Synthesis and Anticonvulsant Activities of α-Heterocyclic α-Acetamido-*N*-benzylacetamide Derivatives

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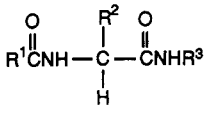
Earlier studies showed that (*R,S*)-α-acetamido-*N*-benzylacetamides (**2**) containing a five- and six-membered aromatic or heteroaromatic group appended at the C(α) site displayed outstanding activity in the maximal electroshock-induced seizure (MES) test in mice. An expanded set of C(α)-heteroaromatic analogues of **2** have been prepared and evaluated. The observed findings extended the structure–activity relationships previously discerned for this novel class of anticonvulsants and have validated previous trends. The α-furan-2-yl (**4**), α-oxazol-2-yl (**18**), and α-thiazol-2-yl (**19**) α-acetamido-*N*-benzylacetamides afforded excellent protection against MES-induced seizures in mice. The ED_{50} and PI values for these adducts rivaled those reported for phenytoin. The outstanding properties provided by **4** led to an in-depth examination of the effect of structural modification at key sites within this compound on biological activity. The pharmacological data in this series indicated that stringent steric and electronic requirements existed for maximal activity and revealed the outstanding activity of (*R*)-(−)-α-acetamido-*N*-(4-fluorobenzyl)-α-(furan-2-yl)acetamide [(*R*)-**30**].

Non-naturally occurring amino acid derivatives constitute an increasing resource of new chemotherapeutic agents that include antibacterial and CNS agents and enzyme inhibitors.[1] In recent years, we have reported on the anticonvulsant properties of functionalized amino acid derivatives **1**.[2-7] Our studies demonstrated that α-acetamido-*N*-benzylacetamides (**2**)containing a five- and six-membered aromatic or heteroaromatic group appended at the C(α)-site afforded excellent protection against maximal electroshock (MES)-induced seizures in mice (Table I).[3,6] For example, the ED_{50} values against MES seizures for the racemic α-phenyl (**3**) (32.1 mg/kg) and α-furan-2-yl (**4**) (10.3 mg/kg) derivatives[6] compared favorably with phenobarbital (21.8 mg/kg) and phenytoin (9.5 mg/kg).[8] Examination of the individual enantiomers of **3** and **4** demonstrated the importance of stereochemistry at the C(α) site in **2** on biological activity.[5,6] In both **3** and **4**, the (*R*)-stereoisomer was 10 times more potent in the control of MES seizures than the (*S*)-enantiomer. This difference in activity is the greatest eudismic ratio reported to date for MES-selective anticonvulsant agents.



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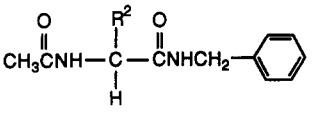

2

In the present study we report the synthesis and pharmacological activities of a carefully selected series of C(α)-heteroaromatic analogues of **2**. Information is provided on the effect of type, number, and site of heteroatom substitution within the C(α)-substituent on anticonvulsant activity (Table I). The outstanding properties provided by α-acetamido-*N*-benzyl-α-(furan-2-yl)acetamide (**4**) against MES seizures led to an in-depth examination of the effect of structural modification at key sites in **4** on biological activity (Table II). Included in this study was also the preparation of several enantiopure congeners of (*R*)-**4** to demonstrate that this absolute configuration afforded compounds with marked anticonvulsant activity.

Selection of Compounds

Our investigation proceeded in two stages. First, we determined the effect of the C(α)-heteroaromatic group in **2** on anticonvulsant activity (Table I). Amino acid derivatives **4**-**8**[6] (Table I) served as the reference compounds for this investigation. The placement of additional heteroatoms within these derivatives or the preparation of isomeric adducts led to multiple effects. These included perturbations in the electron density of the aromatic ring, changes in the spatial orientation of the nonbonding electrons, and alterations in the basicity and bioavailability of the drug candidates. These multifaceted electronic, structural, and physical effects complicated the interpretation of the biological data. Nonetheless, the pronounced improvement in MES-induced seizure protection previously observed by the placement of an electron-rich aromatic ring at the C(α)-site in **2** (i.e., **3** (ED_{50} = 32.1 mg/kg) versus **4** (ED_{50} = 10.3 mg/kg); **7** (ED_{50} = 44.8 mg/kg) versus **5** (ED_{50} = 16.1 mg/kg) versus **4** (ED_{50} = 10.3 mg/kg)) prompted us to provide additional documentation for this trend. The compounds selected for synthesis and evaluation were grouped into three categories. The first set (i.e., **9**–**12**) included aza analogues of **5** where the C(α)-heteroaromatic ring was appended by a carbon–carbon bond. Compounds in this series were α-imidazolyl (**9** and **10**), α-triazolyl (**11**), and α-tetrazolyl (**12**). The second category (i.e., **13**–**17**) encompassed the isomeric C(α)-azaromatics where heteroaromatic attachment to the amino acid backbone occurred through a nitrogen–carbon bond. Compounds evaluated were α-pyrrolyl (**13**), α-pyrazolyl (**14**), α-imidazolyl (**15**), α-triazolyl (**16**), and α-tetrazolyl (**17**) adducts. Finally, the third category (i.e., **18**–

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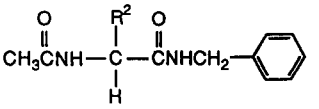
Table I. Physical and Pharmacological Data in Mice for C(α)-Heteroaromatic α-Acetamido-*N*-benzylacetamides[a]



no.	R^2	mp[b]	MES[c] ED_{50}	HS[d] TD_{50}	PI[e]
3[f]		202–203	32.1 (27.5–40.2)	>40	
4[f]		178–179	10.3 (9.1–11.6)	~40	>3.9
5[f]		174–175	16.1 (13.2–19.9)	>30, <100	
6[f]		179–181	~300	*g*	
7[f]		167–169	44.8 (38.9–51.4)	>30, <100	
8[f]		198–199	87.8 (69.9–150)	>100	
9		228–230	>100	*g*	
10		188–191 dec	>100	*g*	
11		205–207	>100	*g*	
12		236–238	>30, <100	*g*	
13		182–184	80.2 (66.6–100.6)	*g*	
14		158–160	16.5 (14.1–22.5)	*g*	
15		146–148	>100	*g*	
16		146–148	>30, <100	*g*	
17		169–171	>300	*g*	
18		164–166	10.4 (9.2–11.6)	38.6[h] (33.8–46.0)	3.7
19		166–167	12.1 (9.5–14.5)	69.1[h] (61.6–78.6)	5.7
20		164–166	>100, <300	*g*	
phenytoin[i]			9.5 (8.1–10.4)	65.5[h] (52.5–72.1)	6.9
phenobarbital[i]			21.8 (15.0–22.5)	69.0[h] (62.8–72.9)	3.2
valproate[i]			272 (247–338)	426[h] (369–450)	1.6

[a] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in milligrams per kilogram. Number 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 0.5 h ("time of peak effect") except for compound 19, which was obtained at 0.25 h. [b] Melting points (°C) are uncorrected. [c] MES = maximal electroshock seizure test. [d] HS TD_{50} = neurologic toxicity determined from horizontal screen unless otherwise noted. [e] PI = protective index (TD_{50}/ED_{50}). [f] Reference 6. [g] Not determined. [h] Neurologic toxicity determined using the rotorod test. [i] Reference 8.

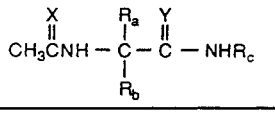
20) contained C(α)-mixed heteroaromatic systems. The three compounds prepared were α-oxazolyl (**18**), α-thiazolyl (**19**), and α-1,2,4-oxadiazolyl (**20**) derivatives. In all cases, the functionalized amino acids were synthesized as the racemates.

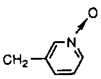
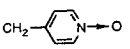
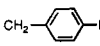
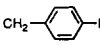
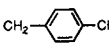
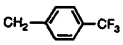
The second phase of this study (Table II) focused on α-acetamido-*N*-benzyl-α-(furan-2-yl)acetamide (**4**), the most active compound evaluated in the initial study. Structural modifications were conducted at key sites in **4**, including the furan ring (i.e., **21**), the C(α)-position (i.e., **22**), the two amide carbonyl groups (i.e., **23**, **24**), and the *N*-benzyl substituent (i.e., **25**–**29**) to discern how these changes influenced biological activity. Moreover, because of the substantial eudismic ratio observed with enantiomers of **4**, enantiopure (*R*)-isomers of several congeners in the present series were prepared (i.e., (*R*)-**30**–(*R*)-**32**) to demonstrate that this absolute configuration afforded compounds with marked anticonvulsant activity.

Chemistry

The novel α-heteroaromatic amino acid derivatives **9**–**20** were prepared from either α-acetamido-*N*-benzyl-α-bro-

Table II. Physical and Pharmacological Data in Mice for α-Acetoamido-*N*-benzyl-α-(furan-2-yl)acetamide (4) Derivatives[a]

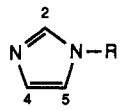


no.	R_a	R_b	R_c	X	Y	mp[b]	MES[c] ED_{50}	HS[d] TD_{50}	PI[e]
4[f]		H	$CH_2C_6H_5$	O	O	178–179	10.3 (9.1–11.6)	~40	>3.9
(*R*)-4[f]		H	$CH_2C_6H_5$	O	O	196–197	3.3 (2.8–3.9)	23.8	7.2
(*S*)-4[f]		H	$CH_2C_6H_5$	O	O	196–197	>25	>200	
21a		H	$CH_2C_6H_5$	O	O	159–161	51.7 (44.4–59.9)	*g*	
21b		H	$CH_2C_6H_5$	O	O	130–132	89.8 (78.4–103.4)	*g*	
22		CH_3	$CH_2C_6H_5$	O	O	–[h]	>300	*g*	
23		H	$CH_2C_6H_5$	S	O	78–80	18.4 (15.9–22.0)	*g*	
24		H	$CH_2C_6H_5$	S	S	99–101	>100	*g*	
25		H		O	O	172–174	~30	*g*	
26		H		O	O	168–170	>100	*g*	
27		H		O	O	159–161	~30	*g*	
28		H		O	O	210–212	>100	*g*	
29		H		O	O	226–228	>100	*g*	
30		H		O	O	188–190	12.7 (10.4–15.1)	144 (123–171)	11.3
(*R*)-30		H		O	O	205–207	3.5 (2.9–4.4)	14.4 (7.3–28.9)	4.1
(*R*)-31		H		O	O	210–212	43.6 (26.1–143)	*g*	
(*R*)-32		H		O	O	193–195	22.8 (15.9–33.4)	*g*	
phenytoin[i]							9.5 (8.1–10.4)	65.5[j] (52.5–72.1)	6.9
phenobarbital[i]							21.8 (15.0–22.5)	69.0[j] (62.8–72.9)	3.2
valproate[i]							272 (247–338)	426[j] (369–450)	1.6

[a] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in milligrams per kilogram. 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 0.5 h ("time of peak effect") except for compound 27 which was obtained at 1 h. [b] Melting points (°C) are uncorrected. [c] MES = maximal electroshock seizure test. Compound was suspended in 30% PEG. [d] HS TD_{50} = neurologic toxicity determined from horizontal screen unless otherwise noted. [e] PI = protective index (TD_{50}/ED_{50}). [f] Reference 6. [g] Not determined. [h] Thick oil. [i] Reference 8. [j] Neurologic toxicity determined using the rotorod test.

moacetamide[7] (33) or α-acetamido-*N*-benzyl-α-cyanoacetamide[9] (34). Addition of a tetrahydrofuran solution of the C(2)-lithio salt of 1-(diethoxymethyl)imidazole[10] (35) to 33 prepared *in situ* afforded 9 after workup. Correspondingly, treatment of 33 with triethylamine followed by introduction of the lithio salt of 1-(*N*,*N*-dimethylsulfamoyl)imidazole[11] (36) gave 37, which upon deprotection with acid furnished 10. The structure of 37 has been tentatively assigned as the C(4)-imidazole-substituted derivative based on a comparison of the NMR chemical shift values for 37 versus the parent heterocycle 36[11] and 1-(*N*,*N*-dimethylsulfamoyl)-4-methylimidazole (38) (Table III). Compound 38 was prepared by the addition of dimethylsulfamoyl chloride to 4-methylimidazole (39) in the presence of triethylamine. NMR and TLC analyses of the crude reaction mixture indicated the presence of only one major compound, and the structure was confirmed by X-ray crystallography (Figure 1, supplementary material). Select ^1H–^{13}C NMR decoupling experiments on 38 provided the assignments listed in Table III and permitted the assignments for the corresponding NMR resonances in 36 and 37. The ^{13}C NMR assignments

