Synthesis and Anticonvulsant Activities of *N*-Benzyl-2-acetamidopropionamide Derivatives

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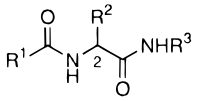
Received November 29, 1995[⊗]

Studies have demonstrated that 2-substituted *N*-benzyl-2-acetamidoacetamides (**2**) are potent anticonvulsants. A recent investigation has led to the hypothesis that an important structural feature in **2** for maximal anticonvulsant activity is the placement of a small, substituted heteroatom moiety one atom from the C(2) site. This paper validates this hypothesis. Twelve derivatives of *N*-benzyl-2-acetamidopropionamide have been prepared in which six different heteroatom substituents (chloro, bromo, iodo, oxygen, nitrogen, and sulfur) were incorporated at the C(3) site. Highly potent activities were observed for the two oxygen-substituted derivatives, *N*-benzyl-2-acetamido-3-methoxypropionamide (**18**) and *N*-benzyl-2-acetamido-3-ethoxypropionamide (**19**). The ED_{50} values in mice following intraperitoneal (ip) dosing for the maximal electroschock-induced seizure test for **18** and **19** were 8.3 and 17.3 mg/kg, respectively. These values compared favorably to the ED_{50} value found for phenytoin (ED_{50} = 6.5 mg/kg). Comparable activities were observed for **18** and **19** upon oral (po) administration to rats (**18**, ED_{50} = 3.9 mg/kg; **19**, ED_{50} = 19 mg/kg; phenytoin, ED_{50} = 23 mg/kg). Evaluation of the individual stereoisomers for **18** demonstrated that the principal anticonvulsant activity resided in the (*R*)-stereoisomer. The ED_{50} value for (*R*)-**18** was 4.5 mg/kg, and the ED_{50} for (*S*)-**18** exceeded 100 mg/kg. This difference in activity for the two stereochemical isomers surpassed comparable values for other members within this class of compounds. The protective indices (PI = TD_{50}/ED_{50}) (where TD_{50} represents a neurotoxic dose impairing rotorod performance) for (*R*)-**18** in mice (ip) and in rats (po) were 6.0 and >130, respectively.

Introduction

Over the past 10 years we have reported on the anticonvulsant properties of functionalized amino acid derivatives that conform to the general structure **1**.[1−9]



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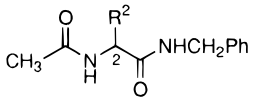

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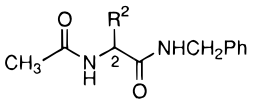
Systematic evaluation of over 100 derivatives has led to our proposal that stringent steric and electronic requirements exist for this novel class of compounds for protection against maximal electroshock (MES)-induced seizure. Our structure−activity studies indicated two important trends. First, in cases where an aromatic moiety was positioned at the C(2) site improved activity was noted for those compounds that contained a small, electron-rich R^2 substituent.[5,7] Second, enhanced protection against MES-induced seizures was observed for C(2) cyclic and acyclic R^2 groups that contained a *substituted heteroatom* one atom from the C(2) site.[6,7,9] Consistent with these contentions were the relative activities (mice, ip) of **3** (ED_{50} = 10 mg/kg) versus the 2-tetrahydrofuran-2-yl diastereomers (**7**) (ED_{50} = 52−90 mg/kg),[7] the relative potencies of 2-furan-2-yl (**3**) (ED_{50} = 10 mg/kg), 2-pyrrol-2-yl (**4**) (ED_{50} = 16 mg/kg), and 2-thien-2-yl (**5**) (ED_{50} = 45 mg/kg) *N*-benzyl-2-acetamidoacetamide derivatives,[5] the decrease in activity of the 2-thien-3-yl (**6**) (ED_{50} = 88 mg/kg) adduct versus the isomeric 2-thien-2-yl (**5**) (ED_{50} = 45 mg/kg) compound, and the dramatic increase in activity for the *O*-methylhydroxylamine (**9**) (ED_{50} = 6.2 mg/kg) and *O*,*N*-dimethylhydroxylamine (**10**) (ED_{50} = 6.7 mg/kg) derivatives versus the C(2) hydroxylamine compound (**8**) ($ED_{50} \approx$ 100 mg/kg).[6] Another critical aspect of the structure−activity profile observed for *N*-benzyl-2-acetamidoacetamide derivatives (**2**) was the discovery that in three different cases the (*R*)-stereoisomer was approximately 10 times more potent in the control of MES seizures than the (*S*)-enantiomer.[1,4,5,7] These differences in activities were the greatest eudismic ratio[10] reported to date for MES-selective anticonvulsant agents.



3 R^2 = 

7 R^2 = 

11 R^2 =

4 R^2 = 

8 R^2 = N(H)OH

12 R^2 =

5 R^2 = 

9 R^2 = N(H)OCH_3

13 R^2 =

6 R^2 = 

10 R^2 = N(CH_3)OCH_3

Recently, we found that the three C(2) *electron-deficient* heteroaromatic compounds (**11**−**13**) possessed

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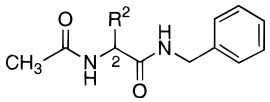
[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1996.

0022-2623/96/1839-1907$12.00/0 © 1996 American Chemical Society

Table 1. Physical and Pharmacological Data in Mice for *N*-Benzyl-2-acetamidopropionamides[a]



no.	R^2	mp[b]	MES[c] ED_{50}	TD_{50}[d]	PI[e]
14[f]	CH_3	138−139	77 [1] (67−89)	450 [0.5] (420−500)	5.9
15	CH_2Cl	143−144	∼100	>100, <300	
16	CH_2Br	123−125	>30, <100	>100, <300	
17	CH_2I	169−170	>30, <100	∼300	
18	CH_2OCH_3	121−122	8.3 [0.5] (7.9−9.8)	43 [0.25] (38−47)	5.2
19	$CH_2OCH_2CH_3$	113−114	17 [0.25] (15−19)	78 [0.25] (64−90)	4.6
20	$CH_2OCH_2CH{=}CH_2$	76−77	>30, <100	>30, <100	
21	CH_2NH_2	119−120	>100	>100	
22	$CH_2N(H)CH_3$	107−108	>100, <300	>100, <300	
23	$CH_2N(H)CH_2CH_3$	90−91	>100	∼100	
24	$CH_2N(CH_3)_2$	125−126	>30, <100	>300	
25	CH_2-morpholino	147−148	>100, <300	>300	
26	CH_2SCH_3	142−143	>30, <100	>100, <300	
27	CH_2OH	201−203	>100, <300	<300[g]	
8	N(H)OH	144−146 dec	∼100 [1]	—[h]	
9	$N(H)OCH_3$	95−97	6.2 [0.5] (5.4−7.2)	46 [0.5][g] (38−56)	7.4
10	$N(CH_3)OCH_3$	165−167	6.7 [0.5] (5.7−7.7)	51 [0.5][g] (40−60)	7.6
	phenytoin[i]		6.5 [2] (5.7−7.2)	43 [0.5] (36−48)	6.6
	phenobarbital[j]		22 [1] (15−23)	69 [0.5] (63−73)	3.1
	valproate[i]		290 [0.25] (240−360)	480 [0.25] (410−570)	1.7

[a] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in mg/kg. Numbers in parentheses are 95% confidence intervals. A dose−response curve was generated for all compounds that displayed sufficient activity. The dose−effect data for these compounds was obtained at the "time of peak effect" (indicated in hours in the brackets). The compounds were tested through the auspices of the National Institute of Neurological and Communicative Disorders and Stroke at the National Institutes of Health, except for compounds **8**−**10** and **27** which were tested at the Eli Lilly Company (Indianapolis, IN). [b] Melting points (°C) are uncorrected. [c] MES = maximal electroshock seizure test. [d] Neurologic toxicity determined using the rotorod test unless otherwise noted. [e] PI = protective index (TD_{50}/ED_{50}). [f] Reference 3. [g] TD_{50} = neurologic toxicity determined from horizontal screen test (ref 22). [h] Test not conducted. [i] Reference 11a. [j] Reference 11b.

outstanding anticonvulsant activities.[9] This discovery ran counter to our original projections of the beneficial properties that accompany incorporation of an electron-rich aromatic substituent at this site and challenged the validity of this aspect of our structure−activity relationship. In this paper we provide additional documentation that the key structural feature for maximal anticonvulsant activity is the placement of a small, substituted heteroatom moiety one atom from the C(2) site. Highlighting this report is the remarkable activity of *N*-benzyl-2-acetamido-3-methoxypropionamide (**18**) (Table 1). In agreement with previous findings,[1,4,5,7] we demonstrate that the activity of this racemate resided preferentially in the (*R*)-stereoisomer.

Selection of Compounds

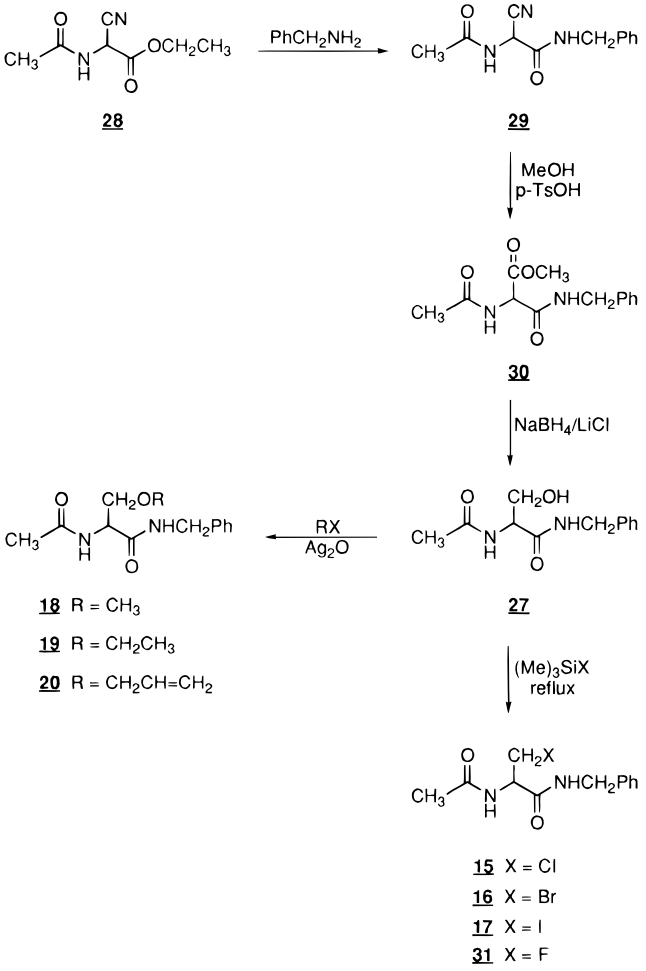
The compounds examined in this study are derivatives of *N*-benzyl-2-acetamidopropionamide[2] (**14**) in which a heteroatom substituent has been attached at the C(3) position (Table 1). Groups placed at this site included halogen (**15**−**17**), oxygen (**18**−**20**), nitrogen (**21**−**25**), and sulfur (**26**) moieties. In all cases, the initially prepared compounds were racemates. Serving as key reference compounds were the methyl (alanyl)[2] (**14**), hydroxymethyl (serinyl) (**27**), and the three C(2)-hydroxylamine[6] (**8**−**10**) derivatives along with the proven antiepileptic agents phenytoin,[11a] phenobarbital,[11b] and valproate.[11a]

Chemistry

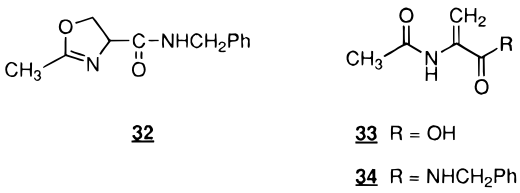
The preferred synthetic route developed for the halogen (**15**−**17**) and the oxygen-substituted (**18**−**20**) adducts is provided in Scheme 1. Beginning with commercially available ethyl acetamidocyanoacetate (**28**), addition of benzylamine gave **29**,[12] which upon dissolution in acidic methanol furnished methyl ester **30**.[13] Reduction of **30** with $NaBH_4$ and LiCl[14] produced **27** in 58% overall yield from **28**. Treatment of serine derivative **27** with the appropriate halotrimethylsilanes[15] afforded **15**−**17** in moderate yields (20−74%).[16] Attempts to prepare the corresponding fluoro derivative (**31**) with fluorotrimethylsilane were not successful and gave **32**. Formation of **15** from **27** with chlorotrimethylsilane was surprising in light of previous literature results.[15,17] The generality and utility of this procedure for the synthesis of β-halo amino acid derivatives for peptide synthesis has been briefly evaluated.[16] Synthesis of ethers **18**−**20** was accomplished by coupling **27** with the appropriate alkyl iodide in the presence of Ag_2O.

