Hz, 1 H, H-N^7); 8.39 (d, J = 10.0 Hz, 1 H, H-N^2); MS exact mass calcd for $C_{66}H_{114}N_{11}O_{13}$ 1268.8595 (M^+H), found (HR-FAB) 1268.8652.

Cyclo[[(2*S*,3*R*,4*R*)-3,5-dihydroxy-4-methyl-2-(methylamino)pentanoyl]-L-2-aminobutyryl-sarcosyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methylvalyl] (28e). A hydrogen stream was bubbled through an ethanol suspension containing 6.3 mg of **28d** and 5 mg of 10% Pd/C for 5.5 h. The mixture was filtered via a pad of Celite and the filtrate was evaporated. The residue was flash chromatographed on 8 g of silica gel with 20% of acetone in hexane to give 5.5 mg (94%) of pure **28e**: R_f 0.19 (40% acetone/hexane); $[\alpha]_D$ -244° (c 0.5, $CHCl_3$); IR ($CHCl_3$) 3310, 2960, 1630 (sh), 1520, 1470, 1410, 1190, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (d, J = 6.5, 3 H, CH_3-C (4^6)); 0.80–1.10 (m, 39 H, CH_3-C(4^1), CH_3-C(3^2), 2 CH_3-C(4^4), 2 CH_3-C(3^5), CH_3-C(4^6), 2 CH_3-C(4^9), 2 CH_3-C(4^{10}), 2 CH_3-C(3^{11})); 1.28 (d, J = 7.0, 3 H, CH_3-C(2^7)); 1.35 (d, J = 7.0, 3 H, CH_3-C(2^7)); 1.10–2.50 (m, 19 H, H-C(4^1), 2 H-C(3^2), 2 H-C(3^4), H-C(4^4), H-C(3^5), 2 H-C(3^6), H-C(4^6), 2 H-C(3^9), H-C(4^9), 2 H-C(3^{10}), H-C(4^{10}), H-C(3^{11}), HO-C(3^1), HO-C(5^1)); 2.67 (s, 6 H, CH_3-N^{10}, CH_3-N^{11}); 3.10 (s, 3 H, CH_3-N^4); 3.16 (s, 3 H, CH_3-N^9); 3.28 (s, 3 H, CH_3-N^6), 3.41 (s, 3 H, CH_3-N^3); 3.48 (s, 3 H, CH_3-N^1); 3.48, 3.57 (2 m, 2 H, 2 H-C(5^1)); 3.19, 4.17 (2 d, J = 15.0, 2 H, 2 H-(3^2)); 4.07 (m, 1 H, H-C(3^1)); 4.45 (m, 1 H, H-C(2^7)); 4.67 (m, 1 H, H-C(2^5)); 4.83 (m, 1 H, H-C(2^8)); 4.97 (m, 1 H, H-C(2^2)); 5.03 (d, J = 11.5, 1 H, H-C(2^{11})); 5.08 (t, J = 6.5, 1 H, H-C(2^{10})); 5.17 (m, 2 H, H-C(2^4), H-C(2^6)); 5.35 (d, J = 9.0, 1 H, H-C(2^1)), 5.67 (dd, J = 4.0, 11.0, 1 H, H-C(2^9)); 7.41 (d, J = 8.0, 1 H, H-N^8); 7.46 (d, J = 8.8, 1 H, H-N^5); 7.85 (d, J = 7.0, 1 H, H-N^7); 8.25 (d, J = 9.5, 1 H, H-N^2). MS exact mass calcd for $C_{59}H_{108}N_{11}O_{13}$ 1178.8127 (M^+H), found (HR-FAB) 1178.8114.

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Registry No. 4, 125782-34-5; **5**, 125782-35-6; **6**, 125782-36-7; **7**, 125782-37-8; **9a**, 63930-46-1; **6b**, 79026-61-2; (*E*)-11, 125782-33-4; (*Z*)-11, 125782-38-9; **12**, 114762-43-5; *anti*-**14**, 125873-80-5; *syn*-**14**, 125873-79-2; **15**, 125872-39-0; **16**, 125872-40-3; **17**, 125782-41-4; **18**, 125782-42-5; **20a**, 125782-43-6; **20b**, 125782-44-7; **20c**, 125782-45-8; **21a**, 125782-46-9; **21b**, 125782-47-0; **21c**, 125782-48-1; **22a**, 125782-49-2; **22b**, 125782-50-5; **22c**, 125782-51-6; **22d**, 125782-52-7; **23**, 81135-30-0; **24a**, 125782-53-8; **24b**, 125801-24-3; **24c**, 125782-54-9; **24d**, 125782-55-0; **25a**, 125782-56-1; **25b**, 125782-57-2; **25c**, 125782-58-3; **25d**, 125782-59-4; **26**, 115141-96-3; **27a**, 125782-60-7; **27b**, 125782-61-8; **27c**, 125782-62-9; **27d**, 125782-63-0; **28a**, 125782-64-1; **28b**, 125801-25-4; **28c**, 125782-65-2; **28c**, 125782-66-3; **28e**, 125782-67-4; trimethyl phosphonoacetate, 5927-18-4; 4-benzoylbenzyl bromide, 32752-54-8.

