Synthesis and Anticonvulsant Activities of α-Acetamido-*N*-benzylacetamide Derivatives Containing an Electron-Deficient α-Heteroaromatic Substituent

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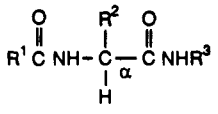
Recent studies have demonstrated that C(α)-substituted α-acetamido-*N*-benzylacetamides displayed excellent anticonvulsant activities in mice. Analysis of the structure–activity relationship for this series of compounds has shown that placement of small, electron-rich aromatic and heteroaromatic groups at the C(α) site led to pronounced protection against MES-induced seizures. In this note, synthetic protocols are reported for the preparation of three novel nonnaturally occurring electron-deficient C(α)-aza aromatic α-acetamido-*N*-benzylacetamides (i.e., pyrid-2-yl (**11**), pyrazin-2-yl (**12**), pyrimid-2-yl (**13**)). Expedient syntheses for **12** and **13** were developed using a phase-transfer, nucleophilic aromatic substitution process. All three adducts exhibited potencies comparable to or greater than phenytoin in the MES test (mice, ip). These findings required us to modify in part the previously proposed structure–activity relationship for this class of anticonvulsants.

Recently, we have reported on the potent anticonvulsant activities of selectively C(α)-substituted functionalized amino acid derivatives **1**.[1–7] Evaluation of the optimal R^2-substituent in **1** (Table 1) revealed that the placement of a small, electron-rich heteroaromatic ring[5,7] at the C(α) position, as well as the incorporation of a heteroatom two atoms removed from this carbon site,[5–7] led to compounds (i.e., **2**, **3**) providing excellent protection against MES-induced seizures in mice. In this note, we describe the pharmacological activities of the three six-membered *electron-deficient* aza aromatic analogues, **11**–**13**. Synthetic strategies are provided for these novel nonnaturally occurring amino acid derivatives. Significantly, the pronounced activities observed for **11**–**13** required us to modify in part the previously proposed structure–activity relationship for this class of anticonvulsants.



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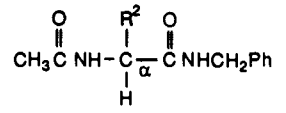
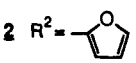
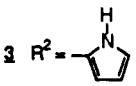
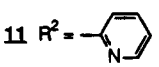
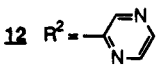
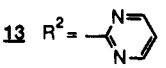


2 

3 

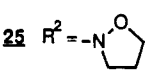
11 

12 

13 

14 R^2 = Br

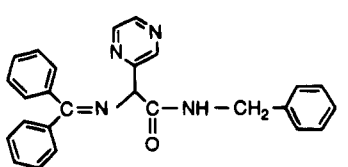
24 R^2 = N(H)OCH_3

25 

Chemistry

Preparation of the pyrid-2-yl derivative **11** was accomplished in 15% yield by treatment of α-acetamido-α-bromo-*N*-benzylacetamide[6] (**14**) with 2-pyridyllithium[8] (2.1 equiv). Attempts to increase the yield for this transformation by varying the mole ratios of the reactants, inversing the order of addition of the reactants, and substituting lithium (2-pyridyl)cyanocuprate[9] for 2-pyridyllithium were unsuccessful.

The low yields observed for the synthesis of **11** suggested that an alternative protocol be used for the preparation of the C(α)-pyrazin-2-yl (**12**) and C(α)-pyrimid-2-yl (**13**) adducts. O'Donnell and co-workers have described a general synthesis of C(α)-alkyl-substituted amino acids from glycine derivatives using a phase-transfer, nucleophilic aliphatic substitution reaction.[10] The corresponding nucleophilic aromatic substitution process has not been reported. Adopting this methodology, commercially available ethyl *N*-(diphenylmethylene)glycinate (**15**) was treated with solid potassium carbonate, tetra-*n*-butylammonium bromide, and either 2-chloropyrazine or 2-chloropyrimidine in 1-methyl-2-pyrrolidinone to afford the C(α)-pyrazin-2-yl (**16**) and C(α)-pyrimid-2-yl (**19**) derivatives, respectively (Scheme 1). Subsequent hydrolysis of **16** and **19** with aqueous 1 N HCl furnished **17** and **20**, respectively, in quantitative yield. Compounds **17** and **20** were acetylated with acetic anhydride and triethylamine in CH_2Cl_2 at room temperature to give **18** and **21**, respectively, and then converted to the desired compounds **12** and **13**, respectively, with benzylamine in EtOH using NaCN as a catalyst.[11] The four-step conversion of ethyl *N*-(diphenylmethylene)glycinate (**15**) to C(α)-pyrazin-2-yl (**12**) and C(α)-pyrimid-2-yl (**13**) proceeded in 33% and 12% overall yield, respectively. We are unaware of other reports describing the syntheses of these novel C(α)-diazinyl amino acid derivatives. Efforts to improve the overall synthetic yield for **12** by first converting **16** to the benzylamide **22** and then deprotecting the amine to give **23**, followed by acetylation, furnished **12** in 12% overall yield. Attempts to use this phase-transfer method to prepare the pyrid-2-yl derivative **11** were unsuccessful. Treatment of **15** with 2-bromopyridine at 150 °C (3 d) led to the recovery of the starting glycinate.



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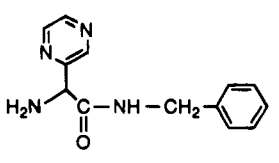

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[⊗] Abstract published in *Advance ACS Abstracts*, November 15, 1994.

