# Sodium Channel Binding and Anticonvulsant Activities for the Enantiomers of a Bicyclic 2,4-Oxazolidinedione and Monocyclic Models

Wayne J. Brouillette,*[,†,‡] Gary L. Grunewald,[§] George B. Brown,[†,‡] Timothy M. DeLorey,[†,‡] M. Shamim Akhtar,[†] and Gang Liang[†]

*Department of Chemistry and The Neuropsychiatry Research Program, University of Alabama at Birmingham, Birmingham, Alabama 35294, and Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045.*
*Received December 1, 1988*

Racemic 7-phenyl-9,10-dioxo-1-aza-8-oxabicyclo[5.2.1]decane (**1**), a bicyclic 2,4-oxazolidinedione that we previously reported was a possible sodium channel anticonvulsant, was resolved into its enantiomeric forms, the absolute configurations were determined, and the stereoisomers were evaluated for relative sodium channel binding and whole animal anticonvulsant activities. Similar studies were carried out with two monocyclic models, 5-ethyl-5-phenyl-2,4-oxazolidinedione (**2**) and 5-ethyl-3-methyl-5-phenyl-2,4-oxazolidinedione (**3**). None of these isomers exhibited stereoselective effects in the sodium channel assay, and only modest enantioselectivities were observed for **2** and **3** in the anticonvulsant assays. (*R*)-(−)-**1** was, however, 4 times more toxic than (*S*)-(+)-**1** in the rotorod test, and due to its larger protective index, (*S*)-(+)-**1** exhibited greater therapeutic potential than either (*R*)-(−)-**1** or racemic **1**.

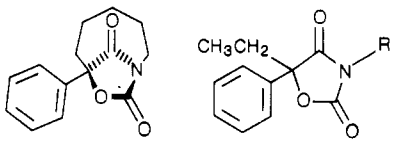
Epilepsy occurs in as many as 2% of all people,[1] yet the currently available drugs cannot provide adequate control for many of these due to problems including tolerance, toxicity, and lack of efficacy for some seizure types. Fortunately, increased interest in the mechanisms of anticonvulsant drug action has resulted in the identification of several receptor sites that are likely responsible for anticonvulsant effects, providing a basis for the more rational design of new agents. Compounds with increased specificity for these sites should provide anticonvulsants with enhanced potency and fewer side effects.

Stereochemistry is one property of chemical structures that might obviously be exploited to provide more specific anticonvulsants, since two enantiomers may present key structural features to the receptor site with different spatial arrangements. Surprisingly, this approach in the past has resulted in only limited success for the anticonvulsants. This is understandable for studies that relied solely on whole animal pharmacological data, since inherent differences in anticonvulsant efficacy could be obscured by differences in absorption, transport, and metabolism. For example, until recently one of the largest anticonvulsant enantioselectivities was reported[2] for the maximal electroshock (MES) activity of Nirvanol (5-ethyl-5-phenylhydantoin), in which the (−)-isomer was 3.8 times more potent than the (+)-isomer. But the more potent isomer has also been shown[3] to have a longer plasma half-life due to stereoselectivity of hepatic hydroxylation. The ability to compare in vitro receptor binding assays with whole animal anticonvulsant effects has greatly improved this situation.

A very recent report[4] has demonstrated, for the first time, that anticonvulsants may be completely stereospecific. In this study (*R*)-*N*-acetylphenylglycine benzylamide exhibited an anti-MES $ED_{50}$ of 26 mg/kg, while that for the *S* enantiomer was >300 mg/kg. The mechanism of action was not reported, but this result clearly demonstrates the potential of stereochemical control for providing more selective anticonvulsants.

A recently proposed anti-MES anticonvulsant receptor site is the neuronal voltage-sensitive sodium channel. Two widely used anti-MES anticonvulsants, diphenylhydantoin (DPH) and carbamazepine (CAR), interact with this site at pharmacologically relevant concentrations.[5,6] Additionally, electrophysiological studies reveal a voltage- and frequency-dependent binding that is consistent with selective effects on hyperactive (epileptic) versus normal neurons. While other actions of DPH and CAR may contribute to their anti-MES effects, the above observations strongly implicate the sodium channel as the most likely anticonvulsant receptor site for these agents. Unfortunately, both DPH and CAR are achiral and cannot be used to investigate enantioselectivity of binding to this site.