Synthesis and Anticonvulsant Activity of 1-Phenylcyclohexylamine Analogues

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Thirty-eight analogues of 1-phenylcyclohexylamine (PCA), a phencyclidine (PCP) derivative, were examined for their activities in the mouse maximal electroshock (MES) seizure test and in a motor-toxicity assay. In addition, we determined the binding affinities of the compounds for PCP acceptor sites in rat brain membranes labeled with [^{3}H]-1-[1-(2-thienyl)cyclohexyl]piperidine. Many of the analogues were protective against MES seizures (ED_{50}s of 5–41 mg/kg, ip) and all of these compounds caused motor toxicity. The potencies in the motor toxicity and MES seizure tests showed a moderate correlation with the affinities for PCP sites. Several analogues exhibited a greater separation of potencies in the motor toxicity and MES seizure tests than did the parent compound PCA. These were obtained by (i) 3-methylation of the cyclohexyl ring trans to the phenyl ring, (ii) methoxylation at the ortho position on the phenyl ring, and (iii) contraction of the cyclohexane ring to form the corresponding cyclopentane.

The effectiveness of phencyclidine (PCP) as an anticonvulsant agent has been largely overshadowed by its notoriety as a drug of abuse. Nevertheless, in rats and mice, PCP is protective in the maximal electroshock (MES),[1,2] pentylenetetrazol,[1,3] and audiogenic[1] seizure models. In addition, PCP increases the threshold of kindled seizures[4] and prolongs the latency of flurothyl-induced seizures.[5] Despite its effectiveness as an anticonvulsant, PCP has a variety of toxicities which limit its clinical usefulness in the treatment of seizure disorders[6] and these toxicities are shared by many PCP-related drugs.[2]

In a recent report by Leccese and co-workers,[7] in which the anticonvulsant actions of PCP and various PCP analogues were examined, it was noted that the primary amine analogue of PCP, 1-phenylcyclohexylamine (PCA, 1), had a particularly potent anticonvulsant action in the MES test. We subsequently demonstrated that PCA has a relatively reduced potency for inducing motor toxicity as compared to the parent compound PCP.[8] The relative potencies of anticonvulsant drugs in motor toxicity and

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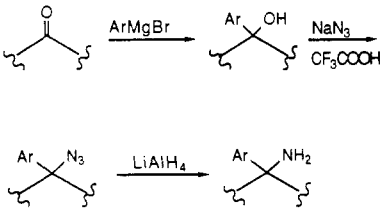
Scheme I. Synthetic Route to α-Phenylamines



MES seizure tests has been used as a measure of their potential clinical utility.[9] This can be quantitatively expressed as the ratio TI = TD_{50}/ED_{50}, where TD_{50} is the dose causing motor toxicity in 50% of animals and ED_{50} is the dose protecting 50% of animals in the MES seizure test. In our prior study, the TI of PCP was approximately 1, whereas PCA exhibited an improved TI (2.3) as did several PCA analogues.[8] In this small series of PCA analogues, we observed that the motor toxicities of the compounds paralleled their affinities for PCP binding sites in brain labeled with [^{3}H]-1-[1-(2-thienyl)cyclohexyl]-piperidine ([^{3}H]TCP) and we postulated that the toxic effects were, at least in part, mediated through an interaction with this site.[8]

In the present study we examined a larger series of PCA analogues to further characterize those structural features critical to anticonvulsant activity and to a favorable ratio of potencies in the motor toxicity and anticonvulsant tests. The structural modifications of PCA reported herein can be classified into four categories. In the first category, an additional carbon has been introduced as a methyl group on the amine nitrogen and at all available positions on the phenyl and cyclohexyl rings. The second category examines the effects of other substituents on the aromatic ring. The third category examines the effects of changing the phenyl ring to some other group. In the final category, the size of the cycloalkyl ring is altered. The prepared compounds were examined for their abilities to prevent seizures in the maximal electroshock (MES) test, their motor toxicities and their in vitro affinities for the PCP binding site in rat brain membranes.

Chemistry. With the exception of compound **16**, all compounds reported in this paper were prepared by using the method of Geneste et al.[10] or a modification thereof. This route, outlined in Scheme I, consists of an initial condensation of a Grignard reagent with the appropriate ketone. Treatment of the resulting tertiary alcohol with trifluoroacetic acid in the presence of sodium azide gave the tertiary azides, which were then reduced to the corresponding amine with lithium aluminum hydride. Treatment of **1** with formalin and sodium cyanoborohydride[11] or with excess methyl iodide in the presence of potassium carbonate provided methylated amines **3** and **4**, respectively. Monomethylamine **2** was obtained through reduction of the *N*-formyl derivative of **1**. The preparation and isolation of **7–10** have been previously described.[12] 2-Methylcyclohexyl derivatives **5** and **6** and 4-methylcyclohexyl derivatives **11** and **12** were prepared as diastereomeric mixtures and separated by chromatography. The configurations of **5**, **6**, **11**, and **12** were determined by conversion to the corresponding PCP derivatives of previously assigned configuration.[10] Compound **29** was prepared from **30** by catalytic hydrogenation over 10% palladium on carbon. The synthesis of compound **16** was accomplished by conversion of the commercially available 1-phenyl-1-carboxycyclohexane to the primary amide followed by reduction with lithium aluminum hydride. The importance of a benzylic tertiary alcohol to the success of the azide conversion is reflected in the low yields obtained for the preparation of compounds **17** and **34**. The low yield of **24** is a consequence of the property of α-halo Grignard reagents to eliminate to form benzynes. The difficulty in preparation of the perfluorophenyl Grignard reagent resulted in a low yield for **33**. Finally, the low yields of **32** and **39** are probably due to the predominance of elimination over carbonium ion formation. The yields for all compounds are unoptimized.