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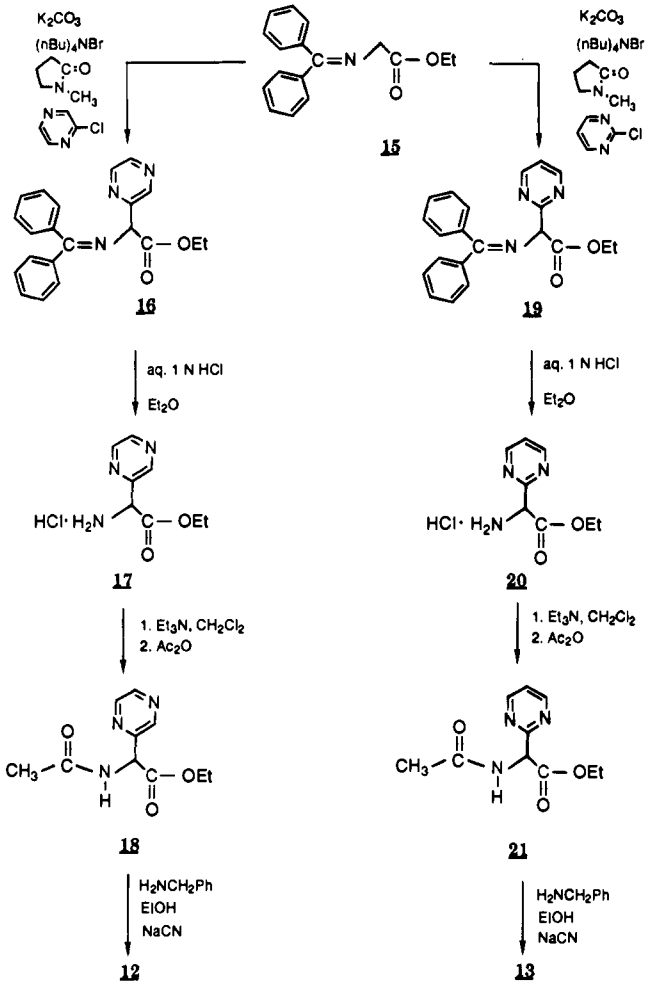
Scheme 1. Synthesis of Compounds **12** and **13**



Pharmacological Evaluation

The racemic aza aromatic amino acid derivatives **11**–**13** were tested for anticonvulsant activity using the procedures described by Krall and co-workers,[12] and these results were compared to the findings previously reported for **2**–**10**.[5,7] All compounds were administered intraperitoneally (ip) to mice. Table 1 lists the ED_{50} values required to prevent tonic extension of the hind limbs in mice in the MES test by **2**–**13**. Included in this table are the median neurologically impairing dose (TD_{50}) values using either the rotorod[13] or horizontal screen[14] test. In those cases when no activity was observed below 100 mg/kg in the MES test, the TD_{50}'s were not determined. The protective index ($PI = TD_{50}/ED_{50}$) for **2**–**13**, where appropriate, is also provided in Table 1.

The ED_{50} values in the MES test for **11**–**13** (ED_{50} = 8.1–14.8 mg/kg) were comparable to those for phenytoin[15] (ED_{50} = 9.5 mg/kg).[16] Significantly, the MES ED_{50} values for **11**–**13** were also similar to those observed for **2** and **3**, indicating that placement of an *electron-deficient* aromatic ring at the C(α) site did not lead to a reduction of activity. Previously, we have suggested that improved activity would result with the incorporation of an *electron-rich* aromatic group at the C(α) site (i.e., **2** (ED_{50} = 10.3 mg/kg), **3** (ED_{50} = 16.1 mg/kg), **4** (ED_{50} = 44.8 mg/kg)).[5,7] We have also presented evidence that placement of a substituted heteroatom two atoms removed from the C(α) site provided enhanced protection against MES-induced seizures (i.e., **4** (ED_{50} = 44.8 mg/kg) vs **5** (ED_{50} = 87.8 mg/kg)).[5–7] In agreement with this latter trend, **13** was more potent than either **11** or **12**. Our findings that **11**–**13** all displayed excellent activity in the MES test indicated that of these two structural determinants the latter was the more important factor for anticonvulsant activity. Consistent with this theory was the notable protection observed for the C(α)-heteroatom adducts **24** (ED_{50} = 6.2 mg/kg) and **25** (ED_{50} = 31.4 mg/kg) in the MES test.[6]

The pronounced activities of **12** and **13** contrasted with the results reported for **7** and **8**.[7] These two C(α)-imidazole adducts exhibited no protection in the MES test at 100 mg/kg, while the corresponding oxazol-2-yl (**6**) (ED_{50} = 10.4 mg/kg) and thiazol-2-yl (**9**) (ED_{50} = 12.1 mg/kg) derivatives provided significant protection against MES-induced seizures.[7] We have attributed the difference in activities of **6**–**9** to the basicities of diazoles **7** and **8**.[7] The activities observed for the two weakly basic diazines **12** and **13**[17] were consistent with this notion.

Conclusions

Three C(α) electron-deficient α-acetamido-*N*-benzylacetamides (**11**–**13**) have been prepared and evaluated. Expedient syntheses are reported for the novel C(α)-pyrazin-2-yl and C(α)-pyrimid-2-yl derivatives. All three C(α)-aza aromatic functionalized amino acid derivatives displayed activity comparable to phenytoin in mice.

