0.089 μM, but propynylbenzimidazolone **46b** was significantly more active, with an IC_{50} value of 0.0053 μM. Both of these compounds remained highly selective, with **46b** being over 1000-fold selective for NR1A/2B receptors. The thiobenzimidazolone analogues **47a** and **47b** were a little weaker than their benzimidazolone counterparts, with the propynyl analogue **47b** again being much more potent than the butynyl analogue **47a**.

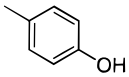
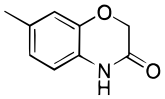
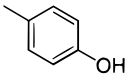
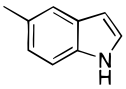
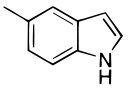
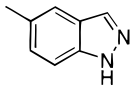
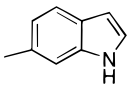
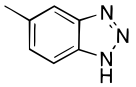
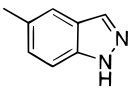
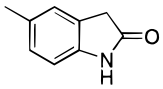
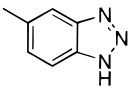
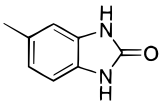
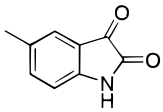
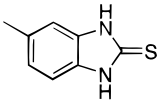
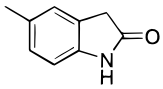
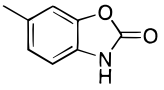
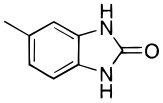
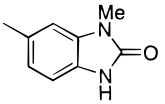
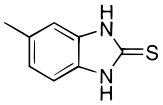
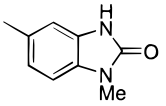
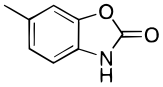
The benzimidazolinone analogues **60a** and **60b** were also potent NR1A/2B receptor antagonists (IC_{50} values 0.12 and 0.049 μM, respectively), although weaker than the benzimidazolones. The benzoxazinone analogue **63** had reduced NR1A/2B potency (IC_{50} 1.1 μM) compared to the five-membered amide heterocycles, and the corresponding propyne analogue was not made.

At this point we concentrated on the propyne benzimidazolone template. Methylation of the *meta* (to the propyne) NH (compound **67**) reduced NR1A/2B potency nearly 20-fold compared to parent **46b**. Methylation of the *para* NH (compound **71**) reduced NR1A/2B potency drastically. This drop in potency reflects not only the importance of the H-bond donor for high potency at NR1A/2B receptors but also suggests that the methyl is causing interference with binding at the receptor − possibly via steric interactions. These results underscore the importance of the *para* H-bond donor for high NR1A/2B potency but also suggest other, more subtle roles for the carbonyl and/or the *meta* NH moiety.

The propynylbenzimidazolone system in compound **46b** seemed to be optimal, and we looked to modifications on the benzylpiperidine system for further optimization of this series. Our previous studies had shown that substitution on the aromatic ring of the benzyl group or 4-hydroxylation of the piperidine ring did not

Table 1. NMDA Receptor Activity for Analogues of **8** and **9**



Compound	n	Het	NR1A/2A[a] IC_{50} μM	NR1A/2B IC_{50} μM	NR1A/2C IC_{50} μM	Compound	n	Het	NR1A/2A[a] IC_{50} μM	NR1A/2B IC_{50} μM	NR1A/2C IC_{50} μM
8	2		>100 (2)[b]	0.17 ± 0.03 (3)	>100 (2)	**63**	2		>100 (1)	1.1 ± 0.1 (4)	>100 (1)
9	1		>100 (2)	0.10 ± 0.01 (5)	>100 (2)	**16b**	1		>100 (1)	15 ± 1.5 (3)	>100 (1)
16a	2		>100 (1)	0.63 ± 0.18 (3)	>100 (1)	**18b**	1		>100 (1)	0.38 ± 0.07 (3)	>100 (1)
17a	2		>100 (1)	6.1 ± 0.7 (3)	>100 (1)	**19b**	1		>100 (1)	0.42 ± 0.05 (3)	>100 (1)
18a	2		95 (1)	0.25 ± 0.05 (4)	>100 (1)	**21b**	1		>100 (1)	0.11 ± 0.01 (3)	>100 (1)
19a	2		>100 (1)	0.22 ± 0.03 (3)	>100 (1)	**46b**	1		35 (2)	0.0053 ± 0.0008 (6)	>100 (4)
20a	2		57 (1)	1.8 ± 1.0 (3)	>100 (1)	**47b**	1		25 (1)	0.016 ± 0.003 (5)	>100 (1)
21a	2		52 (1)	0.32 ± 0.08 (3)	>100 (1)	**60b**	1		pot.(4)[d]	0.049 ± 0.008 (3)	pot.(3)
46a	2		39 (1)	0.089 ± 0.01 (4)	>100 (1)	**67**	1		NT[c]	0.098 ± 0.02 (5)	>100 (1)
47a	2		75 (1)	0.18 ± 0.03 (3)	>100 (1)	**71**	1		89 (1)	62 ± 19 (3)	>100 (1)
60a	2		39 (1)	0.12 ± 0.02 (3)	>100 (1)						

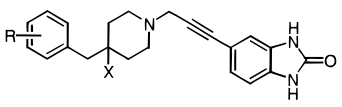
[a] IC_{50} values for inhibition of NMDA responses at cloned NMDA receptors expressed in *Xenopus* oocytes. Number of determinations (*n*) shown in parentheses. Data are presented as mean ± SEM. [b] Less than 50% inhibition at 100 μM. [c] Not tested. [d] Slight potentiation of agonist-induced responses was observed. No attempt was made to investigate the mechanism of this observation.

improve NR1A/2B potency, but these changes did have effects on selectivity − especially with respect to affinity for α-1 adrenergic and D2 dopaminergic receptors. In Table 2, the data for **46b** includes the α-1 adrenergic (0.5 μM) and dopamine D2 (2.6 μM) receptor IC_{50} values. While there is a clear selectivity for NR1A/2B receptor activity versus affinity for these receptors, the selectivity versus α-1 adrenergic receptors in particular is lower than desired. Substitution on the 4-position of the benzyl group of **46b** gave compounds **48**−**51**. There was not a clear preference for electron-withdrawing or -donating substituents for potent NR1A/2B activity, although increasing substituent size may have a minor negative effect on potency. The 3-fluoro analogue **52** had similar potency at NR1A/2B receptors compared to 4-fluoro analogue **48** or unsubstituted parent **46b**. Hence small substituents on the aromatic ring of the benzyl group of **46b** were tolerated. No clear trends in selectivity versus α-1 adrenergic and D2 dopaminergic receptor affinities were seen across this series. However, this tolerance to substitution may give us a means to slow metabolism on the benzyl group, if necessary.

The incorporation of a hydroxyl group on the 4-position of the piperidine moiety (compounds **53** and **54**) caused a 3−4-fold drop in NR1A/2B potency for both compounds. However, there was a much larger drop in α-1 adrenergic and dopamine D2 receptor affinities, resulting in an improved overall selectivity profile for both compounds. For example, compound **53** had >1000-fold selectivity for NR1A/2B receptor IC_{50} versus α-1 adrenergic and dopamine D2 receptor affinities.