2-Acetamidoacrylic acid (**33**) served as the starting material for the remaining compounds in our initial series. Compound **33** was first converted to *N*-benzylamide **34** and then treated with both amine and sulfur nucleophiles in protic solvents to give **21**−**26**.[18,19] The utility of *N*-benzyl-2-acetamido-3-chloropropionamide

Scheme 1. Preparation of *N*-Benzyl-2-acetamidopropionamide Derivatives



(**15**) was also briefly examined for the synthesis of *N*-benzyl-3-substituted-2-acetamidopropionamide derivatives. Treatment of **15** with KOH or NaH provided the elimination product **34**, while addition of sodium methanethiolate to **15** in MeOH gave the substitution product **26** in 89% yield. Information concerning the mechanism of this transformation was obtained by rerunning this reaction in CD_3OD. Under these conditions the C(2) methine site was fully deuterated (NMR analysis, data not shown). This finding coupled with the observation that only 15% C(2)H → C(2)D exchange occurred upon dissolution of **26** in basic CH_3OD indicated that conversion of **15** to **26** proceeded through **34**, rather than by direct S_N2 displacement of the chloride group in **15**.



The pharmacological activity observed for *N*-benzyl-2-acetamido-3-methoxypropionamide (**18**) warranted our preparation of the individual (*R*)- and (*S*)-enantiomers (Table 2). The original preparative route developed took advantage of the commercial availability of both D- and L-serine derivatives (Scheme 2). Treatment of the hydrochloride salts of the optically pure serine methyl esters **36** with benzylamine gave benzylamide **37**, which was then acylated with acetic anhydride to provide **27**. Three criteria were used to assess the enantiopurity of **27**. These were melting point, optical rotation, and the detection of only a single acetyl methyl signal in the ^1H NMR spectrum of **27** upon addition of a saturated solution of (*R*)-(−)-mandelic acid.[20] NMR analysis indicated that conversion of **36** to **27** proceeded to give an approximate 2:1 mixture of the enantiomers. Accordingly, **27** was repeatedly recrystallized until optically pure and then alkylated with MeI and Ag_2O to give the desired ether **18** without racemization.

Table 2. Pharmacological Evaluation of Functionalized (*R,S*)-*N*-Benzyl-2-acetamidopropionamide Derivatives upon Oral Administration to Rats[a]

no.	MES,[b] ED_{50}	Tox,[c] TD_{50}	PI[d]
14	48 [1] (32−72)	−[e]	>21
18	3.8 [2] (2.9−5.5)	390 [1] (320−520)	100
19	19 [0.5] (14−24)	−[f]	>26
phenytoin[g]	23 [2] (21−25)	−[f]	>22
phenobarbital[h]	9.1 [5] (7.6−12)	61 [0.5] (44−96)	6.7
valproate[g]	400 [0.5] (330−440)	860 [0.5] (720−1100)	2.2

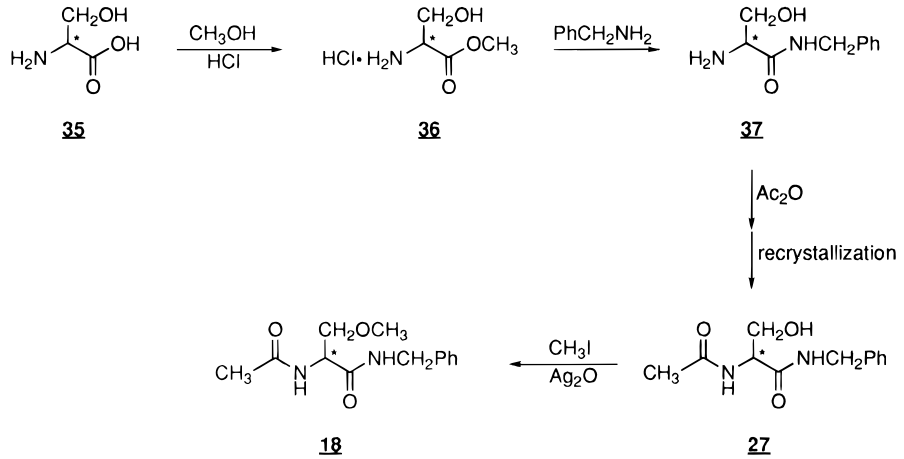
[a] ED_{50} and TD_{50} values are in mg/kg. Numbers in parentheses are 95% confidence intervals. The dose effect data was obtained at the "time of peak effect" (indicated in hours in the brackets). [b] MES = maximal electroshock seizure test. [c] Tox = neurologic toxicity (the rotorod test). [d] PI = protective index (TD_{50}/MES ED_{50}). [e] No ataxia observed up to 1000 mg/kg. [f] No attaxia observed up to 500 mg/kg. [g] Reference 11a. [h] Reference 11b.

The pronounced anticonvulsant activity observed for (*R*)-**18** led us to devise an alternative, more expeditious synthetic route for this compound (Scheme 3). Beginning with D-serine ((*R*)-**35**), treatment with acetic anhydride in acetic acid gave the *N*-acylated derivative **38**, which was converted to *N*-benzylamide (*R*)-**27** using the mixed anhydride coupling procedure.[21] NMR and optical measurements indicated that both steps proceeded without racemization. Alkylation of (*R*)-**27** with MeI and Ag_2O gave (*R*)-*N*-benzyl-2-acetamido-3-methoxypropionamide ((*R*)-**18**) in 30% overall yield. The success of this protocol permitted the rapid synthesis of derivatives of (*R*)-**18** in which the substitution pattern on the benzylamide group was altered (Table 3). Accordingly, treatment of (*R*)-**38** with 3-fluorobenzylamine and 4-fluorobenzylamine provided (*R*)-**39** and (*R*)-**40**, respectively, which were then converted to the methyl ethers (*R*)-**41** and (*R*)-**42**, respectively, with MeI and Ag_2O.

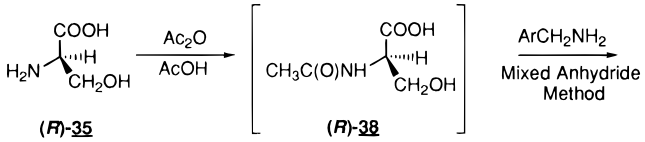
Pharmacological Evaluation

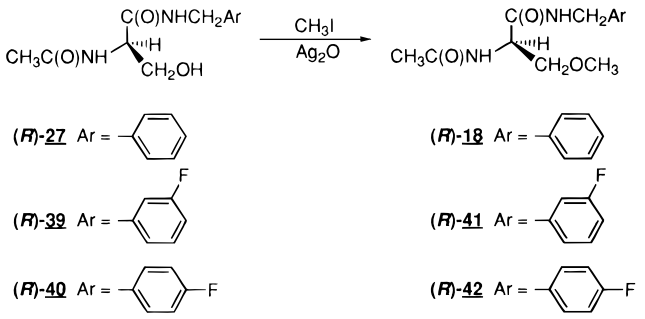
The anticonvulsant activities for 2-acetamido-*N*-benzylpropionamide derivatives **15**−**26** were determined using the procedure described by Kupferberg,[22] and these results compared to **8**−**10**,[6] **14**,[2] **27**, and the clinically proven antiepileptic agents phenytoin,[11a] phenobarbital,[11b] and valproate.[11a] All compounds were administered intraperitoneally (ip) to mice. Table 1 lists the results obtained from the initial mouse identification and quantitation screening studies. They include the ED_{50} values for racemates **15**−**26** that are protective

Scheme 2. Preparation of Enantiopure **18**



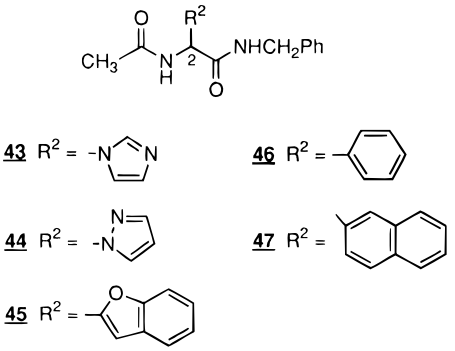
Scheme 3. Improved Procedure for the Preparation of Enantiopure (*R*)-**18** and Related Compounds





in blocking hind limb extension induced in the MES test. Also contained in Table 1 are the median doses for neurological impairment (TD_{50}) using either the rotorod[23] or the horizontal screen[24] (HS) test. In most cases, the TD_{50}s were only determined for those compounds that had good activity in the MES test. The protective index (PI = TD_{50}/ED_{50}) for these adducts, where appropriate, is also shown in Table 1.

Inspection of the composite data in Table 1 provided strong support for our current structure−activity relationship for this class of anticonvulsants. Highlighted were the beneficial value accrued by the placement of a heteroatom one atom from the C(2) site, the need for the heteroatom to be substituted, and the stringent steric requirements that limit the size of the C(2) substituent. Six different heteroatoms (O, N, S, Cl, Br, and I) were incorporated in *N*-benzyl-2-acetamidopropionamide (**14**). Of these, the oxygen-substituted derivatives **18**−**20** proved to be the most effective for the control of MES-induced seizures. The anticonvulsant activities of both **18** (ED_{50} = 8.3 mg/kg) and **19** (ED_{50} = 17 mg/kg) exceeded that of **14** (ED_{50} = 77 mg/kg). Moreover, the MES ED_{50} values and protective indices of racemic **18** and **19** were comparable to those reported for phenytoin[11a] (ED_{50} = 6.5 mg/kg) and phenobarbital[11b] (ED_{50} = 22 mg/kg), respectively. A similar trend with respect to heteroatom substituent was observed for the C(2) aromatic compounds **3** (ED_{50} = 10 mg/kg), **4** (ED_{50} = 16 mg/kg), and **5** (ED_{50} = 45 mg/kg).[5] The comparatively low activity observed for amines **21**−**25** has been tentatively attributed, in part, to the basicity of this substituent. This difference in activity was reminiscent of the decreased activity observed for the C(2) imidazole derivative **43** (ED_{50} >100 mg/kg) versus the less basic, isomeric C(2) pyrazole adduct **44** (ED_{50} = 17 mg/kg).[7]



Support for our suggestion that increased anticonvulsant protection accompanied substitution of the heteroatom moiety was provided by the comparison of the ED_{50} values for methyl ether **18** (ED_{50} = 8.3 mg/kg) and ethyl ether **19** (ED_{50} = 17 mg/kg) versus alcohol **27** (ED_{50} >100, <300 mg/kg). This dramatic increase in protection in the MES test paralleled the previous findings observed for the C(2) *O*-methylhydroxylamines **9** (ED_{50} = 6.2 mg/kg) and **10** (ED_{50} = 6.7 mg/kg) versus the parent compound **8** (ED_{50} ≈ 100 mg/kg).[6]

The effect of size of the C(2) substituent on pharmacological activity could be discerned by the progressive decrease in protection from MES-induced seizures observed in the *O*-alkyl series (**18**−**20**) and the *N*,*N*-disubstituted derivatives **24** and **25**. In both sets of compounds we observed a drop in anticonvulsant activity as the size of the groups attached to the heteroatom increased. Comparable patterns were reported for functionalized C(2) aromatic amino acid derivatives (e.g., **3**, ED_{50} = 10 mg/kg versus **45**, ED_{50} >100, <300 mg/kg;[5] **46**, ED_{50} = 32 mg/kg versus **47**, ED_{50} >300 mg/kg[5]).