Pharmacology

Anticonvulsant and Motor Toxicity Testing. Each compound was administered intraperitoneally to male general purpose Swiss mice (25–30 g) in a 0.9% NaCl solution carrier. Fifteen minutes after the drug injection, the animals were tested for drug-induced motor toxicity by using a modified version of the horizontal screen test[13] as previously described.[8] The mice were then immediately subjected to corneal electroshock (50 mA at 60 Hz for 0.2 s). Animals failing to show the tonic-extensor component of the convulsion were scored as protected. Each drug was tested at five to 10 doses with eight animals per dose. The ED_{50} (TD_{50} in the motor toxicity test) and the 95% confidence intervals were calculated by the log-probit method using the computer programs accompanying Tallarida and Murray.[14]

Binding Assay. Drug affinities for PCP binding sites in rat brain membranes were determined as previously described by Jacobson et al.[15] using a tissue homogenate preparation of whole rat brain minus cerebellum. The homogenate was incubated with [^{3}H]TCP (1.8–2 nM; 53 Ci/mmol) at 5 °C for 60 min and rapidly filtered through membrane filters presoaked in 0.03% polylysine. Nonspecific binding was determined in the presence of 10 μM TCP and typically represented <5% of the total bound radioactivity. K_i values were calculated with the Cheng–Prusoff equation[16] using a K_d for TCP of 16.5 nM as determined by Scatchard analysis. Values listed in Table I are the means of three separate experiments.

Results and Discussion

The structures of the compounds examined as well as the results of the pharmacological screening are displayed in Table I. Many of the analogues were effective anticonvulsants in the MES test. With the exception of the N-methylated derivatives **2** and **3**, the compounds were equal or less potent than PCA as seizure protectants. However, in some cases the TD_{50} was reduced more than the ED_{50}, resulting in an improved TI (e.g., **10**, **11**, **37**).

Despite the enhanced anticonvulsant potencies of **2** and **3**, methylation of the amino nitrogen failed to substantially

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Table I. Comparative Potencies of Phencyclidine and 1-Phenylcyclohexane Analogues in the Mouse MES Seizure Test (MES ED_{50}), in the Motor Toxicity Test (TD_{50}), and in the [^{3}H]TCP Binding Assay (K_i)[a]

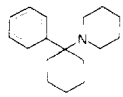
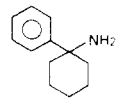
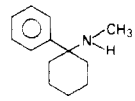
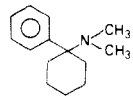
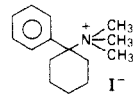
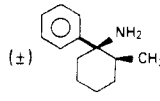
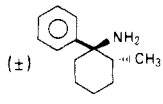
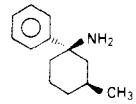
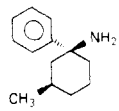
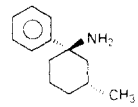
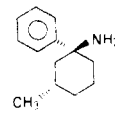
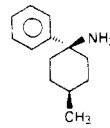
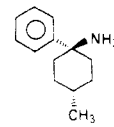
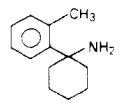
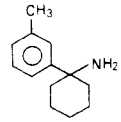
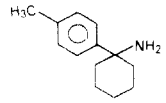
compd	structure	MES ED_{50}, mg/kg	TD_{50}, mg/kg	K_i, nM	TI
PCP		3.1 (2.2–4.0)	2.9 (2.3–3.4)	60–80	0.93 (0.59–1.25)
1		7.04 (5.74–8.62)	16.27 (15.07–17.56)	527	2.31 (1.86–2.87)
2		4.62 (3.35–6.38)	1.56 (1.07–2.28)	347	0.34 (0.20–0.56)
3		4.86 (3.76–6.28)	11.26 (8.50–14.91)	722	2.32 (1.58–3.39)
4		>64	>64	14300	
5		8.01 (5.69–11.27)	5.92 (3.93–8.93)	2000	0.74 (0.43–1.26)
6		16.87 (11.17–25.49)	34.59 (26.30–45.49)	1600	2.05 (1.25–3.36)
7		26.38 (21.40–32.52)	54.8–100	502	
8		8.04 (4.64–13.91)	15.92 (11.48–22.09)	8000	1.98 (1.05–3.75)
9		20.86 (18.24–23.85)	56.13 (46.85–67.25)	1200	2.69 (2.15–3.37)
10		8.01 (6.50–9.88)	24.33 (21.07–28.09)	1640	3.04 (2.36–3.81)
11		13.53 (8.54–21.45)	46.56 (39.20–55.30)	1100	3.44 (2.10–5.62)
12		33.75 (27.72–40.10)	69.33 (63.57–75.61)	8400	2.05 (1.66–2.55)
13		4.93 (3.59–6.77)	7.19 (5.69–9.10)	7800	1.46 (0.98–2.16)
14		19.11 (16.73–21.83)	26.23 (23.83–28.88)	592	1.37 (1.16–1.62)
15		>74	>74	7300	

Table I (Continued)