All of the compounds in Table 2, with the exception of **53**, were tested in the 6-hydroxydopamine-lesioned (6-OHDA) rat model. Compounds **46b**, **48**, **49**, and **50** were dosed at 30 mg/kg orally and showed significant potentiation of the effects of L-DOPA in this model,

Table 2. NMDA Receptor Activity for Analogues of



Compound	R	X	NR1A/2A[a] IC_{50} μM	NR1A/2B IC_{50} μM	NR1A/2C IC_{50} μM	α-1 adrenergic[b] IC_{50} μM	DA D2[c] IC_{50} μM	6-OHDA rat[d] MED mg/kg po
46b	H	H	35 (2)	0.0053 ± 0.0008 (6)	>100 (4)[e]	0.5	2.6	10
48	4-F	H	38 (1)	0.0082 ± 0.002 (5)	>100 (1)	1.2	1.7	30
49	4-Cl	H	pot. (1)[f]	0.019 ± 0.004 (3)	pot. (1)	5.8	3.7	30
50	4-Me	H	pot. (1)	0.017 ± 0.003 (3)	pot. (1)	3.1	14	30
51	4-MeO	H	>100 (2)	0.026 ± 0.006 (3)	>100 (1)	17	9.9	>30
52	3-F	H	>100 (2)	0.0061 ± 0.0007 (3)	>100 (1)	0.7	3.9	>30
53	H	OH	>100 (1)	0.019 ± 0.003 (3)	>100 (1)	55	86	NT[g]
54	4-F	OH	>100 (1)	0.024 ± 0.003 (3)	>100 (1)	18	41	>30

[a] IC_{50} values for inhibition of NMDA responses 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} calculated, $n = 1$. [c] Compounds were evaluated at nine concentrations for the displacement of [^{3}H]raclopride from rat brain striata and an IC_{50} calculated, $n = 1$. [d] Lowest oral dose that shows significant potentiation of total contraversive rotations over 3 h caused by L-DOPA (10 mg/kg sc) in 6-hydroxydopamine-lesioned rats, $n = 8$. [e] Less than 50% inhibition at 100 μM. [f] Slight potentiation of agonist-induced responses was observed. No attempt was made to investigate the mechanism of this observation. [g] Not tested.

while the remainder were inactive at 30 mg/kg. Compound **46b** showed significant activity at 10 mg/kg po. However, **46b** dosed orally or intraperitoneally (ip) has similar potency in this test to phenol **9** dosed ip (all have a minimum effective dose of 10 mg/kg) despite **46b** being 20-fold more potent at NR1A/2B receptors. As **46b** gave similar results dosed ip or po, this suggests good oral bioavailability. In contrast, phenol **9** was inactive at 30 mg/kg orally. These results suggest that **46b** suffers from lower brain penetration than **9**.

In summary, we have discovered several bicyclic heterocyclic systems containing a *para* H-bond donor that are good replacements for a phenol moiety. In particular, compound **46b** is a very potent, selective NR1A/2B receptor antagonist. This compound demonstrated oral activity in a rodent model of Parkinson's disease at 10 and 30 mg/kg.

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 spectra were obtained on Finnigan 4500 or VG Analytical 7070E/HF mass spectrometers. IR spectra were recorded on a Nicolet MX-1 FT spectrophotometer. Robertson Laboratories performed elemental analyses. 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 21-mm i.d. × 300-mm (~80 g of silica gel), 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. Alternatively, disposable Biotage 40- or 90-g of silica gel cartridges were used. 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 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.

5-Iodo-1*H*-benzotriazole (15). A mixture of 5-aminobenzotriazole (2 g, 15 mmol) in 6 N HCl (5 mL) was treated with $NaNO_2$ (1.07 g, 15.5 mmol) in water (2.5 mL) at 0 °C with stirring. The resulting bright red solution was treated with KI (3 g, 18 mmol) in water (6 mL) and allowed to warm to 25 °C. The mixture was allowed to stir for 2 h at 25 °C. Na_2SO_3 (250 mg, 2 mmol) was added followed by water (100 mL) and the mixture warmed over a steam bath. The resulting suspension was filtered. The solids were suspended in EtOAc, filtered and washed with excess EtOAc. The filtrate was concentrated to give **15** as an orange solid (1.18 g, 32%): ^{1}H NMR (DMSO-d_6) δ 8.41 (s, 1H), 7.81 (d, $J = 8.8$ Hz, 1H), 7.76 (d, $J = 8.6$ Hz, 1H).

5-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-1*H*-indole (16a). A mixture of 4-benzyl-1-(3-butynyl)piperidine[15] (**10a**) (908 mg, 4 mmol), 5-bromo-1-(phenylsulfonyl)-1*H*-indole[16] (**11**) (1.34 g, 4 mmol) and $Pd(PPh_3)_4$ (240 mg, 0.2 mmol) was stirred in pyrrolidine (10 mL) and deoxygenated by bubbling N_2 through the mixture for 10 min. The mixture was stirred at 50 °C under N_2 overnight. The pyrrolidine was evaporated and the residue purified by MPLC (200 g of silica gel) loading with CH_2Cl_2 and eluting with 50% → 100% EtOAc/hexanes to give a pale yellow oil (1.55 g, 80%): ^{1}H NMR ($CDCl_3$) δ 7.86 (d, $J = 8.8$ Hz, 1H), 7.81 (d, $J = 7.3$ Hz, 2H), 7.51 (m, 3H), 7.39 (t, $J = 7.8$ Hz, 2H), 7.22−7.29 (m, 3H), 7.09−7.16 (m, 3H), 6.56 (d, $J = 3.7$ Hz, 1H), 2.90 (d, $J = 11.7$ Hz, 2H), 2.52−2.63 (m, 4H), 2.49 (d, $J = 7.1$ Hz, 2H), 1.96 (t, $J = 10.7$ Hz, 2H), 1.58−1.62 (m, 2H), 1.49 (m, 1H), 1.29 (dq, $J = 3.2$, 12.5 Hz, 2H). This oil (1.49 g) was stirred in EtOH (200 mL) and 50% NaOH (1 mL) at room temperature for 2 days. Most of the EtOH was evaporated and the residue diluted with water (500 mL). The precipitate was filtered off, washed copiously with water and dried on the filter. The solid was recrystallized from hot EtOH and dried at 50 °C under high vacuum overnight to give **16a** as an off-white solid (854 mg, 81%): mp 165−166 °C; IR 1469, 1343, 1116, 883, 808, 728, 706 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.16 (s, 1H), 7.51 (s, 1H), 7.31 (t, $J = 2.7$ Hz, 1H), 7.27 (d, $J = 8.3$ Hz, 1H), 7.21 (t, $J = 7.3$ Hz, 2H), 7.09−7.13 (m, 3H), 7.00 (dd, $J = 1.3$, 8.3 Hz, 1H), 6.34 (br s, 1H), 2.82 (d, $J = 11.5$ Hz, 2H), 2.42−2.47 (m, 6H), 1.85 (t, $J = 11.0$ Hz, 2H), 1.47 (d, $J = 12.7$ Hz, 2H), 1.41 (m, 1H), 1.12 (dq, $J = 3.2$, 12.2 Hz, 2H); APCI MS *m*/*z* 343.6 (MH^+, 100); HPLC (60% pH 3 buffer:40% MeCN) 6.17 min (99.01%). Anal. ($C_{24}H_{26}N_2 \cdot 0.10H_2O$) C, H, N, water.

5-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-1*H*-indole (16b). A procedure similar to that above for **16a** using 4-benzyl-1-(2-propynyl)piperidine[15] **(10b)** gave **16b** as a yellow oil (541 mg). This oil was stirred in MeCN (50 mL) and oxalic acid dihydrate (208 mg) in EtOH (5 mL) added. A pale tan solid precipitated on standing in the freezer overnight; it was collected and recrystallized from hot EtOH to give the oxalate salt of **16b** as an off-white solid (348 mg, 52%): mp 185−188 °C; IR 2232, 1723, 1633, 1453, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.32 (s, 1H), 7.67 (s, 1H), 7.33−7.37 (m, 2H), 7.24 (t, $J = 7.4$ Hz, 2H), 7.14 (m, 4H), 6.39 (t, $J = 1.6$ Hz, 1H), 4.00 (br. s, 2H), 3.30 (d, $J = 11.2$ Hz, 2H), 2.73 (t, $J = 11.1$ Hz, 2H), 2.48 (d, $J = 6.3$ Hz, 2H), 1.67−1.71 (m, 3H), 1.33−1.39 (m, 2H); APCI MS *m*/*z* 329.3 (MH^+, 100); HPLC (60% 0.1% TFA in water:40% MeCN) 7.48 min (98.91%). Anal. ($C_{23}H_{24}N_2 \cdot C_2H_2O_4$) C, H, N, water.