The pharmacological activities of racemic **18** and **19** warranted their further evaluation. Table 2 lists the MES ED_{50}, TD_{50}, and PI value for these compounds upon oral administration (po) to rats with similar data

Table 3. Selected Physical and Pharmacological Data for Functionalized *N*-Benzyl-2-acetamidopropionamide Stereoisomers

				mice (ip)[b]			rat (po)[f]		
no.	R^2	Ar	mp[a]	MES,[c] ED_{50}	Tox,[d] TD_{50}	PI[e]	MES,[c] ED_{50}	Tox,[d] TD_{50}	PI[e]
(*R,S*)-**14**	CH_3	Ph	139−141	77 [1][g] (67−89)	450 [0.5] (420−500)	5.9	48 [1] (32−72)	−[h]	>21
(*R*)-**14**	CH_3	Ph	139−141	55 [0.5][i] (50−60)	210 [0.5] (150−260)	3.9	28 [4] (22−35)	−[h]	>36
(*S*)-**14**	CH_3	Ph	139−142	550 [0.5] (460−740)	840 [0.5] (690−950)	1.5	−[j]	−[j]	
(*R,S*)-**18**	CH_2OCH_3	Ph	121−122	8.3 [0.5] (7.9−9.8)	43 [0.25] (38−47)	5.2	3.8 [2] (2.9−5.5)	390 [1] (320−510)	100
(*R*)-**18**	CH_2OCH_3	Ph	143−144	4.5 [0.5] (3.7−5.5)	27 [0.25] (26−28)	6.0	3.9 [0.5] (2.6−6.2)	>500 [0.5]	>130
(*S*)-**18**	CH_2OCH_3	Ph	143−144	>100, <300	>300		>30	>30	
(*R,S*)-**27**	CH_2OH	Ph	201−203	>100, <300	>300		−[j]	−[j]	
(*R*)-**27**	CH_2OH	Ph	148−149	53 [2] (38−67)	>500 [2]	>9.4	−[j]	−[j]	
(*R*)-**41**	CH_2OCH_3	Ph(m-F)	150−151	6.9 [0.25] (6.1−8.0)	46 [0.25] (40−55)	6.7	6.9 [0.5] (4.3−9.9)	>400 [0.5]	>58
(*R*)-**42**	CH_2OCH_3	Ph(p-F)	144−145	4.2 [0.5] (3.5−5.1)	28 [0.25] (22−34)	6.7	2.6 [2] (1.9−3.6)	>125, <250	

[a] Melting points (°C) are uncorrected. [b] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in mg/kg. Numbers in parentheses are 95% confidence intervals. The dose effect data was obtained at the "time of peak effect" (indicated in hours in the brackets). [c] MES = maximal electroshock seizure test. [d] Tox = neurologic toxicity determined from rotorod test. [e] PI = protective index (TD_{50}/MES ED_{50}). [f] The compounds were administered orally. [g] Reference 3. [h] No ataxia observed up to 1000 mg/kg. [i] Reference 4. [j] Data not available.

for racemic **14** and some of the current clinically used antiepileptic agents.[11] Both **18** and **19** provided enhanced protection against MES-induced seizures versus **14**. These results gave further proof that the placement of a small, substituted heteroatom moiety one atom from the C(2) site in this series of compounds leads to improved anticonvulsant activities. Significantly, the MES ED_{50} values for **18** (ED_{50} = 3.8 mg/kg) and **19** (ED_{50} = 19 mg/kg) were better than those reported for phenytoin (ED_{50} = 23 mg/kg). Moreover, the PI value for **18** was 100.

The final group of compounds evaluated were the individual (*R*)- and (*S*)-stereoisomers of **18** and the (*R*)-stereoisomers of **27**, **41**, and **42** (Table 3). A distinguishing feature previously determined for this class of anticonvulsant agents was the marked differences in activity observed for the two enantiomers that comprised the racemate.[1,4,5,7] For example, in mice (ip) the (*R*)-stereoisomer of *N*-benzyl-2-acetamidopropionamide ((*R*)-**14**) was 10 times more effective in the control of MES-induced seizures than the corresponding (*S*)-isomer, (*S*)-**14**. Comparable differences in potencies were observed for the stereoisomers of **3** and **46**. Consistent with these findings, we observed that the anticonvulsant activity for **18** resided in the (*R*)-stereoisomer. The eudismic ratio determined in the MES test in mice (ip) was >22 and surpassed comparable values found for **3**, **14**, and **46**. Similarly, we noted a significant improvement in anticonvulsant activity of (*R*)-**27** (ED_{50} = 53 mg/kg) versus the corresponding racemate (*R,S*)-**27** (ED_{50} >100, <300 mg/kg). Included in this survey were the two monofluorinated derivatives (*R*)-**41** and (*R*)-**42**. These compounds were prepared because we previously observed improvements in the PI values for select monofluorinated *N*-benzyl derivatives of **3** and **14**.[3,7] In keeping with this trend, both (*R*)-**41** (PI = 6.7) and (*R*)-**42** (PI = 6.7) exhibited modest improvements in their PI values versus (*R*)-**18** (PI = 6.0).

Conclusions

The structure−anticonvulsant activity relationship for functionalized amino acid derivatives has been extended to derivatives of *N*-benzyl-2-acetamidopropionamide (**14**) in which a heteroatom moiety has been positioned one atom from the C(2) site. Highly potent activities against MES-induced seizures were observed for both *N*-benzyl-2-acetamido-3-methoxypropionamide (**18**) and *N*-benzyl-2-acetamido-3-ethoxypropionamide (**19**). Evaluation of the individual stereoisomers of **18** demonstrated that the anticonvulsant activity resided in the (*R*)-stereoisomer. The potency of (*R*)-**18** in mice (ip) exceeded the value previously reported for phenytoin. The findings that the anticonvulsant properties of **18** and **19** surpassed that of **14** provided further evidence that placement of small, substituted heteroatom groups one atom from the C(2) site in the functionalized amino acid derivatives leads to improved pharmacological activity.

Experimental Section

General Methods. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on Perkin-Elmer 1330 and 283 and Mattson Genesis spectrometers and were calibrated against the 1601 cm^{-1} band of polystyrene. Absorption values are expressed in wavenumbers (cm^{-1}). Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were taken on Nicolet NT-300 and General Electric QE-300 NMR instruments. Chemical shifts (δ) are in parts per million (ppm) relative to Me_4Si, and coupling constants (*J* values) are in hertz. All chemical ionization mass spectral investigations were conducted at the University of Texas at Austin by Dr. M. Moini on a Finnigan MAT TSQ-70 instrument. Microanalyses were provided by Atlantic Microlab, Inc. (Norcross, GA). Ethyl α-acetamidocyanoacetate (**28**) was obtained from Aldrich Chemical Co. (Milwaukee, WI). Thin-layer chromatography was performed on precoated silica gel GHLF microscope slides (2.5 × 10 cm; Analtech No. 21521).

Synthesis of Methyl α-Acetamido-*N*-benzylmalonamate[13] (30). To a methanolic suspension (800 mL) of **29** (28.5 g, 123.1 mmol) was added *p*-toluenesulfonic acid (24.0 g, 126.2 mmol). The mixture was heated at reflux (12 h). The resulting suspension was concentrated *in vacuo*. The residue was dissolved in a 3:2 mixture of EtOAc and H_2O (3 L). The organic layer was separated and the aqueous layer extracted with EtOAc (2 L). The organic layers were combined, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was recrys-

tallized (1:1 EtOAc/hexanes), and washed with Et_2O (1 L) to give 21.2 g (65%) of **30**: mp 158−159 °C (lit.[13] mp 158−159 °C); R_f 0.36 (6% MeOH−$CHCl_3$); IR (KBr) 2920, 1750, 1630, 1370, 890, 790 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.90 (s, C(O)C**H**$_3$), 3.66 (s, OC**H**$_3$), 4.30 (t, J = 6.3 Hz, C**H**$_2$), 5.14 (d, J = 7.8 Hz, C**H**), 7.21−7.32 (m, 5 Ph**H**), 8.61 (d, J = 7.8 Hz, N**H**), 8.96 (t, J = 6.3 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.1 (C(O)**C**H$_3$), 42.3 (**C**H$_2$), 52.4 (**C**H), 56.5 (O**C**H$_3$), 126.8 (**C$_4$′**), 127.0 (**2C$_2$′** or **2C$_3$′**), 128.2 (**2C$_2$′** or **2C$_3$′**), 138.7 (**C$_1$′**), 165.4 (**C**(O)CH$_3$ or **C**(O)OCH$_3$), 168.3 (**C**(O)CH$_3$ or **C**(O)OCH$_3$), 169.6 (**C**(O)NH) ppm; MS (+CI) 265 (M^+ + 1, 22), 264 (100). Anal. ($C_{13}H_{16}N_2O_4$).

Synthesis of *N*-Benzyl-2-acetamidohydracrylamide (27). To an anhydrous THF solution (400 mL) of **30** (14.4 g, 54.5 mmol) was successively added dry LiCl (4.62 g, 109 mmol), $NaBH_4$ (4.13 g, 109 mmol), and EtOH (200 mL). The reaction mixture was stirred at room temperature (5 h). The suspension was concentrated *in vacuo*. After continuous extraction (12 h) of the product using $CHCl_3$ (1000 mL) and H_2O (250 mL), the organic layer was collected, dried (Na_2SO_4), and removed *in vacuo* to give a crude white solid. The crude product was triturated with Et_2O (500 mL) to give 11.45 g (89%) of **27**: mp 201−203 °C; R_f 0.40 (10% MeOH−$CHCl_3$); IR (KBr) 3287, 3085, 2969, 2859, 1648, 1552, 1456, 1055, 697 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.88 (s, C(O)C**H**$_3$), 3.59 (dd, J = 5.7 Hz, 5.7 Hz, C**H**$_2$O), 4.19−4.35 (m, C**H**$_2$NH, C**H**), 4.92 (t, J = 5.7 Hz, O**H**), 7.10−7.40 (m, 5 Ph**H**), 7.94 (d, J = 5.7 Hz, N**H**), 8.38 (t, J = 5.7 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.2 (C(O)**C**H$_3$), 41.6 (**C**H$_2$N), 54.9 (**C**H), 61.3 (**C**H$_2$OH), 126.2 (**C$_4$′**), 126.5 (**2C$_2$′** or **2C$_3$′**), 127.7 (**2C$_2$′** or **2C$_3$′**), 138.9 (**C$_1$′**), 169.1 (**C**(O)CH$_3$ or **C**(O)NH), 169.9 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 237 (M^+ + 1, 100), 219 (9); M_r (+CI) 237.123 88 [M^+ + 1] (calcd for $C_{12}H_{17}N_2O_3$ 237.123 92). Anal. ($C_{12}H_{16}N_2O_3$) C, H, N.