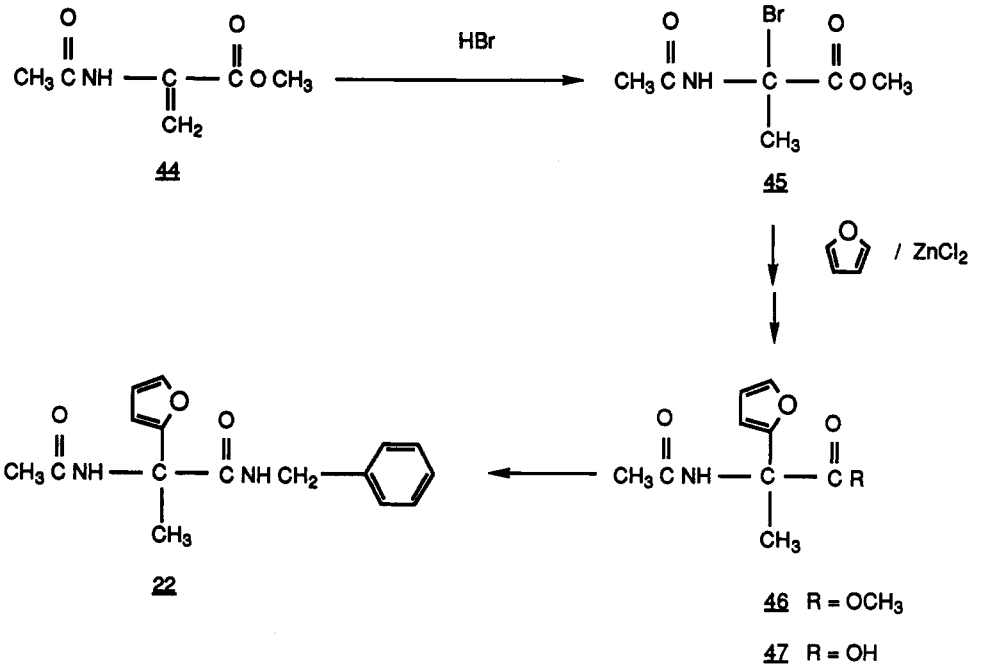
Table III. NMR Assignments for Substituted Imidazoles[a]



	^1H NMR[b]		^{13}C NMR[c]	
compd no.	H(4)	H(5)	C(4)	C(5)
imidazole	7.13	7.13	121.96	121.96
36	7.13	7.56	130.45	118.75
37		7.40	140.26	115.50
38		7.32	138.85	114.34
39		6.75	131.00	118.18
40[d]	7.09[e]	7.47	130.5[f]	115.9

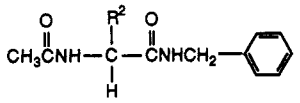
[a] All spectra were recorded in DMSO-d_6 unless otherwise indicated. [b] The number in each entry is the chemical shift value (δ) observed in ppm relative to Me_4Si. ^1H NMR spectra were recorded at 300 MHz. [c] ^{13}C NMR spectra were obtained at 75 MHz. [d] Spectra taken in $CDCl_3$. [e] Reference 12b. [f] Reference 12a.

Scheme I. Preparation of α-Acetamido-*N*-benzyl-α-methyl-α-(furan-2-yl)acetamide (22)



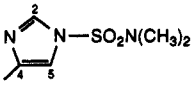
44 45 46 R = OCH3 47 R = OH 22

for **36** were in agreement with the values reported by Chadwick and Ngochindo[11] and follow the pattern cited by Begtrup and co-workers for *N*-acetylimidazole[12a] (**40**). Our NMR decoupling experiments on **36**, however, required a reversal of the previously proposed C(4) and C(5) proton assignments.[11] The revised values mirrored the ^{1}H NMR pattern reported for *N*-acetylimidazole[12b] (**40**). The origin for the formation of the C(4)-imidazole-substituted derivative **37** has not been determined. Previous studies have shown that treatment of the C(2)-lithio salt of **36** with alkyl halides furnished the C(2) substituted product, while addition of electrophiles to the C(2),C(5)-dilithio intermediate provided the C(5)-substituted adduct as a major product.[11]



33 R^2 = Br

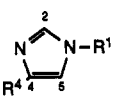
34 R^2 = CN

37 R^2 = 

41 R^2 = $C(O)NH_2$

42 R^2 = $C(S)NH_2$

43 R^2 = $C(NOH)NH_2$



35 R^1 = $CH(OCH_2CH_3)_2$, R^4 = H

36 R^1 = $SO_2N(CH_3)_2$, R^4 = H

38 R^1 = $SO_2N(CH_3)_2$, R^4 = CH_3

39 R^1 = H, R^4 = CH_3

40 R^1 = $C(O)CH_3$, R^4 = H

Comparable protocols were employed for the preparation of the *N*-substituted heteroaromatics **13**–**17** beginning with **33**. Addition of an excess amount of the preformed potassium salt of pyrrole to **33** in tetrahydrofuran yielded **13**, while **14**–**17** were synthesized by initial treatment of **33** with excess triethylamine at −78 °C followed by addition of the parent heterocycle.

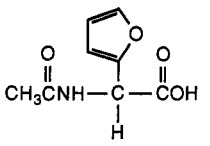
α-Acetamido-*N*-benzyl-α-cyanoacetamide (**34**) served as the starting point for the synthesis of **11**, **12**, and **18**–**20**. Addition of formic hydrazide to **34** in basic ethanol gave **11** upon workup, while treatment of **34** with KN_3 and triethylamine hydrochloride in 1-methyl-2-pyrrolidinone afforded **12**.[13] α-Oxazol-2-yl (**18**) and α-thiazol-2-yl (**19**) derivatives were prepared by initial conversion of **34** to the α-amide[9b] (**41**) and α-thioamide (**42**) adducts, respectively, and then these compounds were condensed with excess bromoacetaldehyde dimethyl acetal[14] in dimethoxyethane. α-Oxadiazol-3-yl (**20**) derivative was generated in two steps from **34**.[15] Addition of NH_2OH·HCl to **34** in basic ethanol gave the α-carboxamide oxime derivative **43**. Treatment of **43** with trimethyl orthoformate and a catalytic amount of boron trifluoride etherate gave **20**.

Several synthetic protocols were utilized for the preparation of compounds **21**–**32**. Catalytic hydrogenation (H_2, Pd/C) of (*R,S*)-**4** gave the tetrahydrofuran-2-yl adduct **21**. Fractional recrystallization of the product mixture from ethyl acetate provided diastereomers **21a** and **21b**. Synthesis of the α-methyl analogue **22** was achieved by a four-step procedure (Scheme I) beginning with methyl 2-acetamidoacrylate[16] (**44**). Addition of HBr to **44** furnished **45**, which was directly treated with furan and $ZnCl_2$ to give the α-amidoalkylation adduct **46**.[6,17] Hydrolysis of **46** to the free acid **47**, followed by treatment of **47** with benzylamine using the mixed carbonic anhydride coupling procedure[6,18] (i.e., isobutyl chloroformate, 4-methylmorpholine), gave **22**.

The two thioamides **23** and **24** were prepared directly from **4** using Lawesson's reagent.[19] Treatment of **4** with this thiation reagent (0.5 molar equiv) at room temperature yielded the monothio derivative **23**. Elevation of the reaction temperature and the relative proportion of Lawesson's reagent (>1 molar equiv) to **4** gave the dithio product **24**.

Synthesis of **25**, **26**, and **29** was accomplished from racemic α-acetamido-α-(furan-2-yl)acetic acid (**48**), isobutyl chloroformate, 4-methylmorpholine, and the appropriate amine or hydrazine, while use of (*R*)-α-acetamido-α-(furan-2-yl)acetic acid[6] [(*R*)-**48**] in this protocol with 4-fluorobenzylamine, 4-methylbenzylamine, and 4-(trifluoromethyl)benzylamine furnished the three optically active *N*-benzylamides (*R*)-**30**–(*R*)-**32**, respectively. This coupling strategy previously provided enantiopure (*R*)-**4** and (*S*)-**4**.[6] Evidence that amide bond formation pro-

ceeded without racemization (<5%) was obtained by examining the ^{1}H NMR spectra ($CDCl_3$) of (*R,S*)-**30** and (*R*)-**30**–(*R*)-**32** both in the absence and the presence of saturating amounts of (*R*)-(−)-mandelic acid.[20] Addition of this chiral solvating reagent to (*R,S*)-**30** led to the appearance of two acetyl methyl signals (~Δ ppm 0.02) of equal intensity,[21] while only a single acetyl methyl singlet was observed in the corresponding ^{1}H NMR spectra for (*R*)-**30**–(*R*)-**32**. Similar results were earlier secured for (*R*)-**4**, (*S*)-**4**, and (*R,S*)-**4**[6] (see the supplementary material for appropriate ^{1}H NMR spectra). Access to the starting material (*R*)-**48** was readily achieved using the protocol advanced by Whitesides and co-workers.[22] Treatment of racemic **48** with acylase I led to the selective hydrolysis of the (*S*)-amino acid derivative providing (*R*)-**48** in 75% yield. Previously, (*R*)-**48** was obtained by fractional



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recrystallization of the corresponding diastereomeric salts formed with (*R*)-α-methylbenzylamine.[6] The two pyridine *N*-oxide adducts **27** and **28** were prepared by treating **25** and **26**, respectively, with *m*-chloroperoxybenzoic acid.

Pharmacological Evaluation

The heteroaromatic amino acid derivatives **9**–**32** were tested for anticonvulsant activity using the procedures described by Krall and co-workers,[23] and these results were compared to the findings previously reported for **3**–**8**.[6] All compounds were administered intraperitoneally (ip) to mice. Tables I and II list the ED_{50} values required to prevent toxic extension of the hind limbs in mice in the MES test by **9**–**32**. Included in these tables are the median neurologically impairing dose (TD_{50}) values using either the horizontal screen[24] (HS) or the rotorod test.[25] 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 Tables I and II.

Our previous studies indicated that placement of electron-rich five- and six-membered aromatic and heteroaromatic moieties at the α-site within functionalized amino acids **2** led to compounds providing excellent protection against MES-induced seizures in mice.[6] Moreover, we noted in this series that improved activity resulted by the positioning of a heteroatom two atoms removed from the C(α)-site. A similar result was observed in α-acyclic derivatives of **2**.[7] The pharmacological data obtained in this study provided evidence in support of these two structure–activity themes.

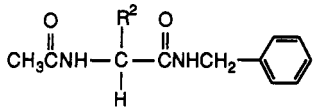
Support for the beneficial value accrued by the placement of an electron-rich aromatic ring at the C(α)-position was obtained by the comparison of the ED_{50} values in the MES-test for pyrrole **5** (ED_{50} = 16.1 mg/kg) versus the azoles **9**–**12** (ED_{50} > 30 mg/kg) (Table I). The data demonstrated that overall reduction of the electron excessive character of the C(α) π-aromatic system by heteroatom incorporation[26] led to decreased biological activity despite the fact that additional nitrogen incorporation often provided a substrate that contained two heteroatoms two atoms removed from the C(α)-site (i.e., **9**, **11**, **12**).

Comparison of the pharmacological activities of the C-substituted azoles **5**, **9**–**12** versus the N-substituted isomers **13**–**17** provided qualitative information concerning the importance of heteroatom substitution versus the C(α)-position. We observed a significant reduction in activity for **13** (ED_{50} = 80.2 mg/kg) versus **5** (ED_{50} = 16.1 mg/kg), and **17** (ED_{50} > 300 mg/kg) versus **12** (ED_{50} >30, <100 mg/kg). In compound **5** one heteroatom exists two atoms removed from the C(α)-site, while in **13** there is none. Similarly, in **12** there are two heteroatoms two atoms removed from the C(α)-site, while in **17** there is only one.