6-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-1*H*-indole (17a). A mixture of 4-benzyl-1-but-3-ynylpiperidine[15] (**10a**) (398 mg, 1.75 mmol), 6-bromoindole (**12**) (343 mg, 1.75 mmol) and $Pd(PPh_3)_4$ (101 mg, 0.09 mmol) in pyrrolidine (10 mL) was deoxygenated with N_2 and stirred at 60 °C for 2 h. The

pyrrolidine was evaporated and the residue purified by MPLC (90-g Biotage silica gel cartridge) eluting with 200:8:1 → 100:8:1 CH_2Cl_2:EtOH:30% aqueous ammonia to give a pale yellow oil (472 mg). This oil was further purified by MPLC (90-g Biotage silica gel cartridge) eluting with 50% → 100% EtOAc/hexanes to give **17a** as a white solid (75 mg, 13%): mp 136−138 °C; IR 1494, 1452, 1321, 1111, 820, 705 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.11 (s, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.33 (m, 2H), 7.21 (t, J = 7.3 Hz, 2H), 7.11 (m, 3H), 6.90 (dd, J = 1.5, 8.3 Hz, 1H), 6.36 (d, J = 2.2 Hz, 1H), 2.82 (d, J = 11.5 Hz, 2H), 2.43−2.48 (m, 6H), 1.85 (t, J = 10.5 Hz, 2H), 1.47 (d, J = 12.7 Hz, 2H), 1.41 (m, 1H), 1.12 (dq, J = 4.2, 12.9 Hz, 2H); APCI MS m/z 343.1 (MH^+, 100); HPLC (65% pH 3 buffer:35% MeCN) 13.00 min (98.83%). Anal. ($C_{24}H_{26}N_2$) C, H, N.

5-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-1*H*-indazole (18a). Coupling of 4-benzyl-1-but-3-ynylpiperidine[15] (**10a**) (454 mg, 2 mmol), 5-iodoindazole[17] (**14**) (488 mg, 2 mmol) as described for **16a** followed by MPLC (200 g of silica gel) eluting with 30% → 100% EtOAc/hexanes gave a white, waxy solid (515 mg). This solid was recrystallized from hot 9:1 EtOH:water to give **18a** as an off-white solid (444 mg, 65%): mp 143−146 °C; IR 1655, 1466, 1297, 953, 812, 749, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.33 (br s, 1H), 7.99 (s, 1H), 7.76 (s, 1H), 7.37 (m, 2H), 7.22−7.26 (m, 2H), 7.09−7.17 (m, 3H), 2.93 (d, J = 11.7 Hz, 2H), 2.56−2.68 (m, 4H), 2.50 (d, J = 7.1 Hz, 2H), 1.99 (dt, J = 2.2, 11.7 Hz, 2H), 1.63 (d, J = 13.2 Hz, 2H), 1.50 (m, 1H), 1.31 (dq, J = 3.9, 12.7 Hz, 2H); APCI MS m/z 344.6 (MH^+, 100); HPLC (70% pH 3 buffer:30% MeCN) 8.08 min (97.71%). Anal. ($C_{23}H_{25}N_3 \cdot 0.25H_2O$) C, H, N, water.

5-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-1*H*-indazole (18b). A procedure similar to that above for **18a** starting with **10b** gave **18b** which was isolated as the oxalate salt (268 mg, 32%): mp 214−216 °C; IR 2240, 1732, 1620, 1452, 939, 704 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.05 (s, 1H), 7.92 (s, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.36 (dd, J = 1.4, 8.5 Hz, 1H), 7.23 (m, 2H), 7.14 (m, 3H), 3.98 (s, 2H), 3.28 (d, J = 11.7 Hz, 2H), 2.70 (t, J = 11.9 Hz, 2H), 2.48 (d, J = 6.6 Hz, 2H), 1.66−1.70 (m, 3H), 1.32−1.38 (m, 2H); APCI MS m/z 330.2 (MH^+, 100); HPLC (60% 0.1% TFA in water:40% MeCN) 2.95 min (100%). Anal. ($C_{22}H_{23}N_3 \cdot C_2H_2O_4 \cdot 0.1H_2O$) C, H, N, water.

5-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-1*H*-benzotriazole (19a). A mixture of 4-benzyl-1-(3-butynyl)piperidine[15] (**10a**) (565 mg, 2.5 mmol), 5-iodo-1*H*-benzotriazole (**15**) (612 mg, 2.5 mmol) and $Pd(PPh_3)_4$ (144 mg, 0.125 mmol) was stirred in pyrrolidine (5 mL) and deoxygenated by bubbling N_2 through the mixture for 10 min. The mixture was stirred at 25 °C under N_2 overnight. The pyrrolidine was evaporated and the residue purified by MPLC (200 g of silica gel) eluting with CH_2Cl_2 → 100:8:1 CH_2Cl_2:EtOH:30% aqueous ammonia to give a semisolid. The semisolid was dissolved in ether and concentrated giving **19a** as a foam (176 mg, 26%): IR 3428, 2930, 2847, 1451, 1207 and 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.24 (s, 1H), 7.64 (m, 3H), 7.19 (m, 1H), 7.09 (m, 3H), 3.16 (d, J = 11.5 Hz, 2H), 2.80 (t, J = 7.3 Hz,2H), 2.68 (t, J = 7.3 Hz, 2H), 2.50 (d, J = 6.8 Hz, 2H), 2.12 (t, J = 11.2 Hz, 2H), 1.71 (d, J = 12.7 Hz, 2H), 1.58 (m, 1H), 1.41 (m, 2H); APCI MS m/z 330.2 (MH^+, 100). Anal. ($C_{22}H_{24}N_4 \cdot 0.31H_2O$) C, H, N, water.

5-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-1*H*-benzotriazole (19b). A procedure similar to that above for **19a** starting with **10b** gave **19b** which was isolated as the oxalate salt: mp 169−176 °C; IR 2240, 1729, 1617, 1453, 1208, 998, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.07 (s, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.23 (m, 2H), 7.14 (m, 3H), 3.99 (s, 2H), 3.26 (d, J = 11.8 Hz, 2H), 2.68 (t, J = 12.0 Hz, 2H), 2.49 (d, J = 6.6 Hz, 2H), 1.66−1.70 (m, 3H), 1.31−1.37 (m, 2H); APCI MS m/z 331.2 (MH^+, 100); HPLC (60% 0.1% TFA in water:40% MeCN) 3.22 min (98.76%). Anal. ($C_{21}H_{22}N_4 \cdot 1.1C_2H_2O_4 \cdot 0.3H_2O$) C, H, N, water.