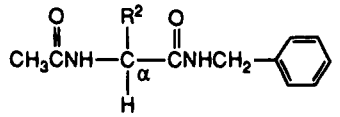
Experimental Section

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 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 mass spectra were taken by Dr. M. Moini at the University of Texas at Austin on a Finnegan MAT TSQ-70 instrument. The *N*-(diphenylmethylene)glycinate (**15**) and BBr_3 were purchased 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 α-Acetamido-α-bromo-*N*-benzylacetamide (14). To a stirred solution of α-acetamido-α-ethoxy-*N*-benzylacetamide[18] (2.00 g, 8 mmol) in dry CH_2Cl_2 (200 mL) was introduced a solution of BBr_3 (16 mL, 16 mmol, 1.0 M in CH_2Cl_2) by means of a syringe under a N_2 atmosphere. The N_2 line was removed, and the reaction mixture was sealed. The yellow solution was stirred at room temperature (20 h) and then concentrated *in vacuo* to give a yellow solid. The solid was successively triturated with distilled Et_2O (3 × 50 mL) and ethanol-free $CHCl_3$ (neutral Al) (2 × 50 mL) and dried under high vacuum (0.1 Torr, 48 h) to give 1.94 g (85%) of **14**: mp 162–163 °C; ^1H NMR (acetone-d_6) δ 2.04 (s, C(O)C**H**$_3$), 4.38 (d, *J* = 15.0 Hz, C**H**H'), 4.49 (d, *J* =15.0 Hz, CH**H**'), 6.66 (s, C**H**), 7.23–7.39 (m, 5 Ph**H**), the two NH protons are believed to be beneath the aromatic signals; ^{13}C NMR (acetone-d_6) 23.03 (C(O)**C**H$_3$), 43.57 (**C**H$_2$), 55.90 (**C**H), 127.99 (**C**$_4$'), 128.29 (**2C**$_2$' or **2C**$_3$'), 129.24 (**2C**$_2$' or **2C**$_3$'), 139.33 (**C**$_1$'), 166.05 (**C**(O)CH$_3$), 169.93 (**C**(O)NH) ppm; MS, CI(−) (rel intensity) 204 (100), 163 (100); M_r (+CI) 285.02368 [M + 1]$^+$ (calcd for $C_{11}H_{14}BrN_2O_2$ 285.02386).

Synthesis of α-Acetamido-*N*-benzyl-α-(pyrid-2-yl)acetamide (11). A cooled (−100 °C) THF solution of 2-pyridyllithium[8] (60 mL, 8.0 mmol) was added dropwise to a cooled

Table 1. Physical and Pharmacological Data in Mice for C(α)-Heteroaromatic α-Acetamido-*N*-benzylacetamides[a]



no.	R^2	mp[b]	MES[c] ED_{50}	tox[d] TD_{50}	PI[e]
2[f,g]		178–179	10.3 (9.1–11.6)	~40	>3.9
3[f,g]		174–175	16.1 (13.2–19.9)	>30, <100	–
4[f,g]		167–169	44.8 (38.9–51.4)	>30, <100	–
5[f,g]		198–199	87.8 (69.9–150)	>100	–
6[h,i]		164–166	10.4 (9.2–11.6)	38.6[j] (33.8–46.0)	3.7
7[g,h]		228–230	>100	*k*	–
8[g,h]		188–191 (d)	>100	*k*	–
9[h,i]		166–167	12.1 (9.5–14.5)	69.1[j] (61.6–78.6)	5.7
10[g,l]		202–203	32.1 (27.5–40.2)	>40	–
11[i]		145–147	10.8 (9.1–12.1)	>25, <100[j]	–
12[i]		185–187	14.8 (12.5–17.2)	58.2[j] (46.3–72.5)	3.9
13[i]		174–176	8.1 (5.5–11.5)	56.7[j] (48.5–64.9)	7.0
	phenytoin[m]		9.5 (8.1–10.4)	65.5[j] (52.5–72.1)	6.9
	phenobarbital[m]		21.8 (15.0–22.5)	69.0[j] (62.8–72.9)	3.2
	valproate[m]		272 (247–338)	426[j] (369–450)	1.6

[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 were obtained at 0.5 h ("time of peak effect") except for compounds **9**, 11, and **13**, which were obtained at 0.25 h. [b] Melting points (°C) are uncorrected. [c] MES = maximal electroshock seizure test. [d] tox TD_{50} = neurologic toxicity determined from horizontal screen unless otherwise noted. [e] PI = protective index (TD_{50}/ED_{50}). [f] Reference 5. [g] The compounds were tested at the Eli Lilly Co. (Indianapolis, IN). [h] Reference 7. [i] The compounds were tested through the auspices of the National Institute of Neurological and Communicative Disorders and Stroke at the National Institutes of Health. [j] TD_{50} value determined from the rotorod test. [k] Not determined. [l] Reference 2. [m] Reference 15.