Synthesis of *N*-Benzyl-2-acetamido-3-chloropropionamide (15). To an CH_3CN suspension (300 mL) of **27** (3.54 g, 15.0 mmol) was added chlorotrimethylsilane (4.76 mL, 37.5 mmol) under N_2. The reaction mixture was heated at reflux (8 h), and then the solvent was removed under reduced pressure. The residue was dissolved in a 1:1 mixture of $CHCl_3$ and H_2O (200 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (200 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated *in vacuo*. The white residue was triturated with Et_2O (150 mL) to give 2.83 g (74%) of **15** as a white solid: mp 143−144 °C; R_f 0.55 (10% MeOH−$CHCl_3$); IR (KBr) 3291, 3061, 3038, 2951, 2930, 1631, 1536, 1370, 753, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (s, C(O)C**H**$_3$), 3.72 (dd, J = 6.3, 11.1 Hz, C**H**H′Cl), 3.94 (dd, J = 6.3, 11.1 Hz, CH**H**′Cl), 4.48 (d, J = 5.7 Hz, NHC**H**$_2$), 4.72−4.81 (m, C**H**), 6.36 (br d, J = 6.3 Hz, N**H**), 6.49 (br s, N**H**), 7.22−7.35 (m, 5 Ph**H**); ^{13}C NMR (DMSO-d_6) 22.5 (C(O)**C**H$_3$), 42.2 (**C**H$_2$N or **C**H$_2$Cl), 44.6 (**C**H$_2$N or **C**H$_2$Cl), 53.9 (**C**H), 126.7 (**C$_4$′**), 127.0 (**2C$_2$′** or **2C$_3$′**), 128.2 (**2C$_2$′** or **2C$_3$′**), 138.4 (**C$_1$′**), 168.4 (**C**(O)CH$_3$ or **C**(O)NH), 169.5 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 257 (M^+ + 1, 28), 255 (M^+ + 1, 81), 220 (100); M_r (+CI) 255.090 85 [M^+ + 1] (calcd for $C_{12}H_{16}ClN_2O_2$ 255.090 03). Anal. ($C_{12}H_{15}ClN_2O_2$) C, H, N.

Synthesis of *N*-Benzyl-2-acetamido-3-bromopropionamide (16). To an CH_3CN suspension (250 mL) of **27** (2.36 g, 10 mmol) was added bromotrimethylsilane (3.30 mL, 25 mmol) under N_2. The reaction mixture was heated at reflux (2 h), and then the solvent was removed *in vacuo*. The product was purified by flash column chromatography on SiO_2 gel (EtOAc) to give 1.25 g of **16**. The crude product was triturated with Et_2O (250 mL) to give 1.09 g (34%) of the desired product: mp 123−125 °C; R_f 0.50 (EtOAc); IR (KBr) 3287, 3067, 2928, 1645, 1551, 1455, 1376, 742, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C(O)C**H**$_3$), 3.59 (dd, J = 4.8, 10.5 Hz, C**H**H′Br), 3.74 (dd, J = 4.8, 10.5 Hz, CH**H**′Br), 4.47 (d, J = 5.7 Hz, NHC**H**$_2$), 4.79−4.83 (m, C**H**), 6.42 (br d, J = 6.6 Hz, N**H**), 6.47 (br s, N**H**), 7.29−7.37 (m, 5 Ph**H**); ^{13}C NMR ($CDCl_3$) 23.1 (C(O)**C**H$_3$), 32.2 (**C**H$_2$Br), 43.8 (**C**H$_2$N), 53.6 (**C**H), 127.6 (**C$_4$′**), 127.7 (**2C$_2$′** or **2C$_3$′**), 128.7 (**2C$_2$′** or **2C$_3$′**), 137.4 (**C$_1$′**), 168.6 (**C**(O)CH$_3$ or **C**(O)NH), 170.4 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 301 (M^+ + 1, 5), 299 (M^+ + 1, 5), 220 (72), 219 (100); M_r (+CI) 299.039 22 [M^+ + 1] (calcd for $C_{12}H_{16}BrN_2O_2$ 299.039 51). Anal. ($C_{12}H_{15}BrN_2O_2$·0.67H_2O) C, H, N.

Synthesis of *N*-Benzyl-2-acetamido-3-iodopropionamide (17). To an CH_3CN suspension (100 mL) of **27** (1.18 g, 5.0 mmol) was added iodotrimethylsilane (0.84 mL, 6.0 mmol) under N_2. The reaction mixture was heated at reflux (1 h), and then the solvent was removed *in vacuo*. The residue was dissolved in a 1:1 mixture of H_2O and $CHCl_3$. The organic layer was separated, washed with a saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was triturated with EtOAc (20 mL) to give 0.35 g (20%) of **17** as a white solid: mp 169−170 °C dec; R_f 0.65 (10% MeOH−$CHCl_3$); IR (KBr) 3287, 3067, 2928, 1645, 1551, 1455, 1376, 742, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (s, C(O)C**H**$_3$), 4.38−4.51 (m, C**H**$_2$I), 4.48 (d, J = 5.7 Hz, NHC**H**$_2$), 4.63−4.70 (m, C**H**), 6.52 (br d, J = 7.2 Hz, N**H**), 6.87 (br s, N**H**), 7.30−7.35 (m, 5 Ph**H**); ^{13}C NMR ($CDCl_3$) 4.8 (**C**H$_2$I), 22.8 (C(O)**C**H$_3$), 43.4 (**C**H$_2$N), 53.3 (**C**H), 127.3 (**C$_4$′**), 127.4 (**2C$_2$′** or **2C$_3$′**), 128.3 (**2C$_2$′** or **2C$_3$′**), 136.9 (**C$_1$′**), 168.4 (**C**(O)CH$_3$ or **C**(O)NH), 169.8 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 220 (20), 219 (100); M_r (+CI) 347.025 81 [M^+ + 1] (calcd for $C_{12}H_{16}IN_2O_2$ 347.025 65). Anal. ($C_{12}H_{15}IN_2O_2$·0.33H_2O) C, H, N.

Synthesis of Dihydrooxazole 32. To an CH_3CN solution (5 mL) of **27** (47 mg, 0.2 mmol) was added fluorotrimethylsilane (0.92 μL, 1 mmol) at −78 °C. The reaction solution was warmed to room temperature and stirred (1 d). The solvent was removed under reduced pressure, and then the product was isolated by preparative TLC (10% MeOH−$CHCl_3$) to give 20 mg (46%) of **32**: mp 129−130 °C; IR (KBr) 3287, 3084, 3067, 1648, 1551, 1055, 742, 697 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.93 (s, C**H**$_3$), 4.21−4.38 (m, NHC**H**$_2$, OC**H**$_2$CH), 4.55−4.61 (m, C**H**), 7.22−7.33 (m, 5 Ph**H**), 8.43 (t, J = 5.7 Hz, N**H**); ^{13}C NMR (CD_3OD) 13.6 (**C**H$_3$), 44.1 (NH**C**H$_2$), 69.7 (**C**H), 71.9 (O**C**H$_2$CH), 128.3 (**C$_4$′**), 128.6 (**2C$_2$′** or **2C$_3$′**), 129.6 (**2C$_2$′** or **2C$_3$′**), 139.6 (**C$_1$′**), 170.7 (**C**(N)O or **C**(O)), 173.7 (**C**(N)O or **C**(O)) ppm; MS (+CI) (rel intensity) 219 (M^+ + 1, 100), 141 (41); M_r (+CI) 219.112 64 [M^+ + 1] (calcd for $C_{12}H_{15}N_2O_2$ 219.113 35).

Synthesis of *N*-Benzyl-2-acetamido-3-methoxypropionamide (18). To an CH_3CN solution (500 mL) of **27** (2.36 g, 10 mmol) were successively added Ag_2O (11.59 g, 50.0 mmol) and CH_3I (6.23 mL, 100 mmol) at room temperature, and then the reaction mixture was stirred at room temperature (4 d). The insoluble salts were filtered, and the solvent was removed *in vacuo* to give a white solid. The residue was triturated with Et_2O (50 mL) to give 2.10 g (84%) of **18**: mp 121−122 °C; R_f 0.47 (10% MeOH−$CHCl_3$); IR (KBr) 3290, 3087, 2924, 2878, 2820, 1637, 1548, 1139, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C(O)C**H**$_3$), 3.38 (s, OC**H**$_3$), 3.43 (dd, J = 7.8, 9.0 Hz, C**H**H′OCH$_3$), 3.82 (dd, J = 4.2, 9.0 Hz, CH**H**′OCH$_3$), 4.48 (d, J = 6.0 Hz, NHC**H**$_2$), 4.51−4.57 (m, C**H**), 6.43 (br d, J = 5.4 Hz, N**H**), 6.74 (br s, N**H**), 7.25−7.37 (m, 5 Ph**H**); ^{13}C NMR ($CDCl_3$) 23.2 (C(O)**C**H$_3$), 43.5 (**C**H$_2$N), 52.4 (**C**H), 59.1 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 127.4 (**C$_4$′** and **2C$_2$′** or **2C$_3$′**), 128.7 (**2C$_2$′** or **2C$_3$′**), 137.8 (**C$_1$′**), 170.0 (**C**(O)CH$_3$ or **C**(O)NH), 170.3 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 251 (M^+ + 1, 100), 219 (100); M_r (+CI) 251.139 39 [M^+ + 1] (calcd for $C_{13}H_{19}N_2O_3$ 251.139 57). Anal. ($C_{13}H_{18}N_2O_3$) C, H, N.

Synthesis of *N*-Benzyl-2-acetamido-3-ethoxypropionamide (19). Using the preceding procedure and **27** (2.36 g, 10 mmol), Ag_2O (11.59 g, 50 mmol), and EtI (12.0 mL, 150 mmol) gave crude **19** after stirring at room temperature (18 h). The insoluble salts were filtered, and the solvent was removed *in vacuo*. The residue was dissolved in MeOH (50 mL), treated with charcoal, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and triturated with Et_2O (100 mL) to give 0.60 g (23%) of **19** as a white solid: mp 113−114 °C; R_f 0.60 (5% MeOH−$CHCl_3$); IR (KBr) 3307, 3277, 3064, 2975, 2861, 1630, 1549, 1392, 1119, 1103, 731, 707 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.09 (t, J = 6.9 Hz, OCH$_2$C**H**$_3$), 1.87 (s, C(O)C**H**$_3$), 3.43 (q, J = 6.9 Hz, OC**H**$_2$CH$_3$), 3.48−3.57 (m, C**H**$_2$OCH$_2$CH$_3$), 4.25−4.35 (m, NHC**H**$_2$), 4.44−4.50 (m, C**H**), 7.10−7.35 (m, 5 Ph**H**), 8.08 (d, J = 7.8 Hz, N**H**), 8.50 (t, J = 5.7 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 15.0 (OCH$_2$**C**H$_3$), 22.6 (C(O)**C**H$_3$), 42.0 (**C**H$_2$N), 52.9 (**C**H), 65.8 (O**C**H$_2$CH$_3$), 126.7 (**C$_4$′**), 126.9 (**2C$_2$′** or **2C$_3$′**), 128.2 (**2C$_2$′** or **2C$_3$′**), 139.3 (**C$_1$′**), 169.5 (**C**(O)CH$_3$ or **C**(O)NH), 169.9 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel

intensity) 265 ($M^+ + 1$, 100), 219 (22); M_r (+CI) 265.155 04 [$M^+ + 1$] (calcd for $C_{14}H_{21}N_2O_3$, 265.155 21). Anal. ($C_{14}H_{20}N_2O_3$) C, H, N.