5-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-1*H*-indole-2,3-dione (20a). A mixture of 4-benzyl-1-(3-butynyl)piperidine[15] (**10a**) (904 mg, 4 mmol), $Pd(PPh_3)_2Cl_2$ (41 mg, 0.1 mmol) and CuI (76 mg, 0.4 mmol) was stirred in Et_3N (4 mL) and DMF (10 mL) and stirred at 25 °C for 30 min. 5-Iodoisatin (**13**) (546 mg, 2 mmol) was added and the mixture was stirred at 25 °C under N_2 overnight. The DMF was evaporated and residue purified by MPLC (200 g of silica gel) eluting with 1:1:0.01 ethyl acetate: hexane: triethylamine to give a solid (238 mg). The solid was recrystallized from 10% water/2-propanol to yield **20a** as orange crystals (152 mg, 26%): mp 140−141 °C; IR 3026, 2923, 1743, 1621, 1482 and 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (s, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.21 (m, 2H), 7.13 (m, 3H), 6.73 (d, J = 8.1 Hz, 1H), 2.97 (d, J = 11.5 Hz, 2H), 2.61 (t, J = 6.8 Hz, 2H), 2.55 (t, J = 6.8 Hz, 2H), 2.50 (d, J = 7.1 Hz, 2H), 1.98 (t, J = 11.7 Hz, 2H), 1.62 (d, J = 13.2 Hz, 2H), 1.52 (m, 1H), 1.29 (m, 2H); APCI MS m/z 373 (MH^+, 39). Anal. ($C_{24}H_{24}N_2O_2 \cdot 1.51H_2O$) C, H, N, water.

5-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-1,3-dihydroindol-2-one (21a). A solution of **20a** (209 mg, 0.6 mmol) in hydrazine hydrate (1.5 mL) was warmed to reflux with stirring. The reaction was cooled after 35 min and quenched with water. The mixture was extracted with EtOAc, dried over $MgSO_4$ and concentrated to give solid. The solid was purified by MPLC (80 g of silica gel) eluting with 400:8:1 CH_2Cl_2:EtOH:30% aqueous ammonia to give a solid (126 mg). This solid was dissolved in MeOH and oxalic acid dihydrate (78 mg) in ether (2 mL) was added. A tan precipitate was filtered off and dried under vacuum for 16 h to give **21a** (80 mg, 18%): mp 164.5−165.4 °C; IR 3425, 3025, 2923, 1698, 1623, 1490, 701 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.54 (s, 1H), 7.29 (t, J = 7.2 Hz, 2H), 7.22 (m, 5H), 6.79 (d, J = 8.4 Hz, 1H), 3.46 (s, 2H), 3.39 (d, J = 10.4 Hz, 2H), 3.14 (m, 2H), 2.80 (m, 4H), 2.55 (m, 2H), 1.73 (d, J = 11.8 Hz, 3H), 1.41 (br d, J = 11.1 Hz, 2H); APCI MS m/z 359.0 (MH^+, 100). Anal. ($C_{24}H_{26}N_2O \cdot 1.03C_2H_4O_4 \cdot 0.1H_2O$) C, H, N, water.

5-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-1,3-dihydroindol-2-one (21b). A procedure similar to that above for **20a**/**21a** starting with **10b** gave **21b** as yellow crystals: mp 164−166 °C; IR 1704, 1488, 1294, 1229, 1108, 819, 699 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.46 (s, 1H), 7.09−7.23 (m, 7H), 6.71 (d, J = 8.3 Hz, 1H), 3.37 (s, 2H), 3.27 (s, 2H), 2.75 (d, J = 11.3 Hz, 2H), 2.44 (m, 2H), 2.04 (t, J = 9.7 Hz, 2H), 1.50 (d, J = 12.2 Hz, 2H), 1.40 (m, 1H), 1.14 (dq, J = 3.6, 12.2 Hz, 2H); APCI MS m/z 345.2 (MH^+, 100); HPLC (60% 0.1% TFA in water:40% MeCN) 2.95 min (100%). Anal. ($C_{23}H_{24}N_2O \cdot 0.07H_2O$) C, H, N, water.

4-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-2-nitrobenzeneamine (30b). Coupling of 4-bromo-2-nitroaniline (**29**) (Maybridge) (5.00 g, 23 mmol) and 4-benzyl-1-prop-2-ynylpiperidine[15] (**10b**) (5.55 g, 26 mmol) as described for **16a** followed by chromatography on silica gel (400 g) eluting with EtOAc gave **30b** (7.33 g, 91%): mp 125−126 °C; ^1H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.32 (dd, J = 2.2, 10.1 Hz, 1H), 7.22 (m, 2H), 7.15 (d, J = 7.1 Hz, 1H), 7.10 (d, J = 7.8 Hz, 2H), 6.68 (d, J = 8.1 Hz, 1H), 6.15 (br s, 2H), 3.43 (s, 2H), 2.95 (d, J = 12.2 Hz, 2H), 2.50 (d, J = 6.8 Hz, 2H), 2.20 (m, 2H), 1.65 (d, J = 12.2 Hz, 2H), 1.50 (m, 1H), 1.27 (m, 2H).

4-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]benzene-1,2-diamine (38b). Five drops of concentrated HCl were added to a refluxing mixture of **30b** (1.0 g, 2.87 mmol) and Fe powder (1 g) in 20% aqueous EtOH (50 mL). After stirring at reflux for 30 min, the mixture was filtered through Celite to remove Fe and some tar and the filtrate was concentrated to a foam. Purification by column chromatography (80 g of silica gel) eluting with 15% 1 N methanolic NH_3 in $CHCl_3$ provided **38b** (0.8 g, 87%): mp 96−97 °C; ^1H NMR (DMSO-d_6) δ 7.22 (m, 2H), 7.15 (m, 3H), 7.05 (m, 2H), 6.50 (s, 1H), 6.40 (dd, J = 1.7, 7.8 Hz, 1H), 6.36 (d, J = 7.8 Hz, 1H), 4.72 (s, 2H), 4.49 (s, 2H), 3.30 (s, 2H), 2.73 (d, J = 11.2 Hz, 2H), 2.49 (m, DMSO+ 2H), 2.01 (t, J = 11.0 Hz, 2H), 1.50 (d, J = 11.7 Hz, 2H), 1.40 (m, 1H), 1.18 (dq, J = 3.7, 12.2 Hz, 2H); APCI MS m/z 320.2 (MH^+, 100). Anal. ($C_{21}H_{25}N_3$) C, H, N.

5-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-1,3-dihydrobenzoimidazol-2-one (46a). 4-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]benzene-1,2-diamine[15] (**38a**) (333 mg, 1 mmol) and carbonyl diimidazole (CDI) (162 mg, 1 mmol) in THF (5 mL) were stirred at room temperature for 1 h. More CDI (100 mg) was added and stirring continued for 1 h. The mixture was diluted with ether (10 mL), the precipitate filtered off and

washed with ether to leave **46a** as a white powder (233 mg, 65%): mp 221−223 °C; IR 1757, 1704, 1497, 699 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.68 (s, 1H), 10.60 (s, 1H), 7.21 (t, J = 7.4 Hz, 2H), 7.08−7.13 (m, 3H), 6.88 (dd, J = 1.2, 8.0 Hz, 1H), 6.79 (dd, J = 4.2, 5.6 Hz, 2H), 2.79 (d, J = 11.5 Hz, 2H), 2.44 (m, 6H), 1.84 (t, J = 10.6 Hz, 2H), 1.46 (d, J = 12.7 Hz, 2H), 1.40 (m, 1H), 1.11 (dq, J = 3.4, 12.0 Hz, 2H); APCI MS m/z 360.6 (MH^+, 100); HPLC (70% pH 3 buffer:30% MeCN) 4.35 min (100%). Anal. ($C_{23}H_{25}N_3O \cdot 0.10H_2O$) C, H, N, water.