(−100 °C) THF solution (100 mL) of compound 14 (0.90 g, 3.9 mmol). The reaction mixture was stirred at −100 °C (2 h), and then the reaction was quenched with a saturated aqueous solution of NH_4Cl (40 mL) at −78 °C. The mixture was warmed to 0 °C, during which time a saturated aqueous solution of Na_2CO_3 was added dropwise until the precipitate dissolved. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, dried (Na_2SO_4), concentrated under vacuum, and then further purified by flash column chromatography on SiO_2 using 5% MeOH/$CHCl_3$ as the eluant to afford 340 mg (15%) of 11. The product was recrystallized from chloroform/hexanes: mp 146–147 °C; R_f 0.40 (5% $CH_3OH/CHCl_3$); ^1H NMR (DMSO-d_6) δ 1.94 (s, C(O)-CH_3), 4.27 (d, J = 6.0 Hz, CH_2), 5.58 (d, J = 8.1 Hz, CH), 7.17–7.34 (m, 5 PhH and C_5H), 7.45 (d, J = 7.2 Hz, C_3H), 7.76–7.82 (m, C_4H), 8.51–8.54 (m, C_6H and NH), 8.76 (t, J = 6.0 Hz, NH); ^{13}C NMR (DMSO-d_6) 22.57 ($C(O)CH_3$), 44.57 (CH_2), 60.22 (CH), 122.65 (C_5), 123.54 (C_3), 127.51 (C_4'), 128.20 ($2C_2'$ or $2C_3'$), 129.37 ($2C_2'$ or $2C_3'$), 138.62 (C_1' or C_4), 139.53 (C_1' or C_4), 150.11 (C_6), 157.10 (C_2), 171.29 ($C(O)CH_3$), 172.10 (C(O)NH) ppm. Anal. ($C_{16}H_{17}N_3O_2$) C, H, N.

Synthesis of Ethyl α-(Pyrazin-2-yl)-*N*-(diphenylmethylene)glycinate (16). A heterogeneous mixture containing **15** (10.00 g, 37.5 mmol), 2-chloropyrazine (8.58 g, 74.9 mmol), tetra-*n*-butylammonium bromide (12.07 g, 37.5 mmol), K_2CO_3 (9.00 g, 112.4 mmol), and 1-methyl-2-pyrrolidinone (70 mL) was heated at 100 °C (3 d). The mixture was diluted with acetone (100 mL) and filtered through Celite. The solvents were removed *in vacuo*, and the residue was purified by flash column chromatography on SiO_2 using 33% ethyl acetate/hexanes as the eluant to give 10.00 g (77%) of **16** as an oil: R_f 0.38 (33% ethyl acetate/hexanes); IR (neat) 3061, 2984, 1738, 1659, 1448, 1398, 1277, 1022, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (t, J = 7.2 Hz, OCH_2CH_3), 4.14 (q, J = 7.2 Hz, OCH_2-CH_3), 5.43 (s, CH), 7.14–7.44 (m, 10 PhH), 8.45 (s, C_5H or C_6H), 8.46 (s, C_5H or C_6H), 8.97 (s, C_3H); ^{13}C NMR ($CDCl_3$)

13.81 (OCH_2CH_3), 61.39 (OCH_2CH_3), 70.06 (**C**H), 127.44, 127.87, 128.12, 128.48, 128.86, 130.62, 135.46, 138.78 ($2C_6H_5$), 143.40 (C_5 and C_6), 144.88 (C_3), 154.18 (C_2), 169.32 (**C**(O)OCH_2CH_3 or **C**(N)), 172.14 (**C**(O)OCH_2CH_3 or **C**(N)) ppm; MS, CI(+) (rel intensity) 346 ($M^+ + 1$, 100), 272 (75); M_r (+CI) 346.15563 [$M^+ + 1$] (calcd for $C_{21}H_{20}N_3O_2$ 346.15555). Anal. ($C_{21}H_{19}N_3O_2 \cdot 0.4H_2O$) C, H, N.

Synthesis of Ethyl α-(Pyrimid-2-yl)-*N*-(diphenylmethylene)glycinate (19). Using the preceding procedure (100 °C, 2 d) and **15** (10.00 g, 37.5 mmol), 2-chloropyrimidine (3.53 g, 74.9 mmol), tetra-*n*-butylammonium bromide (12.07 g, 37.5 mmol), K_2CO_3 (9.00 g, 112.4 mmol), and 1-methyl-2-pyrrolidinone (70 mL) gave 3.30 g (26%) of **19** as an oil: R_f 0.40 (50% ethyl acetate/hexanes); IR (KBr) 3053, 2991, 1735, 1652, 1449, 1397, 1279, 1025, 640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.09 (t, J = 7.2 Hz, OCH_2CH_3), 4.10 (d, J = 7.2 Hz, OCH_2CH_3), 5.28 (s, C**H**), 7.18–7.57 (m, 10 Ph**H** and C_5**H**), 8.81 (d, J = 5.4 Hz, C_4**H** and C_6**H**); ^{13}C NMR (DMSO-d_6) 13.72 (OCH_2CH_3), 61.04 (OCH_2CH_3), 119.49 (C_5), 127.51, 127.59, 128.24, 128.55, 128.87, 130.25, 135.67, 138.94 (2 C_6H_5), 157.14 (C_4 and C_6), 166.83 (C_2), 169.22 (**C**(O)OCH_2CH_3 or **C**(N)), 172.00 (**C**(O)OCH_2CH_3 or **C**(N)) ppm; MS, CI(+) (rel intensity) 346 ($M^+ + 1$, 100), 272 (62); M_r (+CI) 346.15580 [$M^+ + 1$] (calcd for $C_{21}H_{20}N_3O_2$ 346.15555). Anal. ($C_{21}H_{19}N_3O_2 \cdot 0.4H_2O$) C, H, N.