We recently reported[7] that racemic bicyclic 2,4-oxazolidinedione **1**, one of the first two examples of anti-Bredt bicyclic imides that we call "smissmanones," binds to the neuronal voltage-sensitive sodium channel. The efficiency of binding for smissmanone **1** ($IC_{50}$ = 160 μM for the inhibition of binding of [$^3$H]batrachotoxinin A 20α-benzoate, [$^3$H]BTX-B) was comparable to that for carbamazepine ($IC_{50}$ = 131 μM), suggesting that **1** may also cause its anti-MES effect through interaction with the neuronal voltage-sensitive sodium channel. Surprisingly, the monocyclic models **2** and **3**, while exhibiting comparable whole



**1**



**2**: R = H
**3**: R = $CH_3$

animal anticonvulsant effects, were much less potent binders to the voltage-sensitive sodium channel ($IC_{50}$ = >800 and 500 μM, respectively). In order to determine if these effects were stereoselective, we resolved **1**–**3**, assigned

* Address correspondence to this author.
† Department of Chemistry, University of Alabama at Birmingham.
‡ The Neuropsychiatry Research Program, University of Alabama at Birmingham.
§ Department of Medicinal Chemistry, University of Kansas.

(1) Church, J.; Davies, S. N.; Lodge, D. *Neurol. Neurobiol.* **1987**, *24*, 115.
(2) Swinyard, E. A.; Toman, J. E. P. *J. Pharmacol. Exp. Ther.* **1950**, *100*, 151.
(3) Kupfer, A.; Bircher, J.; Preisig, R. *J. Pharmacol. Exp. Ther.* **1977**, *203*, 493.
(4) Kohn, H.; Conley, J. D.; Leander, J. D. *Brain Res.* **1988**, *244*, 666.
(5) Willow, M.; Catterall, W. A. *Mol. Pharmacol.* **1982**, *22*, 627.
(6) Willow, M.; Kuenzel, E. A.; Catterall, W. A. *Mol. Pharmacol.* **1984**, *25*, 228.
(7) Brouillette, W. J.; Brown, G. B.; DeLorey, T. M.; Shirali, S. S.; Grunewald, G. L. *J. Med. Chem.* **1988**, *31*, 2218.

0022-2623/89/1832-1577$01.50/0 

**Table I.** Biological Results

| compd | config | $Na^+$ channel: % inhibn [concn, $\mu$M][b] | anticonvulsant[a] time,[c] h | MES $ED_{50}$ | scMet $ED_{50}$ | rotorod $TD_{50}$ |
|---|---|---|---|---|---|---|
| (±)-1[d,e] | | 50 [160] | 0.25 | 66 [51–84] | 45 [40–48] | 147 [93–226] |
| (+)-1[e] | *S* | 50 [190] | 0.5 (0.25)[f] | 82 [72–90] | <400[g] | 334 [269–394] |
| (−)-1[e] | *R* | 50 [190] | 0.5 | 45 [41–51] | 50 [42–66] | 84 [75–92] |
| (±)-2[d] | | 44 (±3)[h] [500] | 0.5 | 86 [80–94] | 39 [15–45] | 164 [154–173] |
| (+)-2 | *S* | 36 (±5) [500] | 0.5 | 141 [133–149] | 42 [33–52] | 155 [141–169] |
| (−)-2 | *R* | 46 (±2) [500] | 0.5 | 91 [85–99] | 108 [92–106] | 172 [154–187] |
| (±)-3[d] | | 50 [500] | 0.5 | 124 [104–139] | 45 [36–55] | 504 [437–558] |
| (+)-3 | *S* | 45 (±1) [500] | 0.5 | 188 [171–210] | 64 [51–79] | 395 [352–428] |
| (−)-3 | *R* | 49 (±2) [500] | 0.5 | 122 [104–148] | 69 [59–80] | 354 [322–387] |

[a] Unless otherwise noted, all compounds were administered intraperitoneally to mice as suspensions in 30% polyethylene glycol 400. All activities are expressed in milligrams/kilogram and are rounded off to the nearest whole number. Numbers in brackets refer to 95% confidence intervals. [b] Concentrations accompanying 50% inhibition are $IC_{50}$ values determined from dose–response curves (ref 7). All other percent inhibition values were determined at 500 $\mu$M as indicated. [c] Time of test after compound administration. [d] Data taken from ref 7. [e] The vehicle for anticonvulsant administration was 0.5% methylcellulose. [f] Time of rotorod test only. [g] Insufficient compound to complete testing. The following data were obtained [dose (number of animals protected/number of animals tested)]: 25 (0/2); 50 (0/2); 100 (0/2); 200 (1/2); 400 (8/8). [h] Value determined in the present study.

the absolute configurations, and evaluated each enantiomer in both the sodium channel and whole animal anticonvulsant assays. Here we report that the enantiomers of **1–3** do not exhibit significant stereoselective effects in the sodium channel assays and exhibit only modest enantioselectivities in the anticonvulsant assays.

