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

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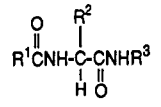
Potent anticonvulsant activity has been reported for (*R,S*)-2-acetamido-*N*-benzyl-2-methylacetamide (**2a**). Select α-heteroatom substituted derivatives of **2a** have been prepared (26 examples) in which the α-methyl group has been replaced by nitrogen (**3a–q**), oxygen (**3r–u**), and sulfur (**3v–z**) containing moieties.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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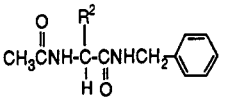

2a R^2 = CH_3
b R^2 = Ph
c R^2 = 2-pyrrolyl
d R^2 = 2-furanyl

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

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† University of Houston.
‡ Lilly Research Laboratories.

(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.; Kupferberg, H. J.; Scoville, B.; White, B. G. *Cleveland Clin. Q.* **1984**, *51*, 293.

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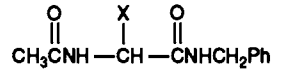
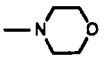
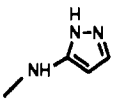
Table I. Selected Physical and Pharmacological Data in Mice for α-Heteroatom-Substituted Functionalized Amino Acid Derivatives **3**[a]



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)

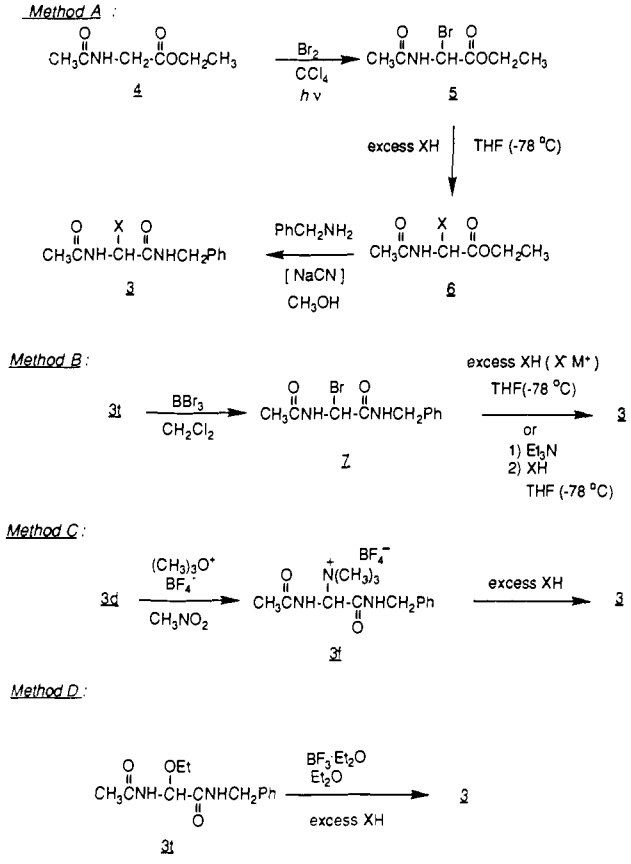
[a] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in milligrams per kilogram. Number in parentheses are 95% confidence intervals. Time of peak effects in hours as determined in the Experimental Section is denoted in brackets. [b] Melting points (°C) are uncorrected. [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 **3w** were prepared.

(8) LeGall, P.; Sawhney, K. N.; Conley, J. D.; Kohn, H. *Int. J. Peptide Protein Res.* **1988**, *32*, 279.

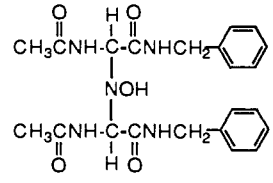
Scheme I. Preparation of α-Heteroatom-Substituted Functionalized Amino Acid Derivatives **3**



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**.



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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-l**, **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. Biochem. Behav.* **1977**, *6*, 351.

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* = 6.8 Hz, 3 H), 1.87 (s, 3 H), 2.48 (q, *J* = 6.7 Hz, 2 H), 4.05 (q,

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), 177 (100). Anal. ($C_{16}H_{21}N_3O_2$·0.25H_2O) C, H, N.

(15) Hurd, C. D. *Inorg. Synth.* **1939**, *1*, 87.

