4-(Tetrazolylalkyl)piperidine-2-carboxylic Acids. Potent and Selective *N*-Methyl-D-aspartic Acid Receptor Antagonists with a Short Duration of Action

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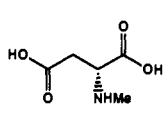
We have prepared a series of *cis*-4-(tetrazolylalkyl)piperidine-2-carboxylic acids as potent and selective *N*-methyl-D-aspartic acid (NMDA) receptor antagonists. NMDA antagonists may prove to be useful therapeutic agents, for instance, as anticonvulsants, in the treatment of neurodegenerative disorders such as Alzheimer's disease and in the prevention of neuronal damage that occurs during cerebral ischemia. The compounds prepared were evaluated in vitro in both receptor binding assays ([^{3}H]CGS-19755, [^{3}H]AMPA, and [^{3}H]kainic acid) and in a cortical-wedge preparation (versus NMDA, quisqualic acid, and kainic acid) to determine affinity, potency, and selectivity. The new amino acids were also evaluated in vivo for their ability to block NMDA-induced convulsions in neonatal rats and NMDA-induced lethality in mice. The most potent compound of this series, **15** (LY233053), selectively displaced [^{3}H]CGS-19755 binding with an IC_{50} of 107 ± 7 nM and selectively antagonized responses due to NMDA in a cortical-wedge preparation with an IC_{50} of 4.2 ± 0.4 μM. Compound **15** blocked both NMDA-induced convulsions in neonatal rats (minimum effective dose (MED) = 20 mg/kg ip) and NMDA-induced lethality in mice (MED = 5 mg/kg ip). This is the first example of an NMDA receptor antagonist that incorporates a tetrazole moiety as an ω-acid bioisostere. These amino acid antagonists are also unique from their phosphonic acid counterparts in that they have a shorter duration of action in vivo. For the treatment of acute disorders such as stroke, where an NMDA antagonist would be administered parenterally, the shorter duration of action may be beneficial, e.g., allowing for better dosage control. The combination of potent NMDA receptor antagonism and a short duration of action may make these compounds useful therapeutic agents in the treatment of a variety of neurological disorders.

The excitatory amino acid (EAA) neurotransmitters glutamate and aspartate are now recognized as important mediators of neuronal function in the central nervous system (CNS).[2] Biochemical[3] and electrophysiological[4] experiments have distinguished at least three distinct EAA receptor subtypes, which are classified by the agonists which selectively activate them. They are *N*-methyl-D-aspartic acid (NMDA, **1**), quisqualic acid (QUIS, **2**), and kainic acid (KA, **3**).



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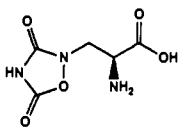

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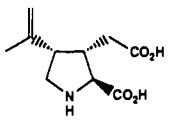

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The NMDA receptor subtype[5] is actually a macromolecular complex of at least four binding sites that gate an ion channel permeable to cations, primarily calcium and sodium[2] (Figure 1). NMDA binds at one site, often referred to as the "competitive" binding site. Phencyclidine (PCP) is an NMDA antagonist[6] that binds at a site distinct from the competitive site. It is thought that this site for PCP exists inside the ion channel,[7] and thus PCP produces a noncompetitive inhibition of glutamate responses. There are also allosteric sites that bind glycine,[8] zinc,[9] and polyamines.[10] While much is now known about the NMDA receptor complex, the exact location of the glycine, zinc, and polyamine sites as well as the delicate balance of interactions between each of these sites that is required for normal neuronal functioning is still unclear.

Excessive stimulation of NMDA receptors may be a significant event leading to cell death both in cerebral ischemia and a variety of neuronal disorders,[11] including Alzheimer's disease and Huntington's chorea. Intervention with an NMDA receptor antagonist may prevent excitatory amino acid overstimulation and thus prevent neuronal degeneration. Ample precedence now exists to support the utility of NMDA antagonists in treating cerebral ischemia and other neuronal disorders, and NMDA antagonists may soon prove to be useful and novel therapeutic agents.[11] However, the use of PCP-like compounds may be precluded by their undesirable human pharmacology[12] (e.g., psychotomimetic effects, amnesic effects, stimulation). While the exact human pharmacology of competitive NMDA antagonists is still unknown, there are certain differences in pharmacology between these two types of compounds in animals[13] that may translate into distinct behavioral differences in man.

We recently reported a series of 4-(phosphonoalkyl)-piperidine-2-carboxylic acids (**4**; Figure 2) which are potent and selective competitive NMDA receptor antagonists.[14]

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Table I. In Vitro and in Vivo Activity of 4-(Tetrazolylalkyl)piperidine-2-carboxylic Acids

compd	[^{3}H]CGS-19755 binding,[a] IC_{50}, nM	antagonism of NMDA-induced responses in cortical wedges,[b] IC_{50}, μM	antagonism of NMDA-induced convulsions in neonatal rats,[c] MED,[e] mg/kg ip	antagonism of NMDA-induced lethality in mice,[d] MED,[e] mg/kg, ip
15	107 ± 7	4.2 ± 0.4	20	5
17	777 ± 204	35.2 ± 7.3	NT	80
19	>10000	NT[f]	NT	>160
25	2280 ± 380	8.1 ± 0.7	100	20
28	5830 ± 910	12.4 ± 1.0	100	10
30	>10000	NT	NT	>160
CGS-19755	54 ± 13	1.7 ± 0.1	5	1.25

[a] See ref 23. [b] See ref 26. There was no significant antagonism of responses due to quisqualic acid (40 μM) or kainic acid (10 μM) at doses up to 100 μM of the compound tested. [c] See ref 27. Male or female 7-day-old Sprague–Dawley rats were injected ip with the test drug 30 min prior to NMDA administration. Animals were then observed for 30 min for overt excitatory amino acid agaonist-induced tonic–clonic convulsions. In saline-treated animals, NMDA (20 mg/kg) produced convulsions in 100% of the animals. [d] See ref 28. Animals were given the test compound 30 min prior to an ip dose of 200 mg/kg of NMDA. All drugs were give intraperitoneally. [e] MED = minimum effective dose. This is the lowest dose where at least three of the five animals tested were free of convulsions (neonatal rats) or survived (mice). [f] NT = not tested.

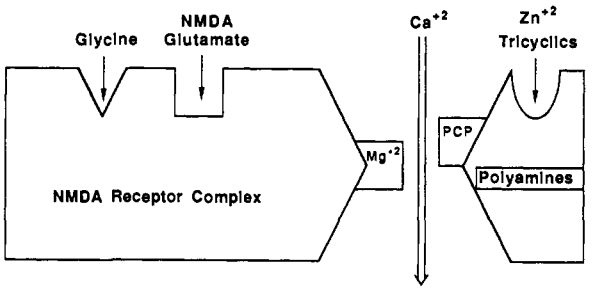


Figure 1. NMDA receptor complex.

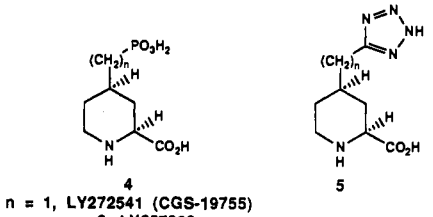
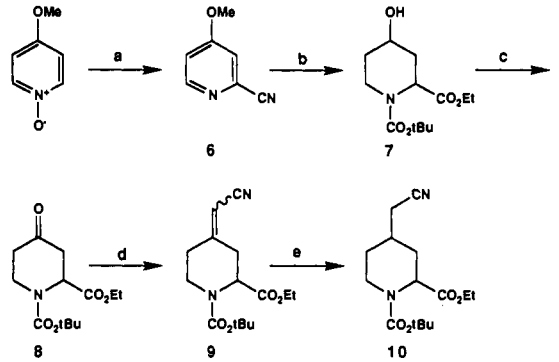


Figure 2. NMDA antagonists.

