was resuspended in 3 times the original volume of buffer and incubated at 37 °C for 15 min, centrifuged again, and resuspended in the original volume of buffer. A binding assay using [^{3}H]-bremazocine (0.5 nM) was carried out as described above.

Acknowledgment. We greatly appreciate receiving samples of benzomorphan standards **1**, its enantiomer, **2**, (2′*R*)- and (2″*S*)-**3**, and the enantiomer of (2″*S*)-**3** from Dr. Herbert Merz, Boehringer Ingelheim KG, Germany. We acknowledge the support of this work by the National Institute on Drug Abuse through research grants DA-03933 and DA-06675.

Registry No. **4**, 134133-69-0; **5**, 134233-45-7; **6**, 134233-46-8; **7**, 134233-47-9; **8**, 134133-70-3; **8**·HCl, 134233-67-3; **9**, 134233-48-0; **9**·HCl, 134308-16-0; (±)-**10**, 52079-30-8; (5*R*)-**11**, 58879-35-9; (5*S*)-**11**, 58879-36-0; **12**, 134133-71-4; **13**, 134233-49-1; **14**, 134133-72-5; **15**, 134233-50-4; **16** (isomer 1), 134133-73-6; **16** (isomer 2), 134233-51-5; **18** (isomer 1), 134133-74-7; **18** (isomer 2), 134233-52-6; **20**, 134133-75-8; **21**, 134233-53-7; **22**, 134233-54-8; **23**, 134233-55-9; **24**, 134233-56-0; **25**, 134233-57-1; **30**, 134233-58-2; **31**, 134233-59-3; **32** (isomer 1), 134133-76-9; **32** (isomer 2), 134233-60-6; **33** (isomer 1), 134133-77-0; **33** (isomer 2), 134233-61-7; **33** (isomer 1)·HCl, 134233-62-8; **33** (isomer 2)·HCl, 134308-15-9; **34** (isomer 1), 134233-63-9; **34** (isomer 2), 134233-64-0; **35** (isomer 1), 134233-65-1; **35** (isomer 2), 134233-66-2.

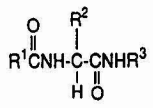
Preparation and Anticonvulsant Activity of a Series of Functionalized α-Heteroatom-Substituted Amino Acids

Harold Kohn,*,† Kailash N. Sawhney,† Philippe LeGall,† David W. Robertson,‡ and J. David Leander‡

Department of Chemistry, University of Houston, Houston, Texas 77204-5641, and Lilly Research Laboratories, Eli Lilly Company, Indianapolis, Indiana 46285. *Received December 4, 1990*

Potent anticonvulsant activity has been reported for (*R*,*S*)-2-acetamido-*N*-benzyl-2-methylacetamide (**2a**). Select α-heteroatom substituted derivatives of **2a** have been prepared (26 examples) in which the α-methyl group has been replaced by nitrogen (**3a–q**), oxygen (**3r–u**), and sulfur (**3v–z**) containing moieties. The functionalized amino acid derivatives were evaluated in the maximal electroshock seizure (MES) and horizontal screen (tox) tests in mice. The most active compounds were (*R*,*S*)-2-acetamido-*N*-benzyl-2-(methoxyamino)acetamide (**3l**), and (*R*,*S*)-2-acetamido-*N*-benzyl-2-(methoxymethylamino)acetamide (**3n**). After ip administration, the MES ED_{50} values for **3l** (6.2 mg/kg) and **3n** (6.7 mg/kg) compared favorably with phenytoin (9.50 mg/kg).

Nonnaturally occurring amino acids have become increasingly important in the design of pharmacologically active peptides and peptidomimetics.[1] Recently we reported the excellent anticonvulsant activity of certain functionalized amino acid derivatives **1**.[2-6] Potent protection against maximal electroshock seizures (MES) in mice was observed for functionalized amino acid racemates containing both an *N*-benzylamide moiety and an acetylated amino group. Systematic variation of the α-substituent revealed that stringent steric and electronic requirements must be met for optimal activity. The median effective dose (ED_{50}) for the α-methyl (**2a**) (76.5 mg/kg) and α-phenyl (**2b**) (20.3 mg/kg) derivatives[4] compared favorably with that observed for phenobarbital[7] (21.8 mg/kg), while those of the α-pyrrolyl (**2c**) (16.1 mg/kg) and α-furanyl (**2d**) (10.3 mg/kg) adducts[6] rivaled that reported for phenytoin[7] (9.50 mg/kg). Furthermore, comparison of the two individual enantiomers of **2a,b,d** revealed that in each case the anticonvulsant activity resided primarily in the *R* stereoisomer.[2,5,6]



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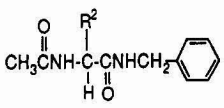


2a R^2 = CH_3
b R^2 = Ph
c R^2 = 2-pyrrolyl
d R^2 = 2-furanyl

In the present study, the synthesis and anticonvulsant properties of a novel series of α-heteroatom-substituted amino acid derivatives (26 examples) are presented. Included in this survey are selected oxygen, nitrogen, and sulfur-functionalized amino acids. Analysis of the composite data set disclosed trends that further define the structure–activity relationships for this class of amino acid derived anticonvulsant agents.