2-Acetamido-*N*-benzyl-2-(4-morpholino)acetamide (3e): yield 0.55 g (71%); mp 171–172 °C (recrystallized from EtOAc); R_f 0.35 (4% MeOH/$CHCl_3$); IR (KBr) 3250, 1620, 1515, 1440, 740, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (s, 3 H), 2.29–2.45 (m, 4 H), 3.51 (t, J = 4.1 Hz, 4 H), 4.23 (dd, J = 6.1, 15.1 Hz, 1 H), 4.28 (dd, J = 6.1, 15.1 Hz, 1 H), 5.08 (d, J = 9.1 Hz, 1 H), 7.12–7.30 (m, 5 H), 8.24 (d, J = 9.1 Hz, 1 H), 8.58 (t, J = 6.1 Hz, 1 H); ^{13}C (DMSO-d_6) 22.39, 42.20, 48.43 (2 C), 66.03, 69.24 (2 C), 126.76, 127.13 (2 C), 128.21 (2 C), 139.42, 168.02, 170.20 ppm; mass spectrum, m/e (relative intensity) 292 (M^+ + 1, 1), 233 (8), 158 (19), 157 (100), 116 (26), 115 (100), 106 (29), 91 (72). Anal. ($C_{15}H_{21}N_3O_3$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(*N*-anilino)acetamide (3g). **6g** (2.00 g, 8.47 mmol), benzylamine (1.09 g, 10.00 mmol), and NaCN (0.04 g, 0.84 mmol) gave a white solid that separated during the course of the reaction. The precipitate was filtered and purified by recrystallization from absolute EtOH to give 1.10 g (44%) of **3g**: mp 183–185 °C; IR (KBr) 3270, 1630, 1520, 1490, 1430, 740, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.84 (s, 3 H), 4.31 (d, J = 5.8 Hz, 2 H), 5.67 (t, J = 8.1 Hz, 1 H), 6.04 (d, J = 8.1 Hz, 1 H), 6.59–6.64 (m, 1 H), 6.70–6.72 (m, 2 H), 7.06–7.11 (m, 2 H), 7.20–7.33 (m, 5 H), 8.41 (d, J = 8.1 Hz, 1 H), 8.72 (t, J = 5.8 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.46, 42.25, 60.42, 113.21 (2 C), 117.22, 126.72, 127.16 (2 C), 128.18 (2 C), 128.77 (2 C), 138.99, 145.88, 168.65, 169.70 ppm; mass spectrum, m/e (relative intensity) 297 (M^+, 2), 239 (7), 164 (28), 163 (100), 122 (20), 121 (100), 106 (47), 104 (65), 93 (63), 91 (77). Anal. ($C_{17}H_{19}N_3O_2$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(3-pyrazolylamino)acetamide (3h). A solution of **6h** (1.60 g, 7.1 mmol) in MeOH (40 mL) containing benzylamine (0.83 g, 7.8 mmol) and NaCN (50 mg, 1 mmol) was stirred at 45–55 °C (18 h). TLC analysis (8% MeOH/$CHCl_3$) of the reaction mixture indicated the presence of only a minor amount of product. A second lot of NaCN (50 mg, 1 mmol) was then added, and the reaction was allowed to proceed at 45–55 °C (6 h) and then at room temperature (48 h). The solvent was removed in vacuo, and the residue was triturated with EtOAc (15 mL). The insoluble solid that remained was filtered and purified by flash column chromatography on SiO_2 gel (7% MeOH/$CHCl_3$) to give 0.90 g (44%) of **3h**: mp 135–137 °C; R_f 0.35 (8% MeOH/$CHCl_3$); IR (KBr) 3230 (br), 1620 (br), 1500 (br), 1430, 730, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.82 (s, 3 H), 4.29 (d, J = 5.9 Hz, 2 H), 5.51–5.55 (m, 3 H), 7.18–7.40 (m, 6 H), 8.36 (br s, 1 H), 8.53 (br s, 1 H), 11.66 (br s, 1 H); ^{13}C NMR (DMSO-d_6) 22.59, 42.29, 61.79, 90.68, 126.67, 127.07 (2 C), 128.17 (2 C), 129.10, 139.41, 153.53, 169.19, 169.67 ppm; mass spectrum, m/e (relative intensity) 288 (M^+ + 1, 64), 287 (M^+, 2), 230 (28), 229 (100), 153 (46). Anal. ($C_{14}H_{17}N_5O_2 \cdot 0.5H_2O$) C, H, N.

Preparation of Functionalized α-Heteroatom-Substituted Amino Acids (3). Method B. General Procedure. A BBr_3 solution (1 M in CH_2Cl_2, 1.1 equiv) was added to a solution of **3t**[6,8] (1 equiv) in CH_2Cl_2 (10 mmol/125 mL). The mixture was stirred at room temperature (5 h) and then concentrated to dryness in vacuo to give **7** as a pale yellow crystalline material. The bromo adduct **7** was then dissolved in THF (10 mmol/250 mL), cooled (−78 °C), and then added over a 15-min interval to a cooled (−78 °C) solution of the heteroatom nucleophile in THF (1 mmol/1 mL). The reaction mixture was stirred at this temperature (30 min) and then at room temperature (90 min). The insoluble salts were filtered, and the filtrate was concentrated in vacuo. The residue was then purified by flash column chromatography on SiO_2 gel (using the indicated solvent as the eluent).

By using this procedure, the following compounds were prepared.