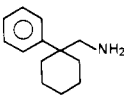
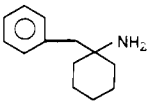
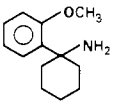
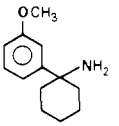
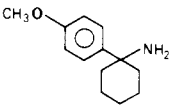
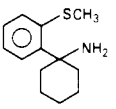
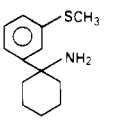
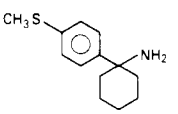
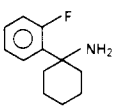
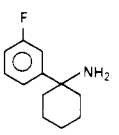
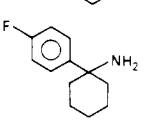
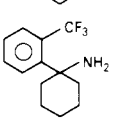
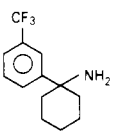
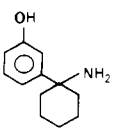
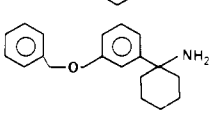
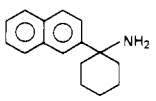
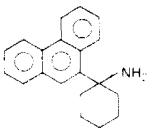
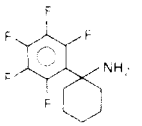
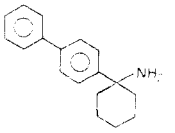
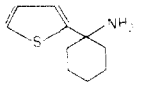
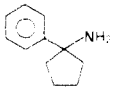
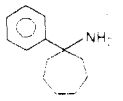
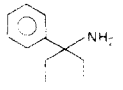
compd	structure	MES ED_{50}, mg/kg	TD_{50}, mg/kg	K_i, nM	TI
16		27.70 (21.26–36.07)	51.88 (41.32–65.14)	5100	1.87 (1.32–2.65)
17		34.52 (25.33–47.04)	67.25 (58.36–77.50)	16000	1.95 (1.39–2.74)
18		11.11 (4.97–24.80)	31.55 (27.65–36.01)	850	2.84 (1.26–6.41)
19		14.78 (11.60–18.84)	21.40 (18.81–24.36)	563	1.45 (1.10–1.91)
20		32.67 (26.48–40.31)	77.94 (63.63–95.47)	121000	2.39 (1.78–3.19)
21		26.18 (19.43–35.27)	29.32 (18.14–47.38)	820	1.12 (0.64–1.97)
22		32.88 (31.47–34.35)	63.70 (58.22–69.69)	2420	1.94 (1.75–2.14)
23		40.80 (31.50–52.85)	77.11 (63.78–93.22)	43000	1.89 (1.37–2.60)
24		22.93 (15.26–34.44)	61.21 (48.24–77.68)	10700	2.67 (1.67–4.28)
25		9.36 (6.57–13.33)	20.16 (18.20–22.32)	675	2.15 (1.49–3.11)
26		26.18 (16.10–42.56)	23.45 (19.36–28.40)	923	0.90 (0.53–1.51)
27		30.36 (25.15–36.65)	39.20 (34.81–44.15)	12400	1.29 (1.03–1.61)
28		24.31 (20.34–29.06)	16.03 (12.27–20.95)	8400	0.66 (0.48–0.91)
29		35.25 (27.97–44.43)	42.70 (35.59–51.22)	222	1.21 (0.90–1.63)
30		29.41 (18.32–47.22)	67.05 (52.06–86.34)	10600	2.28 (1.33–3.90)
31		16.91 (12.87–22.22)	30.85 (27.21–34.97)	34000	1.82 (1.35–2.46)

Table I (Continued)

compd	structure	MES ED_{50}, mg/kg	TD_{50}, mg/kg	K_i, nM	TI
32		16.02 (11.54–22.25)	20.57 (15.82–26.74)	27500	1.28 (0.84–1.95)
33		33.81 (27.15–42.11)	37.93 (29.85–48.19)	10000	1.21 (0.81–1.55)
34		>40.6	40.6–54.8	ND	
35		18.81 (16.82–21.04)	26.68 (21.50–33.11)	86000	1.42 (1.11–1.81)
36		10.50 (6.88–16.02)	4.99 (2.88–8.62)	145	0.47 (0.24–0.95)
37		18.52 (15.05–22.79)	64.57 (54.07–77.11)	10500	3.49 (2.65–4.58)
38		19.73 (12.70–30.66)	43.05 (34.87–53.14)	2600	2.18 (1.34–3.56)
39		31.23 (29.43–33.14)	42.09 (36.00–49.21)	6000	1.35 (1.14–1.59)

[a] Numbers in parentheses give the 95% confidence limits. No protection at the indicated lethal dose is denoted by the > symbol. TI is the ratio TD_{50}/MES ED_{50}. All compounds were tested as HCl salts except 4, which was a methiodide. The data for PCP and 1 are taken from ref 8. ND, not determined.

increase the TI. The poor in vivo activity of the quaternary salt **4** may be a consequence of its inability to penetrate the blood–brain barrier. However, **4** also has a very low affinity for PCP binding sites.

The addition of a methyl substituent to the cyclohexyl ring (compounds **5–12**) had a moderate influence on the behavioral potencies and on the resulting TI values. Of the cyclohexane ring methylated analogues, **11** with phenyl and methyl in the trans configuration showed a considerably improved TI (3.44) relative to the parent compound PCA (TI = 2.31). It is instructive to compare the isomeric compounds **5** and **10**. While the two analogues have identical ED_{50} values for protection against MES seizures, they show markedly different potencies in the motor toxicity test, clearly demonstrating that the anticonvulsant activity of this class of compounds can be dissociated from motor toxicity.