5-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-1,3-dihydrobenzoimidazol-2-one (46b). A mixture of **38b** (0.80 g, 2.5 mmol) and CDI (1.0 g, 6 mmol) in THF (60 mL) was stirred at room temperature for 3 days. After the solvent was removed in vacuo, the residue was purified by column chromatography (80 g of silica gel) eluting with 15% 1 N methanolic NH_3 in $CHCl_3$ to provide **46b** (0.52 g, 61%): mp 212−213 °C; ^1H NMR ($CDCl_3$) δ 10.05 (br s, 1H), 9.95 (br s, 1H), 7.24 (m, 2H), 7.05−7.15 (m, 5H), 6.83 (d, J = 7.0 Hz, 1H), 3.43 (s, 2H), 3.05 (d, J = 11.7 Hz, 2H), 2.50 (d, J = 6.8 Hz, 2H), 2.05 (t, J = 11.7 Hz, 2H), 1.65 (d, J = 12.9 Hz, 2H), 1.45 (m, 1H), 1.11 (dq, J = 4.0, 12.0 Hz, 2H); APCI MS m/z 346.1 (MH^+, 100). Anal. ($C_{22}H_{23}N_3O$) C, H, N.

5-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-1,3-dihydrobenzoimidazole-2-thione (47a). A procedure similar to that above for **46a** employing **38a** and thiocarbonyldiimidazole gave **47a**: mp 245−246 °C; ^1H NMR (DMSO-d_6) δ 12.50 (br s, 1H), 7.10 (m, 2H), 7.05 (m, 3H), 7.00 (m, 3H), 3.46 (s, 2H), 2.80 (d, J = 11.7 Hz, 2H), 2.45 (m, 6H), 1.85 (t, J = 11.7 Hz, 2H), 1.50 (d, J = 12.9 Hz, 2H), 1.40 (m, 1H), 1.10 (dq, J = 4.0, 12.0 Hz, 2H); APCI MS m/z 376.0 (MH^+, 100). Anal. ($C_{23}H_{25}N_3S \cdot 0.4H_2O$) C, H, N, S.

5-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-1,3-dihydrobenzoimidazole-2-thione (47b). A procedure similar to that above for **46b** employing **38b** and thiocarbonyldiimidazole gave **47b**: mp 224−225 °C; ^1H NMR (DMSO-d_6) δ 12.65 (br s, 1H), 12.50 (br s, 1H), 7.25 (m, 2H), 7.15 (m, 3H), 7.05 (m, 3H), 3.40 (s, 2H), 2.85 (d, J = 11.7 Hz, 2H), 2.45 (m, 2H), 2.05 (t, J = 11.7 Hz, 2H), 1.55 (d, J = 12.9 Hz, 2H), 1.40 (m, 1H), 1.15 (dq, J = 4.0, 12.0 Hz, 2H); APCI MS m/z 360.0 (MH^+, 100). Anal. ($C_{22}H_{23}N_3S \cdot 0.2H_2O$) C, H, N, S.

Compounds **48**−**54** were made using the procedure described above for **46b**.

5-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]prop-1-ynyl}-1,3-dihydrobenzoimidazol-2-one (48): mp 206−207 °C; ^1H NMR (DMSO-d_6) δ 10.72 (s, 1H), 10.62 (s, 1H), 7.25 (m, 2H), 7.15 (t, J = 8.1 Hz, 2H), 6.95 (dd, J = 2.2, 8.1 Hz,1H), 6.81 (m, 2H), 3.38 (s, 2H), 2.87 (d, J = 11.7 Hz, 2H), 2.45 (m, 2H), 2.07 (t, J = 11.7 Hz, 2H), 1.52 (d, J = 12.9 Hz, 2H), 1.40 (m, 1H), 1.15 (dq, J = 4.0, 12.0 Hz, 2H); APCI MS m/z 362.0 (MH^+, 100). Anal. ($C_{22}H_{22}N_3FO \cdot 0.2H_2O$) C, H, N, F.

5-{3-[4-(4-Chlorobenzyl)piperidin-1-yl]prop-1-ynyl}-1,3-dihydrobenzoimidazol-2-one (49): mp 225−227 °C; ^1H NMR (DMSO-d_6) δ 10.75 (s, 1H), 10.62 (s, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 6.93 (dd, J = 2.2, 7.5 Hz, 1H), 6.83 (m, 2H), 3.38 (s, 2H), 2.87 (d, J = 11.7 Hz, 2H), 2.45 (m, 2H), 2.05 (t, J = 11.7 Hz, 2H), 1.52 (d, J = 12.9 Hz, 2H), 1.40 (m, 1H), 1.15 (dq, J = 4.0, 12.0 Hz, 2H); APCI MS m/z 378.1 (MH^+, 100). Anal. ($C_{22}H_{22}ClN_3O \cdot 0.4H_2O$) C, H, N, Cl.

5-{3-[4-(4-Methylbenzyl)piperidin-1-yl]prop-1-ynyl}-1,3-dihydrobenzoimidazol-2-one (50): mp 234−235 °C; ^1H NMR (DMSO-d_6) δ 10.72 (s, 1H), 10.60 (s, 1H), 7.05 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 6.93 (dd, J = 2.2, 7.5 Hz, 1H), 6.83 (m, 2H), 3.38 (s, 2H), 2.77 (d, J = 11.7 Hz, 2H), 2.40 (d, J = 7.0 Hz, 2H), 2.20 (s, 3H), 2.05 (t, J = 11.7 Hz, 2H), 1.52 (d, J = 12.9 Hz, 2H), 1.40 (m, 1H), 1.15 (dq, J = 4.0, 12.0 Hz, 2H); APCI MS m/z 358.2 (MH^+, 100). Anal. ($C_{23}H_{25}N_3O \cdot 0.15H_2O$) C, H, N.

5-{3-[4-(4-Methoxybenzyl)piperidin-1-yl]prop-1-ynyl}-1,3-dihydrobenzoimidazol-2-one (51): mp 227−229 °C; ^1H NMR (DMSO-d_6) δ 10.77 (s, 1H), 10.62 (s, 1H), 7.05 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 7.5, 1H), 6.83 (m, 2H), 6.72 (d, J = 8.1 Hz, 2H), 3.65 (s, 3H) 3.38 (s, 2H), 2.77 (d, J = 11.7 Hz, 2H), 2.40 (d, J = 7.0 Hz, 2H), 2.20 (s, 3H), 2.05 (t, J = 11.7 Hz, 2H), 1.52 (d, J = 12.9 Hz, 2H), 1.40 (m, 1H), 1.15 (dq, J = 4.0, 12.0 Hz, 2H); APCI MS m/z 377.2 (MH^+, 100). Anal. ($C_{23}H_{25}N_3O_2$) C, H, N.

5-{3-[4-(3-Fluorobenzyl)piperidin-1-yl]prop-1-ynyl}-1,3-dihydrobenzoimidazol-2-one (52): mp 210−212 °C; ^1H NMR (DMSO-d_6) δ 10.72 (s, 1H), 10.62 (s, 1H), 7.25 (m, 1H), 6.95 (m, 4H), 6.80 (m, 2H), 3.38 (s, 2H), 2.87 (d, J = 11.7 Hz, 2H), 2.55 (m, 2H), 2.07 (t, J = 11.7 Hz, 2H), 1.52 (d, J = 12.9 Hz, 2H), 1.45 (m, 1H), 1.15 (dq, J = 4.0, 12.0 Hz, 2H); APCI MS m/z 362.0 (MH^+, 100). Anal. ($C_{22}H_{22}N_3FO$) C, H, N, F.