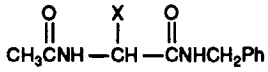
Selection of Compounds

(*R*,*S*)-2-Acetamido-*N*-benzyl-2-methylacetamide[3] (**2a**) represented the parent compound in this study wherein the α-methyl group was replaced by select functionalized nitrogen, oxygen, and sulfur substituents (Table I). In all cases, the racemates were prepared and tested. No attempts were made at this stage to resolve the enantiomeric mixtures. The α-nitrogen-substituted adducts consisted of the parent amino **3a**, the monoalkylamino **3b,c**, the dialkylamino **3d,e**, and the trialkylammonium **3f** derivatives, as well as the corresponding monoaryl analogues **3g** and **3h**. Included in our α-nitrogen subset of compounds were three classes of functionalized amino derivatives. These were the monoacyl derivatives **3i** and **3j**, the *N*-hydroxyamino adducts **3k–o**, and the *N*-hydrazino compounds **3p** and **3q**. The second set of structurally modified amino acid derivatives were the

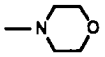
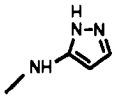
* Author to whom correspondence should be addressed to at the University of Houston.
† University of Houston.

(1) For leading references, see: (a) Shuman, R. T.; Ornstein, P. L.; Paschal, J. W.; Gesellchen, P. D. *J. Org. Chem.* **1990**, *55*, 738. (b) Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770 and references therein.
(2) Kohn, H.; Conley, J. D. *Chem. Br.* **1988**, *24*, 231.
(3) Cortes, S.; Liao, Z.-K.; Watson, D.; Kohn, H. *J. Med. Chem.* **1985**, *28*, 601.
(4) Conley, J. D.; Kohn, H. *J. Med. Chem.* **1987**, *30*, 567.
(5) Kohn, H.; Conley, J. D.; Leander, J. D. *Brain Res.* **1988**, *457*, 371.
(6) Kohn, H.; Sawhney, K. N.; LeGall, P.; Conley, J. D.; Robertson, D. W.; Leander, J. D. *J. Med. Chem.* **1990**, *33*, 919.
(7) Porter, R. J.; Cereghino, J. J.; Gladding, G. D.; Hessie, B. J.;

Table I. Selected Physical and Pharmacological Data in Mice for α-Heteroatom-Substituted Functionalized Amino Acid Derivatives **3**[a]



3

no.	X	mp[b]	MES[c] ED_{50}	tox[d] TD_{50}
3a	NH_2	131–133	65.1 [0.5] (56.2–75.3)	*e*
3b	$NHCH_3$	115–117	44.5 [0.5] (37.0–52.4)	*e*
3c	$NHCH_2CH_3$	123–125	42.4 [0.5] (37.2–47.8)	*e*
3d	$N(CH_3)_2$	104–106	45.3 [1]	*e*
3e		171–172	>30, <100 [1]	*e*
3f	$N^+(CH_3)_3\ BF_4^-$	171–173 dec	>100	*e*
3g	NHPh	183–185	>300	*e*
3h		135–137	~100 [1]	*e*
3i	$NHCOCH_3$	265–267 dec	>100, <300 [1]	*e*
3j	$NHCOCF_3$	228–230	>300	*e*
3k	NHOH	144–146 dec	~100 [1]	*e*
3l	$NH(OCH_3)$	95–97	6.2 [0.5] (5.4–7.2)	46.0 [0.5] (38.0–56.0)
3m	$N(CH_3)OH$	159–161	~30 [1]	*e*
3n	$N(CH_3)OCH_3$	165–167	6.7 [0.5] (5.7–7.7)	50.5 [0.5] (40.4–59.9)
3o		149–151	31.4 [0.5] (26.7–37.8)	*e*
3p	NHNHPh	132–134	~100 [0.5]	*e*
3q	$NHNHCO_2CH_2Ph$	152–154	55.6 [0.5] (49.3–63.9)	*e*
3r	OH	136–138	80.1 [1] (70.6–91.0)	*e*
3s[f]	OCH_3	145–146	98.3 [0.5] (84.4–114.0)	>100, <300 [0.5]
3t[f]	OCH_2CH_3	153–155	62.0 [1] (51.1–78.4)	>112
3u	OPh	125–128	>100[g]	*e*
3v	SCH_3	155–157	>100	*e*
3w	SCH_2CH_3	140–142	>30, <100 [0.5]	*e*
3x[f]	SPh	165–167	>300	*e*
3y-1	$S(O)CH_2CH_3$	135–137	>100	*e*
3y-mix	$S(O)CH_2CH_3$	135–137	>100	*e*
3z	$S(O_2)CH_2CH_3$	161–163	>100	*e*
2a[h]	CH_3	138–139	76.5 (66.6–89.0)	453.9[i] (416.6–501.0)
2b[j]	Ph	202–203	20.3 (16.9–24.5)	96.9[i] (79.8–118.4)
2c[k]	2-pyrrolyl	174–175	16.1 (13.2–19.9)	>30, <100
2d[k]	2-furanyl	178–179	10.3 (9.1–11.6)	~40
phenytoin[l]			9.5 (8.1–10.4)	65.5[i] (52.5–72.1)
phenobarbital[l]			21.8 (15.0–22.5)	69.0[i] (62.8–72.9)
valproate[l]			272 (247–338)	426[i] (369–450)