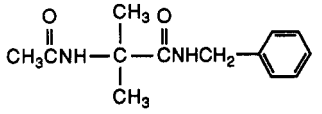
The delicate interplay of the π-electron character of the appended C(α)-heteroaromatic group, the site of the heteroatom incorporation, and the identity of the heteroatom on anticonvulsant activity was reinforced by comparison of the biological activities of the α-oxazol-2-yl (**18**), α-imidazol-2-yl (**9**), and α-thiazol-2-yl (**19**) derivatives. Of these three compounds, **18** was the most active (ED_{50} = 10.4 mg/kg), displaying protection similar to that reported for phenytoin (ED_{50} = 9.5 mg/kg).[8] The slight decrease in protection in the MES test afforded by **19** (ED_{50} = 12.1 mg/kg) versus **18** paralleled the larger difference previously observed for α-furan-2-yl (**4**) (ED_{50} = 10.3 mg/kg) and α-thien-2-yl (**7**) (ED_{50} = 44.8 mg/kg) adducts.[6] Surprisingly, the α-imidazol-2-yl (**9**) derivative failed to protect the mice from MES-induced seizures at dosages of 100 mg/kg or less. Previously, we observed that the anticonvulsant activity of **2** decreased in proceeding from oxygen to nitrogen to sulfur containing C(α)-heteroaromatic derivatives.[6] The low potency of **9** may be a reflection in part of the increased basicity of this compound versus **18** and **19**.[26]

The pyrazole derivative **14** provided protection in the MES test (ED_{50} = 16.5 mg/kg) comparable to phenobarbital (ED_{50} = 21.8 mg/kg),[8] and this compound was considerably more potent than the isomeric imidazoles **9**, **10**, and **15**. Our results do not provide information concerning the underlying factors that contribute to this difference in activity. We do note that pyrazoles are substantially less basic than imidazoles.[26]

Inspection of the composite data set for analogues of α-acetamido-*N*-benzyl-α-(furan-2-yl)acetamide (**4**) revealed that most structural changes at the α-carbon, amide carbonyl, and *N*-benzylamide site in **4** led to decreased potency of the compounds as anticonvulsants (Table II). This result is in agreement with previous findings demonstrating that stringent steric and electronic factors governed the anticonvulsant activities of this class of compounds.[3,4,6,7] Examination of the individual test results led to several important observations. First, reduction of the furan ring in **4** to the tetrahydrofuran analogues **21a** and **21b** led to a decrease, but not an abolition, of activity in the MES test (i.e., ED_{50} < 90 mg/kg). The decreased activity of **21** versus **4** can be attributed to the loss of the aromatic ring at the α-carbon site, since previous findings have demonstrated that substantial improvement in activity accompanied the placement of a small aromatic group at this position.[6] The potency of **21a** and **21b** was greater than that observed for **49** (ED_{50} > 100 mg/kg).[9b] This observation provided support for our suggestion that increased anticonvulsant activity generally accompanied the placement of a substituted (alkylated) heteroatom two atoms removed from the amino acid α-carbon.[7] Second, replacement of the α-carbon proton in **4** by a methyl group led to a sharp decrease in anticonvulsant activity of the drug candidate. This decreased potency in the MES test



49 $R^2 = CH_2OH$
50 $R^2 = CH_3$



51

was surprising in light of the near equipotency previously observed for **50** (ED_{50} = 51.0 mg/kg)[5] versus **51** (ED_{50} > 40, < 100 mg/kg).[27] Third, isosteric replacement of the amide carbonyl groups in **4** by a thioamide moiety resulted in decreased potency in the MES test. Of the two amide groups, modification of the benzylamide moiety (i.e., **24**) appeared to affect the MES activity more than modification of the acetamide site (i.e., **23**). Fourth, alteration of the *N*-benzylamide group affected the pharmacological profile of the functionalized amino acid test candidate. Conversion of the *N*-benzylamide substituent in **4** to the 3-pyridinylmethyl (**25**) or the corresponding *N*-oxide (**27**) led to small decreases in anticonvulsant activity, whereas the isomeric 4-pyridinylmethyl adduct (**26**) and *N*-oxide (**28**) were devoid of anticonvulsant activity at doses less than 100 mg/kg. Similarly, the 2′-pyridine hydrazide (**29**) displayed no protective effects in the MES test at doses of 100 mg/kg or less. Fifth, the pharmacological stereospecificity that distinguishes this novel class of anticonvulsant agents[4-6] was reaffirmed by the biological data obtained for (*R*)-**30**, (*R*)-**31**, and (*R*)-**32**. We noted a significant improvement in anticonvulsant activity of (*R*)-**30** (ED_{50} = 3.5 mg/kg) versus the corresponding racemate **30**[6] (ED_{50} = 12.7 mg/kg). Moreover, the potency of (*R*)-**30** exceeded the value previously reported for phenytoin (ED_{50} = 9.5 mg/kg).[8]

Conclusions

Synthetic protocols have been developed for the generation of C(α)-heteroaromatic α-acetamido-*N*-benzylacetamides. The pharmacological activities of these unique amino acid derivatives (i.e., **9–20**) along with the modified analogues of α-acetamido-*N*-benzyl-α-(furan-2-yl)acetamide (i.e., **21–32**) extended the structure–activity relationships previously obtained for this class of anticonvulsant agents.[2-7] Significantly, the α-furan-2-yl (**4**), α-oxazol-2-yl (**18**), and α-thiazol-2-yl (**19**) α-acetamido-*N*-benzylacetamides afforded excellent protection to MES-induced seizures in mice. The observed ED_{50} and PI values rivaled those reported for phenytoin.[8] The experimental findings provided further documentation of the beneficial properties gained by the incorporation of aromatic groups at the C(α)-site and the importance of heteroatom location within the aromatic ring system for maximal biological activity. Protection against MES-induced seizures proved to be sensitive to changes at the C(α)-site in **2** and to modifications conducted at each of the other key functional groups in these compounds.

Experimental Section

Chemistry. 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 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. Low-resolution mass spectra (MS) were recorded at an ionizing voltage of 70 eV with a Varian MAT CH-5 spectrometer at the Lilly Research Laboratories. High-resolution electron-impact mass spectra were performed on a VG ZAB-E instrument by Dr. M. Moini at the University of Texas—Austin. Microanalyses were provided by the Physical Chemistry Department of the Lilly Research Laboratories. Ethyl acetamidocyanoacetate and Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide] were obtained from Aldrich Chemical Co., Milwaukee, WI. Thin-layer chromatography was performed on precoated silica gel GHLF microscope slides (2.5 x 10 cm; Analtech No. 21521).

Synthesis of α-Acetamido-*N*-benzyl-α-(imidazol-2-yl)-acetamide (9). *n*-BuLi (2.5 M in hexane, 6.8 mL, 17.0 mmol) was added to a cooled (−46 °C) solution of **35**[10] (2.90 g, 17.06 mmol) in THF (45 mL) under N_2, and then stirred at -46 °C (15 min). The lithio salt solution of **35** was then added dropwise (15 min) into a cooled (−78 °C) THF solution (130 mL) of **33** (prepared from α-acetamido-*N*-benzyl-α-ethoxyacetamide[17] (2.00 g, 8.0 mmol) and BBr_3 (1 M in CH_2Cl_2, 10 mL, 10.0 mmol)).[7] The reaction was stirred at −78 °C (1 h) and then quenched with a saturated aqueous NH_4Cl (50 mL) solution. The mixture was stirred at room temperature (30 min) and made basic (pH 9.2) with aqueous K_2CO_3. The aqueous mixture was extracted with EtOAc (3 × 100 mL), and the combined extracts were dried (Na_2SO_4). The solvents were removed *in vacuo*, and the residue was purified by flash column chromatography on SiO_2 gel (2.5% MeOH/$CHCl_3$) to give 0.14 g (7%) of **9**: mp 228–230 °C (recrystallized from EtOH); R_f 0.46 (10% MeOH/$CHCl_3$); IR (KBr) 3200 (br), 1610, 1500 (br), 1430, 1350, 740, 680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.91 (s, C(O)CH_3), 4.29 (d, *J* = 5.6 Hz, CH_2), 5.51 (d, *J* = 7.7 Hz, CH), 6.85 (br s, C_4H), 7.05 (br s, C_5H), 7.18–7.30 (m, 5 PhH), 8.42 (d, *J* = 7.7 Hz, NH), 8.65 (t, *J* = 5.6 Hz, NH), 11.91 (br s, NH); ^{13}C NMR (DMSO-d_6) 22.49 (C(O)CH_3), 42.21 (CH_2), 51.62 (CH), 126.60 (C_4'), 126.98 ($2C_2'$ or $2C_3'$), 127.21 (C_4), 128.09 ($2C_2'$ or $2C_3'$), 128.32 (C_5), 139.05 (C_1'), 143.74 (C_2), 168.12 (C(O)NH), 169.30 (C(O)CH_3) ppm; mass spectrum, FD (relative intensity), 273 (M^+ + 1, 65), 272 (M^+, 100). Anal. ($C_{14}H_{16}N_4O_2$) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-(imidazol-4-yl)-acetamide (10). A 75% aqueous EtOH (16 mL) solution of **37** (0.85 g, 3.05 mmol) was acidified (pH ~1.5) with ethanolic HCl, and the solution was heated to reflux (8 h). The reaction was neutralized with a saturated aqueous $NaHCO_3$ solution and the EtOH–H_2O azeotrope removed by distillation *in vacuo*. The remaining aqueous layer was made basic (pH 10) with aqueous NaOH. The aqueous mixture was extracted with EtOAc (3 × 50 mL), and the combined extracts were dried (Na_2SO_4). The reaction mixture was concentrated *in vacuo* to give 0.35 g (57%) of **10**: mp 189–191 °C dec (recrystallized from acetone); R_f 0.19 (10% MeOH/$CHCl_3$); IR (KBr) 3400, 3260, 1650, 1600, 1500, 1430, 1360, 1330, 730, 710 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.88 (s, C(O)CH_3), 4.28 (d, *J* = 5.9 Hz, CH_2), 5.38 (d, *J* = 6.8 Hz, CH), 6.97 (br s, C_5H), 7.15–7.30 (m, 5 PhH), 7.60 (s, C_2H), 8.26 (br s, NH), 8.53 (br s, NH), 12.01 (br s, NH); ^{13}C NMR (CD_3OD) 22.45 (C(O)CH_3), 44.15 (CH_2), 127.88 (C_5 or C_4'), 128.01 (C_4' or C_5), 128.37 ($2C_2'$ or $2C_3'$), 129.44 ($2C_2'$ or $2C_3'$), 136.88 (C_2), 139.74 (C_1'), 172.13 (C(O)NH), 173.00 (C(O)CH_3) ppm (a weak signal was observed at δ 54 and has been tentatively attributed to CH); mass spectrum, FD, 273 (M^+ + 1). Anal. ($C_{14}H_{16}N_4O_2$) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-(1,2,4-triazol-3-yl)-acetamide (11). An ethanolic solution (250 mL) of **34**[9] (3.00 g, 13.0 mmol), formic hydrazide (1.60 g, 26.0 mmol), and K_2CO_3 (6.00 g, 2.90 mmol) was heated at reflux (20 h). The reaction mixture was allowed to cool and filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on SiO_2 gel using 13% MeOH/$CHCl_3$ as the eluant to give 1.40 g (40%) of the desired product. Compound **11** was purified by recrystallization from EtOH: mp 205–207 °C; R_f 0.35 (16% MeOH/$CHCl_3$); IR (KBr) 3285, 3080, 2930, 1690,

1650, 1510 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.92 (s, C(O)C**H$_3$**), 4.30 (d, J = 5.7 Hz, C**H$_2$**), 5.62 (d, J = 7.8 Hz, C**H**), 7.18–7.32 (m, 5 Ph**H**), 8.53 (s, C$_5$**H**), 8.56 (d, J = 7.8 Hz, N**H**), 8.71 (t, J = 5.7 Hz, N**H**), 13.98 (s, N**H**); ^{13}C NMR (DMSO-d_6) 22.48 (C(O)**C**H$_3$), 42.41 (**C**H$_2$), 51.30 (**C**H), 126.63 (**C**$_4$'), 127.08 (**2C**$_2$' or **2C**$_3$'), 128.11 (**2C**$_2$' or **2C**$_3$'), 139.05 (**C**$_1$'), 167.92 (**C**(O)NH), 169.32 (**C**(O)CH$_3$) ppm (the two triazole carbon signals were not detected); mass spectrum, FD (relative intensity), 274 (M$^+$ + 1, 100), 273 (66). Anal. (C$_{13}$H$_{15}$N$_5$O$_2$) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-(tetrazol-5-yl)-acetamide (12). A mixture of **34** (1.00 g, 4.33 mmol), KN_3 (1.70 g, 20.96 mmol), and Et_3N·HCl (1.78 g, 13.0 mmol) in 1-methyl-2-pyrrolidinone (125 mL) was stirred at 110 °C (7 h). After cooling, aqueous concentrated HCl (1 mL) was added, and the reaction mixture was filtered. The solvent was removed *in vacuo*. The residue was dissolved in aqueous 1 N NaOH (20 mL), and then aqueous 1 N HCl (20 mL) was added. The precipitate was filtered to give 0.77 g (65%) of the desired product. Compound **12** was recrystallized from EtOH: mp 236–238 °C; R_f 0.20 (30% MeOH/$CHCl_3$); IR (KBr) 3300, 3260, 3080, 1680, 1645, 1500 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.94 (s, C(O)C**H$_3$**), 4.33 (d, J = 5.7 Hz, C**H$_2$**), 5.89 (d, J = 7.8 Hz, C**H**), 7.18–7.33 (m, 5 Ph**H**), 8.86 (d, J = 7.8 Hz, N**H**), 8.92 (t, J = 5.7 Hz, N**H**), 16.54 (br s, N**H**); ^{13}C NMR (DMSO-d_6) 22.21 (C(O)**C**H$_3$), 42.37 (**C**H$_2$), 48.13 (**C**H), 126.67 (**C**$_4$'), 127.00 (**2C**$_2$' or **2C**$_3$'), 128.05 (**2C**$_2$' or **2C**$_3$'), 138.52 (**C**$_1$'), 166.18 (**C**(O)NH), 169.58 (**C**(O)CH$_3$) ppm (the tetrazole carbon signal was not detected); mass spectrum, FD (relative intensity), 275 (M$^+$ + 1, 73), 274 (100); M_r (+CI) 274.119201 (calcd for $C_{12}H_{14}N_6O_2$ 274.117824).