**Chemistry.** Racemic compounds **1–3** were prepared as previously described.[7,8] Smissmanone **1** was preparatively resolved directly on a Chiralcel OD chiral HPLC column (10 mm i.d. × 25 cm L). Complete separation was demonstrated by reinjection on an analytical column (4.6 mm i.d. × 25 cm L). Compound **2**, whose enantiomers could not be separated on the Chiralcel OD column, was resolved by recrystallization of the quinone salt from absolute ethanol to give the (+)-isomer. The resulting (+)-**2** was demonstrated to be optically pure by a $^1H$ NMR chiral shift reagent study which employed tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III). In this study a mixture of racemic **2** (100 mg/mL) and the shift reagent (216 mg/mL) in $CDCl_3$ resulted in a $^1H$ NMR spectrum that contained the ethyl triplet of **2** as two overlapping triplets (one for each diastereomeric complex) centered at 3.0 ppm. When the spectrum of (+)-**2** was recorded under the same conditions, only a single triplet was visible. Recovered **2** from the mother liquors was then reacted with quinidine and the resulting salt recrystallized from ethanol to give (−)-**2**, the high optical purity of which was demonstrated by the observation of a nearly equal and opposite rotation to that found for (+)-**2**. The (+)- and (−)-enantiomers of **2** were each methylated according to the procedure we reported[7] for racemic **3** to give, respectively, (+)- and (-)-**3**.

The absolute configuration of (+)-**2** was determined to be *S* by hydrolysis in aqueous NaOH to give (+)-2-ethylmandelic acid (**4**) of known configuration.[9] This also established the *S* configuration for (+)-**3**. The circular dichroism (CD) spectrum of (+)-**2** exhibited a single band of positive ellipticity centered at 242 nm, and the CD spectrum of (+)-**1** was identical (other than a greater intensity), establishing the *S* configuration for (+)-**1**.

**Biology.** The enantiomers of **1–3** were each evaluated in synaptoneurosomal preparations from rat cerebral cortex as inhibitors of the specific binding of [$^3H$]BTX-B to the voltage-sensitive sodium channel. The $IC_{50}$ values for **1** were determined according to our previously reported method.[7] The percent inhibition values for **2** and **3** were obtained at a single concentration, 500 $\mu$M. (The $IC_{50}$ values for **2** and **3** were not determined since the enantiomers exhibited only small differences in activity at the above concentration.) All experiments were performed in triplicate and included a control that contained 40 $\mu$M diphenylhydantoin (the $IC_{50}$ value). The results are given in Table I.

The enantiomers of **1–3** were also evaluated as anticonvulsants in mice by the Antiepileptic Drug Development Program of the National Institute of Neurological and Communicative Disorders and Stroke. In this screening procedure, which has been described in detail,[10] the compounds were injected intraperitoneally into mice as suspensions in either 30% polyethylene glycol 400 or 0.5% methylcellulose. The median effective dose ($ED_{50}$) was determined for both an MES and scMet screen, and the median toxic dose ($TD_{50}$) was determined in a rotorod test. Table I gives the results.

## Results and Discussion

The sodium channel binding activities and quantitative whole animal anticonvulsant effects for the enantiomers of **1–3** are given in Table I. For reference, also included are data for racemic **1–3**, which were obtained in a previous study.[7]

Racemic compounds **2** and **3** were previously observed to be relatively poor binders to the sodium channel, and, as anticipated, the enantiomers were also poor binders

(8) Brouillette, W. J.; Einspahr, H. M. *J. Org. Chem.* **1984**, *49*, 5113.
(9) McKenzie, A.; Ritchie, A. *Chem. Ber.* **1937**, *70*, 23. Mitsui, S.; Imaizumi, S.; Konno, K. *Chem. Ind. (London)* **1964**, 233.
(10) Krall, R. L.; Penry, J. K.; White, B. G.; Kupferburg, H. J.; Swinyard, E. A. *Epilepsia* **1978**, *19*, 409. Porter, R. J.; Cereghino, J. J.; Gladding, G. G.; Hessie, B. J.; Kupferburg, H. J.; Scoville, B.; White, B. G. *Cleve. Clin. Q.* **1984**, *51*, 293.