Synthesis of *N*-Benzyl-2-acetamido-3-(allyloxy)propionamide (20). Utilizing the procedure employed for **18** and using **27** (2.36 g, 10 mmol), Ag_2O (11.59 g, 50 mmol), and allyl iodide (9.1 mL, 100 mmol) gave crude **20** after stirring at 45 °C (6 d). The insoluble salts were removed *in vacuo* to give an oily residue. The residue was purified by flash column chromatography on SiO_2 gel (3% MeOH−$CHCl_3$). After removal of the solvent the residue was dried *in vacuo* and then triturated with a 1:1 mixture of Et_2O/hexanes (40 mL) to give 1.20 g (44%) of **20**: mp 76−77 °C; R_f 0.57 (5% MeOH−$CHCl_3$); IR (KBr) 3288, 3090, 3064, 2859, 1635, 1541, 1108, 696 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.86 (s, C(O)C**H$_3$**), 3.49−3.58 (m, CHC**H$_2$**O), 3.94 (d, J = 5.1 Hz, OC**H$_2$**CHCH$_2$), 4.21−4.34 (m, NHC**H$_2$**), 4.44−4.51 (m, C**H**), 5.12−5.27 (m, OCH$_2$CHC**H$_2$**), 5.77−5.91 (m, OCH$_2$C**H**CH$_2$), 7.20−7.31 (m, 5 Ph**H**), 8.09 (d, J = 7.5 Hz, N**H**), 8.50 (t, J = 5.4 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.5 (C(O)**C**H$_3$), 42.0 (**C**H$_2$NH), 52.8 (**C**H), 69.8 (CH**C**H$_2$O), 71.1 (O**C**H$_2$CHCH$_2$), 116.6 (OCH$_2$CH**C**H$_2$), 126.6 (**C$_4$′**), 126.9 (**2C$_2$′** or **2C$_3$′**), 128.1 (**2C$_2$′** or **2C$_3$′**), 134.9 (OCH$_2$**C**HCH$_2$), 139.2 (**C$_1$′**), 169.4 (**C**(O)CH$_3$ or **C**(O)NH), 169.5 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 277 ($M^+ + 1$, 100), 219 (19); M_r (+CI) 277.155 74 [$M^+ + 1$] (calcd for $C_{15}H_{21}N_2O_3$ 277.155 22). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

Synthesis of *N*-Benzyl-2-acetamidoacrylamide (34). To a THF solution (300 mL) containing **33** (3.70 g, 28.6 mmol) were successively added 4-methylmorpholine (3.5 mL, 31.5 mmol), isobutyl chloroformate (4.1 mL, 31.5 mmol), and benzylamine (3.4 mL, 31.5 mmol) at room temperature. The reaction mixture was stirred at room temperature (1 h), then the insoluble salts were filtered, and the solvent was removed *in vacuo*. The product was purified by flash column chromatography on SiO_2 gel (5% MeOH−$CHCl_3$) to give 4.50 g (72%) of **34** as a white solid: mp 124−125 °C; R_f 0.58 (5% MeOH−$CHCl_3$); IR (KBr) 3345, 1685, 1655, 1632, 1499, 878 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.80 (s, C(O)C**H$_3$**), 4.16 (d, J = 5.5 Hz, C**H$_2$**), 5.23 (s, C**H**H′), 5.81 (s, CH**H**′), 7.03−7.14 (m, 5 Ph**H**), 8.70 (d, J = 5.5 Hz, N**H**), 8.92 (s, N**H**); ^{13}C NMR (DMSO-d_6) 24.0 (C(O)**C**H$_3$), 42.6 (**C**H$_2$NH), 103.4 (**C**H$_2$), 126.9 (**C$_4$′**), 127.3 (**2C$_2$′** or **2C$_3$′**), 128.4 (**2C$_2$′** or **2C$_3$′**), 136.3 (**C**), 139.4 (**C$_1$′**), 164.3 (**C**(O)CH$_3$ or **C**(O)NH), 169.5 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 219 ($M^+ + 1$, 100), 177 (55); M_r (+CI) 219.112 52 [$M^+ + 1$] (calcd for $C_{12}H_{15}N_2O_2$, 219.113 35). Anal. ($C_{12}H_{14}N_2O_2$) C, H, N.

Synthesis of *N*-Benzyl-2-acetamido-3-aminopropionamide (21). NH_3 (2.40 g, 141 mmol) was passed into a stirred methanolic solution (50 mL) of **34** (1.53 g, 7 mmol). The reaction solution was stirred at room temperature (10 d), and then the solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography on SiO_2 gel (30% MeOH−$CHCl_3$) and then further purified by recrystallization from EtOAc to give 0.37 g (22%) of **21** as a white solid: mp 119−120 °C; R_f 0.52 (30% MeOH−$CHCl_3$); IR (KBr) 3348, 3288, 3244, 3206, 3059, 2931, 1655, 1590, 1545, 1305, 1273, 1179, 939, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C(O)C**H$_3$**), 2.70 (dd, J = 8.1, 12.0 Hz, C**H**H′NH$_2$), 3.36 (dd, J = 2.4, 12.0 Hz, CH**H**′NH$_2$), 4.28−4.34 (m, C**H**), 4.45 (d, J = 6.0 Hz, NHC**H$_2$**), 6.85 (br d, J = 5.1 Hz, N**H**), 7.25−7.36 (m, 5 Ph**H**), 7.91 (br s, N**H**); ^{13}C NMR ($CDCl_3$) 22.6 (C(O)**C**H$_3$), 43.0 (**C**H$_2$NH$_2$ or **C**H$_2$Ph), 43.5 (**C**H$_2$Ph or **C**H$_2$NH), 54.2 (**C**H), 127.0 (**C$_4$′**), 127.1 (**2C$_2$′** or **2C$_3$′**), 128.3 (**2C$_2$′** or **2C$_3$′**), 137.8 (**C$_1$′**), 170.7 (**C**(O)CH$_3$ or **C**(O)NH), 170.8 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 236 ($M^+ + 1$, 100), 219 (27), 218 (76); M_r (+CI) 236.140 07 [$M^+ + 1$] (calcd for $C_{12}H_{18}N_3O_2$, 236.139 90). Anal. ($C_{12}H_{17}N_3O_2$) C, H, N.

Synthesis of *N*-Benzyl-2-acetamido-3-(*N*-methylamino)propionamide (22). Using the preceding procedure and **34** (1.53 g, 7 mmol) and a methanolic solution of $MeNH_2$ (2 M, 70 mL, 140 mmol) gave crude **22** after stirring at room temperature (18 h). The resulting residue was triturated with Et_2O (50 mL) to give 1.61 g (93%) of **22** as a white solid: mp 107−108 °C; R_f 0.46 (30% MeOH−$CHCl_3$); IR (KBr) 3376, 3290, 3207, 2940, 2816, 1648, 1572, 1537, 753, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (s, C(O)C**H$_3$**), 2.40 (s, NHC**H$_3$**), 2.53 (dd, J = 8.4, 11.7 Hz, C**H**H′N(H)CH$_3$), 3.14 (dd, J = 3.3, 11.7 Hz, CH**H**′N(H)CH$_3$), 4.30−4.34 (m, C**H**), 4.33−4.51 (m, NHC**H$_2$**), 6.87 (br d, J = 3.9 Hz, N**H**), 7.24−7.35 (m, 5 Ph**H**), 8.25 (br s, N**H**); ^{13}C NMR ($CDCl_3$) 23.0 (C(O)**C**H$_3$), 36.1 (N(H)**C**H$_3$), 43.2 (**C**H$_2$NH), 52.7 (**C**H), 52.8 (**C**H$_2$N(H)CH$_3$), 127.2 (**C$_4$′** or **2C$_2$′** or **2C$_3$′**), 127.3 (**C$_4$′** or **2C$_2$′** or **2C$_3$′**), 128.5 (**C$_4$′** or **2C$_2$′** or **2C$_3$′**), 138.1 (**C$_1$′**), 170.5 (**C**(O)CH$_3$ or **C**(O)NH), 171.2 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 250 ($M^+ + 1$, 100); M_r (+CI) 250.156 82 [$M^+ + 1$] (calcd for $C_{13}H_{20}N_3O_2$ 250.155 52). Anal. ($C_{13}H_{19}N_3O_2$) C, H, N.

Synthesis of *N*-Benzyl-2-acetamido-3-(*N*-ethylamino)propionamide (23). Utilizing the procedure for **21** and using **34** (1.53 g, 7 mmol) and $EtNH_2$ (6.31 g, 140 mmol) gave crude **23** after stirring at room temperature (18 h). The resulting residue was triturated with Et_2O (50 mL) to give 1.70 g (92%) of **23** as a white solid: mp 90−91 °C; R_f 0.32 (10% MeOH−$CHCl_3$); IR (KBr) 3271, 3103, 2961, 1680, 1628, 1567, 1543, 745, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (t, J = 7.2 Hz, N(H)-CH$_2$C**H$_3$**), 2.01 (s, C(O)C**H$_3$**), 2.50−2.72 (m, C**H**H′N(H)CH$_2$CH$_3$ and N(H)C**H$_2$**CH$_3$), 3.16−3.21 (m, CH**H**′N(H)CH$_2$CH$_3$), 4.31−4.37 (m, C**H**), 4.35−4.51 (m, N(H)C**H$_2$**), 6.94 (br d, J = 5.4 Hz, N**H**), 7.24−7.35 (m, 5 Ph**H**), 8.43 (br s, N**H**); ^{13}C NMR ($CDCl_3$) 15.0 (N(H)CH$_2$**C**H$_3$), 22.9 (C(O)**C**H$_3$), 43.2 (N(H)**C**H$_2$-CH$_3$ or **C**H$_2$NH), 43.7 (N(H)**C**H$_2$CH$_3$ or **C**H$_2$NH), 50.5 (**C**H or **C**H$_2$N(H)CH$_2$CH$_3$), 51.8 (**C**H or **C**H$_2$N(H)CH$_2$CH$_3$), 127.1 (**C$_4$′**), 127.2 (**2C$_2$′** or **2C$_3$′**), 128.4 (**2C$_2$′** or **2C$_3$′**), 138.1 (**C$_1$′**), 170.4 (**C**(O)-CH$_3$ or **C**(O)NH), 171.2 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 264 ($M^+ + 1$, 100); M_r (+CI) 264.171 77 [$M^+ + 1$] (calcd for $C_{14}H_{22}N_3O_2$ 264.171 20). Anal. ($C_{14}H_{21}N_3O_2$) C, H, N.