The most potent compounds from this series are LY272541 (CGS-19755) and LY257883 (**4**, where n = 1 and 3, respectively). The structure–activity relationship paralleled that which was observed for a series of acyclic ω-phosphono-α-amino acids prepared by Watkins,[6,15] namely, the compounds with four and six atoms separating the two acidic groups (AP5 and AP7) were the best NMDA antagonists. Our concern that the polar phosphonic acid group may be limiting in vivo activity led us to explore the development of amino acids substituted with other ω-acid bioisoteres. Phosphonic acid substituted amino acids also have a long duration of action in vivo,[16b] and we believed that a shorter acting antagonist may be beneficial in the treatment of acute conditions such as cerebral ischemia. We now report the successful use of the tetrazole moiety as a replacement for phosphonic acid and the subsequent preparation of a series of *cis*-4-(tetrazolylalkyl)-piperidine-2-carboxylic acids (**5**) as potent and selective NMDA receptor antagonists.[16]

Scheme I[a]



[a] (a) TMSCN, Me_2NCOCl, CH_2Cl_2, room temperature; (b) (i) 48% HBr, reflux, (ii) EtOH, HCl, reflux, (iii) H_2, 5% Rh/Al_2O_3, EtOH, 100 °C, 1000 psi (iv) Di-*tert*-butyl dicarbonate, *i*-Pr_2NEt, CH_2Cl_2, EtOH, room temperature; (c) PCC, 4-Å sieves, CH_2Cl_2, room temperature; (d) $(EtO)_2P(O)CH_2CN$, NaH, THF, room temperature; (e) H_2, 5% Pd/C, EtOH, room temperature, 60 psi.

Chemistry

Commercially available 4-methoxypyridine *N*-oxide was treated with cyanotrimethylsilane and *N*,*N*-dimethylcarbamoyl chloride in dichloromethane[17] to afford 2-cyanopyridine **6**[18] (Scheme I). Dealkylation of the methyl ether and hydrolysis of the nitrile was effected with refluxing aqueous HBr to yield the corresponding hydroxy acid, which was directly esterified with ethanolic HCl and then hydrogenated and BOC-protected to afford **7** in 40% yield from **6**. This alcohol was efficiently oxidized to the corresponding ketone **8** (96%) with pyridinium chlorochromate (PCC) and powdered 4-Å molecular sieves in dichloromethane. Reaction of **8** with the sodium salt of diethyl (cyanomethyl)phosphonate gave cyanomethylidine compound **9** in 88% yield. The ^{1}H NMR of **9** suggests a mixture of (*E*)- and (*Z*)-olefin isomers, but these assignments are complicated by the presence of amide rotamers. Hydrogenation of **9** (5% Pd/C in ethanol, room temperature, 60 psi) afforded the cyanomethyl compound **10** in

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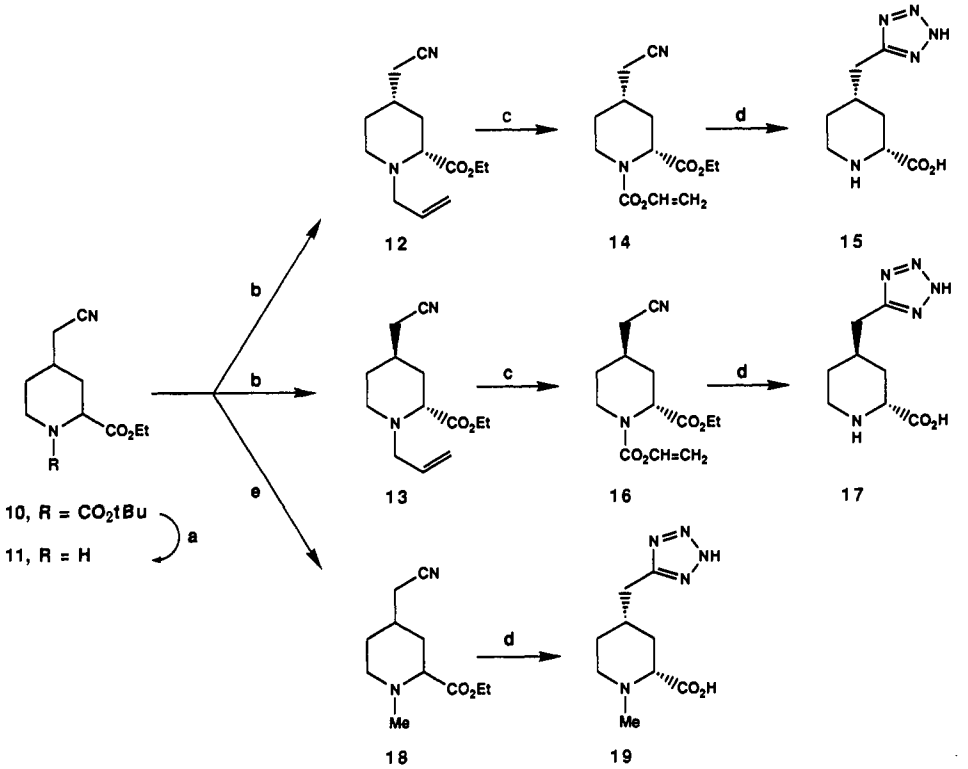
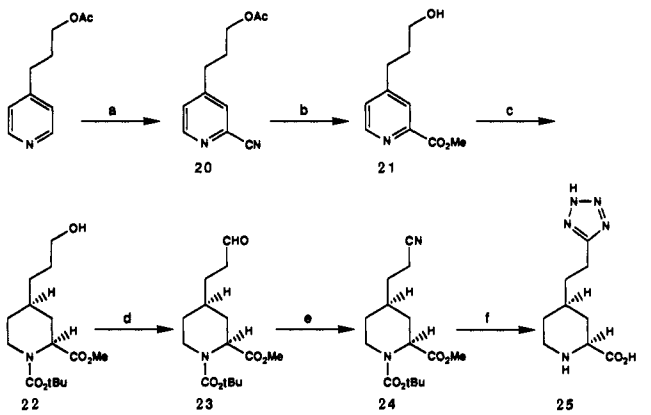
Scheme II[a]



[a] (a) TFA, CH_2Cl_2, room temperature; (b) $NaHCO_3$, DMSO, allyl bromide; (c) vinyl chloroformate, Proton Sponge, $ClCH_2CH_2Cl$, reflux; (d) (i) n-Bu_3SnN_3, 80 °C, (ii) 6 N HCl, reflux; (e) HCHO, HCO_2H, 80 °C.

Scheme III[a]



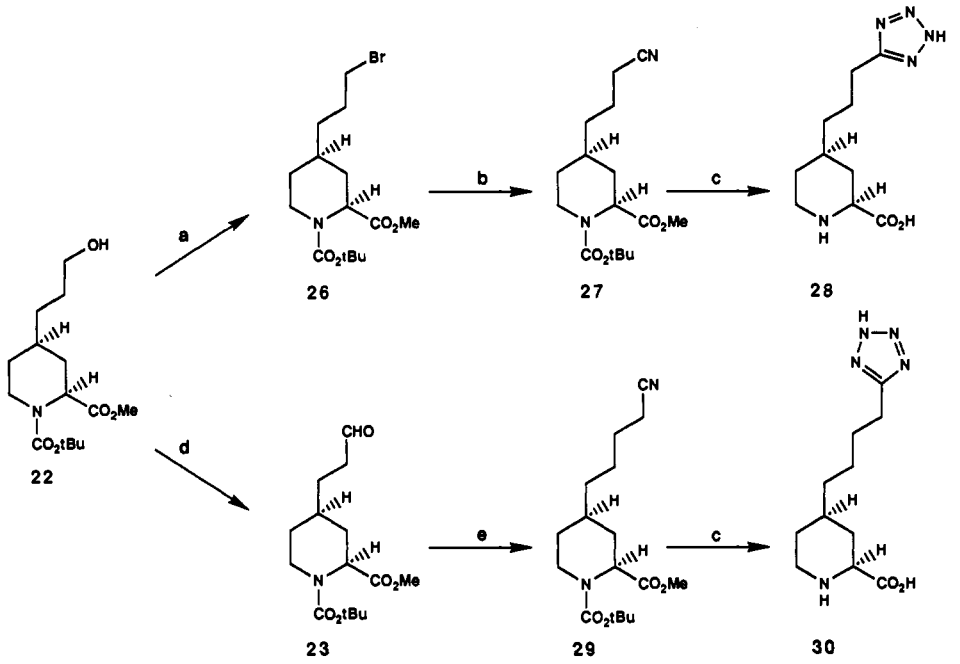
[a] (a) (i) m-CPBA, acetone, room temperature, (ii) TMSCN, Me_2NCOCl, CH_2Cl_2, room temperature; (b) (i) NaOH, MeOH, H_2O, reflux, (ii) HCl, MeOH, reflux; (c) (i) H_2, 5% Rh/Al_2O_3, MeOH, 60 °C, 60 psi, (ii) di-*tert*-butyl dicarbonate, i-Pr_2NEt, CH_2Cl_2, room temperature; (d) PCC, 4-Å sieves, CH_2Cl_2, room temperature; (e) (i) NH_2OH·HCl, pyridine, CH_2Cl_2, MeOH, (ii) $PhP(O)Cl_2$, pyridine, CH_2Cl_2, 0 °C, (f) (i) n-Bu_3SnN_3, 80 °C, (ii) 6 N HCl, reflux.