Synthesis of 2-Acetamido-*N*-benzyl-2-(dimethylamino)acetamide (3d). By making use of **3t** (3.00 g, 12.0 mmol), BBr_3 (1 M in CH_2Cl_2, 13.2 mL, 13.2 mmol), and Me_2NH (5–6 equiv), a brown residue was obtained that was purified by flash column chromatography on SiO_2 gel (2.5% MeOH/$CHCl_3$) to give 1.20 g (40%) of **3d**. The product was recrystallized from ethyl acetate/hexane to give light yellow cubic crystals: mp 104–106 °C; R_f 0.39 (5% MeOH/$CHCl_3$); IR (KBr) 3280, 1670 (br), 1500 (br), 1460, 760, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.91 (s, 3 H), 2.11 (s, 6 H), 4.22 (dd, J = 5.2, 14.7 Hz, 1 H), 4.34 (dd, J = 6.1, 14.7 Hz, 1 H), 5.11 (d, J = 8.3 Hz, 1 H), 7.23–7.31 (m, 5 H), 8.18 (d, J = 8.3 Hz, 1 H), 8.55 (br s, 1 H); ^{13}C NMR (DMSO-d_6) 22.43, 40.33 (2 C), 42.28, 69.42, 126.73, 127.27 (2 C), 128.21 (2 C), 139.49, 168.49, 170.31 ppm; mass spectrum (FD) 250 (M^+ + 1). Anal. ($C_{13}H_{19}N_3O_2$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(hydroxyamino)acetamide (3k). Use of **3t** (2.00 g, 8.0 mmol), BBr_3 (1 M in CH_2Cl_2, 8.8 mL, 8.8 mmol), and anhydrous NH_2OH[15] (5–6 equiv) gave an oily residue. The residue was separated into three components by flash chromatography on SiO_2 gel (7.5% MeOH/$CHCl_3$).

2-Acetamido-*N*-benzyl-2-(hydroxyamino)acetamide (3k): yield 0.14 g (7%); mp 144–146 °C dec (recrystallized from EtOH); R_f 0.30 (8% MeOH/$CHCl_3$); IR (KBr) 3320 (br), 1660 (br), 1540 (br), 1460, 750, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.88 (s, 3 H), 4.31 (d, J = 5.7 Hz, 2 H), 5.08 (dd, J = 4.4, 8.1 Hz, 1 H), 5.94 (dd, J = 2.8, 4.4 Hz, 1 H), 7.19–7.35 (m, 5 H), 7.52 (d, J = 2.8 Hz, 1 H), 8.26 (d, J = 8.1 Hz, 1 H), 8.42 (t, J = 5.7 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.69, 42.25, 67.86, 126.69, 127.14 (2 C), 128.18 (2 C), 139.08, 168.53, 169.67 ppm; mass spectrum (FD) 238 (M^+ + 1). Anal. ($C_{11}H_{15}N_3O_3$) C, H, N.

Compound 8a: yield 0.05 g (3%); mp 177–179 °C (recrystallized from EtOH); R_f 0.27 (8% MeOH/$CHCl_3$); IR (KBr) 3240 (br), 1640 (br), 1510 (br), 1450, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.82 (s, 6 H), 4.25–4.34 (m, 4 H), 5.21 (d, J = 9.3 Hz, 2 H), 7.20–7.33 (m, 10 H), 8.16 (d, J = 9.3 Hz, 2 H), 8.26 (t, J = 5.8 Hz, 2 H), 8.51 (s, 1 H); ^{13}C NMR (DMSO-d_6) 22.54 (2 C), 42.30 (2 C), 67.55 (2 C), 126.63 (2 C), 127.13 (4 C), 128.11 (4 C), 139.02 (2 C), 168.24 (2 C), 169.33 (2 C) ppm; mass spectrum (FD) 442 (M^+ + 1). Anal. ($C_{22}H_{27}N_5O_5$) C, H, N.

Compound 8b: yield 0.10 g (6%); mp 184–186 °C (recrystallized from MeOH); R_f 0.18 (8% MeOH/$CHCl_3$); IR (KBr) 3300 (br), 1660 (br), 1530 (br), 1450, 740, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (6 H), 4.20 (dd, J = 5.3, 15.3 Hz, 2 H), 4.44 (dd, J = 6.2, 15.3 Hz, 2 H), 5.28 (d, J = 9.0 Hz, 2 H), 7.15–7.31 (m, 10 H), 8.00 (d, J = 9.0 Hz, 2 H), 8.39 (dd, J = 5.3, 6.2 Hz, 2 H), 8.51 (s, 1 H); ^{13}C NMR (DMSO-d_6) 22.50 (2 C), 42.58 (2 C), 69.98 (2 C), 126.73 (2 C), 127.23 (4 C), 128.22 (4 C), 139.08 (2 C), 167.60 (2 C), 169.57 (2 C) ppm; mass spectrum (FD) 442 (M^+ + 1). Anal. ($C_{22}H_{27}N_5O_5$) C, H, N.

Improved Synthesis of 2-Acetamido-*N*-benzyl-2-(hydroxyamino)acetamide (3k). Compound **7** (prepared from **3t** (3.00 g, 12.0 mmol) and BBr_3 (1 M in CH_2Cl_2, 17.2 mL, 17.2 mmol)) was dissolved in THF (250 mL), cooled (−10 °C), and then added dropwise (30 min) to a suspension of NH_2OH (5–6 equiv) in THF (50 mL) at −10 °C. The reaction mixture was stirred (30 min) at this temperature and then allowed to warm to room temperature (1 h). The insoluble materials were filtered, and the filtrate was concentrated in vacuo. The residue was separated into two components by flash column chromatography on SiO_2 gel (7.5% MeOH/$CHCl_3$).