which displayed essentially no stereoselectivity. However, moderate enantioselective effects were observed in the whole animal anticonvulsant screen. For **2**, the more potent anti-MES agent was the *R*-(−)-isomer, although its $ED_{50}$ was essentially the same as that for racemic **2**. (*S*)-(+)-**2** was the more potent enantiomer in the scMet screen, where the greatest anticonvulsant enantioselectivity was observed, and again its activity was nearly identical with that for racemic **2**. Compound **3** exhibited minor enantioselectivity only in the MES screen, where (*R*)-(−)-**3** was slightly more potent and equal in activity to racemic **3**. Both **2** and **3** exhibited very little stereoselectivity in the rotorod test. While the reasons for the slight enantioselective effects of **2** and **3** are not apparent, it is clear that the enantiomers provide no potential therapeutic advantage over the racemate.

The racemate of smissmanone **1**, in contrast to **2** and **3**, was previously observed to be a relatively effective binder to the neuronal voltage-sensitive sodium channel. Surprisingly, like **2** and **3**, the enantiomers of **1** also exhibited no stereoselectivity in the sodium channel assay and were each nearly as active as the racemate. Furthermore, in the MES screen the enantiomers of **1** were each equipotent with the racemate (when confidence intervals are compared). This observation is consistent with our earlier suggestion that **1** may represent a new sodium channel anticonvulsant,[7] since the sodium channel assay correctly predicted the lack of stereoselectivity for the enantiomers of **1**. We were unable to evaluate stereoselectivity in the scMet assay due to an insufficient supply of (*S*)-(+)-**1**, although (*R*)-(−)-**1** was observed to be equipotent with the racemate. Finally, there appeared to be significant stereoselectivity for **1** in the rotorod test, where (*R*)-(−)-**1** was 4 times more toxic than (*S*)-(+)-**1**, and the racemate toxicity was, considering confidence interals, the average of the enantiomer toxicities. Therefore, due to its larger protective index ($PI = TD_{50}/ED_{50}$), (*S*)-(+)-**1** appears to offer greater therapeutic potential as an anticonvulsant than either (*R*)-(−)-**1** or racemic **1**.

In summary, the lack of stereoselectivity for the enantiomers of **1** in both the sodium channel and anti-MES anticonvulsant assays is consistent with our previous suggestion[7] that **1** may represent a new sodium channel anticonvulsant. Additionally, since the enantiomers of **1** contain highly defined stereochemistries, these results may provide insight for beginning to elucidate gross structural features of this receptor site.

## Experimental Section

Racemic compounds **1**–**3** were prepared as previously described.[7,8] All HPLC separations were performed on a Rainin Rabbit HPLC system that included an Apple IIe controlled Gilson Data Master and a Hitachi Model 100-40 variable-wavelength detector. The preparative resolution of racemic **1** was accomplished on a Chiralcel OD HPLC column (10 mm i.d. × 25 cm L, supplied by J. T. Baker Chemical Co.) using 9% iPrOH/hexane (2 mL/min). Up to 50 mg of **1** (as an iPrOH solution) could be applied to the column and maintain base-line resolution (monitoring at 255 nm), and under these conditions retention times for (+)- and (−)-**1** were 18.8 and 26.5 min, respectively. For (+)-**1**: $[\alpha]^{25}_D = +184°$ (*c* 1.12, $CHCl_3$). For (−)-**1**: $[\alpha]^{25}_D = -180°$ (*c* 1.16, $CHCl_3$). A total of 3.0 g of **1** was resolved in this manner. (*S*)-(+)-**3** and (*R*)-(−)-**3** were prepared by the methylation of (*S*)-(+)-**2** and (*R*)-(−)-**2**, respectively, according to the procedure we previously reported[7] for converting racemic **2** to **3**. For (*S*)-(+)-**3**: $[\alpha]^{27}_D = +39.5°$ (*c* 1.28, EtOH). For (*R*)-(−)-**3**: $[\alpha]^{27}_D = -39.9°$ (*c* 1.12, EtOH).