5-[3-(4-Benzyl-4-hydroxypiperidin-1-yl)prop-1-ynyl]-1,3-dihydrobenzoimidazol-2-one (53): mp 237−239 °C; IR 1715, 1497, 1472, 702 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.72 (s, 1H), 10.63 (s, 1H), 7.10−7.21 (m, 5H), 6.94 (dd, J = 1.5, 8.1 Hz, 1H), 6.83 (m, 2H), 4.10 (s, 1H), 3.34 (s, 2H), 2.60 (s, 2H), 2.40−2.46 (m, 4H), 1.45 (dt, J = 4.6, 11.8 Hz, 2H), 1.33 (d, J = 12.7 Hz, 2H); APCI MS m/z 362.1 (MH^+, 100); HPLC (75% pH 3 buffer:25% MeCN) 2.48 min (100%). Anal. ($C_{22}H_{23}N_3O_2$) C, H, N, water.

5-{3-[4-(4-Fluorobenzyl)-4-hydroxypiperidin-1-yl]prop-1-ynyl}-1,3-dihydrobenzoimidazol-2-one (54): mp 230−232 °C; ^1H NMR (DMSO-d_6) δ 10.72 (s, 1H), 10.60 (s, 1H), 7.15 (m, 2H), 7.05 (t, J = 8.1 Hz, 2H), 6.95 (d, J = 8.1 Hz, 1H), 6.81 (m, 2H), 4.10 (s, 1H), 3.38 (s, 2H), 2.60 (s, 2H), 2.42 (m, 4H), 1.45 (t, J = 11.7 Hz, 2H), 1.30 (d, J = 12.9 Hz, 2H); APCI MS m/z 380.0 (MH^+, 100). Anal. ($C_{22}H_{22}N_3FO_2 \cdot 0.2H_2O$) C, H, N, F.

5-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-2-nitrophenol (56). A mixture of 4-benzyl-1-(3-butynyl)piperidine[15] (**10a**) (10.63 g, 47 mmol), 5-bromo-2-nitrophenol[19] (**55**) (9.32 g, 43 mmol), $Pd(PPh_3)_2Cl_2$ (600 mg, 0.85 mmol) and CuI (93 mg, 0.85 mmol) was stirred in Et_3N (18 mL) and dichloroethane (100 mL) and deoxygenated by bubbling N_2 through the mixture for 30 min. The mixture was stirred at reflux for 16 h. The reaction was cooled, concentrated and purified by MPLC (200 g of silica gel) eluting with CH_2Cl_2 → 400:8:1 CH_2Cl_2:EtOH:30% aqueous ammonia to give **56** as a semisolid (5.85 g): ^1H NMR ($CDCl_3$) δ 7.98 (d, J = 8.8 Hz, 1H), 7.24 (m, 2H), 7.09 (m, 4H), 6.89 (dd, J = 1.7, 8.8 Hz, 1H), 2.87 (br d, J = 11.5 Hz, 2H), 2.61 (m, 4H), 2.49 (d, J = 7.1 Hz, 2H), 1.96 (dt, J = 2.4, 11.7 Hz, 2H), 1.64 (d, J = 12.9 Hz, 2H), 1.49 (m, 1H), 1.29 (dt, J = 3.7, 12.4 Hz, 2H).

5-Bromo-2-nitrophenyl Ethyl Carbonate (57). A mixture of 5-bromo-2-nitrophenol[19] (**55**) (1.78 g, 8.18 mmol), ethyl chloroformate (939 μL, 9.82 mmol) and K_2CO_3 (1.70 g, 12.3 mmol) in MeCN (150 mL) was stirred at room temperature overnight. The mixture was filtered and evaporated to leave **57** as a yellow solid (2.38 g, 100%): ^1H NMR ($CDCl_3$) δ 7.98 (d, J = 8.8 Hz, 1H), 7.53 (dd, J = 2.0, 8.8 Hz, 1H), 7.48 (d, J = 1.7 Hz, 1H), 4.34 (d, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H).

5-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-2-nitrophenyl Ethyl Carbonate (58a). A mixture of **56** (547 mg, 1.5 mmol), ethyl chloroformate (0.22 mL, 1.8 mmol) and K_2CO_3 (228 mg, 1.65 mmol) was stirred at 25 °C in MeCN (100 mL) for 1.5 h. The reaction was quenched with water (100 mL) and concentrated to ∼100 mL. The aqueous was extracted with EtOAc to give crude solid (768 mg). This solid was purified by MPLC (90-g silica gel cartridge) loading in toluene and eluting with 25% EtOAc:hexanes to give **58a** as a yellow solid (305 mg, 47%): ^1H NMR ($CDCl_3$) δ 8.02 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.25 (m, 3H), 7.16−7.09 (m, 3H), 4.33 (q, J = 7.1 Hz, 2H) 2.89 (br d, J = 11.5 Hz, 2H), 2.60 (m, 3H), 2.51 (d, J = 7.1 Hz, 2H), 1.96 (t, J = 11.7 Hz, 2H), 1.63 (br d, J = 13.7 Hz, 2H) 1.52 (m, 3H), 1.37 (t, J = 7.1 Hz, 2H), 1.29 (dq, J = 3.2, 12.0 Hz, 2H).

5-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-2-nitrophenyl Ethyl Carbonate (58b). A mixture of **57** (1.28 g, 4.4 mmol), 4-benzyl-1-(2-propynyl)piperidine[15] (**10b**) (852 mg, 4 mmol), CuI (15.2 mg, 0.08 mmol) and Et_3N (1.7 mL, 12 mmol) in CH_2Cl_2 (25 mL) was deoxygenated by bubbling N_2 though for 15 min. $Pd(PPh_3)_2Cl_2$ (56 mg, 0.08 mmol) was added and the mixture stirred at reflux under N_2 overnight. The solvents were evaporated and the residue purified by MPLC (90-g silica gel cartridge) eluting with CH_2Cl_2 → 100:8:1

CH_2Cl_2:EtOH:30% aqueous ammonia to give **58b** as a brown oil (1.44 g, 85%): ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 8.5 Hz, 1H), 7.37 (dd, J = 1.7, 8.5 Hz, 1H), 7.30 (d, J = 1.7 Hz, 1H), 7.22−7.27 (m, 2H), 7.09−7.19 (m, 3H), 4.33 (d, J = 7.2 Hz, 2H), 3.50 (s, 2H), 2.91 (d, J = 11.5 Hz, 2H), 2.51 (d, J = 7.1 Hz, 2H), 2.17 (t, J = 10.7 Hz, 2H), 1.67 (d J = 12.0 Hz, 2H), 1.51 (m, 1H), 1.33−1.39 (m, 5H including 1.37 (t, J = 7.1 Hz, 3H)).

5-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-2-aminophenyl Ethyl Carbonate (59a). Reduction of **58a** (300 mg, 0.7 mmol) as described for **38b** followed by MPLC (80 g of silica gel) eluting with CH_2Cl_2 → 400:8:1 CH_2Cl_2:EtOH:30% aqueous ammonia to give **59a** as an off-white solid (152 mg, 53%): ^{1}H NMR ($CDCl_3$) δ 7.43 (d, J = 8.1 Hz, 1H), 7.25 (m, 1H), 7.18−7.09 (m, 3H), 6.97 (s, 1H), 6.86 (dd, J = 1.7, 8.3 Hz, 1H), 6.80 (s, 1H), 4.22 (q, J = 7.3 Hz, 2H), 3.69 (q, J = 6.8 Hz, 1H), 2.98 (br d, J = 12.0 Hz, 2H), 2.67 (t, J = 7.6 Hz, 3H), 2.55 (t, J = 7.3 Hz, 2H), 2.50 (d, J = 7.1 Hz, 2H), 2.01 (t, J = 11.9 Hz, 2H), 1.62 (br d, J = 13.7 Hz, 2H) 1.50 (m, 3H), 1.32 (m, 2H), 1.20 (t, J = 7.1 Hz, 2H).