Synthesis of *N*-Benzyl-2-acetamido-3-(*N*,*N*-dimethylamino)propionamide (24). Utilizing the procedure for **21** and using **34** (1.53 g, 7 mmol) and *N*,*N*-dimethylamine (7.0 g, 155.6 mmol) gave crude **24** after stirring at room temperature (24 h). The residue was triturated with Et_2O (100 mL) to give a white solid, and the solid was filtered to give 1.70 g (92%) of **24**: mp 125−126 °C; R_f 0.60 (10% MeOH−$CHCl_3$); IR (KBr) 3250, 3096, 3050, 2942, 2827, 1632, 1573, 1553, 1457, 1428, 1275, 1246, 1044, 739 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.83 (s, C(O)C**H$_3$**), 2.15 (s, N(C**H$_3$**)$_2$), 2.32−2.49 (m, C**H$_2$**N(CH$_3$)$_2$), 4.25−4.28 (m, NHC**H$_2$**), 4.36−4.44 (m, C**H**), 7.20−7.37 (m, 5 Ph**H**), 7.99 (br d, J = 7.8 Hz, N**H**), 8.55 (br t, J = 5.4 Hz, N**H**); ^{13}C NMR ($CDCl_3$) 23.1 (C(O)**C**H$_3$), 43.3 (**C**H$_2$NH), 45.0 (N(**C**H$_3$)$_2$), 49.7 (**C**H), 60.5 (**C**H$_2$N(CH$_3$)$_2$), 127.2 (**C$_4$′** or **2C$_2$′** or **2C$_3$′**), 127.3 (**C$_4$′** or **2C$_2$′** or **2C$_3$′**), 128.6 (**C$_4$′** or **2C$_2$′** or **2C$_3$′**), 138.3 (**C$_1$′**), 170.3 (**C**(O)CH$_3$ or **C**(O)NH), 171.3 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 264 ($M^+ + 1$, 100); M_r (+CI) 264.171 72 [$M^+ + 1$] (calcd for $C_{14}H_{22}N_3O_2$ 264.171 20). Anal. ($C_{14}H_{21}N_3O_2$) C, H, N.

Synthesis of *N*-Benzyl-2-acetamido-3-morpholinopropionamide (25). A morpholine (7.85 mL, 90 mmol) solution of **34** (1.31 g, 6 mmol) was stirred at room temperature (4 d). The excess morpholine was removed *in vacuo*, and the resulting residue was triturated with Et_2O (50 mL) to give a white solid. The solid was purified by flash column chromatography on SiO_2 gel (5% MeOH−$CHCl_3$) and then further purified by recrystallization from EtOAc to give 1.30 g (72%) of **25**: mp 147−148 °C; R_f 0.31 (5% MeOH−$CHCl_3$); IR (KBr) 3295, 3244, 3086, 2968, 2859, 2819, 1648, 1562, 1543, 1275, 1114, 863, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, C(O)C**H$_3$**), 2.29−2.42 (m, C**H**H′N(C**H**H′CH$_2$)$_2$O), 2.71−2.79 (m, CH**H**′N(CH**H**′CH$_2$)$_2$O), 3.45−3.56 (m, N(CH$_2$C**H$_2$**)$_2$O), 4.31 (dd, J = 4.2, 14.4 Hz, NHC**H**H′), 4.34−4.39 (m, C**H**), 4.58 (dd, J = 6.3, 14.4 Hz, NHCH**H**′), 6.58 (br d, J = 3.3 Hz, N**H**), 7.26−7.37 (m, 5 Ph**H**), 8.33 (br s, N**H**); ^{13}C NMR ($CDCl_3$) 23.1 (C(O)**C**H$_3$), 43.6 (**C**H$_2$-NH), 48.9 (N(**C**H$_2$CH$_2$)O), 53.3 (**C**H), 59.7 (**C**H$_2$N(CH$_2$CH$_2$)O), 66.8 (N(CH$_2$**C**H$_2$)O), 127.6 (**C$_4$′** or **2C$_2$′** or **2C$_3$′**), 127.7 (**C$_4$′** or **2C$_2$′** or **2C$_3$′**), 128.8 (**C$_4$′** or **2C$_2$′** or **2C$_3$′**), 137.9 (**C$_1$′**), 170.2 (**C**(O)CH$_3$ or **C**(O)NH), 170.8 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 306 ($M^+ + 1$, 100); M_r (+CI) 306.181 68 [$M^+ + 1$] (calcd for $C_{16}H_{24}N_3O_3$ 306.181 77). Anal. ($C_{16}H_{23}N_3O_3$·0.25H_2O) C, H, N.

Synthesis of *N*-Benzyl-2-acetamido-3-(methylthio)propionamide (26). To a stirred methanolic solution (150 mL) of **34** (2.18 g, 10 mmol) was added NaSMe (2.10 g, 30 mmol). The reaction solution was stirred at room temperature (3 h).

The solvent was removed under reduced pressure, and the residue was dissolved in a 4:1 mixture of $CHCl_3$ and H_2O (250 mL). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. The white residue was triturated with Et_2O (200 mL) to give 2.30 g (86%) of **26**: mp 142−143 °C; R_f 0.41 (10% MeOH−$CHCl_3$); IR (KBr) 3274, 3090, 3059, 2918, 1642, 1545, 1371, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, C(O)C**H$_3$**), 2.15 (s, SC**H$_3$**), 2.78 (dd, J = 7.8, 13.8 Hz, C**H**H′SCH$_3$), 2.90 (dd, J = 5.4, 13.8 Hz, CH**H**′SCH$_3$), 4.46 (d, J = 5.7 Hz, NHC**H$_2$**), 4.52−4.57 (m, C**H**), 6.56 (br d, J = 6.6 Hz, N**H**), 6.93 (br s, N**H**), 7.26−7.36 (m, 5 Ph**H**); ^{13}C NMR ($CDCl_3$) 15.8 (S**C**H$_3$), 23.0 (C(O)**C**H$_3$), 36.3 (**C**H$_2$SCH$_3$), 43.6 (**C**H$_2$NH), 52.2 (**C**H), 127.4 (**C$_4$′**), 127.6 (**2C$_2$′** or **2C$_3$′**), 128.6 (**2C$_2$′** or **2C$_3$′**), 137.5 (**C$_1$′**), 170.3 (**C**(O)CH$_3$ or **C**(O)NH), 170.4 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 267 (M^+ + 1, 100), 219 (6); M_r (+CI) 267.116 26 [M^+ + 1] (calcd for $C_{13}H_{19}N_2O_2S$ 267.116 73). Anal. ($C_{13}H_{18}N_2O_2S$) C, H, N.

Synthesis of (*S*)-enriched *N*-Benzyl-2-aminohydracrylamide ((*S*)-37). To a stirred methanolic solution (250 mL) of L-serine methyl ester hydrochloride ((*S*)-**36**) (20.00 g, 128 mmol) was added benzylamine (55.9 mL, 512 mmol), and then the reaction solution was heated at reflux (18 h). The solvent was removed under reduced pressure, the insoluble salts were filtered, and the excess benzylamine was removed under high vacuum (Kugelrohr). The residue was dissolved in H_2O (100 mL), and the product was extracted with $CHCl_3$ (8 × 200 mL). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was triturated with Et_2O (150 mL) and filtered to give 8.50 g (34%) of the product as a white solid: mp 76−80 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = +1.3°; R_f 0.30 (10% MeOH−$CHCl_3$); ^1H NMR (DMSO-d_6) δ 1.84 (br s, N**H$_2$**), 3.23 (t, J = 5.4 Hz, C**H**), 3.39−3.55 (m, C**H$_2$**OH), 4.28 (d, J = 5.7 Hz, NHC**H$_2$**), 4.76 (t, J = 5.4 Hz, CH$_2$O**H**), 7.18−7.32 (m, 5 Ph**H**), 8.33 (t, J = 5.7 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 41.8 (NH**C**H$_2$), 57.0 (**C**H), 64.3 (**C**H$_2$OH), 126.6 (**C$_4$′**), 127.0 (**2C$_2$′** or **2C$_3$′**), 128.2 (**2C$_2$′** or **2C$_3$′**), 139.5 (**C$_1$′**), 179.3 (**C**(O)NH) ppm; MS (+CI) (rel intensity) 195 (M^+ + 1, 100), 117 (30); M_r (+CI) 195.113 48 [M^+ + 1] (calcd for $C_{10}H_{15}N_2O_2$ 195.113 35).

Synthesis of (*R*)-enriched *N*-Benzyl-2-aminohydracrylamide ((*R*)-37). HCl (8.00 g, 219.4 mmol) was passed into MeOH (250 mL), and then D-serine ((*R*)-**35**) (20.00 g, 190.3 mmol) was added. The reaction solution was heated at reflux (18 h), then benzylamine (81.6 mL, 761 mmol) was added, and then the reaction mixture was heated for additional 18 h. The solvent was removed under reduced pressure, the insoluble salts were filtered, and the excess benzylamine was removed under high vacuum (Kugelrohr). The residue was dissolved in H_2O (100 mL), and the product was extracted with $CHCl_3$ (8 × 200 mL). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was triturated with Et_2O (150 mL) and filtered to give 10.0 g (27%) of the product as a white solid: mp 74−78 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = −1.6°; R_f 0.30 (10% MeOH−$CHCl_3$); ^1H NMR (DMSO-d_6) δ 1.87 (br s, N**H$_2$**), 3.23 (t, J = 5.4 Hz, C**H**), 3.39−3.55 (m, C**H$_2$**OH), 4.28 (d, J = 5.7 Hz, NHC**H$_2$**), 4.76 (t, J = 5.4 Hz, CH$_2$O**H**), 7.18−7.32 (m, 5 Ph**H**), 8.34 (t, J = 5.7 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 41.8 (NH**C**H$_2$), 56.9 (**C**H), 64.3 (**C**H$_2$OH), 126.6 (**C$_4$′**), 127.0 (**2C$_2$′** or **2C$_3$′**), 128.1 (**2C$_2$′** or **2C$_3$′**), 139.5 (**C$_1$′**), 173.3 (**C**(O)NH) ppm; MS (+CI) (rel intensity) 195 (M^+ + 1, 53), 117 (100); M_r (+CI) 195.113 56 [M^+ + 1] (calcd for $C_{10}H_{15}N_2O_2$ 195.113 35).

Synthesis of (*S*)-*N*-Benzyl-2-acetamidohydracrylamide ((*S*)-27). To a stirred CH_2Cl_2 suspension (100 mL) of enriched (*S*)-**37** (8.50 g, 43.7 mmol) was added Ac_2O (5.0 mL, 52.4 mmol), and then the reaction suspension was stirred at room temperature (1 h). The solvent was removed under reduced pressure to give a white solid. The product was triturated with Et_2O (250 mL) to give 8.50 g (82%) of enriched (*S*)-**27** as a white solid. The reaction product was recrystallized (3×) using EtOH to give 1.89 g (18%) of (*S*)-**27**: mp 147−148 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = −22.0°; R_f 0.40 (10% MeOH−$CHCl_3$); IR (KBr) 3289, 3088, 2965, 2855, 1642, 1570, 1551, 1053, 698 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.86 (s, C(O)C**H$_3$**), 3.57 (dd, J = 5.7, 5.7 Hz, C**H$_2$**OH), 4.26−4.31 (m, C**H**), 4.27 (d, J = 5.7 Hz, NHC**H$_2$**), 4.94 (t, J = 5.7 Hz, CH$_2$O**H**), 7.18−7.32 (m, 5 Ph**H**), 7.96 (d, J = 7.8 Hz, N**H**), 8.39 (t, J = 5.7 Hz, N**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**27** gave only one signal for the acetyl methyl protons; ^{13}C NMR (DMSO-d_6) 22.7 (C(O)**C**H$_3$), 42.0 (**C**H$_2$NH), 55.3 (**C**H), 61.7 (**C**H$_2$OH), 126.6 (**C$_4$′**), 126.9 (**2C$_2$′** or **2C$_3$′**), 128.1 (**2C$_2$′** or **2C$_3$′**), 139.4 (**C$_1$′**), 169.4 (**C**(O)CH$_3$ or **C**(O)NH), 170.2 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 237 (M^+ + 1, 100), 219 (33); M_r (+CI) 237.124 03 [M^+ + 1] (calcd for $C_{12}H_{17}N_2O_3$ 237.123 92). Anal. ($C_{12}H_{16}N_2O_3$) C, H, N.