Optical rotations were measured on a Perkin-Elmer 141 polarimeter in a 1-mL cell. Circular dichroism spectra were obtained in $CH_3OH$ (0.3 mg/mL) on a JASCO 500A spectropolarimeter. Melting points were recorded on a Thomas-Hoover or Electrothermal melting point apparatus and are uncorrected. $^1H$ NMR spectra for the shift reagent study of **2** were recorded on a Varian EM 360 spectrometer using tetramethylsilane (TMS) as internal standard.

[$^3H$]Batrachotoxinin A 20$\alpha$-benzoate with a specific activity of 50 Ci/mmol was prepared as described.[11] This compound is currently available from New England Nuclear.

**Resolution of 5-Ethyl-5-phenyl-2,4-oxazolidinedione (2).** Racemic **2** (53.5 g, 0.261 mol) was dissolved in absolute EtOH (600 mL), and quinine monohydrate (46.2 g, 0.135 mol) was added. The solution was heated at reflux for 18 h, reduced in volume to 400 mL on a steam bath, cooled, and filtered to yield white needles (56.0 g, 74.0%). The salt was recrystallized from absolute EtOH (four recrystallizations) until no further change occurred in melting point or rotation to yield the quinine salt of (−)-**2** (33.8 g, 47.0%): mp 214.5–215.5 °C; $[\alpha]^{27}_D = -75.4°$ (*c* 0.665, EtOH). This salt was shaken with a mixture of 5% HCl (200 mL) and $Et_2O$ (300 mL), the aqueous layer removed, and the ether layer extracted, respectively, with 5% HCl (2 × 75 mL), water (2 × 75 mL), and saturated aqueous NaCl (75 mL). The organic layer was dried ($MgSO_4$) and concentrated on a rotary evaporator to yield a colorless oil. Distillation afforded (+)-**2** (11.8 g, 93.0%) as a viscous oil: bp 125 °C (0.02 mm); $[\alpha]^{27}_D = +49.1°$ (*c* 2.99, EtOH). The $^1H$ NMR and IR spectra were identical with those for racemic material.[4]

The mother liquor from the first crystallization was concentrated under vacuum. The residue was dissolved in $Et_2O$ and extracted, respectively, with 10% HCl (2 × 50 mL), water (50 mL), and saturated aqueous NaCl (50 mL). The ethereal solution was dried ($MgSO_4$) and concentrated under vacuum to yield a clear oil which consisted mainly of (−)-**2** (29.0 g, 0.141 mol): $[\alpha]^{27}_D = -35.4°$. This oil was dissolved in absolute EtOH (100 mL) and a solution of anhydrous quinidine (42.3 g, 0.130 mol) in absolute EtOH (300 mL) was added. After heating at reflux for 3 h, the solution was cooled to give a white solid (56.0 g). Recrystallization from absolute EtOH until no further change occurred in melting point or rotation (three recrystallizations) yielded the quinidine salt of (−)-**2** (29.0 g, 42.2%) as white needles: mp 201–202 °C; $[\alpha]^{27}_D = +119°$ (*c* 0.795, EtOH). The salt was then acidified as described above for (+)-**2** and the product distilled to give (−)-**2** (9.8 g, 87%): bp 125 °C (0.02 mm); $[\alpha]^{27}_D = -49.5°$ (*c* 1.14, EtOH). The $^1H$ NMR and IR spectra were identical with those for racemic **2**.[7]

**(*S*)-(+)-2-Ethylmandelic Acid (4).** A suspension of (+)-**2** {100 mg, 0.49 mmol; $[\alpha]^{24}_D = +47.5°$ (*c* 1.05, $CH_3OH$); 97% enantiomeric excess} in 10% NaOH (10 mL) was heated at gentle reflux for 2 h and then allowed to stand overnight at room temperature. This was extracted with EtOAc (3 × 10 mL), and the water layer was adjusted to pH 2 with concentrated HCl. The aqueous solution was extracted with EtOAc (3 × 20 mL), the organic layers were dried ($MgSO_4$), and the mixture was concentrated under vacuum to give crude (*S*)-(+)-**4** (85 mg, 97%) as a light yellow solid (mp 114–120 °C). This was recrystallized from benzene to give a white solid: mp 124–126 °C; $[\alpha]^{24}_D = +31°$ (*c* 0.94, $CH_3OH$; 95% enantiomeric excess) [lit.[9] mp 128–129 °C; lit.[9] $[\alpha]^{20}_D = +32.7°$ (*c* 3.996, EtOH)].