6-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-3*H*-benzooxazol-2-one (60a). A mixture of **59a** (135 mg, 0.3 mmol) and K_2CO_3 (135 mg, 1.0 mmol) in MeCN (100 mL) was stirred at reflux. After 3 h, the reaction was cooled and filtered. The filtrate was concentrated and purified by MPLC (40-g silica gel cartridge) eluting with CH_2Cl_2 → 400:8:1 CH_2Cl_2:EtOH:30% aqueous ammonia to give **60a** as an off-white solid (98 mg, 90%): mp 135.1−135.5 °C; IR 2924, 2847, 1771, 1498, 1261, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.24 (m, 2H), 7.15−7.07 (m, 4H), 7.01 (d, J = 8.1 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 3.00 (d, J = 11.7 Hz, 2H), 2.63 (t, J = 6.8 Hz, 2H), 2.55 (t, J = 6.6 Hz, 2H), 2.50 (d, J = 7.1 Hz, 2H), 1.97 (t, J = 12.4 Hz, 2H), 1.66 (broad d, J = 12.7 Hz, 2H) 1.52 (m, 1H), 1.31 (dt, J = 3.1, 12.7 Hz, 2H); APCI MS m/z 361.0 (MH^+, 100). Anal. ($C_{23}H_{24}N_2O_2\cdot 0.15H_2O$) C, H, N, water.

6-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-3*H*-benzooxazol-2-one (60b). Compound **58b** (1.44 g, 3.4 mmol) was reduced as described for **38b** and purified by MPLC (90-g silica gel cartridge) eluting with CH_2Cl_2 → 100:8:1 CH_2Cl_2:EtOH:30% aqueous ammonia to give a mixture of **59b**, **60b** and aminophenol as a beige solid (853 mg). This solid was stirred in MeCN (200 mL) with K_2CO_3 (1 g) at reflux for 1 h. The mixture was filtered and carbonyl diimidazole (1 g) added. After stirring at room temperature for 1 h, the solvent was evaporated. The residue was triturated with EtOH/ether to give a beige solid (565 mg). The solid was dissolved in EtOH (50 mL) and oxalic acid·2H_2O (206 mg) in EtOH (2 mL) added. The oxalate salt precipitated on standing in the freezer; it was collected, washed with EtOH and dried at 50 °C under high vacuum to give **60b** as a beige powder (507 mg, 27% from **58b**): mp 191−192 °C; IR 1768, 1604, 1497, 1451, 1280, 923, 756, 701 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.34 (s, 1H), 7.18−7.24 (m, 3H), 7.11−7.14 (m, 3H), 7.03 (d, J = 8.1 Hz, 1H), 3.68 (s, 2H), 3.01 (d, J = 11.0 Hz, 2H), 2.46 (m, 2H), 2.37 (t, J = 11.2 Hz, 2H), 1.59 (d, J = 12.7 Hz, 2H), 1.53 (m, 1H), 1.25 (q, J = 12.0 Hz, 2H); APCI MS m/z 347.2 (MH^+, 100); HPLC (60% 0.1% aq TFA:40% MeCN) 3.53 min (96.66%). Anal. ($C_{22}H_{22}N_2O_2\cdot 2.25C_2H_2O_4\cdot 0.25H_2O$) C, H, N, water.

7-Trifluoromethylsulfonyloxy-4*H*-benzo[1,4]oxazin-3-one (62). A mixture of 6-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one[20] (**61**) (500 mg, 3.3 mmol), *N*-phenyltrifluoromethane sulfonimide (2.59 g, 7.26 mmol) and Et_3N (0.45 mL, 7.26 mmol) was stirred at 25 °C in THF (10 mL) for 16 h. The reaction was concentrated and crude mixture purified by MPLC (200 g of silica gel) eluting with 1% MeOH:CH_2Cl_2 to give **62** as an off-white solid (581 mg, 60%): ^{1}H NMR ($CDCl_3$) δ 9.16 (br s, 1H), 7.22 (s, 1H), 6.88 (m, 2H), 4.63 (s, 2H).

7-[4-(4-Benzylpiperidin-1-yl)but-1-ynyl]-4*H*-benzo[1,4]-oxazin-3-one (63). Coupling of 4-benzyl-1-(3-butynyl)piperidine[15] (**10a**) (678 mg, 3 mmol) and triflate **62** (446 mg, 1.5 mmol) as described for **16a** followed by MPLC (80 g of silica gel) eluting with CH_2Cl_2 → 400:8:1 CH_2Cl_2:EtOH:30% aqueous ammonia gave an off-white solid (186 mg). This solid was recrystallized from MeCN to give **63** as white needles (125 mg, 20%): mp 201−202 °C; IR 3170, 3027, 2913, 1693, 1521, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.25 (m, 2H), 7.14 (m, 3H) 6.93 (d, J = 6.6 Hz, 2H), 6.65 (d, J = 8.6 Hz, 1H), 4.56 (s, 2H), 2.90 (d, J = 11.5 Hz, 2H), 2.62−2.48 (m, 6H), 1.95 (t, J = 11.8 Hz, 2H), 1.62 (br d, J = 12.7 Hz, 2H), 1.48 (m, 1H), 1.28 (dq, J = 2.9, 12.2 Hz, 2H); APCI MS m/z 375.2 (MH^+, 100). Anal. ($C_{24}H_{26}N_2O_2$) C, H, N.

5-Bromo-*N*-methyl-2-nitroaniline (64). A solution of 1,3-dibromo-4-nitrobenzene (1.5 g, 5.34 mmol) and 40% aqueous $MeNH_2$ (40 mL) in EtOH (40 mL) was heated to reflux for 2 h. The reaction mixture was allowed to sit 18 h and the resulting shiny yellow plates were collected by filtration to give **64** (0.93 g, 75%): mp 115−116 °C; ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1H), 8.0 (d, J = 7.5 Hz, 1H), 6.95 (s, 1H), 6.7 (dd, J = 2.2, 7.5 Hz, 1H) 3.0 (d, J = 2.2 Hz, 3H); APCI MS m/z 231.0 (MH^+, 100).

5-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-*N*-methyl-2-nitroaniline (65). A mixture of **64** (0.93 g, 4.03 mmol), 4-benzyl-1-(2-propynyl)piperidine[15] (**10b**) (0.87 g, 4.1 mmol), CuI (0.154 g, 0.81 mmol), $Pd(PPh_3)_2Cl_2$ (0.082 g, 0.12 mmol), Et_3N (5 g, 5 mmol) and DMF (15 mL) was stirred under N_2 for 18 h at 50 °C. The solvents were removed in vacuo and the residue was purified by MPLC (80 g of silica gel) eluting with EtOAc to provide **65** as dark red crystals (0.85 g, 58%): mp 102−105 °C; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 7.5 Hz, 1H), 7.92 (s, 1H), 7.22 (m, 2H), 7.10 (m, 1H), 7.05 (m, 2H), 6.82 (s, 1H), 6.58 (d, J = 7.5 Hz, 1H), 3.42 (s, 2H), 2.95 (d, J = 2.2 Hz, 3H), 2.9 (d, J = 11.7 Hz, 2H), 2.5 (d, J = 7.5 Hz, 2H), 2.12 (t, J = 12.9 Hz, 2H), 1.65 (d, J = 12.9 Hz, 2H), 2.12 (t, J = 12.0 Hz, 2H), 1.62 (d, J = 12.0 Hz, 2H), 1.45 (m, 1H), 1.30 (dq, J = 2.2, 12.0 Hz, 2H).

6-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-1-methylbenzene-1,2-diamine (66). Compound **65** (0.8 g, 2.2 mmol) was reduced as described for **38b** followed by MPLC (80 g of silica gel) eluting with 10:1 $CHCl_3$:1 N NH_3/MeOH and the homogeneous fractions concentrated to provide **66** (0.4 g, 50%), which was used immediately without any characterization due to its instability.