Synthesis of α-Acetamido-*N*-benzyl-α-(1-pyrrolyl)acetamide (13). A cooled (−78 °C) THF solution (225 mL) of **33** (prepared from α-acetamido-*N*-benzyl-α-ethoxyacetamide (2.00 g, 8.0 mmol) and BBr_3 (1 M CH_2Cl_2 solution, 8.8 mL, 8.8 mmol)) was added under N_2 to a cooled (−78 °C) suspension of potassium pyrrole (2.71 g, 25.8 mmol) in THF (25 mL). The reaction mixture was stirred at −78 °C (1 h) and then at room temperature (1 h) and then treated with H_2O (10 mL) and acidified (pH 4.0) with 5% citric acid. The reaction was made basic with aqueous saturated Na_2CO_3 solution, the aqueous mixture was extracted with EtOAc (2 x 250 mL), and the combined organic layers were dried (Na_2SO_4). The volatile materials were removed *in vacuo*, and the residue was purified by flash column chromatography on SiO_2 gel using 3% MeOH/$CHCl_3$ as the eluant to give 0.40 g (18%) of the desired product. Compound **13** was purified by recrystallization from EtOH: mp 182–184 °C; R_f 0.44 (4% MeOH/$CHCl_3$); IR (KBr) 3400, 3280, 1630, 1520, 1370, 740, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.91 (s, C(O)C**H$_3$**), 4.30 (d, J = 5.5 Hz, C**H$_2$**), 6.01 (s, 2 × C$_3$**H**), 6.38 (d, J = 8.7 Hz, C**H**), 6.85 (s, 2 × C$_2$**H**), 7.11-7.35 (m, 5 Ph**H**), 8.96 (t, J = 5.5 Hz, N**H**), 9.14 (d, J = 8.7 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.22 (C(O)**C**H$_3$), 42.15 (**C**H$_2$), 62.86 (**C**H), 107.79 (**2C**$_3$), 119.19 (**2C**$_2$), 126.76 (**C**$_4$'), 127.01 (**2C**$_2$' or **2C**$_3$'), 128.11 (**2C**$_2$' or **2C**$_3$'), 138.34 (**C**$_1$'), 166.37 (**C**(O)NH), 169.41 (**C**(O)CH$_3$) ppm; mass spectrum, FD (relative intensity), 272 (M$^+$ + 1, 22), 271 (M$^+$, 100). Anal. ($C_{15}H_{17}N_3O_2$·0.2H_2O) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-(1-pyrazolyl)-acetamide (14). To a cooled (−78 °C) solution (250 mL) of **33** (prepared from α-acetamido-*N*-benzyl-α-ethoxyacetamide (3.60 g, 14.4 mmol) and BBr_3 (1 M CH_2Cl_2 solution, 15.8 mL, 15.8 mmol)) was added Et_3N (2.91 g, 28.8 mmol) in THF (20 mL), followed by pyrazole (1.17 g, 17.28 mmol) in THF (30 mL). The mixture was stirred at −78 °C (30 min) and at room temperature (1 h). The insoluble materials were filtered and the solvents removed *in vacuo*. The residue was purified by flash column chromatography on SiO_2 gel using 4% MeOH/$CHCl_3$ as the eluant to give 0.80 g (22%) of the desired product. Compound **14** was recrystallized from EtOAc as a white solid: mp 158–160 °C; R_f 0.51 (6% MeOH/$CHCl_3$); IR (KBr) 3400, 3180, 1650, 1530, 1470, 1370, 1350, 740, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.93 (s, C(O)C**H$_3$**), 4.29 (d, J = 5.8 Hz, C**H$_2$**), 6.26 (s, C$_4$**H**), 6.57 (d, J = 8.8 Hz, C**H**), 7.15-7.33 (m, 5 Ph**H**), 7.48 (br s, C$_5$**H**), 7.76 (br s, C$_3$**H**), 8.96 (t, J = 5.8 Hz, N**H**), 9.23 (d, J = 8.8 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.41 (C(O)**C**H$_3$), 42.40 (**C**H$_2$), 65.51 (**C**H), 105.37 (**C**$_4$), 126.87 (**C**$_4$'), 127.14 (**2C**$_2$' or **2C**$_3$'), 128.25 (**2C**$_2$' or **2C**$_3$'), 129.00 (**C**$_5$), 138.59 (**C**$_3$), 139.17 (**C**$_1$'), 165.68 (**C**(O)NH), 169.81 (**C**(O)CH$_3$) ppm; mass spectrum, FD (relative intensity), 273 (M$^+$ + 1, 11), 272 (M$^+$, 2), 139 (83), 138 (100), 92 (37). Anal. ($C_{14}H_{16}N_4O_2$) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-(1-imidazolyl)-acetamide (15). Using the preceding procedure, α-acetamido-*N*-benzyl-α-ethoxyacetamide (2.00 g, 8.0 mmol), BBr_3 (1 M CH_2Cl_2 solution, 8.8 mL, 8.8 mmol), Et_3N (1.62 g, 1.60 mmol), and imidazole (0.60 g, 8.8 mmol) gave 0.60 g (30%) of **15**. The desired compound was recrystallized from ethyl acetate/hexane as a beige-colored solid: mp 146–148 °C; R_f 0.30 (7% MeOH/$CHCl_3$); IR (KBr) 3400 (br), 1640, 1560, 1480, 1360, 720, 670 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.85 (s, C(O)C**H$_3$**), 4.30 (br s, C**H$_2$**), 6.53 (d, J = 8.0 Hz, C**H**), 6.89 (s, C$_5$**H**), 7.12–7.33 (m, C$_4$**H**, 5 Ph**H**), 7.69 (s, C$_2$**H**), 9.06 (br s, N**H**), 9.29 (d, J = 8.0 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.28 (C(O)**C**H$_3$), 42.36 (**C**H$_2$), 61.18 (**C**H), 117.56 (**C**$_5$), 126.92 (**C**$_4$'), 127.16 (**2C**$_2$' or **2C**$_3$'), 128.19 (**C**$_4$), 128.26 (**2C**$_2$' or **2C**$_3$'), 136.21 (**C**$_2$), 138.27 (**C**$_1$'), 165.72 (**C**(O)NH), 169.77 (**C**(O)CH$_3$) ppm; mass spectrum, FD (relative intensity), 274 (M$^+$ + 2, 12), 273 (M$^+$ + 1, 77), 272 (100), 205 (34), 274 (18). Anal. ($C_{14}H_{16}N_4O_2$) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-(1,2,4-triazol-1-yl)-acetamide (16). Using α-acetamido-*N*-benzyl-α-ethoxyacetamide (4.00 g, 16.0 mmol), BBr_3 (1 M CH_2Cl_2 solution, 17.6 mL, 17.6 mmol), Et_3N (4.85 g, 48.0 mmol), and 1,2,4-triazole (1.43 g, 20.8 mmol), the desired product was obtained in 28% yield (1.20 g). Compound **16** was recrystallized from EtOAc as an amorphous white solid: mp 146–148 °C; R_f 0.48 (6% MeOH/$CHCl_3$); IR (KBr) 3400, 1660, 1470, 1370, 830 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.85 (s, C(O)C**H$_3$**), 4.32 (br s, C**H$_2$**), 6.70 (d, J = 7.8 Hz, C**H**), 7.21–7.29 (m, 5 Ph**H**), 8.01 (s, C$_3$**H**), 8.57 (s, C$_5$**H**), 9.04 (br s, N**H**), 9.39 (d, J = 7.8 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.39 (C(O)**C**H$_3$), 42.59 (**C**H$_2$), 65.02 (**C**H), 126.97 (**C**$_4$'), 127.25 (**2C**$_2$' or **2C**$_3$'), 128.32 (**2C**$_2$' or **2C**$_3$'), 138.47 (**C**$_1$'), 143.93 (**C**$_5$), 151.50 (**C**$_3$), 164.77 (**C**(O)NH), 170.23 (**C**(O)CH$_3$) ppm; mass spectrum, FD (relative intensity), 274 (M$^+$ + 1, 100), 273 (11), 205 (19), 204 (13), 140 (67), 139 (31). Anal. ($C_{13}H_{15}N_5O_2$) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-(1-tetrazolyl)-acetamide (17). Making use of α-acetamido-*N*-benzyl-α-ethoxyacetamide (3.00 g, 12.0 mmol), BBr_3 (1 M CH_2Cl_2 solution, 13.2 mL, 13.2 mmol), Et_3N (2.42 g, 24.0 mmol), and tetrazole (1.10 g, 15.6 mmol), the desired product was obtained in 27% yield (0.90 g) as a white solid. Compound **17** was recrystallized from EtOH: mp 169–171 °C; R_f 0.22 (4% MeOH/$CHCl_3$); IR (KBr) 3300 (br), 1660, 1510, 1360, 870, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.97 (s, C(O)C**H$_3$**), 4.25–4.40 (m, C**H$_2$**), 7.05 (d, J = 8.4 Hz, C**H**), 7.21–7.38 (m, 5 Ph**H**), 9.23 (t, J = 5.5 Hz, N**H**), 9.44 (s, C$_5$**H**), 9.69 (d, J = 8.4 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.38 (C(O)**C**H$_3$), 42.78 (**C**H$_2$), 63.62 (**C**H), 127.10 (**C**$_4$'), 127.39 (**2C**$_2$' or **2C**$_3$'), 128.38 (**2C**$_2$' or **2C**$_3$'), 138.26 (**C**$_1$'), 143.67 (**C**$_5$), 163.88 (**C**(O)NH), 170.62 (**C**(O)CH$_3$) ppm; mass spectrum, FD (relative intensity), 275 (M$^+$, 79), 273 (14), 206 (100), 205 (50). Anal. ($C_{12}H_{14}N_6O_2$) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-(oxazol-2-yl)acetamide (18). A mixture of **41** (2.50 g, 10 mmol) and bromoacetaldehyde dimethyl acetal (8.50 g, 52 mmol) in DME (250 mL) was heated to reflux (1 d). The reaction mixture was cooled and filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on SiO_2 gel using 2% MeOH/EtOAc as the eluant to give 0.96 g (36%) of the desired product. Compound **18** was purified by recrystallization from ethyl acetate/hexane: mp 164–166 °C; R_f 0.35 (2% MeOH/EtOAc); IR (KBr) 3280, 3200, 3100, 3025, 2905, 1665, 1635, 1430, 1320, 1290, 1215, 905, 620 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.91 (s, C(O)C**H$_3$**), 4.31 (d, J = 6.0 Hz, C**H$_2$**), 5.72 (d, J = 8.1 Hz, C**H**), 7.21–7.33 (m, 5 Ph**H**, C$_4$**H**), 8.11 (s, C$_5$**H**), 8.33 (d, J = 8.1 Hz, N**H**), 8.90 (t, J = 6.0 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.27 (C(O)**C**H$_3$), 42.33 (**C**H$_2$), 51.08 (**C**H), 126.83 (**C**$_4$' or **C**$_4$), 127.09 (**2C**$_2$' or **2C**$_3$'), 127.17 (**C**$_4$ or **C**$_4$') 128.26 (**2C**$_2$' or **2C**$_3$'), 138.82 (**C**$_1$'), 140.28 (**C**$_5$), 159.92 (**C**$_2$), 166.30 (**C**(O)NH), 169.49 (**C**(O)CH$_3$) ppm; mass spectrum, CI(+) 274 (M$^+$ + 1); M_r (FAB+) 274.11927 (calcd for $C_{14}H_{16}N_3O_3$ 274.11917). Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.09; H, 5.59; N, 15.25.