**Sodium Channel Binding Assay.** We previously described the details of this procedure.[7] Briefly, synaptoneurosomes (which are resealed postsynaptic elements containing attached resealed presynaptic elements, approximately 980 $\mu$g) were incubated for 40 min at 25 °C with the test compound (500 $\mu$M) in a total volume of 320 $\mu$L containing 10 nM [$^3H$]BTX-B and 50 $\mu$g/mL of scorpion venom. Incubations were terminated by dilution with ice-cold buffer and filtration through a Whatman GF/C filter paper. Filters were counted in a Beckmann scintillation counter. Specific binding was determined by subtracting the nonspecific binding, which was measured in the presence of 250 $\mu$M veratridine, from the total binding of [$^3H$]BTX-B. All experiments were performed in triplicate and included a control tube containing 40 $\mu$M diphenylhydantoin.

**Anticonvulsant Assays.** All whole animal anticonvulsant and neurotoxicity assays were conducted by the Anticonvulsant Drug Development Program of the Epilepsy Branch, National

(11) Brown, G. B.; Daly, J. W. *Cell Mol. Neurobiol.* **1981**, *1*, 361.

Institute of Neurological and Communicative Disorders and Stroke. Compounds were injected intraperitoneally into mice as suspensions in either 30% polyethylene glycol 400 or 0.5% methylcellulose. After the time indicated in Table I, the animal was subjected to either a subcutaneous Metrazol (scMet) challenge (85 mg/kg), a maximal electroshock (MES) challenge (produced with 60 cycle AC at 50 mA for 0.2 s via corneal electrodes), or a rotorod toxicity test. The details of these procedures have been published.[10]

**Acknowledgment.** We thank Gill Gladding and James Stables of the Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke, for the whole animal anticonvulsant assays. We are also indebted to Dr. Michael Henry at J. T. Baker Chemical Co. for identifying the Chiralcel OD column as appropriate for the resolution of **1**. Finally, we thank the NIH for generous support of this work (Grant No. NS23866).

**Registry No.** (±)-**1**, 120666-79-7; (+)-**1**, 120710-26-1; (−)-**1**, 120710-27-2; (±)-**2**, 101053-00-3; (+)-**2**, 77207-58-0; (−)-**2**, 120710-28-3; (±)-**3**, 120666-80-0; (+)-**3**, 120710-29-4; (−)-**3**, 120710-30-7; **4**, 24256-91-5.

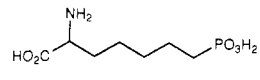
# Exploration of Phenyl-Spaced 2-Amino-(5–9)-phosphonoalkanoic Acids as Competitive *N*-Methyl-D-aspartic Acid Antagonists

Christopher F. Bigge,[†] James T. Drummond,[†] Graham Johnson,*[,†] Thomas Malone,[†] Albert W. Probert, Jr.,[‡] Frank W. Marcoux,[‡] Linda L. Coughenour,[‡] and Laura J. Brahce[‡]

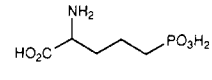
*Departments of Chemistry and Pharmacology, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105.* *Received December 7, 1988*

To investigate the preferred spatial relationship of the distal phosphonic acid to the α-amino acid group of the established competitive *N*-methyl-D-aspartic acid (NMDA) antagonists APH (**1**) and APV (**2**), we have prepared a series of ortho-, meta-, and para-substituted (phosphonoalkyl)phenylglycine and -phenylalanine derivatives. With use of a [$^3$H]CPP receptor binding assay, significant binding activity was observed to be critically dependent on both the position of substitution and length of alkyl spacing groups. Two compounds, 4-(phosphonomethyl)-phenylglycine (**6**, PD 129635) and 3-(phosphonomethyl)phenylalanine (**15**, PD 130527), displayed receptor-binding affinity comparable to that of APH. Like APH, these compounds were also effective in antagonizing both the proconvulsant and lethal action of NMDA-administered retrobulbar in the mouse. Data are also provided which compare directly the binding efficacy of these compounds against that disclosed recently for the related NMDA antagonist **18** (NPC 451). A preliminary comparison of the structures showing good receptor-binding affinity and in vivo antagonist activity suggests that the NMDA receptor prefers a "folded" rather than "extended" conformation.