96% yield as an 85:15 mixture of cis and trans isomers (by GC of the corresponding free amine compound **11** prepared below[19]). While we found that the mixture of carbamates were inseparable by chromatography, we were able to separate the cis and trans isomers by conversion to the *N*-allylpiperidine (Scheme II). Removal of the *tert*-butyl carbamate (TFA, dichloromethane) was followed by alkylation with allyl bromide in DMSO to yield 62% of the cis isomer **12** and 9% of the trans isomer **13**. The assignment of stereochemistry for the 2,4-disubstituted piperidine isomers **12** and **13** was made by examination of the ^1H NMR's of these compounds.[20] Allylamine **12** was readily converted to the corresponding vinyl carbamate **14**

(19) GC spectra were recorded on a Hewlett-Packard HP5890A gas chromatograph using an HP1 (methyl silicone gum) column (10 m × 0.53 mm × 2.65 μm film thickness). The temperature program used was an initial column temperature of 110 °C for 1 min then increase 15 °C/min to 250 °C and then 250 °C for 5 min. Retention times for **11** were t_R = 4.96 min for the trans isomer and t_R = 5.22 min for the cis isomer. Retention times were t_R = 6.14 for **12** and t_R = 5.89 for **13**.

(20) The assignment of **15** as the *cis*-2,4-disubstituted piperidine and **17** as the *trans*-2,4-disubstituted piperidine was made through measurement of the ^1H NMR coupling constants of the intermediates **12** and **13**. The proton H_2 (δ 2.93) in **12** displays coupling constants of 12.0 and 2.8 Hz to H_{3ax} and H_{3eq}, respectively, requiring H_2 to be axial. The proton H_4 (δ 1.76) has coupling constants of 12.0 Hz to H_{3ax} and 12.3 Hz to H_{5ax}, which is consistent with H_4 being axial. Assuming a chairlike conformation for the piperidine ring, these NMR assignments are consistent with cis stereochemistry for **12** and the derived compound **15**. Proton H_2 (δ 3.64) in **13** displays coupling constants of 5.5 and 2.8 Hz to the H_3 protons, necessitating an equitorial orientation. The proton H_4 (δ 1.95) has coupling constants of 12.7 Hz to both H_{3ax} and H_{5ax}, consistent with an axial orientation. Assuming a chairlike conformation for the piperidine ring, the assignment of trans stereochemistry to the intermediate **13** and the derived compound **17** is consistent. Compounds **12** and **13** are diastereomeric, and epimerization of **12** or **13** in subsequent reactions would ultimately give **17** or **15**, respectively, as a byproduct. Since we do not observe this phenomenon, i.e., both **15** and **17** are obtained in a stereochemically homogenous fashion, the assignment of stereochemistry for the intermediates translates to the derived products. The amino acids **25**, **28**, and **30** all derive from the same piperidine intermediate **22**, and were shown to be 2,4-cis-disubstituted by ^1H NMR examination of the *O*-trifluoroacetate ester piperidine trifluoroacetate salt derived from **22** by treatment with trifluoroacetic acid in dichloromethane and concentration in vacuo (^1H NMR analysis of **22** was inconclusive). The coupling constants between H_2 and H_{3ax} and H_4 and H_{3ax} were 11.8 and 12.5 Hz, respectively. In addition, there is an NOE at H_2 when H_4 is irradiated. From these data we conclude that, assuming a chair-like conformation for the piperidine ring, the stereochemistry of **22b** is cis.

Scheme IV[a]



[a] (a) $Ph_3P{\cdot}Br_2$, CH_2Cl_2, pyridine, 0 °C; (b) NaCN, DMSO, 50 °C; (c) (i) n-Bu_3SnN_3, 80 °C, (ii) 6 N HCl, reflux; (d) PCC, 4-Å sieves, CH_2Cl_2, room temperature; (e) $(EtO)_2P(O)CH_2CN$, NaH, THF, room temperature, (iii) H_2, 5% Pd/C, EtOH, room temperature, 60 psi.

in 85% yield by treatment with vinyl chloroformate and 1,8-bis(dimethylamino)naphthalene in refluxing dichloroethane.[21] Formation of the tetrazole was best accomplished by heating a solution of nitrile **14** and 2 equiv of azidotri-n-butylstannane[22] in the absence of solvent at 80 °C for 3 days. Without purification, the crude tetrazole was deprotected with 6 N aqueous HCl to afford amino acid **15** (LY233053) in 69% yield after ion-exchange chromatography (Dowex 50-X-8). By the same sequence of reactions, *trans*-piperidine **13** was converted to vinyl carbamate **16** (88%) and then amino acid **17** (68%). The mixture of *cis*- and *trans*-nitriles **10** could be deprotected to **11** and methylated (Scheme II) to afford amine **18** (75%), which was converted to N-methyltetrazole **19** (34%) as before.

The compounds with two, three, and four methylene units between the tetrazole and piperidine rings were prepared by starting from 4-(3-acetoxyprop-1-yl)pyridine (Scheme III). This pyridine derivative was oxidized to the corresponding N-oxide with m-CPBA in acetone and the N-oxide was converted to the nitrile as above to afford 2-cyanopyridine **20** in 69% yield. Conversion of **20** to an intermediate hydroxy acid with aqueous sodium hydroxide in methanol was followed by esterification with methanolic HCl to yield 77% of ester **21**. Hydrogenation of **21** to the piperidine (H_2, 5% Rh/Al_2O_3, 60 °C, 60 psi) was followed by N-protection as the *tert*-butyl carbamate to afford *cis*-ester **22**[20] in 79% yield. This compound was oxidized to aldehyde **23** in 69% yield with PCC and 4-Å sieves followed by a two-step conversion to the corresponding nitrile **24** by (1) formation of the oxime (mixture of isomers by ^1H NMR) with hydroxylamine hydrochloride and pyridine in methanol and dichloromethane at room temperature and then (2) dehydration of the oxime to the nitrile with phenylphosphinoyl dichloride and pyridine in dichloromethane. The resultant nitrile **24** was converted as before to the *cis*-amino acid **25**. Alternatively, hydroxy ester **22** was brominated with triphenylphosphine dibromide in dichloromethane to give bromide **26** (Scheme IV) (97%), which was converted to nitrile **27** (88%) with sodium cyanide in DMSO and subsequently to *cis*-tetrazole amino acid **28** (61%). Aldehyde **23** was also condensed (Scheme IV) with the sodium salt of diethyl (cyanomethyl)phosphonate in tetrahydrofuran and the resultant E,Z mixture of olefins was hydrogenated with 5% Pd/C in ethanol to afford nitrile **29** (59%). Conversion of nitrile **29** as previously described yielded *cis*-amino acid **30** (47%).