6-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-1-methyl-1,3-dihydrobenzoimidazol-2-one (67). A mixture of **66** (0.2 g, 0.58 mmol) and carbonyldiimidazole (0.4 g, 2.47 mmol) was stirred at room temperature in THF (50 mL) for 18 h. The concentrated reaction mixture was purified MPLC (80 g of silica gel) eluting with 25:1 $CHCl_3$:2 N NH_3/MeOH. After the homogeneous fractions were combined and concentrated, the resulting residue was triturated with ether to provide **67** (0.1 g, 48%): mp 196−198 °C; ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 7.25 (m, 2H), 7.15 (m, 4H), 6.98 (s, 1H), 6.92 (d, J = 7.5 Hz, 1H), 3.45 (s, 2H), 3.38 (s, 3H), 2.92 (d, J = 11.7 Hz, 2H), 2.52 (d, J = 7 Hz, 2H), 2.15 (t, J = 11.7 Hz, 2H), 1.65 (d, J = 12.9 Hz, 2H), 1.50 (m, 1H), 1.15 (dq, J = 4.0, 12.0 Hz, 2H); APCI MS m/z 360.2 (MH^+, 100). Anal. ($C_{23}H_{25}N_3O\cdot 0.3H_2O$) C, H, N.

***N*-(4-Bromo-2-nitrophenyl)-*N*-methyl Methyl Carbamate (68).** To a solution of 4-bromo-2-nitroaniline (3 g, 13.8 mmol) and methyl chloroformate (6.48 g, 69 mmol) in THF (100 mL) was added sodium hydride (60%, 0.69 g, 17.27 mmol) and the mixture was heated to reflux for 18 h. The cooled reaction mixture was poured over cold saturated NH_4Cl (100 mL) and extracted with EtOAc (300 mL). A TLC of the organic layer indicated 2:1 of product:starting material. The organic layer was concentrated and the residue purified by MPLC (200 g of silica gel) eluting with 3:1 hexanes:EtOAc and trituration with ether provided the carbamate (1.8 g, 47%): mp 105−107 °C; ^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1H), 8.45 (d, J = 7.5 Hz, 1H), 8.25 (d, J = 2.2 Hz, 1H), 7.65 (dd, J = 2.2, 7.5 Hz, 1H) 3.90 (s, 3H). A solution of the carbamate (1.7 g, 6.2 mmol) in DMF (20 mL) was treated with MeI (1.93 mL, 31 mmol) followed by NaH (0.37 g, 60%, 9.25 mmol) and stirred at RT for 18 h. The mixture was cooled to 0 °C and treated with saturated NH_4Cl (20 mL) and ether (200 mL). The organic layer was backwashed with saturated aq. NaCl, dried over $MgSO_4$ and concentrated to an oil. Trituration with hexane provided **68** (1.53 g, 85%): ^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 2.2 Hz, 1H),

7.65 (dd, J = 2.2, 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 3.55 and 3.75 (2s, rotamers, 3H), 3.23 (s, 3H); APCI MS m/z 289.0 (MH^+, 100).

***N*-{4-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-2-nitrophenyl}-*N*-methyl Methyl Carbamate (69).** Coupling of **68** (1.53 g, 5.29 mmol) and 4-benzyl-1-(2-propynyl)piperidine[15] (**10b**) (1.28 g, 6 mmol) as described for **16a** followed by MPLC (200 g of silica gel) eluting with 5% 1 N NH_3/MeOH in $CHCl_3$ gave 1.2 g of material that was a 50:50 mixture of the desired **69** and the deformylated methylamine. A small amount of the mixture was purified to give pure **69**: ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 2.2, 7.5 Hz, 1H), 7.20 (m, 3H), 7.12 (d, J = 7.5 Hz, 1H), 7.07 (d, J = 7.5 Hz, 2H), 3.57 and 3.72 (2s, rotamers, 3H), 3.23 (s, 3H), 2.86 (d, J = 11.7 Hz, 2H), 2.46 (d, J = 7.0 Hz, 2H), 2.12 (t, J = 11.7 Hz, 2H), 1.65 (d, J = 12.9 Hz, 2H), 1.47 (m, 1H), 1.25 (dq, J = 2.0, 12.0 Hz, 2H).

***N*-{4-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-2-nitrophenyl}-*N*-methyl Methyl Carbamate (70).** Crude **69** was reduced as described for **38b** followed by MPLC (200 g of silica gel) eluting with 5% 2 N NH_3/MeOH in $CHCl_3$ to give **70** as a gum (0.75 g): ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 2H), 7.15 (d, J = 7.5 Hz, 1H), 7.08 (m, 2H), 6.90 (d, J = 7.5 Hz, 1H), 6.75 (m, 2H), 3.60 (br s, 2H), 3.43 (s, 3H), 3.12 (s, 3H), 2.86 (d, J = 11.7 Hz, 2H), 2.50 (d, J = 7.0 Hz, 2H), 2.15 (t, J = 11.7 Hz, 2H), 1.65 (d, J = 12.9 Hz, 2H), 1.47 (m, 1H), 1.30 (dq, J = 2.0, 12.0 Hz, 2H); APCI MS m/z 392.2 (MH^+, 100).

5-[3-(4-Benzylpiperidin-1-yl)prop-1-ynyl]-1-methyl-1,3-dihydrobenzoimidazol-2-one (71). A mixture of **70** (0.6 g, 1.5 mmol) and NaH (0.2 g, 5 mmol) in THF (50 mL) was heated under reflux for 18 h, cooled, quenched with saturated NH_4Cl (20 mL) and partitioned between water and EtOAc. The dried (K_2CO_3) layer was concentrated to an oil and purified by MPLC (80 g of silica gel) eluting with 3% 2 N NH_3/MeOH. The homogeneous fractions were combined, concentrated, and the resulting solid triturated with ether to provide **71** (0.15 g, 28%): mp 154−156 °C; ^{1}H NMR ($CDCl_3$) δ 9.35 (s, 1H), 7.22 (m, 3H), 7.18 (m, 4H), 6.85 (d, J = 7.5 Hz, 1H), 3.35 (s, 3H), 2.95 (d, J = 11.7 Hz, 2H), 2.50 (d, J = 7.0 Hz, 2H), 2.15 (t, J = 11.7 Hz, 2H), 1.65 (d, J = 12.9 Hz, 2H), 1.47 (m, 1H), 1.30 (dq, J = 2.0, 12.0 Hz, 2H); APCI MS m/z 360.2 (MH^+, 100). Anal. ($C_{23}H_{25}N_3O \cdot 0.2H_2O$) C, H, N.

Pharmacological Methods. 1. Electrophysiology. Oocytes were obtained from mature female *Xenopus* laevis and were prepared and maintained as described previously.[26] Individual oocytes were microinjected with a mixture of NMDA receptor-encoding cRNAs, provided by Dr. P. H. Seeburg (Heidelberg University, Heidelberg, Germany).[27] 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.[22] 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 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.[28] Data in the text are mean ± standard error (SE).

2. 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, San Diego, CA).

3. α-1 Adrenergic Receptor Binding. The [^{3}H]prazosin binding assay was modified from previously described methods.[23] 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 1000g for 10 min at 4 °C. The supernatant was centrifuged at 40000g 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 40000g for 30 min. The pellet was resuspended in prazosin binding buffer, 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, 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.

4. D2 Dopaminergic Receptor Binding. The [^{3}H]-raclopride binding assay was modified from previously described methods.[24] 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 20000g 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 20000g 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, 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.

5. 6-Hydroxydopamine-Lesioned Rat.[25] 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/h 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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