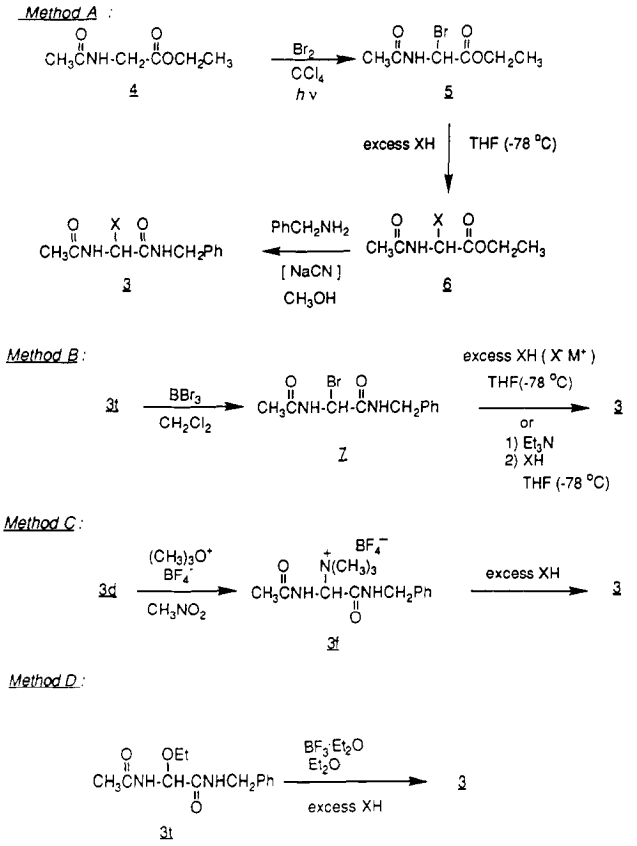
[a] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in milligrams per kilogram. Number in parentheses are 95% confidence intervals. Time of peak effects in hours as determined in the Experimental Section is denoted in brackets. [b] Melting points (°C) are uncorrected. [c] MES = maximal electroshock seizure test. Compound was suspended in 30% PEG unless otherwise noted. [d] Tox = neurologic toxicity determined from horizontal screen unless otherwise noted. [e] Not determined. [f] Reference 8. [g] Compound **3u** was suspended in acacia. [h] Reference 3. [i] Neurologic toxicity determined using the rotorod test. [j] Reference 4. [k] Reference 6. [l] Reference 7.

α-oxygen-substituted compounds **3r–u**. This group was comprised of the α-hydroxy adduct **3r**, the two α-alkoxy derivatives **3s** and **3t**,[8] and the α-phenoxy compound **3u**.

A similar battery of α-sulfur-substituted compounds (i.e., **3v–x**[8]) was selected for evaluation. Attempts to synthesize the parent α-thiol derivative in the series were unsuccessful, however. In addition to **3v–x**, both the sulfoxide **3y** and the sulfone **3z** derivatives of the ethylthio adduct

(8) LeGall, P.; Sawhney, K. N.; Conley, J. D.; Kohn, H. *Int. J.*

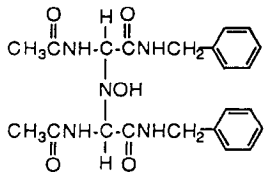
Scheme I. Preparation of α-Heteroatom-Substituted Functionalized Amino Acid Derivatives 3



Chemistry

Four different synthetic approaches (Scheme I, methods A–D) were employed for the preparation of most of the α-heteroatom-substituted, functionalized amino acid derivatives **3**. In the first route (method A), the α-bromo ester **5** was prepared in near quantitative yield using the protocol of Kober and Steglich[9] from commercially available[10] ethyl acetamidoacetate (**4**). Treatment of **5** with an excess of the nucleophilic heteroatom species furnished the corresponding ethyl 2-substituted-2-acetamidoacetate **6** (61–92% yields). Formation of **6** is presumed to proceed through the intermediacy of ethyl 2-(acetylimino)acetate. In most cases, **6** was isolated as a thick oil and used directly in the subsequent step without extensive purification. Treatment of **6** with benzylamine and a catalytic amount of NaCN[11] gave the desired product in moderate yields (29–74%). This method was used to synthesize compounds **3a–c**, **3e**, **3g**, and **3h**. Attempts to utilize this protocol to prepare **3d**, **3k**, **3m**, and **3n** were unsatisfactory. In these cases the final benzylamine-mediated step did not proceed cleanly.