In Vitro Excitatory Amino Acid Activity

We evaluated the compounds we prepared for affinity at the three major subtypes of excitatory amino acid receptors using the receptor-specific ligands [^{3}H]CGS-19755,[23] [^{3}H]AMPA,[24] and [^{3}H]KA.[25] The use of [^{3}H]-CGS-19755 as a ligand for the NMDA receptor was recently reported by Williams,[23] offering a distinct advantage over [^{3}H]CPP with the use of rapid filtration. All of the compounds prepared, except for N-methyl derivative **19** and tetrazolylbutyl compound **30**, showed affinity for the NMDA receptor (Table I). Most notable was *cis*-tetrazolylmethyl compound **15**, with an IC_{50} of 107 ± 7 nM. The corresponding *trans*-tetrazolylmethyl compound **17**, while showing good affinity for the NMDA receptor (IC_{50} = 777 ± 204 nM), was considerably less potent than *cis*-tetrazole **15**. None of the compounds prepared showed a significant displacement of [^{3}H]AMPA or [^{3}H]KA binding at 10 μM and are therefore selective for the NMDA subtype of excitatory amino acid receptors.

In order to determine whether the compounds that significantly inhibited [^{3}H]CGS-19755 binding were

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NMDA agonists or antagonists, we examined their activity in a cortical-wedge preparation.[26] When tested alone, none of the compounds displayed any agonist-like activity. Importantly, compounds **15**, **17**, **25**, and **28** selectively antagonized responses to 40 μM NMDA with no antagonist effect against 40 μM QUIS or 10 μM KA (Table I). The order of potency for these compounds to antagonize depolarizations due to NMDA correlated well with the order of potency for these compounds to displace [^{3}H]CGS-19755 binding.

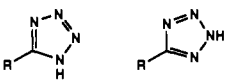
In Vivo Activity at the NMDA Receptor

We evaluated all of the compounds that we prepared in two in vivo assays for NMDA receptor activity, namely, NMDA-induced convulsions in neonatal rats[27] and NMDA-induced lethality in mice.[28] All of the compounds that were active in displacing NMDA receptor binding and that antagonized NMDA responses in the cortical wedge blocked NMDA-induced responses in vivo (Table I). The assay for NMDA-induced convulsions in 7-day-old neonatal rats utilizes animals that have an immature blood–brain barrier, so the activity that is measured should compare with that seen in in vitro assays, i.e., not dependent on blood–brain-barrier penetrability. Indeed, we observed that the most potent tetrazole in vitro, **15**, was also the most potent compound in blocking NMDA-induced convulsions in neonates, with an MED (minimum effective dose, the dose at which >50% of the animals tested were protected from convulsions) of 20 mg/kg (ip). Other amino acids were active at doses comparable to their potencies in displacing [^{3}H]CGS-19755 binding and antagonizing NMDA responses in cortical wedges.

The most striking in vivo results with these tetrazole-substituted amino acids were observed in the assay for NMDA-induced lethality in mice (Table I). In this test, the mice do have a mature blood–brain barrier, so the activity observed is reflective of the compounds ability to penetrate the CNS. Compound **15** was the most potent in blocking NMDA lethality in mice, with an MED of 5 mg/kg (ip). The amino acids **17**, **25**, and **28** also blocked NMDA-induced lethality in mice, with MED's of 80, 20, and 10 mg/kg (ip), respectively.

Discussion

One important goal in the development of therapeutically useful NMDA receptor antagonists is improved in vivo activity. We have previously demonstrated[14a] that significant improvement of both in vitro and in vivo activity could be achieved by conversion of the acyclic amino acid AP5 to the piperidine amino acid **4a** (CGS-19755). We were concerned that the polar ω-phosphonic acid group might be a significant impediment to effective penetration of amino acids into the CNS and sought to develop compounds that incorporated other acid bioisosteres that may be less polar. The tetrazole moiety (whose pK_a is nearly identical with that of a carboxylic acid[29]) has substituted effectively for the carboxylic acid group in a number of biologically active molecules, including prostaglandins,[29] leukotriene antagonists,[30] and angiotensin-converting enzyme inhibitors.[31] Incorporation of the tetrazole as an ω-acid bioisostere has led to the successful development of these compounds as NMDA receptor antagonists.



31a **31b**

Figure 3.

While certain aspects of the activity of these tetrazole amino acids parallels that observed for the acyclic (e.g. AP5) and cyclic (e.g. CGS-19755) phosphono amino acids, some distinctions are notable. In the phosphono series (both acyclic and cyclic such as **4**), activity is observed only in the case where there are four and six carbon atoms separating the two acidic moieties. However, the tetrazole amino acids with four, five, and six carbon atoms separating the acidic groups are active, with maximal activity observed for amino acid **15** (LY233053). Methylation of the piperidine ring nitrogen gave a compound (**19**) devoid of activity, which may imply either strict steric demands in the receptor around that nitrogen or the requirement for a hydrogen-bond donor. This same phenomenon was observed for phosphono amino acids such as **4**.[14b]

The tetrazole group can exist in two tautomeric forms, the 1*H* form **31a** and the 2*H* form **31b** (Figure 3). Alkyl-substituted tetrazoles exist as a nearly 1:1 mixture of both tautomeric forms.[32] The combination of planar tetrazole and more delocalized charge or proton may account for the different structural requirements for activity with the tetrazole-substituted versus the corresponding phosphonate-substituted amino acids.

The level of activity of the amino acids **25** and **28** in blocking NMDA-induced lethality in mice is much higher than one would predict on the basis of their in vitro activity. The basis for this phenomenon, however, remains unclear.

A final distinction between the tetrazole-substituted amino acids and their phosphonic acid counterparts is the observed duration of action. Tetrazole **17** (LY233053) has about a 4-h duration of action compared to a >12-h duration for the phosphonate CGS-19755 (**4**, n = 1) in blocking NMDA-induced convulsions in neonatal rats.[16b]

We have demonstrated that 4-(tetrazolylalkyl)-piperidine-2-carboxylic acids are potent and selective NMDA antagonists, with a shorter duration of action than the corresponding phosphonic acid counterparts. We believe that these novel NMDA antagonists will prove to be therapeutically useful in treating neurological disorders related to overstimulation of NMDA receptors.

Experimental Section

General Experimental Procedures. All experiments were run under a positive pressure of dry nitrogen. Tetrahydrofuran (THF) was distilled from sodium or sodium/benzophenone ketyl prior to use. All other solvents and reagents were used as obtained. "Workup A" refers to partitioning the reaction mixture between neutral, acidic or basic aqueous solution and organic solvent, separation, and then extraction of the aqueous layer twice more with the solvent. "Workup B" refers to addition of organic solvent and washing twice with the indicated aqueous solution. In each case, the combined organic extracts were dried over $MgSO_4$, filtered, concentrated in vacuo, and then purified as indicated. The aqueous solution and organic solvent used are provided in the text. "Preparative HPLC" refers to chromatographic sepa-

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ration on a Waters Prep 500 HPLC, using a linear gradient of hexane to the solvent indicated in parentheses in the text. ^{1}H NMR spectra were obtained on a GE QE-300 spectrometer at 300.15 MHz or a Bruker AM-500 spectrometer at 500 MHz, and ^{13}C NMR spectra were obtained on a GE QE-300 spectrometer at 75.48 MHz with tetramethylsilane as an internal standard. Where indicated, a small amount of 40% aqueous KOD was added to aid solution of NMR samples run in D_2O.