The effect of homologous extensions of benzylamine **1** to the phenethylamine derivatives can be seen in the two analogues **16** and **17**; both compounds exhibited lower efficacy.

Compounds **13–15** and **18–30** were synthesized to explore the effect of various substitutions on the phenyl ring. These analogues examine the effect of group size and substituents with different electron-donating versus electron-withdrawing ability at each position on the ring. The most interesting phenyl-substituted PCA analogues were seen within the ortho-substituted derivatives. With the exception of the fluorinated derivatives **24** and **27**, these compounds (**13**, **18**, **21**) had greater potencies in the MES test than did the corresponding meta and para analogues. In particular, *o*-methyl derivative **13** displays one of the lowest ED_{50} values within the series for protection against MES-induced seizures, although it also has a relatively higher potency for inducing motor toxicity. *o*-Methoxy compound **18** showed a modest increase in the TI compared with that of **1**. The effect of an *o*-methyl group in increasing anticonvulsant efficacy has some precedence. In examining the anticonvulsant action of a series of 4-amino-*N*-phenylbenzamides, Clark et al.[17] found that the mono- and di-*o*-methyl derivatives showed the best overall therapeutic ratios for the series.

Compounds **31–36** represent analogues of PCA in which the phenyl group is replaced by an alternate structure. While changing the phenyl ring to butyl (**34**) or to an aromatic system (**31–33**, **35**) other than thienyl (**36**) raised the effective toxic dose and diminished the affinity for PCP binding sites in comparison with **1**, such changes were also detrimental to the anticonvulsant activity. All of these compounds showed lower TIs than the parent compound **1**. Compound **36**, the primary amine derivative of the potent PCP analogue 1-[1-(2-thienyl)cyclohexyl]piperidine (TCP),[19] showed an exceptionally low TD_{50} for motor

(17) Clark, C. R.; Sansom, R. T.; Lin, C.-M.; Norris, G. N. *J. Med. Chem.* **1985**, *28*, 1259.

(18) Zukin, S. R.; Zukin, R. S. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 5372. Vignon, J.; Chicheportiche, R.; Chicheportiche, M.; Kamenka, J. M.; Geneste, P.; Lazdunski, M. *Brain Res.* **1983**, *280*, 194.

toxicity in accord with its strong affinity for PCP binding sites.

Interesting results were obtained through modification of the cycloalkyl ring size. Contraction to a cyclopentyl system (37) or expansion to a cycloheptyl system (38) led to a decrease in potency in the MES test. A corresponding decrease in the motor toxicity resulted in similar (38) and improved (37) TI values compared to that of 1. Compound 39, which represents a noncyclic analogue of 37, did not offer encouraging results; the conformationally restricted compound 37 was more potent in protecting against MES-induced seizures and had a higher TI.

Leander et al.[2] have recently shown a high correlation between the ability of certain PCP-related compounds to block *N*-methyl-D-aspartate-induced lethality in mice (which is related to their binding affinities for PCP acceptor sites) and protection against MES seizures. They therefore concluded that the anticonvulsant effects of the compounds occurred as a result of their interaction with PCP sites. To determine whether this conclusion applies to the novel PCA analogues described herein, we studied the relationship between the potencies of the analogues in the MES seizure and motor toxicity tests and their affinities for PCP binding sites. There was a moderate correlation between the effective doses in the two in vivo tests and the binding data (no attempt was made to correct for differences in bioavailability or blood–brain barrier penetration among the analogues). The Spearman rank correlation coefficient comparing the K_i values in the binding assay and the MES ED_{50} values was 0.39 (P = 0.018) whereas a similar comparison with the motor toxicity TD_{50} values gave a correlation coefficient of 0.48 (P = 0.004). Thus both in vivo measures are to some degree correlated with binding affinity although the correlation is greater for the motor toxicity values. These observations suggest that anticonvulsant activity and possibly also the motor toxicity for this class of compounds are dependent upon distinct pharmacophores from that which determine PCP receptor binding affinity.

Conclusions

A series of 1-phenylcyclohexylamine (1) analogues were tested for their abilities to protect against MES-induced seizures and to produce motor impairment in mice. The results reported herein indicate that subtle changes in the structure of 1 can afford modest improvement in the ratio of potencies (TI) in the motor toxicity and MES tests. The most favorable overall improvements were obtained with (i) certain stereochemically orientated cyclohexane ring methyl substituents as in 11, (ii) ortho substituents on the phenyl ring as in 18, and (iii) through contraction of the cyclohexane ring as in 37. Both in vivo measures of activity showed a moderate correlation with the affinities for the PCP binding site, but the correlation was greater for the motor toxicity values. These results demonstrate that anticonvulsant activity of this class of compounds may be dependent upon an interaction with a site distinct from the PCP acceptor.

Experimental Section

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Gas chromatographic analysis was performed on a Hewlett-Packard 5880 instrument using a flame-ionization detector. ^1H NMR spectra were recorded on a Varian XL-300 instrument. Chemical shifts are in δ (ppm) downfield from the tetramethylsilane signal. Mass spectra were obtained with a Finnigan 1015D instrument. Infrared spectra were obtained with a Beckman 4230 instrument. Where elemental analyses are indicated only by symbols of the elements, results obtained were within 0.4% of the theoretical values. Hydrochloride salts were prepared by dissolving the free base in ethyl acetate followed by addition of a solution of HCl(g) in ethyl acetate. Yields and melting points are presented in Table II.