The difficulty encountered in converting several α-functionalized esters **6** to the corresponding benzylamides **3** led to the development of the second procedure (method B) depicted in Scheme I. In this route the benzylamide moiety was incorporated within the framework of the amino acid derivative prior to the introduction of the α-heteroatom substituent. Treatment of **3t** with BBr_3 in CH_2Cl_2 led to the formation of the presumed α-bromo derivative **7**. This adduct could not be fully purified or characterized due to the sensitivity of **7** to moisture and its poor solubility in nonhydroxylic solvents. Accordingly, either the addition of an excess of the heteroatom species or the sequential addition of triethylamine and the nucleophilic heteroatom-containing reagent to a THF mixture containing **7** furnished **3** in moderate amounts (21–38% yields from **3t**). This method was employed for the preparation of compounds **3d**, **3k**, **3p**, and **3u–w**. Included in the product mixture for **3k** were the diastereomeric adducts **8a** and **8b** in which 2 equiv of **7** reacted with NH_2OH. Implementation of this procedure for the synthesis of **3l–o** was not successful due to the difficulty encountered in obtaining solutions of the free hydroxyamines in nonhydroxylic solvents. Use of methanolic solutions of the hydroxyamines furnished only **3s**.



8

Employment of the third protocol (method C) outlined in Scheme I provided a convenient procedure to circumvent this obstacle. Methylation of the dimethylamino adduct **3d** with trimethyloxonium tetrafluoroborate[10] in nitromethane furnished the quaternary ammonium derivative **3f** in high yields. Subsequent treatment of **3f** with a methanolic solution containing the requisite hydroxyamine led to production of **3l–o** in good yields (42–82%).

Synthesis of the α-hydroxy (**3r**), α-ethylthio (**3w**), and α-thiophenoxy[8] (**3x**) amino acid derivatives was accomplished using the last technique depicted in Scheme I in which **3t** was treated with $BF_3{\cdot}Et_2O$ in the presence of H_2O, EtSH, and PhSH, respectively (Scheme I, method D). A similar protocol was utilized by us for the preparation of α-heteroaromatic functionalized amino acid derivatives.[6,8] This procedure proved superior than that of method B for the preparation of **3w**.

Two of the remaining compounds listed in Table I, **3i** and **3j**, were obtained by treatment of **3a** with acetic anhydride and trifluoroacetic anhydride, respectively. The final compounds **3y** and **3z** were prepared directly from the α-ethylthio adduct **3w**. Interestingly, treatment of **3w** with *m*-chloroperbenzoic acid in CH_2Cl_2 led to the stereoselective production of the α-sulfoxide **3y-1**. ^{13}C NMR analysis of the initial reaction mixture indicated the presence of only a single diastereomeric (enantiomeric pair) compound. The precise stereochemical identity of this adduct has not been established. Correspondingly, use of stoichiometric amounts of $NaIO_4$ at room temperature in an aqueous methanolic solution yielded a 2:1 diastereomeric mixture (^{13}C NMR analysis) of **3y-1** and **3y-2** in which the major compound present corresponded to the product generated in the *m*-chloroperbenzoic acid reaction (**3y-1**). Attempts to completely separate these diastereomers by either TLC or recrystallization proved unsuccessful. Accordingly, a 2:3 mixture of **3y-1** and **3y-2** obtained after fractional recrystallization was analyzed for anticonvulsant activity and is identified as **3y-mix**. We have tentatively attributed the diastereoselectivity of the *m*-chloroperbenzoic acid mediated process to the preorganization of the oxidant with **3w** in CH_2Cl_2. Employment of excess $NaIO_4$ with **3w** at elevated temperatures (50–60 °C) gave the α-sulfone **3z** in 32% yield.

Of note, all 17 α,α-diamino acid derivatives (**3a–q**), including the trimethylammonium adduct **3f**, were well-

(9) Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599.
(10) Aldrich Chemical Co.
(11) Hogberg, T.; Strom, P.; Ebner, M.; Ramsby, S. *J. Org. Chem.* 1987, 52, 2033.

defined, stable compounds.[12] Only **3f**, **3i**, and **3k** melted with decomposition.

Pharmacological Evaluation

The α-heteroatom substituted amino acid derivatives **3** were tested for anticonvulsant activity by using the procedures described by Krall et al.[13] All compounds were administered intraperitoneally (ip) to mice. Table I lists the median effective dose (ED_{50}) values required to prevent seizures in the MES test by racemic **3**. Included in this table are the median neurotoxic dose (TD_{50}) values determined for select compounds using the horizontal screen test.[14]