Ethyl 4-Hydroxy-*N*-(*tert*-butoxycarbonyl)piperidine-2-carboxylate (7). A solution of 73.9 g (0.55 mol) of **6** and 1000 mL of 48% aqueous hydrobromic acid were heated for 72 h at reflux and then cooled to room temperature and concentrated in vacuo. To the residue was added 500 mL of anhydrous ethanol, and the mixture was concentrated in vacuo. To the residue was added 2 L of anhydrous ethanol and then HCl gas was bubbled through the solution for 10 min. After heating overnight at reflux, the mixture was cooled to room temperature and concentrated in vacuo to afford 112 g of a white solid. This solid was hydrogenated in 1350 mL of anhydrous ethanol with 36 g of 5% Rh/Al_2O_3 at 100 °C and 1000 psi for 10 h. After cooling to room temperature, the mixture was filtered through Celite and concentrated in vacuo. The residue was dissolved/suspended in 800 mL of dichloromethane, 300 mL of anhydrous ethanol, and 100 mL (71 g, 0.55 mol) of *N*,*N*-diisopropyl-*N*-ethylamine and to this mixture was added 120 mL (114 g, 0.55 mol) of di-*tert*-butyl dicarbonate in 10-mL portions every 15 min. The resultant mixture was stirred overnight at room temperature and then filtered through Celite and concentrated in vacuo. Workup A (2:1 ether–dichloromethane/10% sodium bisulfate) and preparative HPLC (75% ethyl acetate/hexane) afforded 60.6 g (40%, four steps) of **7** as a clear, slightly yellow oil. ^{1}H NMR ($CDCl_3$) δ: 4.70 (m, 1 H), 4.19 (m, 3 H), 3.84 (m, 1 H), 3.38 (m, 2 H), 2.43 (m, 1 H), 2.12 (m, 1 H), 1.90 (m, 1 H), 1.69 (m, 2 H), 1.46 (s, 9 H), 1.27 (t, J = 7.5 Hz, 3 H). Anal. ($C_{13}H_{23}NO_5$) C, H, N.

Ethyl 4-Oxo-*N*-(*tert*-butoxycarbonyl)piperidine-2-carboxylate (8). To a solution of 112.6 g (0.52 mol) of PCC, 112.6 g of powdered 4-Å molecular sieves, and 500 mL of dichloromethane (stirred for 1 h at room temperature and then cooled in a water bath) was added dropwise over 45 min 60.5 g (0.22 mol) of **7** in 350 mL of dichloromethane. After 2 h more at room temperature, 1 L of ether was added and the mixture was filtered through a 0.75-in. pad of Celite (bottom) and a 0.75-in. pad of flash chromatography silica gel in a 2 L medium-porosity sintered-glass funnel, the solids being washed well with 4 L more of ether. The filtrate was concentrated in vacuo, then 400 mL of ether was added to the residue and the solution was filtered through a 1.25-in. pad of flash chromatography silica gel, washing the solids with another 1600 mL of ether. This new filtrate was concentrated in vacuo to afford 57.7 g (96%) of the desired ketone **8** as a yellow green oil. ^{1}H NMR ($CDCl_3$) δ: 5.10 and 4.85 (m, 1 H, amide rotamers), 4.20 (q, J = 7.5 Hz, 2 H), 4.05 (dt, J = 14.0, 6.0 Hz, 1 H), 3.67 (m, 1 H), 2.78 (m, 2 H), 2.52 (m, 2 H), 1.48 and 1.46 (s, 9 H, amide rotamers), 1.27 (t, J = 7.5 Hz, 3 H). Anal. ($C_{13}H_{21}NO_5$) C, H, N.

Ethyl (*E*)- and (*Z*)-4-(Cyanomethylidine)-*N*-(*tert*-butoxycarbonyl)piperidine-2-carboxylate (9). To a suspension of 4.52 g (60% by weight in oil, 112.9 mmol) of sodium hydride (washed three times with hexane) in 160 mL of THF was added 20.0 g (112.9 mmol) of diethyl (cyanomethyl)phosphonate over a 10-min period. The mixture was stirred for 30 min at room temperature and then 21.4 g (78.9 mmol) of **8** in 50 mL of THF was added dropwise over 30 min. (The reaction is slightly exothermic. No effort is made to control this exotherm other than by the slow addition of ketone.) After 30 min more at room temperature, workup A (water/ether) and preparative HPLC (50% ethyl acetate/hexane) afforded 20.5 g (88%) of **9** as a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 5.23 (s, 1 H), 4.80–5.20 (m, 1 H), 4.19 (m, 3 H), 3.40 (m, 1 H), 3.07 (m, 1 H), 2.85 (m, 1 H), 2.56 (m, 1 H), 2.35 (m, 1 H), 1.48 (s, 9 H), 1.32 and 1.26 (t, J = 7.5 Hz, 3 H, amide rotamers). Anal. ($C_{15}H_{22}N_2O_4 \cdot 0.2H_2O$) C, N; H: calcd, 7.57; found, 6.91.

Ethyl 4-(Cyanomethyl)-*N*-(*tert*-butoxycarbonyl)-piperidine-2-carboxylate (10). A solution of 20.5 g (69.6 mmol) of **9** in 378 mL of anhydrous ethanol was hydrogenated with 2.05 g of 5% Pd/C at room temperature and 60 psi for 1.5 h. The mixture was filtered through Celite and concentrated in vacuo. Ether was added; the residue was again filtered through Celite and concentrated in vacuo to afford 19.9 g (96%) of **10** as a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 4.39 (t, J = 6.2 Hz, 1 H), 4.18 (q, J = 7.0 Hz, 2 H), 3.67 (m, 1 H), 3.30 (m, 1 H), 2.32 (m, 2 H), 1.80–2.20 (m, 4 H), 1.53 (m, 1 H), 1.41 (s, 9 H), 1.27 (t, J = 7.0 Hz, 3 H). Anal. ($C_{15}H_{24}N_2O_4$) C, H, N.

Ethyl *cis*- and *trans*-4-(Cyanomethyl)piperidine-2-carboxylate (11). To a solution of 20.4 g (68.8 mmol) of **10** in 75 mL of dichloromethane was added 65 mL of trifluoroacetic acid; the mixture was stirred for 3 h at room temperature and then concentrated in vacuo. To the residue was added 100 mL of dichloromethane, and the solution was again concentrated in vacuo. Workup A (dichloromethane/saturated sodium bicarbonate) afforded 13.0 g (96%) of **11**. GC analysis[19] showed an 85:15 mixture of cis:trans isomers. ^{1}H NMR ($CDCl_3$) δ: 4.19 (q, J = 7.5 Hz, 2 H), 3.32 (m, 1 H), 3.20 (m, 1 H), 2.63 (m, 1 H), 2.29 (d, J = 7.0 Hz, 2 H), 2.18 (m, 1 H), 1.82 (m, 4 H), 1.24 (m, 4 H).

Ethyl *cis*- and *trans*-4-(Cyanomethyl)-*N*-allylpiperidine-2-carboxylate (12 and 13). To a solution of 11.6 g (59.1 mmol) of **11** in 60 mL of DMSO was added 9.9 g (118.2 mmol) of sodium bicarbonate and 5.7 mL (7.9 g, 65.0 mmol) of allyl bromide. After 1 h at room temperature, another 1.1-mL portion of allyl bromide was added, and the mixture was stirred another 2 h at room temperature. Workup A (1:1 water–brine/extraction five times with dichloromethane and once with ether) and preparative HPLC (50% ethyl acetate/hexane) afforded 8.63 g (62%) of **12** and 1.24 g (9%) of **13**, both of which were >99.9% one isomer by GC.[19] Cis isomer **12**, ^{1}H NMR ($CDCl_3$) δ: 5.88 (dddd, J = 16.2, 11.3, 8.3, 5.2 Hz, 1 H), 5.18 (d, J = 16.2 Hz, 1 H), 5.16 (d, J = 11.3 Hz, 1 H), 4.22 (q, J = 7.0 Hz, 2 H), 3.28 (dd, J = 13.2, 5.2 Hz, 1 H), 3.12 (dt, J = 11.9, 3.6 Hz, 1 H), 2.93 (dd, J = 12.0, 2.8 Hz, 1 H), 2.83 (dd, J = 13.2, 8.3 Hz, 1 H), 2.30 (d, J = 7.0 Hz, 2 H), 2.05 (m, 2 H), 1.83 (m, 1 H), 1.76 (dddd, J = 12.3, 12.0, 5.0, 3.6 Hz, 1 H), 1.47 (m, 2 H), 1.29 (t, J = 7.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ: 172.8, 133.8, 118.7, 117.9, 65.7, 61.0, 59.0, 51.1, 35.4, 32.8, 30.9, 23.9, 14.2. Anal. ($C_{13}H_{20}N_2O_2$) C, H, N. Trans isomer **13**, ^{1}H NMR ($CDCl_3$) δ: 5.80 (ddt, J = 17.1, 10.2, 6.6 Hz, 1 H), 5.18 (dd, J = 17.1, 1.5 Hz, 1 H), 5.13 (dd, J = 10.2, 1.5 Hz, 1 H), 4.17 (q, J = 7.0 Hz, 2 H), 3.64 (dd, J = 5.5, 2.8 Hz, 1 H), 3.27 (d, J = 6.6 Hz, 2 H), 3.10 (ddd, J = 12.4, 12.1, 3.0 Hz, 1 H), 2.74 (ddd, J = 12.1, 4.7, 3.0 Hz, 1 H), 2.28 (d, J = 6.6 Hz, 2 H), 2.09 (ddd, J = 13.2, 5.8, 2.8, 1 H), 1.95 (m, 1 H), 1.81 (m, 1 H), 1.61 (dt, J = 12.7, 5.5 Hz, 1 H), 1.39 (dq, J = 12.4, 5.0 Hz, 1 H), 1.28 (t, J = 7.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ: 172.6, 135.6, 118.1, 117.6, 60.2, 59.3, 58.3, 46.2, 33.5, 31.1, 29.2, 24.1, 14.4. Anal. ($C_{13}H_{20}N_2O_2$) C, H, N.