Synthesis of Ethyl α-(Pyrazin-2-yl)glycinate Hydrochloride (17). Compound **16** (6.00 g, 17.4 mmol) was dissolved in Et_2O (100 mL), and an aqueous 1 N HCl solution (21 mL, 21.0 mmol) was slowly added, and the mixture was stirred at room temperature (20 h). The layers were separated, and the aqueous layer was washed with Et_2O (3 × 30 mL). The aqueous layer was kept, and the solvent was removed *in vacuo*. The residue was triturated with acetone to give 3.20 g (95%) of **17**: mp 165–167 °C (dec); IR (KBr) 2990, 2908, 2654, 1748, 1524, 1421, 1252, 1157, 1020, 856 cm^{-1}; ^1H NMR (CD_3OD) δ 1.10 (t, J = 7.2 Hz, OCH_2CH_3), 4.17 (q, J = 7.2 Hz, OCH_2CH_3), 5.56 (s, C**H**), 8.69 (s, C_5**H** or C_6**H**), 8.71 (s, C_5**H** or C_6**H**), 8.86 (s, C_3**H**); ^{13}C NMR (CD_3OD) 14.23 (OCH_2CH_3), 54.66 (**C**H), 63.50 (OCH_2CH_3), 145.01 (C_3 or C_5 or C_6), 145.51 (C_3 or C_5 or C_6), 146.21 (C_3 or C_5 or C_6), 147.80 (C_2), 166.92 (**C**(O)OCH_2CH_3) ppm; MS, CI(+) (rel intensity) 182 ($M^+ + 1$, 100); M_r (+CI) 182.09279 [$M^+ + 1$] (calcd for $C_8H_{12}N_3O_2$ 182.09295). Anal. ($C_8H_{11}N_3O_2$) C, H, N.

Synthesis of Ethyl α-(Pyrimid-2-yl)glycinate Hydrochloride (20). Using the preceding protocol (room temperature, 3 h) and **19** (3.30 g, 9.6 mmol), Et_2O (50 mL), and aqueous 1 N HCl (10 mL, 10.0 mmol) gave 1.80 g (87%) of **20**: mp 156–158 °C (dec); IR (KBr) 2978, 2864, 2623, 1744, 1570, 1499, 1422, 1373, 1260, 1211, 1055, 854 cm^{-1}; ^1H NMR (CD_3OD) δ 1.25 (t, J = 7.2 Hz, OCH_2CH_3), 4.29 (q, J = 7.2 Hz, OCH_2CH_3), 5.44 (s, C**H**), 7.61 (t, J = 4.8 Hz, C_5**H**), 8.94 (d, J = 4.8 Hz, C_4**H** and C_6**H**); ^{13}C NMR (CD_3OD) 14.26 (OCH_2CH_3), 59.44 (**C**H), 64.27 (OCH_2CH_3), 123.01 (C_5), 159.46 (C_4 and C_6), 162.03 (C_2), 167.18 (**C**(O)OCH_2CH_3) ppm; MS, CI(+) (rel intensity) 182 ($M^+ + 1$, 100); M_r (+CI) 182.09275 [$M^+ + 1$] (calcd for $C_8H_{12}N_3O_2$ 182.09295). Anal. ($C_8H_{11}N_3O_2$) C, H, N.

Synthesis of Ethyl α-Acetamido-α-(pyrazin-2-yl)acetate (18). Compound **17** (3.20 g, 14.7 mmol) was dissolved in CH_2Cl_2 (50 mL), and then Et_3N (2.05 mL, 14.7 mmol) was slowly added and the reaction mixture was stirred at room temperature (30 min). Ac_2O (1.95 g, 19.1 mmol) was added slowly, and the reaction mixture was stirred (20 h). The solution was washed with H_2O (30 mL) and dried (Na_2SO_4), and the solvent was removed to afford 3.10 g (94%) of **18** as an oil: R_f 0.24 (EtOAc); IR (neat) 3053, 2987, 1734, 1670, 1525, 1408, 1375, 1157, 988 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (t, J = 7.2 Hz, OCH_2CH_3), 2.10 (s, C(O)C**H**$_3$), 4.20 (q, J = 7.2 Hz, OCH_2CH_3), 5.94 (d, J = 7.8 Hz, C**H**), 7.92 (d, J = 7.8 Hz, N**H**), 8.54 (s, C_5**H** or C_6**H**), 8.58 (s, C_5**H** or C_6**H**), 8.84 (s, C_3**H**); ^{13}C NMR ($CDCl_3$) 13.28 (OCH_2CH_3), 21.95 (C(O)**C**H$_3$), 54.89 (**C**H), 61.42 (OCH_2CH_3), 143.31 (C_3 or C_5 or C_6), 143.61 (C_3 or C_5 or C_6), 144.23 (C_3 or C_5 or C_6), 150.73 (C_2), 168.39 (**C**(O)OCH_2CH_3 or **C**(O)CH_3), 169.61 (**C**(O)OCH_2CH_3 or **C**(O)CH_3) ppm; MS, CI(+) (rel intensity) 224 ($M^+ + 1$, 100); M_r (+CI) 224.10307 [$M^+ + 1$] (calcd for $C_{10}H_{14}N_3O_3$ 224.10352). Anal. ($C_{10}H_{13}N_3O_3$) C, H, N.