Evaluation of the results listed in Table I revealed several important observations. First, the α-amino (**3a**), α-alkylamino (**3b–e**), and α-trimethylammonium (**3f**) derivatives all displayed anticonvulsant activities comparable to that observed for the α-methyl analogue **2a**.[3,4] Second, the α-arylamino derivatives **3g** and **3h** were devoid of activity at doses below 100 mg/kg. A comparable reduction in activity has been observed in proceeding from the α-methyl derivative (**2a**) to the corresponding α-benzyl adduct[4] and has been attributed (in part) to the stringent steric requirements that exist for maximal anticonvulsant activity in this class of compounds. Third, conversion of the α-amino derivative **3a** to the corresponding α-acylamino adducts **3i** and **3j** led to a decrease in activity of the test compound. Fourth, incorporation of an α-*N*-alkoxyamino moiety (i.e., **3l**, **3n**, **3o**) within the backbone of the compound led to a pronounced improvement of the potency of the compound in the MES test compared to either **2a** or **3a**. A corresponding enhancement in activity was not observed for the two *N*-hydroxyamino adducts **3k** and **3m**. The anticonvulsant activities of racemic **3l** (ED_{50} = 6.2 mg/kg) and **3n** (ED_{50} = 6.7 mg/kg) were comparable to that of the (*R*,*S*)-2-furanyl derivative **2d**[6] (ED_{50} = 10.3 mg/kg) and phenytoin[7] (ED_{50} = 9.5 mg/kg). Importantly, in the most potent analogues (**2d**, **3l**, and **3n**), a *functionalized* oxygen atom existed two atoms removed from the α-carbon atom. This pattern suggests that a substituted β-heteroatom may be necessary for maximal activity. Fifth, the α-hydrazine derivatives **3p** and **3q** did not display significant anticonvulsant activity. Once again this property has been attributed (in part) to the steric size of these substituents. Sixth, the α-hydroxy (**3r**) and the two α-alkoxy adducts (**3s**, **3t**) displayed activity comparable to that reported for **2a**. The potency of the α-oxygen series was somewhat diminished from that observed for the corresponding α-amino derivatives (**3a–c**). In agreement with previous findings[4] the α-phenoxy adduct **3u** displayed no activity at doses of 100 mg/kg or less. Seventh, within the α-sulfur series, only the α-ethylthio adduct **3w** exhibited anticonvulsant activity at doses less than 100 mg/kg. Eighth, no enhancement of activity was noted for the three sulfur-oxygenated derivatives **3y-1**, **3y-mix**, and **3z** versus **3w**. This observation is consistent with the results obtained for the two *N*-hydroxyamino adducts **3k** and **3m** versus **3a**.

(12) For recent reports on the preparation of α,α-diamino acid derivatives and related compounds, see: (a) Katritzky, A. R.; Urogdi, L.; Mayence, A. *J. Chem. Soc., Chem. Commun.* **1989**, 337. (b) Katritzky, A. R.; Urogdi, L.; Mayence, A. *J. Org. Chem.* **1990**, *55*, 2206. (c) Bock, M. G.; DiPardo, R. M.; Freidinger, R. M. *Ibid.* **1986**, *51*, 3718. (d) Fischer, B.; Hassner, A. *Ibid.* **1990**, *55*, 5225 and references therein.

(13) Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. *Epilepsia* **1978**, *19*, 409.

(14) Coughenour, L. L.; McLean, R. R.; Parker, R. B. *Pharmacol.*

Conclusions

Straightforward procedures have been employed for the preparation of α-heteroatom-substituted amino acid derivatives. Despite the fact that these compounds have geminal heteroatoms α to the carbonyl, they are chemically well-defined and are expected to serve as useful substrates in future chemical and pharmacological studies. The pharmacological data obtained in this investigation provided additional information concerning the structure–activity profile of functionalized amino acid anticonvulsants. The biological activities for **3** reinforced our notions that stringent steric and electronic requirements exist for maximal anticonvulsant activity in this class of compounds. The potencies of **3l** and **3n** in the MES test were comparable to those of phenytoin and **2d**. Additional studies in progress are aimed at investigating the generality of this class of compounds, as well as their mode of action.

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. Microanalyses were provided by the Physical Chemistry Department of the Lilly Research Laboratories. Benzyl carbazate was obtained from Lancaster Synthesis Ltd., Windham, NH. Thin-layer chromatography were run on precoated silica gel GHLF microscope slides (2.5 × 10 cm; Analtech No. 21521).

Preparation of α-Heteroatom-Substituted Amino Acids (3). Method A. Synthesis of Ethyl 2-Acetamido-2-substituted-acetates. General Procedure. A cooled (−78 °C) solution of **5**[9] (1 equiv) in THF (1 mmol/10 mL) was added slowly to a THF (1 mmol/4 mL) solution of the nitrogen nucleophile (5–10 equiv) at −78 °C. The reaction was stirred at this temperature (0.5 h) and then at room temperature (1 h). The insoluble materials were filtered and washed with THF. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on SiO_2 gel (using the indicated solvent as the eluent) to give the desired product.

By use of this procedure, the following compounds were prepared.

Synthesis of Ethyl 2-Acetamido-2-aminoacetate (6a). Compound **5** (2.00 g, 8.93 mmol) and liquid NH_3 (5–6 equiv) yielded a light brown residue, which on purification by flash column chromatography on SiO_2 gel (5% MeOH/$CHCl_3$) gave 1.00 g (70%) of **6a** as a yellow oil: R_f 0.21 (5% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3 H), 2.03 (s, 3 H), 2.61 (br s, 2 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 5.21 (d, *J* = 7.1 Hz, 1 H), 7.50 (d, *J* = 7.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 13.72, 22.68, 59.70, 61.73, 170.40, 170.68 ppm.