Synthesis of α-Acetamido-*N*-benzyl-α-(thiazol-2-yl)-acetamide (19). A mixture of **42** (3.00 g, 11.30 mmol) and bromoacetaldehyde dimethyl acetal (9.55 g, 56.50 mmol) in DME (250 mL) was heated to reflux (10 h) and then was allowed to remain at room temperature (20 h). The reaction mixture was allowed to cool and filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on SiO_2 gel using 1% MeOH/EtOAc as the eluant to give 1.83 g (54%) of the desired product. Compound **19** was purified by

recrystallization from chloroform/hexane: mp 166–167 °C; R_f 0.42 (1% MeOH/EtOAc); IR (KBr) 3260, 3030, 1640, 1620, 1520, 1365, 1255, 1135, 790, 685, 595, 500 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.95 (s, C(O)C**H$_3$**), 4.33 (d, J = 5.7 Hz, C**H$_2$**), 5.87 (d, J = 8.1 Hz, C**H**), 7.21–7.34 (m, 5 Ph**H**), 7.69 (d, J = 3.3 Hz, C$_4$**H** or C$_5$**H**), 7.78 (d, J = 3.3 Hz, C$_5$**H** or C$_4$**H**), 8.89 (d, J = 8.1 Hz, N**H**), 8.99 (t, J = 5.7 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 21.99 (C(O)**C**H$_3$), 42.02 (**C**H$_2$), 54.48 (**C**H), 120.37 (**C$_5$**), 126.46 (**C$_4$'**), 126.79 (**2C$_2$'** or **2C$_3$'**), 127.87 (**2C$_2$'** or **2C$_3$'**), 138.47 (**C$_1$'**), 141.92 (**C$_4$**), 167.13 (**C$_2$**), 167.56 (**C**(O)NH), 169.14 (**C**(O)CH$_3$) ppm; mass spectrum, CI(+) 290 (M$^+$ + 1); M_r (FAB+) 290.09727 (calcd for $C_{14}H_{16}N_3O_2S$ 290.09632). Anal. ($C_{14}H_{16}N_3O_2S$) C, H, N.

Synthesis of α-Acetamido-N-benzyl-α-(1,2,4-oxadiazol-3-yl)acetamide (20). Compound **43** (0.90 g, 3.4 mmol) was dissolved in trimethyl orthoformate (10 mL) containing BF_3·Et_2O (6 drops). The solution was warmed to 55 °C (20 min) and then evaporated under reduced pressure to give a white-blue solid. The material was dissolved in MeOH, treated with norit, filtered, and evaporated under reduced pressure to furnish the crude product (0.79 g, 85%). Compound **20** was purified by recrystallization from chloroform/hexane: mp 164–166 °C; R_f 0.37 (6% MeOH/$CHCl_3$); IR (KBr) 3260, 3060, 1620, 1520 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.92 (s, C(O)C**H$_3$**), 4.31 (d, J = 6.0 Hz, C**H$_2$**), 5.82 (d, J = 8.4 Hz, C**H**), 7.15–7.34 (m, 5 Ph**H**), 8.88 (d, J = 8.4 Hz, N**H**), 8.96 (t, J = 6.0 Hz, N**H**), 9.62 (s, C$_5$**H**); ^{13}C NMR (DMSO-d_6) 22.22 (C(O)**C**H$_3$), 42.35 (**C**H$_2$), 49.44 (**C**H), 126.77 (**C$_4$'**), 127.06 (**2C$_2$'** or **2C$_3$'**), 128.18 (**2C$_2$'** or **2C$_3$'**), 138.70 (**C$_1$'**), 166.25 (**C**(O)NH), 166.74 (**C$_3$**), 167.24 (**C**(O)CH$_3$), 169.52 (**C$_5$**) ppm; mass spectrum, FD (relative intensity), 275 (M$^+$ + 1, 28), 274 (100). Anal. ($C_{13}H_{14}N_4O_3$) C, H, N.

Synthesis of α-Acetamido-N-benzyl-α-(tetrahydrofuran-2-yl)acetamide (21). A methanolic solution (70 mL) of **4** (3.50 g, 12.9 mmol) was hydrogenated (35–40 psi) for 44 h in the presence of Pd/C (10%, 0.44 g). The catalyst was filtered through celite and washed with MeOH (10 mL), and the filtrate was concentrated to dryness *in vacuo* to give **21a** and **21b** (3.50 g) as a white solid. The products were fractionally recrystallized from EtOAc to give 1.30 g (37%) of **21a**: mp 159–161 °C; R_f 0.38 (6% MeOH/$CHCl_3$); IR (KBr) 3340 (br), 3000, 1600, 1550 (br), 1420, 1350, 720, 680 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.66–1.90 (m, C$_3$**H$_2$**, C$_4$**H$_2$**), 1.85 (C(O)C**H$_3$**), 3.62–3.68 (m, C$_5$**HH'**), 3.75–3.80 (m, C$_5$**HH'**), 3.98–4.00 (m, C$_2$**H**), 4.26–4.38 (m, C**H**, C**H$_2$**), 7.18–7.32 (m, 5 Ph**H**), 8.11 (d, J = 8.8 Hz, N**H**), 8.52 (t, J = 5.8 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.52 (C(O)**C**H$_3$), 24.78 (**C$_3$**), 27.82 (**C$_4$**), 41.96 (**C**H$_2$), 55.67 (**C**H), 67.54 (**C$_5$**), 78.48 (**C$_2$**), 126.58 (**C$_4$'**), 127.97 (**2C$_2$'** or **2C$_3$'**), 128.12 (**2C$_2$'** or **2C$_3$'**), 139.27 (**C$_1$'**), 169.09 (**C**(O)NH), 170.09 (**C**(O)CH$_3$) ppm; mass spectrum, EI, *m/e* (relative intensity) 277 (M$^+$ + 1, 4), 206 (52), 142 (13), 106 (38), 91 (100), 71 (97). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

The mother liquors from the EtOAc recrystallization were concentrated to half its volume, and hexane was added dropwise while heating until the solution became turbid. A white solid (0.65 g, 18%) separated on cooling and was collected by filtration to give diastereoisomer **21b**: mp 130–132 °C; R_f 0.38 (6% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 1.55–1.86 (m, C$_3$**H$_2$**, C$_4$**H$_2$**), 1.89 (s, C(O)C**H$_3$**), 3.55–3.64 (m, C$_5$**HH'**), 3.70–3.78 (m, C$_5$**HH'**), 4.08–4.11 (m, C$_2$**H**), 4.27 (d, J = 5.8 Hz, C**H$_2$**), 4.36 (dd, J = 4.7, 8.6 Hz, C**H**), 7.21–7.32 (m, 5 Ph**H**), 7.94 (d, J = 8.6 Hz, N**H**), 8.39 (t, J = 5.8 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.45 (C(O)**C**H$_3$), 25.16 (**C$_4$**), 27.53 (**C$_3$**), 42.04 (**C**H$_2$), 55.48 (**C**H), 67.53 (**C$_5$**), 78.26 (**C$_2$**), 126.59 (**C$_4$'**), 127.04 (**2C$_2$'** or **2C$_3$'**), 128.10 (**2C$_2$'** or **2C$_3$'**), 139.21 (**C$_1$'**), 169.55 (**C**(O)NH), 169.79 (**C**(O)CH$_3$) ppm; mass spectrum, EI, *m/e* (relative intensity) 277 (M$^+$ + 1, 4), 206 (50), 142 (23), 106 (39), 91 (100), 71 (96). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

Synthesis of α-Acetamido-N-benzyl-α-methyl-α-(furan-2-yl)acetamide (22). Employing the mixed carbonic anhydride coupling procedure[6,18] with **47** (2.40 g, 12.2 mmol), 4-methylmorpholine (1.23 g, 12.2 mmol), isobutyl chloroformate (1.83 g, 13.4 mmol), and benzylamine (1.43 g, 12.7 mmol) gave **22** (1.50 g, 43%) as a thick oil: R_f 0.29 (2% MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.94 (s, C**H$_3$**), 1.98 (s, C(O)C**H$_3$**), 4.40 (d, J = 5.6 Hz, C**H$_2$**), 6.20 (br s, N**H**), 6.34–6.37 (m, C$_3$**H**, C$_4$**H**), 7.05–7.36 (m, N**H**, C$_5$**H**, 5 Ph**H**); ^{13}C NMR ($CDCl_3$) 22.31 (C(O)**C**H$_3$), 23.81 (**C**H$_3$), 43.77 (**C**H$_2$), 58.50 (**C**(CH$_3$)), 107.94 (**C$_4$**), 110.67 (**C$_3$**), 126.99 (**2C$_2$'** or **2C$_3$'**), 127.41 (**C$_4$'**), 128.60 (**2C$_2$'** or **2C$_3$'**), 137.52 (**C$_1$'**), 142.38 (**C$_5$**), 152.94 (**C$_2$**), 169.03 (**C**(O)NH), 171.16 (**C**OCH$_3$) ppm; mass spectrum, EI, *m/e* (relative intensity) 287 (M$^+$ + 1, 4), 228 (4), 153 (99), 152 (96), 138 (15), 111 (63), 110 (100), 91 (75); M_r (EI) 286.13074 (calcd for $C_{16}H_{18}N_2O_3$ 286.13174).

Synthesis of α-Thioacetamido-N-benzyl-α-(furan-2-yl)acetamide (23). A THF solution (80 mL) of **4** (1.00 g, 3.7 mmol) and Lawesson's reagent (0.73 g, 1.8 mmol) was stirred at room temperature (4 h). The THF was removed *in vacuo*, and the residue was purified by flash column chromatography on SiO_2 gel using 1% MeOH/$CHCl_3$ to give 0.75 g (71%) of **23**: mp 78–80 °C; R_f 0.51 (1% MeOH/$CHCl_3$); IR (KBr) 3200 (br), 1630, 1500, 1440, 1350, 790, 710, 680 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.46 (s, C(S)C**H$_3$**), 4.27–4.35 (m, C**H$_2$**), 6.22 (d, J = 7.7 Hz, C**H**), 6.32 (d, J = 3.3 Hz, C$_3$**H**), 6.41–6.44 (m, C$_4$**H**), 7.15–7.33 (m, 5 Ph**H**), 7.64 (s, C$_5$**H**), 8.81 (t, J = 5.9 Hz, N**H**), 10.54 (d, J = 7.7 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 32.70 (s, C(S)**C**H$_3$), 42.39 (**C**H$_2$), 56.82 (**C**H), 108.76 (**C$_3$**), 110.67 (**C$_4$**), 126.81 (**C$_4$'**), 127.12 (**2C$_2$'** or **2C$_3$'**), 128.23 (**2C$_2$'** or **2C$_3$'**), 139.98 (**C$_1$'**), 143.06 (**C$_5$**), 149.53 (**C$_2$**), 166.55 (**C**(O)NH), 200.68 (**C**(S)CH$_3$) ppm; mass spectrum, (FD), 288 (M$^+$). Anal. ($C_{15}H_{16}N_2O_2S$) C, H, N.

Synthesis of α-Thioacetamido-N-benzyl-α-(furan-2-yl)thioacetamide (24). A THF solution (90 mL) of **4** (2.00 g, 7.4 mmol) and Lawesson's reagent (3.27 g, 8.1 mmol) was heated to reflux (4 h). The THF was removed *in vacuo*, and the residue was purified by two successive flash column chromatographies on SiO_2 gel using 0.5% MeOH/$CHCl_3$ as the eluant in the first chromatography and $CHCl_3$ in the second chromatography. Compound **24** (0.50 g, 22%) was then further purified by preparative TLC ($CHCl_3$): mp 99–101 °C; R_f 0.74 (1% MeOH/$CHCl_3$); IR (KBr) 3100, 1580, 1500 (br) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.58 (s, C(S)C**H$_3$**), 4.86 (dd, J = 5.4, 15.0 Hz, CH**H**), 4.96 (dd, J = 5.4, 15.0 Hz, CH**H**), 6.49–6.55 (m, C$_3$**H**, C$_4$**H**), 6.65 (d, J = 7.5 Hz, C**H**), 7.31–7.43 (m, 5 Ph**H**), 7.75 (s, C$_5$**H**), 10.64 (d, J = 7.5 Hz, N**H**), 10.95 (t, J = 5.4 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 32.79 (s, C(S)**C**H$_3$), 48.30 (**C**H$_2$), 61.88 (**C**H), 108.50 (**C$_3$**), 110.53 (**C$_4$**), 127.05 (**C$_4$'**), 127.48 (**2C$_2$'** or **2C$_3$'**), 128.19 (**2C$_2$'** or **2C$_3$'**), 136.67 (**C$_1$'**), 142.91 (**C$_5$**), 150.15 (**C$_2$**), 197.45 (**C**(S)NH), 200.56 (**C**(S)CH$_3$) ppm; mass spectrum, FD, 304 (M$^+$). Anal. ($C_{15}H_{16}N_2OS_2$) C, H, N.