Ethyl *cis*-4-(Cyanomethyl)-*N*-[(vinyloxy)carbonyl]-piperidine-2-carboxylate (14). A solution of 8.6 g (36.4 mmol) of **12**, 15.6 g (72.8 mmol) of 1,8-bis(dimethylamino)naphthalene, and 6.2 mL (7.8 g, 72.8 mmol) of vinyl chloroformate in 140 mL of dichloromethane was heated to reflux for 6 h (after 4 h of reflux, an additional 1 mL of vinyl chloroformate was added to the reaction). The mixture was cooled to room temperature and concentrated in vacuo, and then workup B (ether/twice with 10% sodium bisulfate and once with saturated sodium bicarbonate) and preparative HPLC (40% ethyl acetate/hexane) afforded 8.3 g (85%) of **14** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.17 (dd, J = 14.0, 6.2 Hz, 1 H), 4.79 (bd, J = 14.0 Hz, 1 H), 4.59 (t, J = 5.5 Hz, 1 H), 4.48, (d, J = 6.2 Hz, 1 H), 4.22 (q, J = 7.1 Hz, 2 H), 3.86 (m, 1 H), 3.40 (m, 1 H), 2.40 (dd, J = 17.0, 8.0 Hz, 1 H), 2.33 (dd, J = 17.0, 6.5 Hz, 1 H), 2.18 (m, 1 H), 2.14 (m, 2 H), 1.92 (m, 1 H), 1.60 (m, 1 H), 1.30 (t, J = 7.1 Hz, 3 H). Anal. ($C_{13}H_{18}N_2O_4$) C, H, N.

***cis*-4-(2*H*-Tetrazol-5-ylmethyl)piperidine-2-carboxylic Acid (15).** A mixture of 8.0 g (30.0 mmol) of **16** and 20.0 g (60.0 mmol) of azidotributylstannane were heated for 44 h at 80 °C, at which time 5 g (15.0 mmol) of azidotributylstannane was added and heating continued for an additional 4 h. The reaction was cooled to room temperature, then treated with 75 mL of 6 N aqueous HCl, and heated to 80 °C for 1.5 h (CO_2 evolution) and 105 °C for 3 h. The mixture was cooled to room temperature and extracted three times with ether, and the aqueous layer was concentrated in vacuo. Ion-exchange chromatography (Dowex 50-X-8-100, the compound was loaded on the column as the hydrochloride salt in water, eluted with water until the pH was

6–7, and then eluted from the column with 10% pyridine/water; the compound was detected by spotting fractions on a silica gel TLC plate and staining with *p*-anisaldehyde, whereby the product-containing fractions stained yellow) afforded a solid after lyophilization. This solid was refluxed in methanol for 30 min, filtered, washed with methanol and acetone, then suspended in acetone, and refluxed for 1 h. The solid was filtered, washed with acetone and ether, and dried in vacuo at 80 °C to afford 4.4 g (69%) of **17**. Mp: 283–284.5 °C (foams). ^{1}H NMR (D_2O/KOD) δ: 2.98 (m, 2 H), 2.71 (m, 2 H), 2.45 (m, 1 H), 1.84 (m, 2 H), 1.41 (m, 1 H), 0.98 (m, 2 H). ^{13}C NMR (D_2O/KOD) δ: 181.2, 161.8, 60.5, 44.3, 35.9, 35.8, 31.5, 31.3. Anal. ($C_8H_{13}N_5O_2$) C, H, N.

Ethyl *trans*-4-(Cyanomethyl)-*N*-[(vinyloxy)carbonyl]-piperidine-2-carboxylate (16). As for **14**, 2.1 g (8.7 mmol) of **13**, 1.9 g (1.5 mL, 17.4 mmol) of vinyl chloroformate, and 3.7 g (17.4 mmol) of 1,8-bis(dimethylamino)naphthalene in 34 mL of dichloroethane gave 2.1 g (88%) of **16**. ^{1}H NMR ($CDCl_3$) δ (doubling due to amide rotamers): 7.18 (dt, J = 14.0, 5.5 Hz, 1 H), 5.02 and 4.96 (bd, J = 5.5 Hz, 1 H), 4.82 and 4.76 (dd, J = 14.0, 1.1 Hz, 1 H), 4.49 (t, J = 6.0 Hz, 1 H), 4.21 (m, 3 H), 3.14 and 3.00 (dt, J = 13.3, 2.7 Hz, 1 H), 2.33 (m, 3 H), 1.82 (m, 2 H), 1.53 (m, 1 H), 1.32 (m, 1 H), 1.27 (t, J = 7.1 Hz, 3 H). Anal. ($C_{13}H_{18}N_2O_4$) C, H, N.

***trans*-4-(2*H*-Tetrazol-5-ylmethyl)piperidine-2-carboxylic Acid (17).** As for **15**, 3.4 g (12.7 mmol) of **16** and 11.0 g (33.1 mmol) of azidotributylstannane gave 1.8 g (68%) of **17**. Mp: 263–265 °C. ^{1}H NMR (D_2O) δ: 4.00 (t, J = 4.8 Hz, 1 H), 3.27 (m, 2 H), 3.04 (m, 2 H), 2.17 (m, 2 H), 1.80 (m, 2 H), 1.49 (m, 1 H). ^{13}C NMR (D_2O) δ: 172.3, 154.5, 54.7, 40.1, 29.6, 29.3, 26.9, 26.2. Anal. ($C_8H_{13}N_5O_2$) C, H, N.

Ethyl *cis*- and *trans*-4-(Cyanomethyl)-*N*-methylpiperidine-2-carboxylate (18). A solution of 4.1 g (19.5 mmol) of **11** in 16 mL of formic acid and 16 mL of 37% aqueous formaldehyde was heated to 80 °C for 4.5 h and then cooled and concentrated in vacuo. Workup A (2 N sodium hydroxide/dichloromethane) and chromatography on 200 g of silica gel eluting with 5% ethanol/ethyl acetate afforded 3.3 g (75%) of **18**. ^{1}H NMR ($CDCl_3$) δ: 4.22 (q, J = 7.5 Hz, 2 H), 3.00 (m, 1 H), 2.71 (m, 1 H), 2.34 (d, J = 7.0 Hz, 2 H), 2.25 (s, 3 H), 2.10 (m, 2 H), 1.81 (m, 2 H), 1.48 (m, 2 H), 1.29 (t, J = 7.5 Hz, 3 H). Anal. ($C_{11}H_{18}N_2O_2 \cdot 0.1H_2O$) C, N; H: calcd, 8.64; found, 8.00.