Synthesis of Ethyl 2-Acetamido-2-(methylamino)acetate (6b). Use of **5** (2.00 g, 8.93 mmol) and $MeNH_2$ (2.50 g, 80.6 mmol) gave an oily residue (1.50 g). The residue was purified by flash column chromatography on SiO_2 gel (3% MeOH/$CHCl_3$) to yield 1.00 g (65%) of **6b** as an oil: R_f 0.30 (3% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3 H), 2.07 (s, 3 H), 2.36 (s, 3 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 5.20 (d, *J* = 7.4 Hz, 1 H), 6.60 (br s, 1 H) (the remaining amino proton was not detected); ^{13}C NMR ($CDCl_3$) 14.02, 23.06, 30.84, 62.04, 65.72, 170.09, 170.40 ppm.

Synthesis of Ethyl 2-Acetamido-2-(ethylamino)acetate (6c). Employing **5** (2.10 g, 9.38 mmol) and $EtNH_2$ (1.40 g, 31.04 mmol) gave a brown residue. The residue was purified by flash column chromatography on SiO_2 gel (3% MeOH/$CHCl_3$) to yield 0.90 g (51%) of **6c** as a light yellow oil: R_f 0.36 (4% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.93 (t, *J* = 6.7 Hz, 3 H), 1.12 (t, *J*

J = 6.8 Hz, 2 H), 5.05 (d, J = 7.1 Hz, 1 H), 7.09 (d, J = 7.1 Hz, 1 H) (the remaining amino proton was not detected); ^{13}C NMR ($CDCl_3$) 13.64, 14.55, 22.53, 39.06, 61.38, 64.14, 170.09, 170.20 ppm.

Synthesis of Ethyl 2-Acetamido-2-(dimethylamino)acetate (6d). Compound **5** (2.00 g, 8.93 mmol) and Me_2NH (5–6 equiv) gave **6d** (1.50 g, 89%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3 H), 2.02 (s, 3 H), 2.23 (s, 6 H), 4.10–4.25 (m, 2 H), 5.24 (d, J = 8.3 Hz, 1 H), 6.59 (d, J = 8.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 14.05, 23.00, 40.28 (2 C), 61.84, 69.24, 169.38, 170.57 ppm.

Synthesis of Ethyl 2-Acetamido-2-(4-morpholino)acetate (6e). Use of morpholine (1.71 g, 19.64 mmol) and **5** (2.00 g, 8.93 mmol) gave an oily residue, which was purified by flash column chromatography on SiO_2 gel (2% MeOH/$CHCl_3$) to give 1.90 g (93%) of **6e** as a thick oil: R_f 0.29 (3% MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 6.8 Hz, 3 H), 2.07 (s, 3 H), 2.43–2.72 (m, 4 H), 3.58–3.78 (m, 4 H), 4.26 (q, J = 6.8 Hz, 2 H), 5.27 (d, J = 7.9 Hz, 1 H), 6.39 (d, J = 7.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 14.21, 23.25, 48.47 (2 C), 62.06, 66.71 (2 C), 69.22, 169.00, 170.46 ppm.

Synthesis of Ethyl 2-Acetamido-2-(*N*-anilino)acetate (6g). Use of aniline (1.83 g, 19.6 mmol) and **5** (2.00 g, 8.93 mmol) provided a brown residue, which was purified by flash column chromatography on SiO_2 gel ($CHCl_3$–2% MeOH/$CHCl_3$ gradient) to yield 1.80 g (85%) of **6g**: mp 87–89 °C (recrystallized from ethyl acetate/petroleum ether); R_f 0.52 (4% MeOH/$CHCl_3$); IR (KBr) 3340, 1720, 1635, 1590, 1490, 730, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3 H), 1.84 (s, 3 H), 4.27 (q, J = 7.1 Hz, 2 H), 5.89 (d, J = 8.2 Hz, 1 H), 6.43 (d, J = 8.2 Hz, 1 H), 6.68–6.71 (m, 2 H), 6.80–6.83 (m, 1 H), 7.17–7.22 (m, 2 H) (the remaining amino proton was not detected); ^{13}C NMR ($CDCl_3$) 13.96, 22.98, 60.19, 62.41, 113.87 (2 C), 119.29, 129.37 (2 C), 144.09, 169.77, 170.14 ppm; mass spectrum (FD) 237 (M^+ + 1). Anal. ($C_{12}H_{16}N_2O_3$) C, H, N.