2-Acetamido-*N*-benzyl-2-(hydroxyamino)acetamide (3k): yield 0.66 g (23%); mp 144–146 °C dec (recrystallized from EtOH).

Compound 8b: yield 0.10 g (5%); mp 184–186 °C (recrystallized from MeOH).

Compound 8a was not observed under these conditions.

Synthesis of 2-Acetamido-*N*-benzyl-2-(N^2-phenylhydrazino)acetamide (3p). Use of **3t** (2.00 g, 8.0 mmol), BBr_3 (1 M in CH_2Cl_2, 10.0 mL, 10.0 mmol), and phenylhydrazine (2.60 g, 24.0 mmol) gave a pale yellow oily residue, which was purified by flash column chromatography on SiO_2 gel (2% MeOH/$CHCl_3$) to give 0.75 g (29%) of **3p**. The product was recrystallized from chloroform/hexane as a light yellow solid: mp 132–134 °C; R_f 0.26 (2% MeOH/$CHCl_3$); IR (KBr) 3300, 1640 (br), 1610, 1520 (br), 1460, 760, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.89 (s, 3 H), 4.28 (d, J = 5.8 Hz, 2 H), 4.89 (d, J = 5.2 Hz, 1 H), 5.09 (dd, J = 5.2, 7.4 Hz, 1 H), 6.61 (t, J = 7.4 Hz, 1 H), 6.70–7.28 (m, 10 H), 8.29 (d, J = 7.4 Hz, 1 H), 8.60 (t, J = 5.8 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.88, 42.22, 66.22, 112.66 (2 C), 117.57, 126.65, 127.08 (2 C), 128.15 (2 C), 128.53 (2 C), 139.12, 149.90, 168.66, 170.04 ppm; mass spectrum (FD) 313 (M^+ + 1). Anal. ($C_{17}H_{20}N_4O_2$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(N^2-(benzyloxycarbonyl)hydrazino)acetamide (3q). By employing **3t** (3.00 g, 12.0 mmol), BBr_3 (1 M in CH_2Cl_2, 15.0 mL, 15.0 mmol), and benzyl carbazate (4.58 g, 27.6 mmol), 0.95 g (21%) of **3q** was obtained. The product was recrystallized from chloroform/hexane to give a white amorphous solid: mp 152–154 °C; R_f 0.32 (2% MeOH/$CHCl_3$); IR (KBr) 3325, 1620 (br), 1500 (br), 1440, 740, 680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.85 (s, 3 H), 4.27 (d, J = 4.4