Synthesis of α-Acetamido-N-(3-pyridinylmethyl)-α-(furan-2-yl)acetamide (25). Using racemic **48** (3.00 g, 16.4 mmol), 4-methylmorpholine (1.66 g, 16.4 mmol), isobutyl chloroformate (2.24 g, 16.4 mmol), and 3-(aminomethyl)pyridine (1.77 g, 16.4 mmol) in the mixed carbonic anhydride protocol[6,18] gave 3.35 g (75%) of **25**: mp 172–174 °C (recrystallized from EtOAc); R_f 0.27 (8% MeOH/$CHCl_3$); IR (KBr) 3400, 3300, 1640, 1540, 1420, 1360, 820, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.89 (s, C(O)C**H$_3$**), 4.32 (d, J = 5.8 Hz, C**H$_2$**), 5.55 (d, J = 7.9 Hz, C**H**), 6.28–6.29 (m, C$_3$**H**), 6.41–6.43 (m, C$_4$**H**), 7.32 (dd, J = 4.8, 7.7 Hz, C$_5$'**H**), 7.58–7.62 (m, C$_4$'**H**, C$_5$**H**), 8.44 (br s, C$_2$'**H**, C$_6$'**H**), 8.62 (d, J = 7.9 Hz, N**H**), 8.81 (t, J = 5.8 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.31 (C(O)**C**H$_3$), 39.98 (**C**H$_2$), 50.94 (**C**H), 107.67 (**C$_4$**), 110.54 (**C$_3$**), 123.38 (**C$_5$'**), 134.57 (**C$_3$'**), 134.83 (**C$_4$'**), 142.64 (**C$_5$**), 148.06 (**C$_6$'**), 148.55 (**C$_2$'**), 150.94 (**C$_2$**), 168.19 (**C**(O)NH), 169.26 (**C**(O)CH$_3$) ppm; mass spectrum, FD, 274 (M$^+$ + 1). Anal. ($C_{14}H_{15}N_3O_3$) C, H, N.

Synthesis of α-Acetamido-N-(4-pyridinylmethyl)-α-(furan-2-yl)acetamide (26). Making use of racemic **48** (3.00 g, 16.4 mmol), 4-methylmorpholine (1.66 g, 16.4 mmol), isobutyl chloroformate (2.24 g, 16.4 mmol), and 4-(aminomethyl)pyridine (1.77 g, 16.4 mmol) in the mixed carbonic anhydride method[6,18] gave 3.40 g (76%) of **26**: mp 168–170 °C (recrystallized from EtOAc); R_f 0.31 (8% MeOH/$CHCl_3$); IR (KBr) 3180, 1650 (br), 1480, 1400, 1340, 780, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.90 (s, C(O)C**H$_3$**), 4.32 (d, J = 5.7 Hz, C**H$_2$**), 5.57 (d, J = 7.8 Hz, C**H**), 6.32–6.34 (m, C$_3$**H**), 6.42–6.43 (m, C$_4$**H**), 7.19 (d, J = 4.9 Hz, C$_3$'**H**, C$_5$'**H**), 7.64 (s, C$_5$**H**), 8.46 (d, J = 4.9 Hz, C$_2$'**H**, C$_6$'**H**), 8.64 (d, J = 7.8 Hz, N**H**), 8.84 (t, J = 5.7 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.27 (C(O)**C**H$_3$), 41.26 (**C**H$_2$), 50.99 (**C**H), 107.74 (**C$_4$**), 110.54 (**C$_3$**), 121.87 (**C$_3$'**, **C$_5$'**), 142.63 (**C$_5$**), 148.17 (**C$_4$'**), 149.35 (**C$_2$'**, **C$_6$'**), 150.82 (**C$_2$**), 168.35 (**C**(O)NH), 169.29 (**C**(O)CH$_3$) ppm; mass spectrum, FD, 274 (M$^+$ + 1). Anal. ($C_{14}H_{15}N_3O_3$) C, H, N.

Synthesis of α-Acetamido-N-[(1-oxo-3-pyridinyl)methyl]-α-(furan-2-yl)acetamide (27). A solution of **25** (1.50 g, 5.5 mmol) and *m*-chloroperoxybenzoic acid (1.90 g, 6.0 mmol) in THF (175 mL) was heated to reflux (3 h) and then cooled to room temperature. The THF solution was concentrated to approximately half its volume and then cooled to give 1.00 g (63%) of **27**: mp 159–161 °C (recrystallized from EtOH); R_f 0.30 (20% MeOH/$CHCl_3$); IR (KBr) 3400 (br), 1620, 1500 (br), 1420, 1350,

750 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.89 (s, C(O)C**H$_3$**), 4.27 (d, J = 5.0 Hz, C**H$_2$**), 5.53 (d, J = 7.6 Hz, C**H**), 6.31 (br s, C$_3$**H**), 6.42 (br s, C$_4$**H**), 7.14–7.18 (m, 1 Ar**H**), 7.31–7.37 (m, 1 Ar**H**), 7.61 (br s, C$_5$**H**), 8.07 (s, 2 Ar**H**), 8.63 (br s, N**H**), 8.80 (br s, N**H**); ^{13}C NMR (DMSO-d_6) 22.29 (C(O)**C**H$_3$), 39.36 (**C**H$_2$), 50.99 (**C**H), 107.79 (**C**$_4$), 110.56 (**C**$_3$), 124.03 (**C**$_4'$), 126.10 (**C**$_5'$), 137.16 (**C**$_3'$), 137.31 (**C**$_6'$), 138.70 (**C**$_2'$), 142.69 (**C**$_5$), 150.72 (**C**$_2$), 168.40 (**C**(O)NH), 169.32 (**C**(O)CH$_3$) ppm; mass spectrum, FD, 289 (M$^+$); M_r (EI) 289.10554 (calcd for $C_{14}H_{15}N_3O_4$ 289.10626). Anal. Calcd for $C_{14}H_{15}N_3O_4 \cdot 2.0H_2O$: C, 51.69; H, 5.89; N, 12.92. Found: C, 52.03; H, 5.56; N, 13.36.

Synthesis of α-Acetamido-*N*-[(1-oxo-4-pyridinyl)methyl]-α-(furan-2-yl)acetamide (28). Via the preceding procedure and using **26** (1.50 g, 5.5 mmol) and *m*-chloroperoxybenzoic acid (1.90 g, 6.0 mmol), a light yellow solid (0.96 g, 60%) was obtained directly upon cooling the THF solution. The precipitate was filtered and recrystallized from EtOH to give **28**: mp 210–212 °C dec; R_f 0.25 (20% MeOH/CHCl$_3$); IR (KBr) 3300, 1620, 1500, 1410, 1350, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.89 (s, C(O)C**H$_3$**), 4.26 (d, J = 5.8 Hz, C**H$_2$**), 5.52 (d, J = 7.7 Hz, C**H**), 6.30 (br s, C$_3$**H**), 6.41–6.42 (m, C$_4$**H**), 7.21 (d, J = 6.8 Hz, C$_3'$**H**, C$_5'$**H**), 7.63 (s, C$_5$**H**), 8.14 (d, J = 6.8 Hz, C$_2'$**H**, C$_6'$**H**), 8.62 (d, J = 7.7 Hz, N**H**), 8.82 (t, J = 5.8 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.35 (C(O)-**C**H$_3$), 40.68 (**C**H$_2$), 51.14 (**C**H), 107.87 (**C**$_4$), 110.62 (**C**$_3$), 124.83 (**C**$_3'$, **C**$_5'$), 137.43 (**C**$_4'$), 138.39 (**C**$_2'$, **C**$_6'$), 142.72 (**C**$_5$), 150.77 (**C**$_2$), 168.48 (**C**(O)NH), 169.45 (**C**(O)CH$_3$) ppm; mass spectrum, FD, 289 (M$^+$). Anal. ($C_{14}H_{15}N_3O_4$) C, H, N.

Synthesis of α-Acetamido-α-(furan-2-yl)-2′-(pyridin-2-yl)acetohydrazide (29). Via the mixed carbonic anhydride procedure,[6,18] and using racemic **48** (2.00 g, 10.4 mmol), 4-methylmorpholine (1.10 g, 10.9 mmol), isobutyl chloroformate (1.49 g, 10.9 mmol), and 2-hydrazinopyridine (1.20 g, 11.0 mmol), an insoluble material was obtained upon workup containing **29** and 4-methylmorpholine hydrochloride. The reaction products were suspended in EtOH (25 mL), and **29** (1.00 g) was collected by filtration. Concentration of the THF filtrate and trituration of the residue with EtOAc gave an additional 0.70 g of **29** to give a combined yield of 1.70 g (64%): mp 226–228 °C (recrystallized from EtOH); R_f 0.30 (10% MeOH/CHCl$_3$); IR (KBr) 3400, 1650, 1580, 1440, 1360, 1320, 770, 730 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.83 (s, C(O)C**H$_3$**), 5.64 (d, J = 8.0 Hz, C**H**), 6.41–6.50 (m, C$_3$**H**, C$_4$**H**, C$_5'$**H**), 6.67 (dd, J = 5.4, 6.7 Hz, C$_3'$**H**), 7.44–7.52 (m, C$_4'$**H**), 7.66 (s, C$_5$**H**), 8.02 (d, J = 4.0 Hz, C$_6'$**H**), 8.40 (s, C(O)NHN**H**), 8.66 (d, J = 8.0 Hz, N**H**), 10.20 (s, C(O)N**H**NH); ^{13}C NMR (DMSO-d_6) 22.26 (C(O)**C**H$_3$), 49.56 (**C**H), 105.93 (**C**$_3'$), 107.87 (**C**$_3$), 110.57 (**C**$_4$), 114.50 (**C**$_5'$), 137.48 (**C**$_4'$), 142.76 (**C**$_5$), 147.45 (**C**$_6'$), 150.60 (**C**$_2$), 159.59 (**C**$_2'$), 167.88 (**C**(O)NH), 169.28 (**C**(O)CH$_3$) ppm; mass spectrum, FD, 274 (M$^+$); M_r (EI) 274.10649 (calcd for $C_{13}H_{14}N_4O_3$ 274.10659). Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15; N, 20.43. Found: C, 56.42; H, 5.22; N, 19.72.

Synthesis of (*R*)-(−) α-Acetamido-*N*-(4-fluorobenzyl)-α-(furan-2-yl)acetamide [(*R*)-30]. Using (*R*)-**48** (0.94 g, 5.1 mmol), 4-methylmorpholine (0.52 g, 5.1 mmol), isobutyl chloroformate (0.70 g, 5.1 mmol), and 4-fluorobenzylamine (0.65 g, 5.2 mmol) in the mixed carbonic anhydride method[6,18] gave 1.00 g (68%) of (*R*)-**30**: mp 205–207 °C (recrystallized from EtOAc); R_f 0.30 (4% MeOH/CHCl$_3$); $[\alpha]^{26}_D$ = −77.42 (c = 1, MeOH); IR (KBr) 3400 (br), 1620, 1580, 1500 (br), 1350, 770, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.89 (s, C(O)C**H$_3$**), 4.27 (d, J = 5.9 Hz, C**H$_2$**), 5.54 (d, J = 8.0 Hz, C**H**), 6.27 (d, J = 3.0 Hz, C$_3$**H**), 6.41 (dd, J = 1.9, 3.0 Hz, C$_4$**H**), 7.08–7.15 (m, 2 Ar**H**), 7.20–7.26 (m, 2 Ar**H**), 7.61 (d, J = 1.9 Hz, C$_5$**H**), 8.58 (d, J = 8.0 Hz, N**H**), 8.74 (t, J = 5.9 Hz, N**H**) ppm, addition of (*R*)-(−)-mandelic acid to a CDCl$_3$ solution of (*R*)-**30** gave only one signal for the acetamide methyl protons; mass spectrum, FD, 290 (M$^+$). Anal. ($C_{15}H_{15}FN_2O_3$) C, H, N.