Synthesis of Ethyl 2-Acetamido-2-(3-pyrazolylamino)acetate (6h). Use of **5** (2.00 g, 8.93 mmol) and 3-aminopyrazole (1.85 g, 22.32 mmol) and purification of the reaction product by chromatography on SiO_2 gel (2% MeOH/$CHCl_3$) gave 1.80 g (89%) of **6h** as a yellow oil: R_f 0.35 (8% MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 3 H), 1.89 (s, 3 H), 4.20 (q, J = 7.1 Hz, 2 H), 5.64 (d, J = 1.8 Hz, 1 H), 5.71 (br s, 1 H), 5.73 (d, J = 7.1 Hz, 1 H), 7.29 (d, J = 1.8 Hz, 1 H), 7.98 (d, J = 7.1 Hz, 1 H) (the remaining amino proton was not detected); ^{13}C NMR ($CDCl_3$) 13.73, 22.49, 61.41, 62.02, 91.79, 130.53, 153.02, 169.96, 170.93 ppm.

Synthesis of Ethyl 2-Acetamido-2-(hydroxyamino)acetate (6k). Use of **5** (2.10 g, 9.38 mmol) and anhydrous NH_2OH[15] (0.93 g, 28.00 mmol) gave an oily residue. The residue was purified by flash column chromatography on SiO_2 gel (5% MeOH/$CHCl_3$) to give 1.00 g (61%) of **6k**. The product was recrystallized from EtOH to give a white flaky solid: mp 119–121 °C; R_f 0.24 (5% MeOH/$CHCl_3$); IR (KBr) 3300, 1750, 1660, 1540, 1390, 610 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.19 (t, J = 6.9 Hz, 3 H), 1.87 (s, 3 H), 4.10 (q, J = 6.9 Hz, 2 H), 5.09 (dd, J = 4.0, 8.0 Hz, 1 H), 6.06 (br s, 1 H), 7.63 (s, 1 H), 8.50 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 14.05, 22.46, 60.82, 67.37, 169.19, 169.48 ppm; mass spectrum (FD) 177 (M^+ + 1). Anal. ($C_6H_{12}N_2O_4$) C, H, N.

Synthesis of Ethyl 2-Acetamido-2-(methylhydroxyamino)acetate (6m). MeNHOH (17.39 mmol) (prepared from MeNHOH·HCl (2.00 g, 23.95 mmol) and NaOMe (0.94 g, 17.39 mmol)) and **5** (1.00 g, 4.46 mmol) gave an oily residue. The residue was triturated with EtOAc (5 mL) and the solid (0.70 g, 82%) that remained was filtered and recrystallized from EtOH to give **6m** as a white solid: mp 148–150 °C; R_f 0.34 (5% MeOH/$CHCl_3$); IR (KBr) 3320, 3200 (br), 1760, 1660, 1530, 1470, 720, 640 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.17 (t, J = 7.0 Hz, 3 H), 1.89 (s, 3 H), 2.37 (s, 3 H), 4.00–4.20 (m, 2 H), 5.04 (d, J = 9.2 Hz, 1 H), 8.17 (s, 1 H), 8.43 (d, J = 9.2 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 14.04, 22.28, 43.78, 60.79, 71.46, 168.29, 170.23 ppm; mass spectrum (FD) 192 (M^+ + 1). Anal. ($C_7H_{14}N_2O_4$·0.25H_2O) C, H, N.

Synthesis of Ethyl 2-Acetamido-2-(methoxymethylamino)acetate (6n). MeNHOMe (17.40 mmol) (prepared from MeNHOMe·HCl (2.18 g, 22.32 mmol) and NaOMe (0.94 g, 17.40 mmol)) and **5** (1.00 g, 4.46 mmol) gave a residue, which was purified by flash column chromatography on SiO_2 gel (1% MeOH/$CHCl_3$) to give 0.60 g (66%) of **6n** as an oil: R_f 0.53 (2% MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.0 Hz, 3 H), 2.12 (s, 3 H), 2.62 (s, 3 H), 3.46 (s, 3 H), 4.30 (q, J = 7.0 Hz, 2 H), 5.36 (d, J = 8.9 Hz, 1 H), 6.66 (d, J = 8.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 14.06, 22.89, 40.30, 60.01, 61.89, 70.16, 168.14, 170.53 ppm.

Synthesis of 2-Acetamido-*N*-benzyl-2-substituted-acetamides (3). General Procedure. A mixture of **6** (1 equiv), benzylamine (1.2 equiv), and NaCN (0.1 equiv) in MeOH (1 mmol/25 mL) was stirred at 45–50 °C (18 h). The solvent was removed in vacuo, and the residue was purified with either trituration with EtOAc or flash column chromatography on SiO_2 gel (using the indicated solvent as the eluent).

By use of this procedure, the following compounds were prepared.