Synthesis of Ethyl α-Acetamido-2-(pyrimid-2-yl)acetate (21). Using the preceding procedure and **20** (1.40 g, 6.4 mmol), CH_2Cl_2 (40 mL), Et_3N (0.96 mL, 6.4 mmol), and Ac_2O (0.92 g, 9.0 mmol) furnished 1.20 g (84%) of **21** as an oil: R_f 0.21 (EtOAc); IR (neat) 3048, 2982, 1746, 1661, 1530, 1408, 1275, 1020, 853, 787 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, OCH_2CH_3), 2.12 (s, C(O)C**H**$_3$), 4.23 (q, J = 7.2 Hz, OCH_2CH_3), 5.84 (d, J = 6.9 Hz, C**H**), 7.22 (d, J = 6.9 Hz, N**H**), 7.31 (t, J = 4.8 Hz, C_5**H**), 8.77 (d, J = 4.8 Hz, C_3**H** and C_6**H**); ^{13}C NMR ($CDCl_3$) 14.05 (OCH_2CH_3), 23.00 (C(O)**C**H$_3$), 59.18 (**C**H), 62.19 (OCH_2CH_3), 120.42 (C_5), 157.62 (C_4 and C_6), 164.27 (C_2), 169.09 (**C**(O)CH_3 or **C**(O)OCH_2CH_3), 169.80 (**C**(O)CH_3 or **C**(O)OCH_2CH_3) ppm; MS, CI(+) (rel intensity) 224 ($M^+ + 1$, 100), 210 (88); M_r (+CI) 224.10296 [$M^+ + 1$] (calcd for $C_{10}H_{14}N_3O_3$ 224.10352). Anal. ($C_{10}H_{13}N_3O_3 \cdot 0.35\ H_2O$) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-(pyrazin-2-yl)acetamide (12). A methanolic (33 mL) solution of **18** (2.60 g, 11.7 mmol), benzylamine (1.50 g, 14.0 mmol), and NaCN[11] (0.06 g, 1.2 mmol) was heated at reflux (2 d). The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography on SiO_2 using 10% MeOH/$CHCl_3$ as the eluant to give 1.80 g (54%) of **12**. The product was recrystallized from EtOAc: mp 185–187 °C; R_f 0.25 (10% MeOH/$CHCl_3$); IR (KBr) 3052, 1744, 1662, 1518, 1441, 1408, 1375, 1236, 1148 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.94 (s, C(O)C**H**$_3$), 4.28 (d, J = 5.7 Hz, C**H**$_2$), 5.69 (d, J = 7.8 Hz, C**H**), 7.22–7.30 (m, 5 Ph**H**), 8.58 (d, J = 2.5 Hz, C_5**H** or C_6**H**), 8.62 (d, J = 2.5 Hz, C_5**H** or C_6**H**), 8.72–8.75 (m, N**H** and C_3**H**), 8.91 (t, J = 5.7 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 22.38 (C(O)**C**H$_3$), 42.22 (**C**H$_2$), 56.49 (**C**H), 126.68 (C_4'), 126.98 ($2C_2'$ or $2C_3'$), 128.14 ($2C_2'$ or $2C_3'$), 138.90 (C_1'), 143.74 (C_3 and C_5 and C_6), 153.19 (C_2), 168.23 (**C**(O)CH_3 or **C**(O)NH), 169.41 (**C**(O)CH_3 or **C**(O)NH) ppm; MS, CI(+) (rel intensity) 285 ($M^+ + 1$, 46), 108 (100); M_r (+CI) 285.13477 [$M^+ + 1$] (calcd for $C_{15}H_{17}N_4O_2$ 285.13515). Anal. ($C_{15}H_{16}N_4O_2$) C, H, N.

Synthesis of α-Acetamido-*N*-benzyl-α-(pyrimid-2-yl)acetamide (13). Using the previous protocol and methanol (150 mL), **21** (1.20 g, 5.4 mmol), benzylamine (0.69 g, 6.5 mmol), and NaCN (0.06 g, 1.0 mmol) gave 1.00 g (64%) of **13**: mp 174–176 °C; R_f 0.25 (10% MeOH/$CHCl_3$); IR (KBr) 3059, 2953, 1750, 1663, 1543, 1423, 1381, 1240, 702 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.94 (s, C(O)C**H**$_3$), 4.29 (d, J = 5.7 Hz, C**H**$_2$), 5.68 (d, J = 8.4 Hz, C**H**), 7.19–7.28 (m, 5 Ph**H**), 7.44 (t, J = 4.8 Hz, C_5**H**), 8.52 (d, J = 8.4 Hz, N**H**), 8.80–8.82 (m, C_4**H**, C_6**H** and N**H**); ^{13}C NMR (DMSO-d_6) 22.43 (**C**H$_3$), 42.14 (**C**H$_2$), 59.45 (**C**H), 120.31 (C_5), 126.56 (C_4'), 126.90 ($2C_2'$ or $2C_3'$), 128.05 ($2C_2'$ or $2C_3'$), 139.07 (C_1'), 157.38 (C_4 and C_6), 165.75 (C_2), 168.17 (**C**(O)CH_3 or **C**(O)NH), 169.27 (**C**(O)CH_3 or **C**(O)NH); MS, CI(+) 285 ($M^+ + 1$); M_r (+CI) 285.13577 [$M^+ + 1$] (calcd for $C_{15}H_{17}N_4O_2$ 285.13515). Anal. ($C_{15}H_{16}N_4O_2 \cdot 0.2\ H_2O$) C, H, N.