***cis*- and *trans*-4-(2*H*-Tetrazol-5-ylmethyl)-*N*-methylpiperidine-2-carboxylic Acid (19).** As for **15**, 3.2 g (15.0 mmol) of **18** and 10.0 g (30.0 mmol) of azidotributylstannane gave (after crystallization from water) 1.16 g (34%) of **13**. Mp: 261–263 °C. ^{1}H NMR (D_2O) δ: 3.53 (m, 2 H), 3.04 (m, 3 H), 2.84 (s, 3 H), 2.21 (m, 2 H), 1.93 (m, 1 H), 1.55 (m, 2 H). ^{13}C NMR (D_2O) δ: 173.2, 154.7, 68.4, 66.5, 53.8, 42.2, 33.7, 32.0, 28.1. Anal. ($C_9H_{15}N_5O_2$) C, H, N.

3-(2-Cyanopyrid-4-yl)prop-1-yl Acetate (20). By our previously reported procedure,[13] 164.3 g (0.96 mol) of 3-pyrid-4-yl-prop-1-yl acetate was reacted with 248 g (1.15 mol of 80% by weight) of *m*-CPBA in 800 mL of acetone to give the corresponding pyridine *N*-oxide, which was treated with 90 g (0.91 mol) of cyanotrimethylsilane and 98 g (0.91 mol) of *N*,*N*-dimethylcarbamoyl chloride to afford after preparative HPLC (50% ethyl acetate/hexane) 129 g (69%) of **20** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 8.62 (d, J = 5.0 Hz, 1 H), 7.60 (s, 1 H), 7.41 (d, J = 5.0 Hz, 1 H), 4.12 (t, J = 7.0 Hz, 2 H), 2.81 (t, J = 7.0 Hz, 2 H), 2.06 (s, 3 H), 2.03 (m, 2 H). Anal. ($C_{11}H_{12}N_2O_2$) C, H, N.

Methyl 4-(3-Hydroxyprop-1-yl)pyridine-2-carboxylate (21). A solution of 66 g (0.32 mol) of **20** in 380 mL of methanol and 256 mL of 5 N aqueous sodium hydroxide was heated overnight at reflux and then cooled and concentrated in vacuo. The residue was treated with methanolic HCl (exothermic, cooled with a water bath as necessary), and after a brief period of stirring, more HCl gas was bubbled through the solution until the pH was 1. The mixture was heated to reflux for 30 min, then cooled and concentrated in vacuo, suspended in 1.8 L of methanol, and treated with gaseous HCl for 10 min. The resulting mixture was heated to reflux overnight, cooled, and concentrated in vacuo. Workup A (dichloromethane/20% potassium bicarbonate) gave 48.5 g (77%) of **21**. ^{1}H NMR ($CDCl_3$) δ: 8.60 (d, J = 5.0 Hz, 1 H), 7.35 (d, J = 5.0 Hz, 1 H), 4.00 (s, 3 H), 3.71 (m, 2 H), 3.13 (bs, 1 H), 2.82 (t, J = 7.0 Hz, 2 H), 1.94 (quintet, J = 7.0 Hz, 2 H). Anal. ($C_{10}H_{13}NO_3$) C, H, N.

Methyl *cis*-4-(3-Hydroxyprop-1-yl)-*N*-(*tert*-butoxycarbonyl)piperidine-2-carboxylate (22). After treatment of 65.5 g (0.34 mol) of **21** with methanolic HCl and concentration in vacuo, the residue was hydrogenated with 36 g of 5% Rh/Al_2O_3 in 575 mL of methanol at 50 °C and 60 psi overnight. The residue was filtered and concentrated in vacuo and then suspended in 400 mL of dichloromethane and 118 mL (87.9 g, 0.68 mmol) of diisopropylethylamine and treated with 83 mL of di-*tert*-butyl dicarbonate in 21-mL portions every 10 min. After stirring for 30 min more at room temperature, workup B (ether/10% sodium bisulfate) and preparative HPLC (75% ethyl acetate/hexane) afforded 80.2 g (79%) of **22** as a clear oil. ^{1}H NMR ($CDCl_3$) δ: 4.32 (t, J = 5.3 Hz, 1 H), 3.73 (s, 3 H), 3.61 (m, 3 H), 3.36 (m, 1 H), 1.50–2.05 (m, 7 H), 1.45 (s, 9 H), 1.34 (m, 3 H). Anal. ($C_{15}H_{27}NO_5$): C, H, N.

Methyl *cis*-4-(3-Oxoprop-1-yl)-*N*-(*tert*-butoxycarbonyl)piperidine-2-carboxylate (23). As for **8**, 11.6 g (38.4 mmol) of **22**, 18.0 g (83.5 mmol) of PCC, and 18.0 g of powdered 4-Å molecular sieves in 170 mL of dichloromethane gave 10.1 g (88%) of **23**. ^{1}H NMR ($CDCl_3$) δ: 9.74 (s, 1 H), 4.31 (t, J = 6.4 Hz, 1 H), 3.70 (s, 3 H), 3.54 (m, 1 H), 3.35 (m, 1 H), 2.44 (t, J = 7.1 Hz, 2 H), 1.94 (m, 1 H), 1.80 (m, 3 H), 1.58 (m, 3 H), 1.41 (s, 9 H).

Methyl *cis*-4-(2-Cyanoeth-1-yl)-*N*-(*tert*-butoxycarbonyl)piperidine-2-carboxylate (24). To a room-temperature solution of 3.3 g (11.0 mmol) of **23** in 60 mL of dichloromethane and 15 mL of methanol was added 1.8 mL (1.7 g, 22.1 mmol) of pyridine followed by 0.77 g (11.0 mmol) of hydroxylamine hydrochloride. After 15 min, the reaction was homogenous, and after stirring for 1.5 h at room temperature, the mixture was concentrated in vacuo. The residue was dissolved in 50 mL of dichloromethane and 1.8 mL (22.1 mmol) of pyridine, cooled to 0 °C, and then treated with 3.1 mL (4.3 g, 22.1 mmol) of phenylphosphinoyl dichloride and stirred for 1 h at room temperature. Workup B (ether/saturated sodium bicarbonate then 10% sodium bisulfate) and chromatography on 150 g of silica gel eluting with 35% ethyl acetate/hexane afforded 2.87 g (88%) of **24** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 4.39 (m, 1 H), 3.73 (s, 3 H), 3.62 (m, 1 H), 3.32 (m, 1 H), 2.38 (t, J = 7.0 Hz, 2 H), 2.00 (m, 1 H), 1.83 (m, 3 H), 1.61 (, 3 H), 1.46 (s, 9 H). Anal. ($C_{15}H_{24}N_2O_4$) C, H, N.

***cis*-4-[2-(2*H*-Tetrazol-5-yl)eth-1-yl]piperidine-2-carboxylic Acid (25).** As for **28**, 7.6 g (25.5 mmol) of **24** and 17.0 g (51.1 mmol) of azidotributylstannane gave 4.49 g of **25**, isolated by crystallization from water at 0 °C after formation of the inner salt with propylene oxide. Recrystallization from water afforded 3.2 g (48%) of **25** after drying in vacuo at 60 °C. Mp: 271–272 °C. ^{1}H NMR (D_2O/KOD) δ: 2.82 (m, 2 H), 2.66 (m, 2 H), 2.24 (m, 1 H), 1.84 (m, 1 H), 1.42 (m, 3 H), 1.14 (m, 1 H), 0.77 (m, 2 H). ^{13}C NMR (D_2O/KOD) δ: 181.5, 163.6, 60.7, 44.5, 36.0, 35.3, 35.0, 31.4 21.3. Anal. ($C_9H_{15}N_5O_2$) C, H, N.