Hz, 2 H), 5.00 (s, 2 H), 5.14 (dd, J = 3.1, 8.0 Hz, 1 H), 5.23 (t, J = 3.1 Hz, 1 H), 7.25–7.35 (m, 10 H), 8.26 (d, J = 8.0 Hz, 1 H), 8.56 (br s, 1 H), 8.66 (br s, 1 H); ^{13}C NMR (DMSO-d_6) 22.71, 42.23, 65.56, 65.97, 126.69, 127.16 (2 C), 127.61 (2 C), 127.77, 128.13 (2 C), 128.27 (2 C), 136.74, 138.87, 168.04, 169.95 ppm; mass spectrum (FD) 371 (M^+ + 1). Anal. ($C_{19}H_{22}N_4O_4$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-phenoxyacetamide (3u). Use of **3t** (3.00 g, 12.0 mmol), BBr_3 (1 M in CH_2Cl_2, 15.0 mL, 15.0 mmol), and NaOPh (4.18 g, 30 mmol) gave a brown oily residue, which was purified by flash column chromatography on SiO_2 gel using first $CHCl_3$ and then 2% MeOH/$CHCl_3$ as the eluents to give 0.80 g (22%) of **3u**. The compound was recrystallized from chloroform/hexane: mp 125–128 °C (softens at 122 °C); R_f 0.58 (3% MeOH/$CHCl_3$); IR (KBr) 3300, 1650 (br), 1600, 1530 (br), 1490, 1450, 760, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.83 (s, 3 H), 4.35 (d, J = 5.7 Hz, 2 H), 6.18 (d, J = 9.4 Hz, 1 H), 6.94–6.99 (m, 2 H), 7.02–7.33 (m, 8 H), 8.98 (t, J = 5.7 Hz, 1 H), 9.10 (d, J = 9.4 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.54, 42.24, 76.44, 116.09 (2 C), 121.78, 126.84, 127.26 (2 C), 128.25 (2 C), 128.44 (2 C), 138.84, 155.97, 166.63, 170.73 ppm; mass spectrum (FD) 299 (M^+ + 1). Anal. ($C_{17}H_{18}N_2O_3 \cdot 0.5H_2O$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(methylthio)acetamide (3v). A cooled (−78 °C) solution of Et_3N (4.85 g, 48.0 mmol) in THF (20 mL) was added to a cooled (−78 °C) solution of **7** (prepared from **3t** (4.00 g, 16.0 mmol) and BBr_3 (1 M in CH_2Cl_2, 20.0 mL, 20.0 mmol)) in THF (275 mL). A cooled (−78 °C) solution of excess MeSH (5–6 equiv) in THF (55 mL) was then added. The reaction mixture was stirred at this temperature (30 min) and then at room temperature (1 h). The insoluble materials were filtered, and the filtrate was evaporated to dryness in vacuo. The oily residue obtained was purified by flash column chromatography on SiO_2 gel (2% MeOH/$CHCl_3$) to give 1.10 g (27%) of **3v** as a yellow orange oil. The product was purified by a second flash column chromatography on SiO_2 gel (2% MeOH/$CHCl_3$) to give 0.72 g of the pure product as a white solid: mp 155–157 °C; R_f 0.65 (3% MeOH/$CHCl_3$); IR (KBr) 3320, 1650 (br), 1520 (br), 1460, 750 cm^{-1}; ^{1}H NMR (CD_3NO_2) δ 1.98 (s, 3 H), 2.08 (s, 3 H), 4.39 (dd, J = 6.1, 15.2 Hz, 1 H), 4.49 (dd, J = 6.1, 15.2 Hz, 1 H), 5.51 (d, J = 7.8 Hz, 1 H), 7.15 (d, J = 7.8 Hz, 1 H), 7.17–7.41 (m, 6 H); ^{13}C NMR (CD_3NO_2) 12.28, 22.94, 44.26, 56.03, 128.46, 128.60 (2 C), 129.77 (2 C), 140.17, 169.19, 171.06 ppm; mass spectrum (FD) 253 (M^+ + 1). Anal. ($C_{12}H_{16}N_2O_2S$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(ethylthio)acetamide (3w). By using the procedure described for the synthesis of **3v**, **3t** (2.00 g, 8.0 mmol) and EtSH (0.65 g, 10.4 mmol) were converted to 0.80 g (38%) of **3w**. The compound was further purified by recrystallization from chloroform/hexane to give a beige solid: mp 146–148 °C; R_f 0.60 (4% MeOH/$CHCl_3$); IR (KBr) 3240, 1620 (br), 1510 (br), 1415, 680, 640 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.56 (t, J = 7.4 Hz, 3 H), 1.88 (s, 3 H), 2.49–2.67 (m, 2 H), 4.23 (dd, J = 5.9, 15.2 Hz, 1 H), 4.32 (dd, J = 5.9, 15.2 Hz, 1 H), 5.55 (d, J = 9.1 Hz, 1 H), 7.20–7.35 (m, 5 H), 8.59 (d, J = 9.1 Hz, 1 H), 8.75 (t, J = 5.9 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 14.73, 22.43, 23.73, 42.10, 53.70, 126.87, 127.14 (2 C), 128.32 (2 C), 139.01, 167.89, 169.02 ppm; mass spectrum (FD) 267 (M^+ + 1). Anal. ($C_{13}H_{18}N_2O_2S \cdot 0.25H_2O$) C, H, N.

Preparation of Functionalized α-Heteroatom-Substituted Amino Acids (3). Method C. General Procedure. A mixture of **3f** (1 equiv), and the nitrogen nucleophile (4–5 equiv) in MeOH (1 mmol/1 mL) was stirred at 55–60 °C (3 h). The solvent was removed in vacuo, and the residue was purified by flash column chromatography on SiO_2 gel by using the indicated solvents as the eluent.

By using this procedure, the following compounds were prepared.