Synthesis of α-*N*-(Diphenylmethylene)-*N*-benzyl-α-(pyrazin-2-yl)acetamide (22). A methanolic (2 mL) solution of **16** (0.50 g, 1.5 mmol), benzylamine (0.60 g, 5.8 mmol), and NaCN (0.01 g, 0.3 mmol) was heated to reflux (2 d). The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography on SiO_2 using 66% ethyl acetate/hexanes as the eluant to give 0.30 g (20%) of **22** as an oil: R_f 0.39 (66% ethyl acetate/hexanes); IR (neat) 2978, 2874, 1746, 1570, 1504, 1424, 1373, 1213, 1057, 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.28 (d, J = 5.7 Hz, C**H**$_2$), 5.31 (s, C**H**), 6.92–7.67 (m, 15 Ph**H**), 7.84 (t, J = 5.7 Hz, N**H**), 8.40 (d, J = 2.4 Hz, C_5**H** or C_6**H**), 8.47 (d, J = 2.4 Hz, C_5**H** or C_6**H**), 8.53 (s, C_3**H**); ^{13}C NMR ($CDCl_3$) 43.37 (**C**H$_2$), 69.83 (**C**H), 127.32, 127.46, 127.57, 128.28, 128.72, 128.89, 128.94, 129.34, 131.16, 135.69, 138.21, 138.65 (3 C_6H_5), 143.63 (C_3 or C_5 or C_6), 144.17 (C_3 or C_5 or C_6), 144.47 (C_3 or C_5 or C_6), 154.79 (C_2), 169.86 (**C**(N) or **C**(O)NH), 172.05 (**C**(N) or **C**(O)NH) ppm; MS, CI(+) (rel intensity) 407 ($M^+ + 1$, 35), 239 (100); M_r (+CI) 407.18636 [$M^+ + 1$] (calcd for $C_{26}H_{23}N_4O_1$ 407.18719).

Synthesis of α-Amino-*N*-benzyl-α-(pyrazin-2-yl)acetamide (23). Compound **22** (0.30 g, 0.9 mmol) was dissolved in Et_2O (10 mL), and then an aqueous 1 N HCl solution (1 mL, 1.0 mmol) was slowly added and the mixture was stirred at room temperature (20 h). The layers were separated, and the

aqueous layer was washed with Et_2O (3 × 2 mL); the aqueous layer was kept, and the solvent was removed *in vacuo*. The residue was triturated with acetone to give 0.17 g (80%) of the hydrochloride salt, and then CH_2Cl_2 (10 mL) and Et_3N (0.06 g, 0.6 mmol) were added and the reaction mixture was stirred (1 h). The organic phase was washed with H_2O (5 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give 0.14 g (100%) of **23** as an oil: R_f 0.45 (10% MeOH/$CHCl_3$); IR (neat) 3426, 3031, 2926, 1657, 1532, 1452, 1238, 1172, 978, 716 cm^{-1}; ^1H NMR (CD_3OD) δ 4.40 (s, C**H**$_2$), 5.33 (s, C**H**), 7.21–7.44 (m, 5 Ph**H**), 8.70 (s, C_5**H** and C_6**H**), 8.88 (s, C_3**H**); ^{13}C NMR (CD_3OD) 44.25 (**C**H_2), 54.14 (**C**H), 128.13 (**C**$_4'$), 128.32 (**2C**$_2'$ or **2C**$_3'$), 129.25, (**2C**$_2'$ or **2C**$_3'$), 138.80 (**C**$_1'$), 144.99 (**C**$_3$ or **C**$_5$ or **C**$_6$), 145.62 (**C**$_3$ or **C**$_5$ or **C**$_7$), 146.36 (**C**$_3$ or **C**$_5$ or **C**$_6$), 149.10 (**C**$_2$), 166.25 (**C**(O)NH) ppm; MS, CI(+) 243 ($M^+ + 1$); M_r (+CI) 243.12455 [$M^+ + 1$] (calcd for $C_{13}H_{15}N_4O_1$ 243.12459).

Synthesis of α-Acetamido-*N*-benzyl-α-(pyrazin-2-yl)-acetamide (12). To a CH_2Cl_2 solution (1 mL) of **23** (0.03 g, 0.1 mmol) was added Ac_2O (0.02 g, 0.17 mmol), and the reaction mixture was stirred at room temperature (20 h). The solvent was removed *in vacuo* to give 0.03 g (99%) of the desired compound: mp 185–187 °C (mixed melting point with authentic material, 185–187 °C); R_f 0.25 (10% MeOH/$CHCl_3$); ^1H NMR (DMSO-d_6) δ 1.93 (s, C(O)C**H**$_3$), 4.28 (d, J = 5.7 Hz, C**H**$_2$), 5.71 (d, J = 7.8 Hz, C**H**), 7.19–7.31 (m, 5 Ph**H**), 8.59 (d, J = 2.4 Hz, C_5**H** or C_6**H**), 8.62 (d, J = 2.4 Hz, C_5**H** or C_6**H**), 8.70–8.73 (m, N**H** and C_3**H**), 8.91 (t, J = 5.7 Hz, N**H**).

Pharmacology. The compounds were tested under the auspices of the National Institutes of Health for anticonvulsant activity (phase I evaluation) using male Carworth Farms No. 1 mice. All compounds were given in three dose levels (30, 100, and 300 mg/kg). Maximal electroshock seizures (MES) were then elicited with a 60-cycle alternating current of 50-mA intensity (5–7 times that which was necessary to elicit minimal electroshock seizures) delivered for 0.2 s via corneal electrodes. A drop of 0.9% saline was instilled in the eye prior to application of the electrodes so as to prevent the death of the animal. Protection in this test was defined as the abolition of the hind limb tonic extension component of the seizure. The effects of the compounds on forced and spontaneous motor activity were evaluated in mice by the rotorod test (tox). The animal was placed on an 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 was defined as the failure of the animal to remain on the rod for 1 min. The MES test was conducted with a single animal, while four mice were utilized for the toxicology test. The dose–effect behavior (phase II quantitative evaluation) was evaluated by using the previously described procedures by the administration of varying dose levels of each compound, treating normally eight mice at each dose.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of compounds **14**, **22**, and **23** (6 pages). Ordering information is given on any current masthead page.