Synthesis of (*R*)-*N*-Benzyl-2-acetamidohydracrylamide ((*R*)-27). Using the preceding procedure and enriched (*R*)-**37** (10.00 g, 51.5 mmol) and Ac_2O (5.8 mL, 61.8 mmol) gave 7.60 g (62%) of enriched (*R*)-**27** as a white solid. The reaction product was recrystallized (2×) using EtOH to give 3.50 g (29%) of (*R*)-**27**: mp 148−149 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = +22.4°; R_f 0.40 (10% MeOH−$CHCl_3$); IR (KBr) 3295, 3090, 2964, 1642, 1533, 1376, 1281, 1051, 705 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.86 (s, C(O)C**H$_3$**), 3.57 (dd, J = 5.7, 5.7 Hz, C**H$_2$**-OH), 4.25−4.31 (m, C**H**), 4.27 (d, J = 5.7 Hz, NHC**H$_2$**), 4.92 (t, J = 5.7 Hz, CH$_2$O**H**), 7.18−7.32 (m, 5 Ph**H**), 7.94 (d, J = 7.8 Hz, N**H**), 8.38 (t, J = 5.7 Hz, N**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**27** gave only one signal for the acetyl methyl protons; ^{13}C NMR (DMSO-d_6) 22.7 (C(O)**C**H$_3$), 42.0 (**C**H$_2$NH), 55.6 (**C**H), 61.8 (**C**H$_2$OH), 126.7 (**C$_4$′**), 127.0 (**2C$_2$′** or **2C$_3$′**), 128.2 (**2C$_2$′** or **2C$_3$′**), 139.4 (**C$_1$′**), 169.5 (**C**(O)CH$_3$ or **C**(O)NH), 170.3 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 237 (M^+ + 1, 100), 219 (8); M_r (+CI) 237.123 88 [M^+ + 1] (calcd for $C_{12}H_{17}N_2O_3$ 237.123 92). Anal. ($C_{12}H_{16}N_2O_3$) C, H, N.

Synthesis of (*S*)-*N*-Benzyl-2-acetamido-3-methoxypropionamide ((*S*)-18). To a stirred CH_3CN solution (300 mL) of (*S*)-**27** (1.65 g, 7 mmol) were successively added Ag_2O (8.11 g, 35 mmol) and MeI (4.4 mL, 70 mmol) at room temperature. The reaction mixture was stirred at room temperature (4 d). The insoluble salts were filtered, and the solvents were removed *in vacuo* to give a white solid. The residue was triturated with Et_2O (100 mL) to give 1.40 g (80%) of (*S*)-**18**: mp 143−144 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = −16.8°; R_f 0.47 (10% MeOH−$CHCl_3$); IR (KBr) 3289, 3086, 2923, 2876, 2806, 1636, 1547, 1138, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C(O)C**H$_3$**), 3.38 (s, OC**H$_3$**), 3.43 (dd, J = 7.8, 9.0 Hz, C**H**H′OCH$_3$), 3.82 (dd, J = 4.2, 9.0 Hz, CH**H**′OCH$_3$), 4.48 (d, J = 6.0 Hz, C**H$_2$**), 4.51−4.57 (m, C**H**), 6.44 (br d, J = 5.4 Hz, N**H**), 6.75 (br s, N**H**), 7.25−7.37 (m, 5 Ph**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**18** gave only one signal for the acetyl methyl and ether methyl protons; ^{13}C NMR ($CDCl_3$) 23.2 (C(O)**C**H$_3$), 43.6 (**C**H$_2$NH), 52.4 (**C**H), 59.1 (O**C**H$_3$), 71.7 (**C**H$_2$-OCH$_3$), 127.4 (**C$_4$′**), 127.5 (**2C$_2$′** or **2C$_3$′**), 128.7 (**2C$_2$′** or **2C$_3$′**), 137.8 (**C$_1$′**), 170.0 (**C**(O)CH$_3$ or **C**(O)NH), 170.3 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 251 (M^+ + 1, 100), 117 (100); M_r (+CI) 251.140 50 [M^+ + 1] (calcd for $C_{13}H_{19}N_2O_3$ 251.139 57). Anal. ($C_{13}H_{18}N_2O_3$) C, H, N.

Synthesis of (*R*)-*N*-Benzyl-2-acetamido-3-methoxypropionamide ((*R*)-18). Using the preceding procedure and (*R*)-**27** (2.36 g, 10 mmol), Ag_2O (11.59 g, 50 mmol), and MeI (6.2 mL, 100 mmol) gave 2.20 g (88%) of (*R*)-**18** after stirring at room temperature (4 d): mp 143−144 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = +16.4°; R_f 0.47 (10% MeOH−$CHCl_3$); IR (KBr) 3289, 3086, 2923, 2876, 2819, 1636, 1547, 1138, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C(O)C**H$_3$**), 3.38 (s, OC**H$_3$**), 3.43 (dd, J = 7.8, 9.0 Hz, C**H**H′OCH$_3$), 3.82 (dd, J = 4.2, 9.0 Hz, CH**H**′OCH$_3$), 4.48 (d, J = 6.0 Hz, NHC**H$_2$**), 4.51−4.57 (m, C**H**), 6.44 (br d, J = 5.4 Hz, N**H**), 6.75 (br s, N**H**), 7.25−7.37 (m, 5 Ph**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**18** gave only one signal for the acetyl methyl and ether methyl protons; ^{13}C NMR ($CDCl_3$) 23.2 (C(O)**C**H$_3$), 43.5 (**C**H$_2$NH), 52.4 (**C**H), 59.1 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 127.4 (**C$_4$′**), 127.5 (**2C$_2$′** or 2**C$_3$′**), 128.7 (**2C$_2$′** or **2C$_3$′**), 137.9 (**C$_1$′**), 169.9 (**C**(O)CH$_3$ or **C**(O)NH), 170.3 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 251 (M^+ + 1, 100), 219 (6); M_r (+CI) 251.139 76 [M^+ + 1] (calcd for $C_{13}H_{19}N_2O_3$ 251.139 57). Anal. ($C_{13}H_{18}N_2O_3$) C, H, N.

Improved Synthesis of (*S*)-*N*-Benzyl-2-acetamidohydracrylamide ((*S*)-27). To a stirred AcOH (20 mL) suspension of L-serine ((*S*)-**35**) (2.63 g, 25 mmol) was added Ac_2O (2.5 mL, 26.3 mmol), and then the reaction suspension was stirred at room temperature (24 h). The AcOH was removed *in vacuo*

to give an oily residue, and then THF (150 mL) was added to the residue. The THF suspension was cooled to −78 °C under N_2, and 4-methylmorpholine (5.5 mL, 50 mmol) was added. After stirring (2 min), isobutyl chloroformate (6.5 mL, 50 mmol) was added leading to the precipitation of white solid. The reaction was allowed to proceed for an additional 2 min, and then benzylamine (5.5 mL, 50 mmol) was added at −78 °C. The reaction mixture was allowed to stir at room temperature (30 min), and then the 4-methylmorpholine hydrochloride salt was filtered. The organic layer was concentrated *in vacuo*. The product was purified by flash column chromatography on SiO_2 gel (10% MeOH−$CHCl_3$) to give 2.20 g (37%) of (*S*)-**27** as a white solid: mp 146−147 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = −21.5°; ^{1}H NMR (DMSO-d_6) δ 1.86 (s, C(O)C**H$_3$**), 3.57 (dd, J = 5.1 Hz, 5.1 Hz, C**H$_2$**O), 4.25−4.32 (m, C**H$_2$**NH, C**H**), 4.91 (t, J = 5.1 Hz, O**H**), 7.20−7.33 (m, 5 Ph**H**), 7.93 (d, J = 8.1 Hz, N**H**), 8.37 (t, J = 5.7 Hz, N**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**27** gave only one signal for the acetyl methyl protons.

Improved Synthesis of (*R*)-*N*-Benzyl-2-acetamidohydracrylamide ((*R*)-27). Using the preceding procedure and D-serine ((*R*)-**35**) (5.26 g, 50 mmol), Ac_2O (4.7 mL, 50 mmol), 4-methylmorpholine (11.0 mL, 100 mmol), isobutyl chloroformate (13.0 mL, 100 mmol), and benzylamine (10.4 mL, 100 mmol) gave 3.89 g (33%) of (*R*)-**27** as a white solid after purification: mp 147−148 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = +21.7°; ^{1}H NMR (DMSO-d_6) δ 1.86 (s, C(O)C**H$_3$**), 3.57 (dd, J = 5.1, 5.1 Hz, C**H$_2$**O), 4.27−4.31 (m, C**H$_2$**NH, C**H**), 4.90 (t, J = 5.1 Hz, O**H**), 7.20−7.31 (m, 5 Ph**H**), 7.93 (d, J = 8.1 Hz, N**H**), 8.37 (t, J = 6.0 Hz, N**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**27** gave only one signal for the acetyl methyl protons.

Synthesis of (*R*)-*N*-(3-Fluorobenzyl)-2-acetamidohydracrylamide ((*R*)-39). Utilizing the improved procedure for (*S*)-**27** and D-serine ((*R*)-**35**) (5.26 g, 50 mmol), Ac_2O (5.7 mL, 60 mmol), 4-methylmorpholine (11.0 mL, 100 mmol), isobutyl chloroformate (13.0 mL, 100 mmol), and 3-fluorobenzylamine (11.8 mL, 100 mmol) gave 4.20 g (33%) of (*R*)-**39** as a white solid after purification: mp 137−138 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = +20.8°; R_f 0.32 (10% MeOH−$CHCl_3$); IR (KBr) 3282, 3101, 2944, 1636, 1542, 1252, 1050, 779, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.87 (s, C(O)C**H$_3$**), 3.56−3.63 (m, C**H$_2$**OH), 4.29 (d, J = 6.0 Hz, C**H$_2$**NH), 4.25−4.30 (m, C**H**), 4.95 (t, J = 5.4 Hz, CH_2O**H**), 7.00−7.09 (m, 3 Ar**H**), 7.29−7.30 (m, 1 Ar**H**), 7.97 (d, J = 8.1 Hz, N**H**), 8.44 (t, J = 6.0 Hz, N**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**39** gave only one signal for the acetyl methyl protons; ^{13}C NMR (DMSO-d_6) 22.7 (C(O)**C**H$_3$), 41.6 (**C**H$_2$N), 53.4 (**C**H), 61.7 (**C**H$_2$OH), 113.3 (d, J_{CF} = 20.0 Hz, **C$_{2'}$** or **C$_{4'}$**), 113.6 (d, J_{CF} = 20.7 Hz, **C$_{2'}$** or **C$_{4'}$**), 122.9 (**C$_{6'}$**), 130.1 (d, J_{CF} = 8.2 Hz, **C$_{5'}$**), 142.6 (d, J_{CF} = 7.0 Hz, **C$_{1'}$**), 162.3 (d, J_{CF} = 241.4 Hz, **C$_{3'}$**), 169.6 (**C**(O)CH$_3$ or **C**(O)NH), 170.5 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 255 (M$^+$ + 1, 100); M_r (+CI) 255.113 54 [M$^+$ + 1] (calcd for $C_{12}H_{16}FN_2O_3$ 255.114 50). Anal. ($C_{12}H_{15}FN_2O_3$) C, H, N.