Synthesis of 2-Acetamido-*N*-benzyl-2-(methoxyamino)acetamide (3l). Use of a MeOH solution of $MeONH_2$ (prepared from $MeONH_2$·HCl (2.83 g, 33.9 mmol) and NaOMe (1.41 g, 26.1 mmol)) and **3f** (2.70 g, 7.67 mmol) gave an oily residue that was purified by flash column chromatography on SiO_2 gel (2% MeOH/$CHCl_3$) to give 0.80 g (42%) of **3l**. The product was recrystallized from chloroform/hexane: mp 95–97 °C; R_f 0.23 (2% MeOH/$CHCl_3$); IR (KBr) 3300, 1650, 1620, 1510 (br), 1440, 750, 680 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.88 (s, 3 H), 3.38 (s, 3 H), 4.22–4.41 (m, 2 H), 5.18 (dd, J = 4.9, 7.8 Hz, 1 H), 6.78 (d, J = 4.9 Hz, 1 H), 7.21–7.32 (m, 5 H), 8.33 (d, J = 7.8 Hz, 1 H), 8.56 (br s, 1 H); ^{13}C NMR (DMSO-d_6) 22.64, 42.28, 61.42, 66.25, 126.74, 127.19 (2 C), 128.19 (2 C), 139.11, 167.95, 169.66 ppm; mass spectrum (FD) 252 (M^+ + 1). Anal. ($C_{12}H_{17}N_3O_3$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(methylhydroxyamino)acetamide (3m). A MeOH solution (30 mL) of MeNHOH (21.74 mmol) (prepared from MeNHOH·HCl (2.36 g, 28.26 mmol) and NaOMe (1.17 g, 21.74 mmol)) and **3f** (2.20 g, 6.25 mmol) gave a residue that was purified by flash column chromatography on SiO_2 gel (6% MeOH/$CHCl_3$) to give 0.95 g (61%) of **3m** as a white solid. The product was then purified by recrystallization from EtOH: mp 159–161 °C; R_f 0.32 (8% MeOH/$CHCl_3$); IR (KBr) 3440 (br), 3300, 1640, 1530, 1460, 750, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.95 (s, 3 H), 2.43 (s, 3 H), 4.26 (dd, J = 5.7, 15.1 Hz, 1 H), 4.35 (dd, J = 5.7, 15.1 Hz, 1 H), 5.09 (d, J = 9.1 Hz, 1 H), 7.21–7.29 (m, 5 H), 8.05 (s, 1 H), 8.18 (d, J = 9.1 Hz, 1 H), 8.23 (t, J = 5.7 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.40, 42.34, 43.92, 71.49, 126.62, 127.12 (2 C), 128.12 (2 C), 139.14, 167.82, 170.28 ppm; mass spectrum (FD) 252 (M^+ + 1). Anal. ($C_{12}H_{17}N_3O_3$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(methoxymethylamino)acetamide (3n). A MeOH solution (20 mL) of MeNHOMe (17.39 mmol) (prepared from MeNHOMe·HCl (2.20 g, 23.02 mmol) and NaOMe (0.94 g, 17.39 mmol)) and **3f** (2.10 g, 5.97 mmol) gave a solid residue. Flash column chromatography of the solid on SiO_2 gel (2% MeOH/$CHCl_3$) yielded pure **3n** (1.30 g, 82%). The product was recrystallized from EtOH: mp 165–167 °C; R_f 0.39 (2% MeOH/$CHCl_3$); IR (KBr) 3300, 1640 (br), 1540 (br), 1460, 750, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.93 (s, 3 H), 2.43 (s, 3 H), 3.32 (s, 3 H), 4.25 (dd, J = 5.9, 14.9 Hz, 1 H), 4.37 (dd, J = 5.9, 14.9 Hz, 1 H), 5.19 (d, J = 9.4 Hz, 1 H), 7.21–7.35 (m, 5 H), 8.31 (d, J = 9.4 Hz, 1 H), 8.56 (t, J = 5.9 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.36, 39.68, 42.34, 59.16, 70.33, 126.74, 127.41 (2 C), 128.21 (2 C), 139.30, 167.38, 170.30 ppm; mass spectrum (FD) 266 (M^+ + 1). Anal. ($C_{13}H_{19}N_3O_3$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(*N*-isoxazolidino)acetamide (3o). **3f** (1.60 g, 4.55 mmol), isoxazolidine (prepared from isoxazolidine hydrobromide[16] (2.41 g, 15.65 mmol) and NaOMe (0.70 g, 13.04 mmol)) gave 0.80 g (64%) of **3o**. Compound **3o** was recrystallized from chloroform/hexane to give a white amorphous solid: mp 149–151 °C; R_f 0.29 (4% MeOH/$CHCl_3$); IR (KBr) 3400 (br), 3300, 1650, 1530, 1470, 740, 700, 610 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.91 (s, 3 H), 2.05–2.20 (m, 2 H), 2.45–2.89 (m, 1 H), 2.98–3.07 (m, 1 H), 3.74–3.90 (m, 2 H), 4.25 (dd, J = 6.1, 15.3 Hz, 1 H), 4.35 (dd, J = 6.1, 15.3 Hz, 1 H), 5.23 (d, J = 9.2 Hz, 1 H), 7.15–7.35 (m, 5 H), 8.49 (d, J = 9.2 Hz, 1 H), 8.56 (br s, 1 H); ^{13}C NMR (DMSO-d_6) 22.26, 28.26, 42.15, 48.94, 66.19, 68.77, 126.64, 127.02 (2 C), 128.13 (2 C), 139.22, 167.43, 170.27 ppm; mass spectrum (FD) 278 (M^+ + 1). Anal. ($C_{14}H_{19}N_3O_3$) C, H, N.

Preparation of Functionalized α-Heteroatom-Substituted Amino Acids (3). Method D. General Procedure. 2-Acetamido-*N*-benzyl-2-ethoxyacetamide (**3t**) (1 equiv) was suspended in Et_2O (100 mL/10 mmol), and then BF_3·Et_2O (1.6–2.4 equiv) was rapidly added and the resulting solution was stirred (10 min). The nucleophile (H_2O or EtSH) (1.6–4.0 equiv) was then added, and the reaction mixture was stirred at room temperature (18–48 h). The reaction was then quenched by the addition of an aqueous $NaHCO_3$ (100 mL/10 mmol)/ice mixture. The experimental workup varied slightly for **3r** and **3w** and is described in the following sections along with the observed spectral properties.