References

(1) Cortes, S.; Liao, Z.-K.; Watson, D.; Kohn, H. Effect of Structural Modification of the Hydantoin Ring on Anticonvulsant Activity. *J. Med. Chem.* **1985**, *28*, 601–606.
(2) Conley, J. D.; Kohn, H. Functionalized DL-Amino Acid Derivatives. Potent Agents for the Treatment of Epilepsy. *J. Med. Chem.* **1987**, *30*, 567–574.
(3) Kohn, H.; Conley, J. D. New Antiepileptic Agents. *Chem. Br.* **1988**, *24*, 231–233.
(4) Kohn, H.; Conley, J. D.; Leander, J. D. Marked Stereospecificity in a New Class of Anticonvulsants. *Brain Res.* **1988**, *457*, 371–375.
(5) Kohn, H.; Sawhney, K. N.; LeGall, P.; Conley, J. D.; Robertson, D. W.; Leander, J. D. Preparation and Anticonvulsant Activity of a Series of Functionalized α-Aromatic and α-Heteroaromatic Amino Acids. *J. Med. Chem.* **1990**, *33*, 919–926.
(6) Kohn, H.; Sawhney, K. N.; Le Gall, P.; Robertson, D. W.; Leander, J. D. Preparation and Anticonvulsant Activity of a Series of Functionalized α-Heteroatom-Substituted Amino Acids. *J. Med. Chem.* **1991**, *34*, 2444–2452.
(7) Kohn, H.; Sawhney, K. N.; Bardel, P.; Robertson, D. W.; Leander, J. D. Synthesis and Anticonvulsant Activities of α-Acetamido-*N*-benzylacetamide Derivatives. *J. Med. Chem.* **1993**, *36*, 3350–3360.
(8) Parham, W. E.; Piccirilli, R. M. Selective Halogen-Lithium Exchange in 2,5-Dibromobenzenes and 2,5-Dibromopyridine. *J. Org. Chem.* **1977**, *42*, 257–260.
(9) Lipschutz, B. H.; Wilhem, R. S.; Kozlowski, J. A. The Chemistry of Higher Order Organocuprates. *Tetrahedron* **1984**, *40*, 5005–5038.
(10) (a) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. The Synthesis of Amino Acids by Phase-Transfer Reactions. *Tetrahedron Lett.* **1978**, *30*, 2641–2644. (b) Ghosez, L.; Antoine, J.-P.; Deffense, E.; Navarro, M.; Libert, V.; O'Donnell, M. J.; Bruder, W. A. Synthesis of Amino Acids. Alkylation of Aldimine and Ketimine Derivatives of Glycine Ethyl Ester Under Various Phase-Transfer Conditions. *Tetrahedron Lett.* **1982**, *23*, 4255–4258. (c) O'Donnell, M. J.; LeClef, B.; Rusterholz, D. B.; Ghosez, L.; Antoine, J.-P.; Navarro, M. α-Methyl Amino Acids by Catalytic Phase-Transfer Alkylations. *Tetrahedron Lett.* **1982**, *23*, 4259–4262. (d) O'Donnell, M. J.; Polt, R. L. A Mild and Efficient Route to Schiff Base Derivatives of Amino Acids. *J. Org. Chem.* **1982**, *47*, 2663–2666. (e) O'Donnell, M. J.; Wojciechowski, K.; Ghosez, L.; Navarro, M.; Sainte, F.; Antoine, J.-P. Alkylation of Protected α-Amino Acid Derivatives in the Presence of Potassium Carbonate. *Synthesis* **1984**, 313–315.
(11) Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. Cyanide as an Efficient Catalyst in the Aminolysis of Esters. *J. Org. Chem.* **1987**, *52*, 2033–2036.
(12) Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. Antiepileptic Drug Development. II. Anticonvulsant Drug Screening. *Epilepsia* **1978**, *19*, 409–428.
(13) Dunham, N. W.; Miya, T.-S. A Note on a Simple Apparatus for Detecting Neurological Deficit in Rats and Mice. *J. Am. Pharm. Assoc.* **1957**, *46*, 208–209.
(14) Coughenour, L. L.; McLean, R. R.; Parker, R. R. A New Device for the Rapid Measurement of Impaired Motor Function in Mice. *Pharmacol. Biochem. Behav.* **1977**, *6*, 351–353.
(15) Porter, R. J.; Cereghino, J. J.; Gladding, G. D.; Hessie, B. J.; Kupferberg, H. J.; Scoville, B.; White, B. G. Antiepileptic Drug Development Program. *Cleveland Clin. Q.* **1984**, *51*, 293–305.
(16) Compounds **11–13** were not active in the subcutaneous Metrazol test at 300 mg/kg.
(17) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1972.
(18) LeGall, P.; Sawhney, K. N.; Conley, J. D.; Kohn, H. Synthesis of Functionalized Non-natural Amino Acid Derivatives via Amidoalkylation Transformations. *Int. J. Pept. Protein Res.* **1988**, *32*, 279–291.