Table II. Molecular Formulae, Yields, and Melting Points of 1-Phenylcyclohexylamine Analogues

no.	molcular formula	% yield[a]	mp, °C
1	$C_{12}H_{17}N\cdot HCl$	60	244–245
2	$C_{13}H_{19}N\cdot HCl$	43	185–186
3	$C_{14}H_{21}N\cdot HCl$	55	140–141
4	$C_{15}H_{24}N\cdot I$	32	240–245 dec
5	$C_{13}H_{19}N\cdot HCl$	55 (5 + 6)	235–237
6	$C_{13}H_{19}N\cdot HCl$	55	271–274
7	$C_{13}H_{19}N\cdot HCl$	46 (7 + 10)	171–173
8	$C_{13}H_{19}N\cdot HCl$	68 (8 + 9)	220–221
9	$C_{13}H_{19}N\cdot HCl$	68	203–204
10	$C_{13}H_{19}N\cdot HCl$	46	201
11	$C_{13}H_{19}N\cdot HCl$	63 (11 + 12)	280–284 dec
12	$C_{13}H_{19}N\cdot HCl$	63	194–195
13	$C_{13}H_{19}N\cdot HCl$	37	186–188 dec
14	$C_{13}H_{19}N\cdot HCl$	79	209–210
15	$C_{13}H_{19}N\cdot HCl$	61	261–262
16	$C_{13}H_{19}N\cdot HCl$	84	234–235
17	$C_{13}H_{19}N\cdot HCl$	6	169–171
18	$C_{13}H_{19}NO\cdot HCl$	31	212–215
19	$C_{13}H_{19}NO\cdot HCl$	52	195–196
20	$C_{13}H_{19}NO\cdot HCl$	34	233–234
21	$C_{13}H_{19}NS\cdot HCl$	20	181–184
22	$C_{13}H_{19}NS\cdot HCl$	71	177–179
23	$C_{13}H_{19}NS\cdot HCl$	58	264–265
24	$C_{12}H_{16}NF\cdot HCl$	10	267–268
25	$C_{12}H_{16}NF\cdot HCl$	41	231
26	$C_{12}H_{16}NF\cdot HCl$	70	256–257
27	$C_{13}H_{16}NF_3\cdot HCl$	52	274–275
28	$C_{13}H_{16}NF_3\cdot HCl$	48	255–258 dec
29	$C_{12}H_{17}NO\cdot HCl$	52	210–211
30	$C_{19}H_{23}NO\cdot HCl$	58	173–175
31	$C_{16}H_{19}N\cdot HCl$	34	264–265
32	$C_{20}H_{21}N\cdot HCl$	6	234–235
33	$C_{12}H_{12}NF_5\cdot HCl$	4	228
34	$C_{10}H_{21}N\cdot HCl$	1	216–218
35	$C_{18}H_{21}N\cdot HCl$	36	279–281
36	$C_{10}H_{15}NS\cdot HCl$	62	217–218
37	$C_{11}H_{15}N\cdot HCl$	59	221–222
38	$C_{13}H_{19}N\cdot HCl$	75	193
39	$C_{11}H_{17}N\cdot HCl$	12	258–259

[a] Yields are based upon starting ketone, except 16 which is based upon 1-phenyl-1-carboxycyclohexane. All salts were recrystallized from ethyl acetate except for 4 (methiodide) which was recrystallized from 2-propanol.

Representative 1-Arylcycloalkylamine Synthesis. 1-(2-Methylphenyl)cyclohexylamine (13). A solution of 2-methylphenylmagnesium bromide was prepared by the dropwise addition of 2-bromotoluene (6.0 g, 35 mmol) to a vigorously stirred mixture of magnesium turnings (5 g, 205 mmol) in 40 mL of dry tetrahydrofuran (THF). After 2 h, a solution of cyclohexanone (3 g, 31 mmol) in 5 mL of THF was added dropwise. After stirring for 20 min, the reaction mixture was carefully decanted from the excess magnesium into a separatory funnel containing 40 mL of 2.5 N HCl solution and 40 mL of diethyl ether. The ethereal layer was removed, dried ($MgSO_4$), and concentrated to give the crude alcohol (4.6 g, 78%) as a pale yellow oil. The alcohol was dissolved in 50 mL of chloroform, and sodium azide (4.7 g, 73 mmol) was added and the mixture was stirred at 5 °C. To this slurry was added trifluoroacetic acid (13.8 g, 121 mmol) dropwise over 5 min. The reaction was stirred and allowed to come to room temperature overnight. The mixture was poured into a separatory funnel containing 200 mL of water and 200 mL of diethyl ether. The aqueous layer was discarded. The ethereal layer was washed with a further 200 mL of water followed by washing with 200 mL of a 1.0 N NH_4OH solution. The organic layer was dried ($MgSO_4$) and concentrated to give the tertiary azide (2.3 g, 42%) as an oil. The azide was dissolved in 20 mL of diethyl ether, which was then added dropwise over 20 min to a solution of lithium aluminum

(19) Kalir, A.; Edery, H.; Pelah, Z.; Balderman, D.; Porath, G. *J. Med. Chem.* **1969**, *12*, 473.