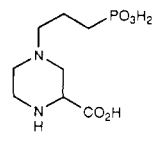
The growing awareness of a critical role for excitatory amino acids in the pathology of increasing numbers of neurodegenerative disorders,[1–4] combined with the availability of several selective receptor ligands, has stimulated significant interest in the search for new and more potent excitatory amino acid antagonists. Particularly interesting from their potential pharmaceutical use in the treatment of cerebral infarction (resulting, for example, from hypoglycemia[5] and ischemia[6]) are antagonists specific for the *N*-methyl-D-aspartate (NMDA) preferring receptor. Recent advances in the understanding of this area have been made possible by the availability of selective NMDA antagonists such as 2-amino-7-phosphonoheptanoic acid (APH)[7] (**1**), 2-amino-5-phosphonovaleric acid[8] (APV) (**2**),



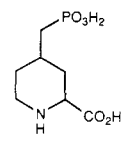

**1**




**2**




**3**




**4**

4-(3-phosphonopropyl)-2-piperazinecarboxylic acid (CPP)[9,10] (**3**), and most recently *cis*-4-(phosphonomethyl)-2-piperidinecarboxylic acid (CGS 19755)[11] (**4**).

Several reports have described the synthesis and biochemical and electrophysiological action of conformationally restricted NMDA-receptor agonists.[12–16b] Combined, these studies have afforded limited insight into the

[†] Department of Chemistry.
[‡] Department of Pharmacology.

(1) Greenamyre, J. T. *Arch. Neurol.* **1986**, *43*, 1058.
(2) Engelsen, B. *Acta Neurol. Scand.* **1986**, *74*, 337.
(3) Meldrum, B. In *Neurotoxins and their Pharmacological Implications*; Jenner, P., Ed.; Raven Press: New York, 1987; pp 33–53.
(4) Spencer, P. S.; Nunn, P. B.; Hugon, J.; Ludolph, A. C.; Ross, S. M.; Roy, D. N.; Robertson, R. C. *Science* **1987**, *237*, 517.
(5) Wieloch, T. *Science* **1985**, *230*, 681.
(6) Simon, R. P.; Swan, J. H.; Griffiths, T.; Meldrum, B. S. *Science* **1984**, *226*, 850.
(7) Perkins, M. N.; Stone, T. W.; Collins, J. F.; Curry, K. *Neurosci. Lett.* **1981**, *23*, 333.
(8) Davies, J.; Fancis, A. A.; Jones, A. W.; Watkins, J. C.; Neurosci. *Lett.* **1981**, *21*, 77.
(9) Davies, J.; Evans, R. H.; Herrling, A. W.; Jones, A. W.; Olverman, H. J.; Pook, P.; Watkins, J. C. *Brain Res.* **1986**, *382*, 169.
(10) Harris, E. W.; Ganong, A. H.; Monaghan, D. T.; Watkins, J. C.; Cotman, C. W. *Brain Res.* **1986**, *382*, 174.
(11) (a) Lehmann, J.; Hutchison, A. J.; McPherson, S. E.; Mondadori, C.; Schmutz, M.; Sinton, C. M.; Tsai, C.; Murphy, D. E.; Steel, D. J.; Williams, M.; Cheney, D. L.; Wood, P. L. *J. Pharm. Exp. Ther.* **1988**, *246*, 65. (b) Boast, C. A.; Gerhardt, S. C.; Pastor, G.; Lehmann, J.; Etienne, P. E.; Liebman, J. M. *Brain Res.* **1988**, *442*, 345.
(12) Davies, J.; Evans, R. H.; Francis, A. A.; Jones, A. W.; Smith, A. S.; Watkins, J. C. *Neurochem. Res.* **1982**, *7*, 1119.
(13) Curry, K.; Magnuson, D. S. K.; McLennan, H.; Peet, M. J. *Can. J. Physiol. Pharmacol.* **1987**, *65*, 2196.
(14) Yamanoi, K.; Yasufumi, O. *Tetrahedron Lett.* **1988**, *29*, 1181.
(15) Pellicciari, R.; Natalini, M.; Marinozzi, M.; Selvi, L.; Chiorri, C.; Monahan, J. B.; Lanthorn, T. H.; Snyder, J. P. In *Frontiers in Excitatory Amino Acid Research*; Cavalheiro, E. A., Lehman, J., Turski, L., Eds.; Alan R. Liss, Inc.: New York, 1988; pp 67–70; or *Neurochem. Int.* **1988**, *12*, Suppl. 1, 26.

0022-2623/89/1832-1580$01.50/0 