Methyl *cis*-4-(3-Bromoprop-1-yl)-*N*-(*tert*-butoxycarbonyl)piperidine-2-carboxylate (26). Triphenylphosphine dibromide was generated from 39.3 g (0.15 mol) of triphenylphosphine and 8 mL (24.0 g, 0.15 mol) of bromine in 300 mL of dichloromethane at 0 °C. A mixture of 42.9 g (0.14 mmol) of **22** and 17 mL (16.6 g, 0.21 mol) of pyridine in 80 mL of dichloromethane was added dropwise to the suspension of triphenylphosphine dibromide in dichloromethane over 15 min. After an additional 2 h at 0 °C, 12 g of triphenylphosphine dibromide [from 7.4 g (0.028 mol) of triphenylphosphine and 1.5 mL (4.6 g, 0.028 mol) of bromine] in 50 mL of dichloromethane and 3.5 mL of pyridine was added to the reaction and the mixture stirred for 15 min more at 0 °C. Workup B (ether/10% sodium bisulfate then saturated sodium bicarbonate) and preparative HPLC (50% ethyl acetate/hexane) afforded 50.1 g (97%) of **26** as a clear oil. ^{1}H NMR ($CDCl_3$) δ: 4.34 (t, J = 5.3 Hz, 1 H), 3.74 (s, 3 H), 3.68 (m, 1 H), 3.38 (t, J = 7.0 Hz, 2 H), 3.35 (m, 1 H), 1.97 (m, 1 H), 1.60–1.94 (m, 5 H), 1.42 (s, 9 H), 1.40 (m, 3 H). Anal. ($C_{15}H_{26}BrNO_4$) C, H, N.

Methyl *cis*-4-(3-Cyanoprop-1-yl)-*N*-(*tert*-butoxycarbonyl)piperidine-2-carboxylate (27). To a solution of 50.1 g (0.14 mol) of **26** in 180 mL of DMSO was added 10.8 g (0.22 mol) of powdered sodium cyanide, and the mixture was heated to 50 °C for 30 min. After cooling to room temperature, workup as for **12** and **13** and preparative HPLC (50% ethyl acetate/

hexane) afforded 37.5 g (88%) of **27**. ^{1}H NMR ($CDCl_3$) δ: 4.34 (t, J = 5.3 Hz, 1 H), 3.74 (s, 3 H), 3.57 (m, 1 H), 3.36 (m, 1 H), 2.33 (t, J = 7.0 Hz, 2 H), 1.97 (m, 1 H), 1.60–1.90 (m, 5 H), 1.44 (s, 9 H), 1.41 (m, 3 H). Anal. ($C_{16}H_{26}N_2O_4$): C, H, N.

***cis*-4-[3-(2*H*-Tetrazol-5-yl)prop-1-yl]piperidine-2-carboxylic Acid (28).** A solution of 37.5 g (0.12 mol) of **27** and 80.5 g (0.24 mol) of azidotributylstannane was heated to 80 °C for 3 days. The mixture was cooled to room temperature and treated with 250 mL of methanolic HCl for 2 h (CO_2 evolution) and then concentrated in vacuo. The residue was dissolved in 200 mL of 6 N aqueous HCl and extracted three times with 150 mL each of ether. The aqueous layer was concentrated in vacuo, dissolved in 400 mL of 6 N aqueous HCl, heated to reflux overnight, cooled to room temperature, and concentrated in vacuo. The residue was dissolved in 50 mL of water and treated with 25 mL (21 g, 0.36 mol) of propylene oxide and heated to 50 °C for 1 h, at which time the pH of the solution was ≈4. The mixture was concentrated in vacuo and then suspended in 500 mL of ethanol and refluxed for 45 min. The solid that formed was cooled to 0 °C, filtered, and washed with ethanol and acetone. The solid was resuspended in 200 mL of acetone and refluxed 1 h, cooled to room temperature, filtered, washed with acetone and ether, and dried in vacuo at 60 °C overnight to afford 17.7 g (61%) of **28** as a white solid. Mp: 253–256 °C. ^{1}H NMR (D_2O/KOD) δ: 2.94 (m, 2 H), 2.73 (t, J = 7.5 Hz, 2 H), 2.40 (dt, J = 12.7, 2.6 Hz, 1 H), 1.88 (bd, J = 12.7 Hz, 1 H), 1.65 (quintet, J = 7.5 Hz, 2 H), 1.53 (bd, J = 13.3 Hz, 1 H), 1.34 (m, 1 H), 1.12 (m, 2 H), 0.83 (m, 2 H). ^{13}C NMR (D_2O/KOD) δ: 182.5, 164.6, 61.8, 45.5, 37.3, 36.7, 36.1, 32.6, 25.8, 25.1. Anal. ($C_{10}H_{17}N_5O_2$) C, H, N.

Methyl *cis*-4-(4-Cyanobut-1-yl)-*N*-(*tert*-butoxycarbonyl)piperidine-2-carboxylate (29). To a 0 °C solution of 46.0 mmol of diethyl (sodiocyanomethyl)phosphonate (prepared as for **9**) in 100 mL of THF was added 10.1 g (33.7 mmol) of **23** in 20 mL of THF. The mixture was stirred for 2 h at 0 °C, overnight at room temperature, and 1 h at reflux and then cooled to room temperature. Workup A (water/ether) and preparative HPLC (40% ethyl acetate/hexane) afforded 8.6 g (69%) of methyl (*E*)- and (*Z*)-*cis*-4-(4-cyanobut-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)piperidine-2-carboxylate. This compound was hydrogenated with 0.9 g of 5% Pd/C in 90 mL of ethanol at room temperature and 60 psi overnight, filtered, and concentrated in vacuo. The residue was dissolved in ether, filtered through Celite, and concentrated in vacuo to afford 7.4 g (86%, 59% from **23**) of **29** as a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 4.32 (t, J = 6.3 Hz, 1 H), 3.73 (s, 3 H), 3.55 (m, 1 H), 3.37 (m, 1 H), 2.34 (t, J = 7.0 Hz, 2 H), 1.97 (m, 1 H), 1.78 (m, 2 H), 1.62 (m, 3 H), 1.45 (s, 11 H), 1.30 (m, 3 H). Anal. ($C_{17}H_{28}N_2O_4$) C, H, N.

***cis*-4-[4-(2*H*-Tetrazol-5-yl)but-1-yl]piperidine-2-carboxylic Acid (30).** As for **28**, 7.2 g (22.2 mmol) of **29** and 14.8 g (44.4 mmol) of azidotributylstannane gave 2.7 g (47%) of **30**. Mp: 253–254 °C dec (foams). ^{1}H NMR (D_2O/KOD) δ: 2.93 (m, 2 H), 2.74 (t, J = 7.4 Hz, 2 H), dt. J = 12.7, 2.4 Hz, 1 H), 1.86 (bd, J = 12.7 Hz, 1 H), 1.60 (quintet, J = 7.1 Hz, 2 H), 1.49 (bd, J = 12.9 Hz, 1 H), 1.30 (m, 1 H), 1.15 (m, 4 H), 0.80 (m, 2 H). ^{13}C NMR (D_2O/KOD) δ: 182.6, 164.7, 61.8, 45.5, 37.4, 36.8, 36.3, 32.6, 29.0, 25.9, 24.9. Anal. ($C_{11}H_{19}N_5O_2$) C, H, N.

[^{3}H]CGS-19755 Binding. The method for this assay has been published. See ref 23.

Cortical-Wedge Assay. The method for this assay has been published. See ref 26.

NMDA-Induced Convulsions in Neonatal Rats. The method for this assay has been published. See ref 27.

NMDA-Induced Lethality in Mice. The method for this assay has been published. See ref 28.

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Registry No. 1, 6384-92-5; **6**, 36057-44-0; **7**, 129919-97-7; **8**, 125545-98-4; (*E*)-**9**, 129919-98-8; (*Z*)-**9**, 129919-99-9; *cis*-**10**, 125546-00-1; *trans*-**10**, 129919-94-4; *cis*-11, 129919-95-5; *trans*-11, 129919-96-6; **12**, 129920-00-9; **13**, 129920-01-0; 14, 129920-02-1; **15**, 129920-03-2; **16**, 129920-04-3; **17**, 129920-05-4; *cis*-**18**, 129920-18-9; *trans*-**18**, 129920-19-0; *cis*-**19**, 129920-06-5; *trans*-**19**, 129920-07-6; **20**, 129920-08-7; **21**, 129920-09-8; **22**, 129920-10-1; **23**, 129920-11-2; **24**, 125545-95-1; **25**, 129920-12-3; **26**, 129920-13-4; **27**, 129920-14-5; **28**, 129920-15-6; **29**, 129920-16-7; **30**, 129920-17-8; $(EtO)_2P(O)CH_2CN$, 2537-48-6; 3-pyrid-4-ylprop-1-yl acetate, 38456-25-6.