Synthesis of (*R*)-(−) α-Acetamido-*N*-(4-methylbenzyl)-α-(furan-2-yl)acetamide [(*R*)-31]. Employing the mixed carbonic anhydride procedure[6,18] and making use of (*R*)-**48** (1.50 g, 8.2 mmol), 4-methylmorpholine (0.83 g, 8.2 mmol), isobutyl chloroformate (1.12 g, 8.2 mmol), and 4-methylbenzylamine (0.99 g, 8.2 mmol) gave 1.80 g (77%) of (*R*)-**31**: mp 210–212 °C (recrystallized from EtOAc); R_f 0.54 (4% MeOH/CHCl$_3$); $[\alpha]^{26}_D$ = −74.43 (c = 1, MeOH); IR (KBr) 3400 (br), 1610 (br), 1500 (br), 1350, 1320, 780, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.89 (s, C(O)-C**H$_3$**), 2.25 (s, C**H$_3$**), 4.24 (d, J = 5.5 Hz, C**H$_2$**), 5.56 (d, J = 8.1 Hz, C**H**), 6.28 (br s, C$_3$**H**), 6.41 (br s, C$_4$**H**), 7.09 (br s, 4 Ar**H**), 7.61 (br s, C$_5$**H**), 8.58 (d, J = 8.1 Hz, N**H**), 8.72 (t, J = 5.5 Hz, N**H**), addition of (*R*)-(−)-mandelic acid to a CDCl$_3$ solution of (*R*)-**31** gave only one signal for the acetamide methyl protons; ^{13}C NMR (DMSO-d_6) 20.64 (**C**H$_3$), 22.32 (C(O)**C**H$_3$), 42.00 (**C**H$_2$), 50.88 (**C**H), 107.52 (**C**$_4$), 110.50 (**C**$_3$), 127.06 (**2C**$_2'$ or **2C**$_3'$), 128.77 (**2C**$_2'$ or **2C**$_3'$), 135.82 (**C**$_1'$ or **C**$_4'$), 135.98 (**C**$_1'$ or **C**$_4'$), 142.51 (**C**$_5$), 151.21 (**C**$_2$), 167.87 (**C**(O)NH), 169.17 (**C**(O)CH$_3$) ppm; mass spectrum, FD, 287 (M$^+$ + 1). Anal. ($C_{16}H_{18}N_2O_3$) C, H, N.

Synthesis of (*R*)-(−) α-Acetamido-*N*-[4-(trifluoromethyl)-benzyl]-α-(furan-2-yl)acetamide [(*R*)-32]. Using (*R*)-**48** (1.00 g, 5.5 mmol), 4-methylmorpholine (0.55 g, 5.5 mmol), isobutyl chloroformate (0.75 g, 5.5 mmol), and 4-trifluoromethylbenzylamine (0.96 g, 5.5 mmol) in the mixed carbonic anhydride protocol[6,18] gave 1.15 g (59%) of (*R*)-**32**: mp 193–195 °C (recrystallized from ethyl acetate/hexanes); $[\alpha]^{26}_D$ = −69.27 (c = 1, MeOH); IR (KBr) 3220, 1610, 1520, 1400, 1350, 800, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.89 (s, C(O)C**H$_3$**), 4.37 (d, J = 5.8 Hz, C**H$_2$**), 5.56 (d, J = 7.9 Hz, C**H**), 6.30–6.31 (m, C$_3$**H**), 6.41–6.43 (m, C$_4$**H**), 7.40-7.43 (m, 2 Ar**H**), 7.63–7.68 (m, 2 Ar**H**, C$_5$**H**), 8.61 (d, J = 7.9 Hz, N**H**), 8.44 (t, J = 5.8 Hz, N**H**), addition of (*R*)-(−)-mandelic acid to a CDCl$_3$ solution of (*R*)-**32** gave only one signal for the acetamide methyl protons; mass spectrum, FD, 340 (M$^+$). Anal. ($C_{16}H_{15}F_3N_2O_3$) C, H, N.

Preparation of α-Acetamido-*N*-benzyl-α-cyanoacetamide[9b] (34). Benzylamine (4.72 g, 4.78 mL, 44.0 mmol) was added in one portion to a suspension of ethyl acetamidocyanoacetate (4.90 g, 28.8 mmol) in EtOH (75 mL). The mixture was stirred at room temperature (18 h), and the resulting suspension was evaporated *in vacuo*. The residue was recrystallized (tetrahydrofuran/petroleum ether (35–60 °C)) to give 4.26 g (64%) of **34** as white crystals: mp 179-180 °C; R_f 0.25 (5% MeOH/CHCl$_3$); IR (KBr) 3200, 3040, 1620 (br), 1565 (br), 1505 (br), 1360, 1280, 1210, 1030, 990 (br), 890, 725, 690, 580 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.94 (s, C(O)C**H$_3$**), 4.33 (d, J = 6.0 Hz, C**H$_2$**), 5.59 (d, J = 8.1 Hz, C**H**), 7.20–7.36 (m, 5 Ph**H**), 8.86 (t, J = 6.0 Hz, N**H**), 9.09 (d, J = 8.1 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.07 (C(O)C**H$_3$**), 42.64 (**C**H$_2$), 44.22 (**C**H), 116.45 (**C**N), 126.90 (**2C**$_2'$ or **2C**$_3'$), 127.11 (**2C**$_2'$ or **2C**$_3'$), 128.23 (**C**$_4'$), 138.38 (**C**$_1'$), 162.81 (**C**(O)CH$_3$), 169.69 (**C**(O)NH) ppm; mass spectrum, EI, m/e (relative intensity) 231 (4), 215 (1), 204 (2), 190 (4), 172 (17), 148 (1), 129 (6), 106 (20), 98 (42), 91 (100), 77 (19), 65 (29). Anal. ($C_{12}H_{13}N_3O_2$) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-[1-(dimethylsulfamoyl)imidazol-4-yl]acetamide (37). Using the literature procedure,[11] imidazole (9.54 g, 0.14 mol) was treated with Et$_3$N (13.13 g, 0.13 mol) and dimethylsulfamoyl chloride (17.38 g, 0.12 mol) to provide **36** (17.00 g, 81%) after distillation at 100–112 °C (0.4 Torr): mp 42–44 °C (lit.[11] mp 42–44 °C); ^{1}H NMR (DMSO-d_6) δ 2.59 (s, N(C**H$_3$**)$_2$), 7.13 (s, C$_4$**H**), 7.56 (s, C$_5$**H**), 8.13 (s, C$_2$**H**); ^{1}H NMR (CDCl$_3$) δ 2.86 (s, N(C**H$_3$**)$_2$), 7.15 (s, C$_4$**H**), 7.33 (s, C$_5$**H**), 7.95 (s, C$_2$**H**); ^{13}C NMR (^{1}H-coupled, DMSO-d_6) 37.54 (q, J = 142.5 Hz, N(**C**H$_3$)$_2$), 118.54 (dd, J = 197.8, 17.6 Hz, **C**$_5$), 130.07 (br d, J = 197.8 Hz, **C**$_4$), 137.07 (br d, J = 216.1 Hz, **C**$_2$) ppm; irradiation of the ^{1}H NMR signal at δ 7.13 led to a collapse of the broad doublet at δ 130.07 in the ^{13}C NMR spectrum to a singlet; irradiation of the ^{1}H NMR signal at δ 7.56 led to a collapse of the doublet of doublets at δ 118.54 in the ^{13}C NMR spectrum to an apparent singlet; irradiation of the ^{1}H NMR signal at δ 8.13 led to a collapse of the broad doublet of δ 137.06 in the ^{13}C NMR spectrum to an apparent singlet; ^{13}C NMR (CDCl$_3$) 37.54 (N(**C**H$_3$)$_2$), 117.27 (**C**$_5$), 129.69 (**C**$_4$), 136.06 (**C**$_2$) ppm.

To a cooled (−78 °C) THF solution (150 mL) of **33** (prepared from α-acetamido-*N*-benzyl-α-ethoxyacetamide (2.00 g, 8.0 mmol) and BBr$_3$ (1 M solution in CH$_2$Cl$_2$, 9.0 mL, 9.0 mmol)) was added Et$_3$N (1.62 g, 16.0 mmol), and then a THF solution of the lithio salt of **36**[11] (generated by the addition of *n*-BuLi (2.5 M in hexane, 3.9 mL, 9.68 mmol) into a cooled (−78 °C) THF solution (25 mL) of **36** (1.54 g, 8.8 mmol)) was slowly added (15 min). The reaction mixture was stirred at this temperature (30 min) and then at room temperature (45 min). A saturated aqueous NH$_4$Cl solution (50 mL) and H$_2$O (50 mL) were then successively added, and the aqueous mixture was extracted with EtOAc (3 × 50 mL). The combined extracts were dried (Na$_2$SO$_4$), and the volatile materials were removed by distillation *in vacuo*. The residue was purified by flash column chromatography on SiO$_2$ gel (4% MeOH/CHCl$_3$) to give 0.50 g (17%) of **37**: mp 145–147 °C (recrystallized from ethyl acetate/hexanes); R_f 0.35 (4% MeOH/CHCl$_3$); IR (KBr) 3400, 1640, 1530, 1380, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.96 (s,

C(O)CH$_3$), 2.77 (s, N(CH$_3$)$_2$), 4.25 (dd, J = 6.0, 15.5 Hz, CHH), 4.34 (dd, J = 6.0, 15.5 Hz, CHH), 5.43 (d, J = 8.0 Hz, CH), 7.19–7.30 (m, 5 PhH), 7.40 (s, C$_5$H), 8.17 (s, C$_2$H), 8.42 (d, J = 8.0 Hz, NH), 8.67 (t, J = 6.0 Hz, NH); ^{13}C NMR (DMSO-d_6) 22.42 (C(O)CH$_3$), 37.80 (N(CH$_3$)$_2$), 42.11 (CH$_2$), 51.40 (CH), 115.50 (C$_5$), 126.64 (C$_4$'), 126.94 (2C$_2$' or 2C$_3$'), 128.12 (2C$_2$' or 2C$_3$'), 136.70 (C$_2$), 139.17 (C$_1$'), 140.26 (C$_4$), 168.93 (C(O)NH), 169.09 (C(O)CH$_3$) ppm; mass spectrum, FD (relative intensity), 380 (M$^+$ + 1, 34), 248 (13), 247 (100), 108 (64). Anal. (C$_{16}$H$_{21}$N$_5$O$_4$S) C, H, N.

Preparation of 2-Acetamido-*N*-benzylmalonamide[9b] (41). Compound **34** (2.00 g, 8.65 mmol) and concentrated aqueous HCl (4.20 g, 4 mL, 34.6 mmol) were combined and stirred at 40 °C (15 min). The resulting suspension was filtered, and the white solid was triturated with CHCl$_3$ (20 mL, 5 min), filtered, and then dissolved in 4:1 1-butanol/H$_2$O (150 mL). The organic phase was concentrated to a small volume *in vacuo*, hexanes were added, and the resulting solution was refrigerated (−16 °C) overnight to yield after filtration 1.20 g (55%) of the desired compound as a white solid: mp 191–192 °C; R_f 0.18 (5% MeOH/CHCl$_3$); IR (KBr) 3370, 3300, 3160, 2905, 1665 (br), 1635 (br), 1520, 1480, 1390, 1260, 1050, 730, 690, 665, 600 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.92 (s, C(O)CH$_3$), 4.31 (d, J = 5.7 Hz, CH$_2$), 4.92 (d, J = 7.8 Hz, CH), 7.20–7.34 (m, 5 PhH), 7.36 (s, NHH'), 7.50 (s, NHH'), 8.10 (d, J = 7.8 Hz, NH), 8.60 (t, J = 5.7 Hz, NH); ^{13}C NMR (DMSO-d_6) 22.48 (C(O)CH$_3$), 42.22 (CH$_2$), 57.28 (CH), 126.73 (C$_4$'), 127.02 (2C$_2$' or 2C$_3$'), 128.19 (2C$_2$' or 2C$_3$'), 138.99 (C$_1$'), 166.87 (C(O)NH$_2$), 168.53 (C(O)CH$_3$), 169.41 (C(O)NH) ppm; mass spectrum, EI, m/e (relative intensity) 249 (6), 232 (3), 206 (5), 190 (13), 163 (6), 146 (8), 116 (70), 99 (92), 91 (100), 73 (95), 66 (46); M_r (EI) 249.11101 (calcd for C$_{12}$H$_{15}$N$_3$O$_2$ 249.11134).