Synthesis of 2-Acetamido-*N*-benzyl-2-aminoacetamide (3a). Compound **6a** (1.00 g, 6.25 mmol), benzylamine (0.80 g, 7.5 mmol), and NaCN (0.03 g, 0.61 mmol) gave a residue that solidified on standing (18 h). The reaction mixture was triturated with EtOAc (20 mL). The white solid (1.00 g, 72%) that remained was filtered and then further purified by recrystallization from EtOAc: mp 131–133 °C dec; R_f 0.21 (5% MeOH/$CHCl_3$); IR (KBr) 3300, 1650 (br), 1530 (br), 1450, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.83 (s, 3 H), 2.35 (br s, 2 H), 4.28 (d, J = 4.4 Hz, 2 H), 4.91 (d, J = 7.0 Hz, 1 H), 7.20–7.32 (m, 5 H), 8.31 (br s, 1 H), 8.51 (br s, 1 H); ^{13}C NMR (DMSO-d_6) 22.66, 42.05, 60.29, 126.67, 127.10 (2 C), 128.18 (2 C), 139.23, 169.24, 170.67 ppm; mass spectrum, m/e (relative intensity) 222 (M^+ + 1, 100), 221 (M^+, 29), 133 (8). Anal. ($C_{11}H_{15}N_3O_2$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(methylamino)acetamide (3b). Compound **6b** (1.50 g, 8.63 mmol), benzylamine (1.11 g, 10.35 mmol), and NaCN (0.04 g, 0.82 mmol) gave a brown residue that was purified by flash column chromatography on SiO_2 gel (2% MeOH/$CHCl_3$) to yield 1.00 g (49%) of **3b**: mp 115–117 °C (recrystallized from ethyl acetate/petroleum ether); R_f 0.33 (3% MeOH/$CHCl_3$); IR (KBr) 3240, 1610 (br), 1500 (br), 1430, 725, 670 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.87 (s, 3 H), 2.18 (s, 3 H), 4.20–4.29 (m, 2 H), 4.87 (d, J = 7.9 Hz, 1 H), 7.24–7.35 (m, 5 H), 8.14 (d, J = 7.9 Hz, 1 H), 8.55 (br s, 1 H) (the remaining amino proton was not detected); ^{13}C NMR (DMSO-d_6) 22.52, 31.37, 42.04, 65.99, 126.68, 127.12 (2 C), 128.18 (2 C), 139.28, 169.51, 169.83 ppm. Anal. ($C_{12}H_{17}N_3O_2$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(ethylamino)acetamide (3c). Use of **6c** (0.90 g, 4.79 mmol), benzylamine (0.62 g, 5.75 mmol), and NaCN (0.03 g, 0.51 mmol) gave an oily residue that was purified by flash column chromatography on SiO_2 gel (3% MeOH/$CHCl_3$) to give 0.35 g (29%) of **3c** as a white solid: mp 123–125 °C (recrystallized from ethyl acetate/hexane); R_f 0.34 (4% MeOH/$CHCl_3$); IR (KBr) 3250, 1620 (br), 1510 (br), 1450 (br), 740, 680 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.93 (t, J = 6.8 Hz, 3 H), 1.81 (s, 3 H), 2.08 (br s, 1 H), 2.40–2.48 (m, 2 H), 4.22 (d, J = 5.5 Hz, 2 H), 4.90 (d, J = 7.8 Hz, 1 H), 7.20–7.27 (m, 5 H), 8.08 (d, J = 7.8 Hz, 1 H), 8.48 (t, J = 5.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 15.14, 22.97, 37.65, 43.53, 65.68, 127.44 (2 C), 127.50, 128.64 (2 C), 137.73, 169.75, 171.20 ppm. Anal. ($C_{13}H_{19}N_3O_2$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(4-morpholino)acetamide (3e). Use of **6e** (0.59 g, 2.56 mmol), benzylamine (0.28 g, 2.82 mmol), and NaCN (0.01 g, 0.26 mmol) gave a thick oily residue. The residue was triturated with EtOAc (5 mL), and the white solid (0.35 g) that remained was collected by filtration to give **3e**. The filtrate was concentrated, and the residue was purified by flash column chromatography on SiO_2 gel (2% MeOH/$CHCl_3$). The initial fractions furnished a trace amount (0.09 g) of 2-acetamido-*N*-benzyl-2-(benzylamino)acetamide. Continued elution gave additional amounts (0.20 g) of **3e**.

2-Acetamido-*N*-benzyl-2-(benzylamino)acetamide: yield 0.09 g (11%); mp 135–138 °C; R_f 0.52 (4% MeOH/$CHCl_3$); IR (KBr) 3250 (br), 1630 (br), 1500 (br), 1425, 750, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.83 (s, 3 H), 3.52 (br s, 1 H), 3.56 (d, J = 13.6 Hz, 1 H), 3.66 (d, J = 13.6 Hz, 1 H), 4.23 (d, J = 5.4 Hz, 2 H), 4.89 (d, J = 8.0 Hz, 1 H), 7.05–7.38 (m, 10 H), 8.20 (d, J = 8.0 Hz, 1 H), 8.51 (t, J = 5.4 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.63, 42.11, 48.57, 64.41, 126.70, 127.13 (2 C), 128.00 (2 C), 128.13 (2 C), 128.22 (2 C), 128.30, 139.29, 140.12, 169.61, 169.90 ppm; mass spectrum, m/e (relative intensity) 312 (M^+ + 1, 12), 311 (M^+, 7), 178 (11),

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