Synthesis of 2-Acetamido-*N*-benzyl-2-hydroxyacetamide (3r). Reacting **3t** (1.00 g, 4.0 mmol), BF_3·Et_2O (0.91 g, 6.4 mmol), and H_2O (0.12 g, 6.7 mmol) followed by aqueous $NaHCO_3$ workup gave an aqueous reaction mixture. The solution was then extracted with EtOAc (3 × 50 mL), and the combined EtOAc extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography on SiO_2 gel (3% MeOH/$CHCl_3$) to give 0.30 g (34%) of **3r** as a white solid: mp 136–138 °C; R_f 0.14 (3% MeOH/$CHCl_3$); IR (KBr) 3300, 1620, 1530 (br), 1430 (br), 730, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.85 (s, 3 H), 4.29 (d, J = 5.9 Hz, 2 H), 5.48 (dd, J = 5.5, 8.6 Hz, 1 H), 6.47 (d, J = 5.5 Hz, 1 H), 7.21–7.35 (m, 5 H), 8.52 (t, J = 5.9 Hz, 1 H), 8.59 (d, J = 8.6 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.66, 41.99,

(16) Hine, J.; Evangelista, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 1649.

71.42, 126.66, 127.22 (2 C), 128.13 (2 C), 139.20, 169.47, 169.62 ppm; mass spectrum, *m/e* (relative intensity) 223 ($M^+ + 1$, 1), 163 (11), 134 (9), 106 (46), 91 (100), 77 (22), 65 (38). Anal. ($C_{11}H_{14}N_2O_3$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(ethylthio)acetamide (3w). Use of **3t** (2.00 g, 8.0 mmol), $BF_3{\cdot}Et_2O$ (2.72 g, 19.2 mmol), and EtSH (2.38 g, 38.4 mmol) gave an aqueous reaction mixture. The solution was extracted with $CHCl_3$ (3 × 100 mL). The combined $CHCl_3$ layers were dried (Na_2SO_4) and then concentrated in vacuo to give 1.90 g (89%) of **3w** as a white solid: mp 148–149 °C (mixed melting point with an authentic sample was undepressed); R_f 0.60 (4% MeOH/$CHCl_3$).

Synthesis of 2,2-Diacetamido-*N*-benzylacetamide (3i). Ac_2O (1 mL) was added to a solution of **3a** (1.10 g, 4.98 mmol) in dry pyridine (10 mL), and then CH_2Cl_2 (20 mL) was added. The mixture was stirred at room temperature (4 h), and then the volatile materials were removed in vacuo. The residue was then treated with a saturated aqueous $NaHCO_3$ solution (50 mL). The white solid (1.20 g, 92%) that remained was filtered, dried (Na_2SO_4), and recrystallized from MeOH: mp 265–267 °C dec; IR (KBr) 3260, 1530, 1500, 740, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.84 (s, 6 H), 4.26 (d, J = 5.8 Hz, 2 H), 5.71 (t, J = 7.6 Hz, 1 H), 7.20–7.31 (m, 5 H), 8.44 (d, J = 7.6 Hz, 2 H), 8.48 (t, J = 5.8 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.44 (2 C), 42.26, 56.99, 126.62, 127.02 (2 C), 128.12 (2 C), 139.15, 168.19, 169.39 (2 C) ppm; mass spectrum (FD) 264 ($M^+ + 1$). Anal. ($C_{13}H_{17}N_3O_3$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(trifluoroacetamido)acetamide (3j). Ice-cold trifluoroacetic anhydride (8 mL) was added in one portion to ice-cold **3a** (1.00 g, 4.53 mmol). The reaction was accompanied by the evolution of heat. After stirring (5 min), the volatile materials were removed in vacuo. The residue was treated with a saturated aqueous $NaHCO_3$ solution (20 mL), and the solid that remained was filtered and washed with H_2O to give **3j** (1.00 g, 70%). The product was recrystallized from EtOH: mp 228–230 °C; R_f 0.34 (8% MeOH/$CHCl_3$); IR (KBr) 3300, 1720, 1660, 1520, 1380, 760, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.90 (s, 3 H), 4.30 (d, J = 5.1 Hz, 2 H), 5.85 (d, J = 8.0 Hz, 1 H), 7.21–7.35 (m, 5 H), 8.64 (d, J = 8.0 Hz, 1 H), 8.75 (t, J = 5.1 Hz, 1 H), 10.04 (s, 1 H); ^{13}C NMR (DMSO-d_6) 22.52, 42.52, 57.42, 117.4 (q, J_{CF} = 288.3 Hz), 126.80, 127.16 (2 C), 128.21 (2 C), 138.93, 156.14 (q, J_{CF} = 35.3 Hz), 166.39, 169.88 ppm; mass spectrum (FD) 318 ($M^+ + 1$). Anal. ($C_{13}H_{14}N_3O_3F_3$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(trimethylammonio)acetamide Tetrafluoroborate (3f). A solution of **3d** (1.93 g, 7.76 mmol) in nitromethane (7 mL) was added slowly to an ice-cold solution of trimethyloxonium tetrafluoroborate (1.26 g, 8.54 mmol) in nitromethane (6 mL). The reaction mixture was stirred at this temperature (15 min) and then at room temperature (2 h). Anhydrous Et_2O (~50 mL) was added to the reaction mixture, and the white solid that separated was filtered, washed with Et_2O, and dried in vacuo: yield 1.95 g (72%); mp 171–173 °C dec; IR (KBr) 3300, 1680 (br), 1530, 1490, 710 cm^{-1}; ^1H NMR (CD_3NO_2) δ 2.14 (s, 3 H), 3.18 (s, 9 H), 4.50 (d, J = 5.8 Hz, 2 H), 5.70 (d, J = 9.3 Hz, 1 H), 7.30–7.41 (m, 5 H), 7.57 (d, J = 9.3 Hz, 1 H), 7.70 (br s, 1 H); mass spectrum (FD) 264 (M^+). Anal. ($C_{14}H_{22}N_3O_2BF_4$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(ethylthio)acetamide *S*-Oxide (3y-1). A solution of *m*-chloroperbenzoic acid (1.00 g (~65%), 3.76 mmol) in CH_2Cl_2 (10 mL) was added dropwise into a stirred, cooled (−10 to −15 °C) CH_2Cl_2 solution (125 mL) of **3w** (1.00 g, 3.76 mmol) under N_2. The reaction was stirred (30 min) at this temperature, and then the *m*-chlorobenzoic acid was precipitated as its ammonium salt by passing NH_3 gas over the surface of the reaction solution. The excess NH_3 was removed by passing N_2 gas through the solution (20 min) at room temperature. The ammonium salt was filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on SiO_2 gel (2% MeOH/$CHCl_3$) to give 0.55 g (52%) of the desired product. Compound **3y-1** was recrystallized from chloroform/hexane as a white granular solid: mp 135–137 °C; R_f 0.23 (2% MeOH/$CHCl_3$); IR (KBr) 3300 (br), 1640 (br), 1510 (br), 1370, 1230, 1100, 1020, 900 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.15 (t, J = 7.5 Hz, 3 H), 1.99 (s, 3 H), 2.49–2.56 (m, 1 H), 2.65–2.72 (m, 1 H), 4.34 (d, J = 5.7 Hz, 2 H), 5.55 (d, J = 9.5 Hz, 1 H), 7.23–7.34 (m, 5 H), 8.74 (d, J = 9.5 Hz, 1 H), 8.77 (t, J = 5.7 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 7.03, 22.34, 42.40, 42.47, 67.15, 126.89, 127.27 (2 C), 128.24 (2 C), 138.55, 164.66, 170.18 ppm; mass spectrum (FD) 283 ($M^+ + 1$). Anal. ($C_{13}H_{18}N_2O_3S$) C, H, N.