hydride in diethyl ether (1.0 N, 30 mL). The resulting solution was stirred for 3 h after which the reaction was quenched by the addition of 3 mL of 1.0 NaOH solution. The reaction was filtered through Celite and extracted with 40 mL of a 1.0 N HCl solution. The ethereal layer was discarded. The acidic aqueous fraction was added to a separatory funnel containing 30 mL of diethyl ether and 50 mL of a 1.0 N NH_4OH solution. The ethereal layer was dried ($MgSO_4$) and concentrated to give 1-(2-methylphenyl)-cyclohexylamine (1.8 g, 93%) as a clear oil. The hydrochloride salt was recrystallized from ethyl acetate: mp 186–188 °C dec; ^1H NMR ($CDCl_3$) δ 7.58 (d, J = 6 Hz, 1 H), 7.2–7.4 (m, 3 H), 2.61 (s, 3 H), 2.1 (m, 2 H), 1.2–2.0 (m, 8 H); mass spectrum (CI, NH_3) m/z 190 (M + 1); IR (neat) 3301, 3009, 2905, 1623, 1605, 1460 cm^{-1}. Anal. ($C_{13}H_{20}NCl$) C, H, N.

***trans*-2-Methyl-1-phenylcyclohexylamine (5) and *cis*-2-Methyl-1-phenylcyclohexylamine (6).** A mixture of racemic *cis*- and *trans*-2-methyl-1-phenylcyclohexylazides (31.1 g) [generated from (±)-2-methylcyclohexanone as described above] was dissolved in dry ether (200 mL) and the solution was cooled to 0 °C. To this stirred solution was added (portionwise) lithium aluminum hydride (10.0 g). After the addition was complete, the reaction mixture was refluxed under a nitrogen atmosphere for 3 h, cooled to −10 °C, and treated with ethyl acetate (90 mL). The solution was then poured into 20% aqueous HCl (300 mL) and the ether layer was decanted. The aqueous phase was washed with 2 × 100 mL of ether and the combined ether phase was discarded. Crushed ice (200 g) was added to the aqueous layer followed by enough aqueous ammonia to render the solution basic. Extraction with 3 × 100 mL of $CHCl_3$ followed by drying of the organic layer with Na_2SO_4 and evaporation of the solvent afforded 15.9 g (63% overall yield from 2-methylcyclohexanone) of a 1:1.67 ratio (GC: 110 °C) of **5** and **6**, respectively. The minor isomer **5** had a higher R_f by TLC (solvent system 0.5:4.5:95 concentrated aqueous ammonia–methanol–$CHCl_3$) than **6**. Compounds **5** and **6** were separated by column chromatography on silica gel eluting with 0.25:2.25:97.5 concentrated aqueous ammonia–methanol–$CHCl_3$ to yield 5.82 g (23% overall) of **5** and 9.91 g (39% overall) of **6** as oily bases. Treatment of solutions of **5** and **6** in ethyl acetate with excess HCl gas dissolved in ethyl acetate afforded **5**·HCl and **6**·HCl.

1-Amino-2-phenyl-2,2-pentamethyleneethane (16). 1-Phenylcyclohexanecarboxylic acid (1.0 g, 4.9 mmol) was dissolved in thionyl chloride (5 mL) containing 0.1 mL of dimethylformamide. After 2 h, the excess thionyl chloride was removed in vacuo. The resulting crystalline solid was dissolved in 10 mL of 2-propanol which had been saturated with ammonia gas. After 20 min the reaction mixture was concentrated, dissolved in diethyl ether (30 mL), and treated with lithium aluminum hydride solution (1.0 N, 7 mL). After stirring for 4 h at room temperature the reaction was quenched by the addition of 2 mL of 1.0 N NaOH solution. The reaction mixture was filtered through Celite and extracted with 1.0 N HCl solution (10 mL). The acidic fraction was poured into a separatory funnel containing 20 mL of diethyl ether and 20 mL of a 1.0 N NH_4OH solution. The ethereal layer was dried ($MgSO_4$) and concentrated to give 0.70 g (76%) of the primary amine as a clear oil. The hydrochloride salt was recrystallized from ethyl acetate: mp 234–235 °C; ^1H NMR ($CDCl_3$) δ 7.0–7.4 (m, 5 H), 2.68 (s, 2 H), 1.90–2.30 (m, 4 H), 1.4–1.8 (m, 6 H); mass spectrum (CI, NH_3) m/z 190 (M + 1); IR (neat) 3365, 3290, 2929, 2857, 1602, 1517, 1455 cm^{-1}. Anal. ($C_{13}H_{20}NCl$) C, H, N.

***N*-Methyl-1-phenylcyclohexylamine (2).** The formyl derivative of 1 (1.7 g, 8.4 mmol) was dissolved in 14 mL of tetrahydrofuran and treated with 2.4 equiv (0.77 g) of lithium aluminum hydride in one portion. The reaction was stirred for 2 h before quenching with 100 mL of a 1.0 N HCl solution. The reaction mixture was partitioned between ether (100 mL) and water (100 mL). The ethereal layer was discarded and the aqueous layer was neutralized with a 1.0 N NH_4OH solution. Extraction of the neutralized mixture with ether (2 × 100 mL) followed by drying of the organic fraction and concentration provided the crude monomethylamine (**2**, 1.44 g, 91%). The product was purified by repeated recrystallization of the hydrochloride salt from ethyl acetate [mp 185–186 °C (lit.[19] mp 187–189 °C)].