Synthesis of (*R*)-*N*-(4-Fluorobenzyl)-2-acetamidohydracrylamide ((*R*)-40). Utilizing the improved procedure for (*S*)-**27** and D-serine ((*R*)-**35**) (5.26 g, 50 mmol), Ac_2O (5.7 mL, 60 mmol), 4-methylmorpholine (11.0 mL, 100 mmol), isobutyl chloroformate (13.0 mL, 100 mmol), and 4-fluorobenzylamine (11.8 mL, 100 mmol) gave 4.08 g (32%) of (*R*)-**40** as a white solid after purification: mp 169−170 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = +17.6°; R_f 0.31 (10% MeOH−$CHCl_3$); IR (KBr) 3289, 3101, 3071, 2936, 1632, 1565, 1543, 1508, 1214, 1053, 814 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.86 (s, C(O)C**H$_3$**), 3.56 (t, J = 5.4 Hz, C**H$_2$**-OH), 4.25 (d, J = 6.0 Hz, C**H$_2$**NH), 4.25−4.29 (m, C**H**), 4.91 (t, J = 5.4 Hz, CH_2O**H**), 7.08−7.14 (m, 2C$_{2'}$**H**), 7.25−7.29 (m, 2C$_{3'}$**H**), 7.93 (d, J = 7.8 Hz, N**H**), 8.39 (d, J = 6.0 Hz, N**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**40** gave only one signal for the acetyl methyl protons; ^{13}C NMR (DMSO-d_6) 22.7 (C(O)**C**H$_3$), 41.3 (**C**H$_2$N), 55.3 (**C**H), 61.7 (**C**H$_2$OH), 114.8 (d, J_{CF} = 21.8 Hz, **2C$_{3'}$**), 128.9 (d, J_{CF} = 8.0 Hz, **2C$_{2'}$**), 135.6 (**C$_{1'}$**), 161.1 (d, J_{CF} = 240.1 Hz, **C$_{4'}$**), 169.4 (**C**(O)CH$_3$ or **C**(O)NH), 170.3 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 255 (M$^+$ + 1, 100); M_r (+CI) 255.113 60 [M$^+$ + 1] (calcd for $C_{12}H_{16}FN_2O_3$ 255.114 50). Anal. ($C_{12}H_{15}FN_2O_3$·0.2H_2O) C, H, N.

Improved Synthesis of (*S*)-*N*-Benzyl-2-acetamido-3-methoxypropionamide ((*S*)-18). To a stirred CH_3CN solution (300 mL) of (*S*)-**27** (1.18 g, 5 mmol) were successively added Ag_2O (5.80 g, 25 mmol) and MeI (3.1 mL, 10 mmol) at room temperature. The reaction mixture was stirred at room temperature (4 d). The insoluble salts were filtered, and the solvent was removed *in vacuo* to give a white solid. The white solid was triturated with Et_2O (100 mL) to give 1.00 g (80%) of (*S*)-**18**: mp 143−144 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = −16.4°; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, C(O)C**H$_3$**), 3.38 (s, OC**H$_3$**), 3.43 (dd, J = 7.5, 9.0 Hz, C**H**H′OCH$_3$), 3.81 (dd, J = 4.2, 9.0 Hz, CH**H**′OCH$_3$), 4.47 (d, J = 5.7 Hz, NHC**H$_2$**), 4.52−4.59 (m, C**H**), 6.48 (br d, J = 6.0 Hz, N**H**), 6.81 (br s, N**H**), 7.25−7.37 (m, 5 Ph**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*S*)-**18** gave only one signal for the acetyl methyl and ether methyl protons.

Improved Synthesis of (*R*)-*N*-Benzyl-2-acetamido-3-methoxypropionamide ((*R*)-18). Using the preceding procedure and (*R*)-**27** (1.42 g, 6 mmol), Ag_2O (6.95 g, 30 mmol), and MeI (3.7 mL, 60 mmol) gave 1.30 g (87%) of (*R*)-**18** after stirring at room temperature (4 d): mp 143−144 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = +16.0°; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, C(O)C**H$_3$**), 3.38 (s, OC**H$_3$**), 3.44 (dd, J = 7.5, 9.0 Hz, C**H**H′OCH$_3$), 3.81 (dd, J = 4.2, 9.0 Hz, CH**H**′OCH$_3$), 4.48 (d, J = 5.7 Hz, NHC**H$_2$**), 4.52−4.58 (m, C**H**), 6.46 (br d, J = 5.7 Hz, N**H**), 6.78 (br s, N**H**), 7.25−7.37 (m, 5 Ph**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**18** gave only one signal for the acetyl methyl and ether methyl protons.

Synthesis of (*R*)-*N*-(3-Fluorobenzyl)-2-acetamido-3-methoxypropionamide ((*R*)-41). Utilizing the improved procedure for (*S*)-**18** and using (*R*)-**39** (2.54 g, 10 mmol), Ag_2O (11.59 g, 50 mmol), and MeI (6.2 mL, 100 mmol) gave crude (*R*)-**41** after stirring at room temperature (2 d). The product was further purified by flash column chromatography on SiO_2 gel (10% MeOH−$CHCl_3$) to give 2.00 g (75%) of (*R*)-**41**: mp 150−151 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = +16.5°; R_f 0.50 (10% MeOH−$CHCl_3$); IR (KBr) 3287, 3072, 2928, 2883, 1634, 1548, 1256, 1142, 785 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (s, C(O)C**H$_3$**), 3.40 (s, OC**H$_3$**), 3.44−3.47 (m, C**H**H′OCH$_3$), 3.81−3.85 (m, CH**H**′OCH$_3$), 4.41−4.50 (m, NHC**H$_2$**), 4.53−4.59 (m, C**H**), 6.42 (br s, N**H**), 6.81 (br s, N**H**), 6.93−7.05 (m, 3 Ph**H**), 7.26−7.31 (m, 1 Ph**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**41** gave only one signal for the acetyl methyl protons and ether methyl protons; ^{13}C NMR (DMSO-d_6) 22.8 (C(O)**C**H$_3$), 42.7 (**C**H$_2$N), 52.6 (**C**H), 58.9 (O**C**H$_3$), 72.0 (**C**H$_2$-OCH$_3$), 114.0 (d, J_{CF} = 21.5 Hz, **C$_{2'}$** and **C$_{4'}$**), 122.7 (**C$_{6'}$**), 129.9 (d, J_{CF} = 7.7 Hz, **C$_{5'}$**), 140.6 (d, J_{CF} = 6.8 Hz, **C$_{1'}$**), 162.9 (d, J_{CF} = 244.4 Hz, **C$_{3'}$**), 170.2 (**C**(O)CH$_3$ or **C**(O)NH), 170.5 (**C**(O)-CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 269 (M$^+$ + 1, 100); M_r (+CI) 269.129 31 [M$^+$ + 1] (calcd for $C_{13}H_{18}FN_2O_3$ 269.130 15). Anal. ($C_{13}H_{17}FN_2O_3$) C, H, N.

Synthesis of (*R*)-*N*-(4-Fluorobenzyl)-2-acetamido-3-methoxypropionamide ((*R*)-42). Utilizing the improved procedure for (*S*)-**18** and using (*R*)-**40** (2.54 g, 10 mmol), Ag_2O (11.59 g, 50 mmol), and MeI (6.2 mL, 100 mmol) gave crude (*R*)-**42** after stirring at room temperature (7 d). The product was further purified by flash column chromatography (10% MeOH−$CHCl_3$) to give 2.00 g (75%) of (*R*)-**42**: mp 144−145 °C; $[\alpha]^{23}_D$ (c = 1, MeOH) = +12.0°; R_f 0.52 (10% MeOH−$CHCl_3$); IR (KBr) 3281, 3102, 3072, 2959, 1632, 1547, 1513, 1223, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, C(O)C**H$_3$**), 3.38 (s, OC**H$_3$**), 3.39−3.46 (m, C**H**H′OCH$_3$), 3.80−3.84 (m, CH**H**′OCH$_3$), 4.44 (br d, J = 5.4 Hz, C**H$_2$**NH), 4.48−4.56 (m, C**H**), 6.42 (br s, N**H**), 6.76 (br s, N**H**), 6.99−7.05 (m, 2 Ph**H**), 7.21−7.31 (m, 2 Ph**H**), addition of excess (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**42** gave only one signal for the acetyl methyl protons and ether methyl protons; ^{13}C NMR ($CDCl_3$) 22.9 (C(O)**C**H$_3$), 42.6 (**C**H$_2$N), 52.5 (**C**H), 58.9 (O**C**H$_3$), 72.0 (**C**H$_2$OCH$_3$), 115.3 (d, J_{CF} = 22.0 Hz, **2C$_{3'}$**), 129.0 (d, J_{CF} = 6.9 Hz, **2C$_{2'}$**), 133.7 (**C$_{1'}$**), 161.9 (d, J_{CF} = 245.3 Hz, **C$_{4'}$**), 170.1-(**C**(O)CH$_3$ or **C**(O)NH), 170.4 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) (rel intensity) 269 (M$^+$ + 1, 100); M_r (+CI) 269.129 66 [M$^+$ + 1] (calcd for $C_{13}H_{18}FN_2O_3$ 269.130 15). Anal. ($C_{13}H_{17}$-FN_2O_3) C, H, N.

Pharmacology. Compounds were screened under the auspices of the National Institutes of Health for anticonvulsant activity in both male albino Carthworth Farms No. 1 mice (ip route) and male albino Sprague Dawley rats (oral (po) route). All of the compounds were administered in suspensions of 0.5% (w/v) of methylcellulose in water. The volumes are 0.01 mL/g of body weight and 0.04 mL/10 g of body weight for mice and rats, respectively. Activity was established using the electrical (maximal electroshock or MES) test.[25] In the MES test, a drop of electrolyte solution with anesthetic (0.5% butacaine hemisulfate in 0.9% sodium chloride) was used in the eyes of the animals prior to positioning the corneal electrodes and delivery of current. A 60-cycle alternating current was administered for 0.2 s in both species, 50 mA in mice and 150 mA in rats.[26] Protection endpoints were defined as the abolition of the hind limb tonic extensor component of the induced seizure. In mice, effects of compounds on forced spontaneous motor activity were determined using the rotorod test. The inability of animals to maintain their balance for 1 min on a 1 in. diameter knurled rod rotating at 6 rpm in three successive trials demonstrated motor impairment. Normally under these conditions, a mouse can maintain its balance indefinitely. In rats, motor impairment is assessed by observing for overt evidence of ataxia, abnormal gait and stance, and/or loss of placing response and muscle tone. In the mouse identification screening study all compounds were given at three dose levels (30, 100, and 300 mg/kg) and two time periods (0.5 and 4 h). Typically, in the MES seizures test one animal was used at 30 and 300 mg/kg, and three animals at 100 mg/kg. In the rotorod toxicity test four animals were used at 30 and 300 mg/kg, and eight animals at 100 mg/kg (Tables 1 and 3).

The quantitative determination of the median effective (ED_{50}) and toxic doses (TD_{50}) were conducted at previously calculated times of peak effect. Groups of at least eight animals were tested using different doses of test compound until at least two points were determined between 100 and 0% protection and minimal motor impairment. The dose of candidate substance required to produce the defined endpoint in 50% of the animals in each test, and the 95% confidence interval were calculated by a computer program based on methods described by Finney.[27]

Acknowledgment. We thank Dr. Harvey Kupferberg and the Anticonvulsant Screening Project (ASP) of the National Institute of Neurological and Communication Disorders and Stroke at the National Institutes of Health for kindly performing the pharmacological studies and Dr. J. David Leander (Eli Lilly Co., Indianapolis, IN) for conducting the earlier pharmacological evaluation of **8**−**10** and **27**. Funds for this project were provided in part by the State of Texas Advanced Technology Program.

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JM9508705