Synthesis of 1-(*N*,*N*-Dimethylsulfamoyl)-4-methylimidazole (38). Using the procedure described for compound **36**,[11] 4-methylimidazole (1.00 g, 12.18 mmol) was treated with Et$_3$N (1.16 g, 11.5 mmol) and dimethylsulfamoyl chloride (1.59 g, 11.00 mmol) to provide **38** (1.27 g, 61%) after purification by flash column chromatography on SiO$_2$ (EtOAc): mp 85–87 °C (recrystallized from ethyl acetate/hexanes); R_f 0.38 (EtOAc); IR (KBr) 3160, 1815, 1630, 1425, 1390, 1360, 1140, 1010 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.15 (s, C$_4$CH$_3$), 2.79 (s, N(CH$_3$)$_2$), 7.32 (s, C$_5$H), 8.03 (s, C$_2$H); ^{13}C NMR (DMSO-d_6) 13.27 (C$_4$CH$_3$), 37.79 (N(CH$_3$)$_2$), 114.34 (C$_5$), 136.44 (C$_2$), 138.85 (C$_4$) ppm; mass spectrum, CI(+) 190 (M + 1); M_r (+CI) 189.05733 (calcd for C$_6$H$_{11}$N$_3$O$_2$S 189.05720). Anal. (C$_6$H$_{11}$N$_3$O$_2$S) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-thiocarbamoylacetamide (42). Compound **34** (4.00 g, 34.64 mmol) and *O*,*O*'-diethyl dithiophosphate[28] (6.45 g, 34.64 mmol) were dissolved in a binary MeOH (80 mL)–EtOH (80 mL) solution containing H$_2$O (0.32 mL), and the mixture was heated at 70 °C (6 h) and then allowed to remain at room temperature (13 h). The reaction mixture was filtered, and the solvent was removed *in vacuo*. The residue was triturated with EtOAc to give 2.00 g (44%) of the desired compound. Compound **42** was recrystallized from ethyl acetate/hexanes: mp 170–171 °C; R_f 0.51 (8% MeOH/CHCl$_3$); IR (KBr) 3360, 3310, 2910, 1610, 1580, 1425, 1230, 1090, 890, 725, 685 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.93 (s, C(O)CH$_3$), 4.29 (d, J = 5.0 Hz, CH$_2$), 5.21 (d, J = 8.0 Hz, CH), 7.15–7.31 (m, 5 PhH), 8.03 (d, J = 8.0 Hz, NH), 8.69 (t, J = 5.0 Hz, NH), 9.27 (s, NHH'), 9.91 (s, NHH'); ^{13}C NMR (DMSO-d_6) 22.68 (C(O)CH$_3$), 42.24 (CH$_2$), 62.95 (CH), 126.63 (C$_4$'), 126.96 (2C$_2$' or 2C$_3$'), 128.09 (2C$_2$' or 2C$_3$'), 138.83 (C$_1$'), 166.42 (C(O)NH), 169.10 (C(O)CH$_3$), 200.28 (C(S)NH$_2$) ppm; mass spectrum, FD (relative intensity), 266 (M$^+$ + 1, 42), 265 (100). Anal. (C$_{12}$H$_{15}$N$_3$O$_2$S) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-[(hydroxyimino)-aminomethyl]acetamide (43). A suspension of NH$_2$OH·HCl (1.80 g, 25.9 mmol), K$_2$CO$_3$ (4.85 g, 35.0 mmol), and **34** (2.00 g, 8.65 mmol) in absolute EtOH (150 mL) was heated at reflux (16 h). The reaction mixture was cooled, filtered, and concentrated *in vacuo*. The residue was first purified by flash column chromatography on SiO$_2$ gel using 8% MeOH/CHCl$_3$ as the eluant to give 1.24 g (54%) of the desired product and then recrystallized from ethyl acetate/hexane: mp 172–173 °C; R_f 0.40 (10% MeOH/CHCl$_3$); IR (KBr) 3380, 3320, 3160, 2920, 1650, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.87 (s, C(O)CH$_3$), 4.27 (d, J = 6.0 Hz, CH$_2$), 4.88 (d, J = 8.4 Hz, CH), 5.37 (s, NH$_2$), 7.21–7.30 (m, 5 PhH), 8.21 (d, J = 8.4 Hz, NH), 8.48 (t, J = 6.0 Hz, NH), 9.28 (s, OH); ^{13}C NMR (DMSO-d_6) 22.46 (C(O)CH$_3$), 42.15 (CH$_2$), 53.65 (CH), 126.60 (C$_4$'), 126.99 (2C$_2$' or 2C$_3$'), 128.11 (2C$_2$' or 2C$_3$'), 139.02 (C$_1$'), 149.63 (CNH$_2$), 167.88 (C(O)NH), 169.07 (C(O)CH$_3$) ppm; mass spectrum, FD (relative intensity), 265 (M$^+$ + 1, 36), 264 (100). Anal. (C$_{12}$H$_{16}$N$_4$O$_3$) C, H, N.

Synthesis of Methyl α-Acetamido-α-methyl-α-(furan-2-yl)acetate (46). HBr was bubbled (2.5 min) through a CDCl$_3$ solution (25 mL) of **44**[16] (3.80 g, 26.6 mmol). The excess HBr and CDCl$_3$[29] were removed by evaporating the solution with a continuous stream of Ar (20–30 min). The light yellow oily residue that remained containing **45** was dissolved in THF (100 mL), and then furan (32.76 g, 482.0 mmol) and ZnCl$_2$ (1 M in Et$_2$O, 53.0 mL, 53.0 mmol) were added. The reaction was stirred at room temperature (3.5 h) and then treated with H$_2$O (50 mL). The aqueous mixture was extracted with EtOAc (3 × 100 mL), and the combined extracts were dried (Na$_2$SO$_4$). The volatile materials were removed by distillation *in vacuo* to give 5.00 g (89%) of **46**: R_f 0.35 (50% EtOAc/CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 1.94 (s, CH$_3$), 1.99 (s, C(O)CH$_3$), 3.74 (s, C(O)OCH$_3$), 6.36 (br s, C$_3$H, C$_4$H), 6.83 (s, NH), 7.35 (s, C$_5$H); ^{13}C NMR (CDCl$_3$) 21.43 (CH$_3$), 23.26 (C(O)CH$_3$), 53.03 (C(O)OCH$_3$), 58.36 (C(CH$_3$)), 107.39 (C$_4$), 110.52 (C$_3$), 142.10 (C$_5$), 152.03 (C$_2$), 169.21 (C(O)CH$_3$), 171.34 (C(O)OCH$_3$) ppm.

Synthesis of α-Acetamido-α-methyl-α-(furan-2-yl)acetic Acid (47). A 95% EtOH solution (150 mL) of **46** (5.00 g, 23.6 mmol) and KOH (3.00 g, 53.5 mmol) was stirred at room temperature (48 h). The solvent was removed, and the residue was dissolved in H$_2$O (50 mL). The aqueous solution was washed with Et$_2$O (3 × 50 mL) and then acidified to pH 1.5 with 10% H$_3$PO$_4$. The acidified solution was extracted with EtOAc (3 × 200 mL), and the combined extracts were dried (Na$_2$SO$_4$) and concentrated *in vacuo* to give 2.90 g (62%) of **47**: mp 178–180 °C dec (recrystallized from CH$_3$CN); IR (KBr) 3400 (br), 1700 (br) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.67 (s, CH$_3$), 1.83 (s, C(O)CH$_3$), 6.39 (m, C$_3$H, C$_4$H), 7.59 (s, C$_5$H), 8.34 (s, NH), 12.63 (s, C(O)OH); ^{13}C NMR (DMSO-d_6) 22.20 (C(O)CH$_3$), 22.59 (CH$_3$), 57.65 (C(CH$_3$)), 107.09 (C$_4$), 110.49 (C$_3$), 142.33 (C$_5$), 153.36 (C$_2$), 168.86 (C(O)NH), 171.78 (C(O)OH) ppm; mass spectrum, EI, m/e (relative intensity) 198 (M$^+$ + 1, 4), 143 (97), 152 (63), 140 (23), 111 (73), 110 (100), 94 (24). Anal. (C$_9$H$_{11}$NO$_4$) C, H, N.

Enzymatic Separation of (*R*)-(−)-α-Acetamido-α-(furan-2-yl)acetic Acid [(*R*)-48] from (*R*,*S*)-(±)-α-Acetamido-α-(furan-2-yl)acetic Acid (48). (*R*,*S*)-(±)-α-Acetamido-α-(furan-2-yl)acetic acid (**48**) (2.00 g, 10.9 mmol) was suspended in deionized H$_2$O (600 mL). An aqueous solution of LiOH (1 N) was added to this suspension dropwise until all of the acid had dissolved and the pH was 7.2. Acylase I, Grade II (20 mg, activity: 900 units/mg, Sigma Chemical Co.) was then added to the above solution, and the mixture was stirred at 34–37 °C (41 h).[22] The suspension was then cooled to room temperature and acidified to pH 1.5 with aqueous 1 N HCl. The suspended material was filtered, and the filtrate was saturated with solid NaCl and then extracted with EtOAc (3 × 250 mL). The combined EtOAc extracts were dried (Na$_2$SO$_4$). The solvent was removed *in vacuo*, and the residue was triturated with EtOAc (10 mL). The white solid (0.75 g, 75%) that remained was filtered and gave pure (*R*)-**45**: mp 168–169 °C, mixed mp with an authentic sample 168–169 °C[6]; [α]$^{26}_D$ (c = 1, MeOH) = −184.3°.

Pharmacology. Initial anticonvulsant evaluation of all compounds except **18** and **19** was conducted at the Lilly Research Laboratories with at least three dose levels (10, 30, 100 mg/kg or 30, 100, and 300 mg/kg where sufficient sample quantity existed) administered intraperitoneally. Four mice at each dose level were tested at 0.5, 1, and 4 h after administration to determine if there was protection against MES-induced seizures. All tests were performed with male albino CF-1 mice from Charles River Breeding Laboratories (Portage, MI). Test solutions of all compounds were prepared in 30% poly(ethylene glycol) 400. Seizures were elicited by electrical current (ac 60 cps, 50 mA, 0.2 s) applied via corneal electrodes. A drop of 0.9% saline was instilled on each eye prior to application of the electrodes to ensure electrical contact. Abolition of the hind limb tonic extension component of the seizure was defined as protection in the MES test. Compounds **18** and **19** were tested using comparable protocols including the same mouse strain and supplier under the auspices of the National Institutes of Health Antiepileptic Drug Development Program.

After the time of peak activity and the approximate dose ranges were determined, a dose–response curve was generated at the

time of peak activity with at least three or four doses and 10–12 mice per dose. The MES ED_{50} is the estimated dose from the dose–response data which protects 50% of the mice in the MES test. At the Lilly Research Laboratories, neurological impairment was measured in mice using the horizontal screen test.[24] Previously trained mice were dosed with the compound and then placed individually on top of a square (13 × 13 cm) wire screen (no. 4 mesh) which was mounted on a vertical rod. The rod was then rotated 180°, and the number of mice that returned to the top of the screen within 1 min was determined. To determine the TD_{50} (toxic dose 50%) value, the estimated dose that impaired 50% of the mice in the horizontal screen test, a dose–response curve was determined at the time of peak anticonvulsant activity with at least three to four doses and 10–12 mice per dose. At the National Institutes of Health Antiepileptic Drug Development Program, the effects of **18** and **19** on neurological impairment were evaluated in mice by the rotorod test.[25] The animal is placed on a 1-in.-diameter knurled plastic rod rotating at 6 rpm after the administration of the drug candidate. Normal mice can remain on a rod rotating at this speed indefinitely. Neurologic toxicity is defined as the failure of the animal to remain on the rod for 1 min. The ED_{50} and TD_{50} values for **18** and **19** were determined using the previously described procedures by the administration of varying dose levels of both compounds, treating normally eight mice at each dose.

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Supplementary Material Available: Crystallographic procedure for compound **38**, Tables IV–VIII giving a complete listing of the final cell constants and information pertinent to data collection and refinement, atomic coordinates and equivalent isotropic displacement parameters, bond lengths, and bond angles, ORTEP drawing for **38** and ^{1}H NMR spectra of compounds (*R,S*)-**4**, (*R*)-**4**, (*S*)-**4**, (*R,S*)-**30**, (*R*)-**30**, (*R*)-**31**, and (*R*)-**32** with (*R*)-(−)-mandelic acid and (*R,S*)-**4** and (*R,S*)-**30** without (*R*)-(−)-mandelic acid (16 pages); observed and calculated structure factors for compound **38** (6 pages). Ordering information is given on any current masthead page.

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