***N,N*-Dimethyl-1-phenylcyclohexylamine (3).** To a solution of 1 (520 mg, 3 mmol) in acetonitrile (10 mL) at 0 °C was added 2 mL of 37% formalin solution. Sodium cyanoborohydride (570 mg, 9 mmol) was added in one portion and the reaction was stirred for 30 min. The solution was brought to pH 6.0 by the addition of a 2.5 N acetic acid solution. The reaction was stirred for 45 min. The resulting mixture was then poured into a separatory funnel containing diethyl ether (10 mL) and a 1.0 N NH_4OH solution (20 mL). The ethereal layer was dried ($MgSO_4$) and concentrated to give the crude amine. The product was purified by recrystallization of the hydrochloride salt from ethyl acetate: mp 140–141 °C; ^1H NMR ($CDCl_3$) δ 7.35–7.40 (m, 3 H), 7.30 (m, 2 H), 2.38 (s, 6 H), 2.30 (m, 2 H), 1.40–1.70 (m, 8 H); IR (neat) 3070, 2910, 1552, 1458 cm^{-1}.

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Registry No. 1, 1934-71-0; 1 free base, 2201-24-3; 1 formyl derivative, 17380-56-2; **2**, 2283-62-7; **2** free base, 2201-16-3; **3**, 1934-69-6; **3** free base, 2201-17-4; **4**, 22904-94-5; **5**, 125801-95-8; **5** free base, 125801-96-9; **6**, 125801-97-0; **6** free base, 125801-98-1; **7**, 125874-62-6; **7** free base, 114760-71-3; **8**, 125874-63-7; **8** free base, 114760-69-9; **9**, 125874-64-8; **9** free base, 114760-70-2; **10**, 125874-65-9; **10** free base, 114760-72-4; 11, 125801-99-2; 11 free base, 55040-01-2; **12**, 125802-00-8; **12** free base, 55040-02-3; **13**, 125802-01-9; **13** free base, 118560-04-6; **13** crude alcohol derivative, 6957-09-1; **13** tertiary azide derivative, 125802-02-0; **14**, 107417-36-7; 14 free base, 2201-28-7; **15**, 125802-03-1; **15** free base, 17797-15-8; **16**, 17380-59-5; **16** free base, 17380-54-0; **17**, 20937-30-8; **17** free base, 19165-94-7; **18**, 125802-04-2; **18** free base, 125802-05-3; **19**, 125802-06-4; **19** free base, 125802-07-5; **20**, 125802-08-6; **20** free base, 125802-09-7; **21** free base, 125802-09-7; **21** free base, 125802-11-1; **22**, 125802-12-2; **22** free base, 125802-13-3; **23**, 125802-14-4; **23** free base, 125802-15-5; **24**, 125802-16-6; **24** free base, 125802-17-7; **25**, 125802-18-8; **25** free base, 125827-86-3; **26**, 125802-19-9; **26** free base, 17380-80-2; **27**, 125802-20-2; **27** free base, 125802-21-3; **28**, 125802-22-4; **28** free base, 125802-23-5; **29**, 125802-24-6; **29** free base, 125802-25-7; **30**, 125802-26-8; **30** free base, 125802-27-9; **31**, 125802-28-0; **31** free base, 125802-29-1; **32**, 125802-30-4; **32** free base, 125802-31-5; **33**, 125802-32-6; **33** free base, 125802-33-7; **34**, 125802-34-8; **34** free base, 2626-61-1; **35**, 125802-35-9; **35** free base, 125802-36-0; **36**, 100132-99-8; **36** free base, 100133-00-4; **37**, 5296-90-2; **37** free base, 17380-74-4; **38**, 125802-37-1; **38** free base, 59397-23-8; **39**, 104177-96-0; **39** free base, 30568-46-8; $H_3CCH_2COCH_2CH_3$, 96-22-0; PhBu, 108-86-1; *m*-MeC_6H_4Bu, 591-17-3; *p*-MeC_6H_4Br, 106-38-7; $PhCH_2Br$, 100-39-0; *o*-$MeOC_6H_4Br$, 578-57-4; *m*-$MeOC_6H_4Br$, 2398-37-0; *p*-$MeOC_6H_4Br$, 104-92-7; *o*-$MeSC_6H_4Br$, 19614-16-5; *p*-$MeSC_6H_4Br$, 104-95-0; *o*-FC_6H_4Br, 1072-85-1; *m*-FC_6H_4Br, 1073-06-9; *p*-FC_6H_4Br, 460-00-4; *o*-$F_3CC_6H_4Br$, 392-83-6; *m*-$F_3CC_6H_4Br$, 401-78-5; *m*-HOC_6H_4Br, 591-20-8; *m*-$BrC_6H_4OCH_2Ph$, 53087-13-1; BuBr, 109-65-9; *p*-BrC_6H_4Ph, 92-66-0; 2-bromotoluene, 95-46-5; cyclohexanone, 108-94-1; (±)-*trans*-2-methyl-1-phenylcyclohexyl azide, 125802-38-2; (±)-2-methylcyclohexanone, 24965-84-2; 1-phenylcyclohexanecarboxylic acid, 1135-67-7; (±)-*cis*-2-methyl-1-phenylcyclohexyl azide, 125802-39-3; cyclopentanone, 120-92-3; cycloheptanone, 502-42-1; 9-bromophenanthrene, 573-17-1; 1,2,3,4,5-pentafluorobromobenzene, 344-04-7; 2-bromonaphthalene, 580-13-2; 2-bromothiophene, 1003-09-4.