Synthesis of 2-Acetamido-*N*-benzyl-2-(ethylthio)acetamide *S*-Oxide (3y-1 and 3y-2). A solution of $NaIO_4$ (1.77 g, 8.27 mmol) in H_2O (20 mL) was added dropwise into a stirred solution of **3w** (2.00 g, 7.52 mmol) in MeOH (25 mL). A precipitate appeared rapidly. H_2O (~30 mL) was added to the mixture to dissolve most of the suspension, and the reaction mixture was stirred (4 h) at room temperature. The reaction was concentrated in vacuo, and the remaining aqueous mixture was extracted with $CHCl_3$ (3 × 100 mL). The combined $CHCl_3$ extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. The oily residue (1.95 g, 92%) solidified on drying in vacuo. NMR analysis (DMSO-d_6) of the product showed that it was a 2:1 mixture of the two diastereomers **3y-1** and **3y-2**, respectively. The reaction was recrystallized from EtOAc to give nearly pure diastereomer **3y-1** (1.20 g). The EtOAc mother liquor was concentrated, and the remaining residue (0.75 g) was recrystallized from ethyl acetate/hexane to give a diastereomeric mixture (0.41 g) of **3y-1** and **3y-2** in a 2:3 ratio, respectively: mp 135–137 °C (softens at 117 °C); R_f 0.60 (4% MeOH/$CHCl_3$); IR (KBr) 3300 (br), 1640 (br), 1510 (br), 1370, 1230, 1100, 1020, 900 cm^{-1}; mass spectrum (FD) 283 ($M^+ + 1$). Anal. ($C_{13}H_{18}N_2O_3S$) C, H, N. The following NMR spectral properties have been assigned to compounds **3y-1** and **3y-2**.

Diastereomer 3y-1: ^1H NMR (DMSO-d_6) δ 1.16 (t, J = 7.5 Hz, 3 H), 2.00 (s, 3 H), 2.49–2.72 (m, 2 H), 4.28–4.39 (m, 2 H), 5.56 (d, J = 9.7 Hz, 1 H), 7.21–7.34 (m, 5 H), 8.71–8.77 (m, 2 H); ^{13}C NMR (DMSO-d_6) 7.10, 22.43, 42.48, 42.57, 67.23, 126.98, 127.36 (2 C), 128.33 (2 C), 138.63, 164.73, 170.25 ppm.

Diastereomer 3y-2: ^1H NMR (DMSO-d_6) δ 1.13 (t, J = 7.6 Hz, 3 H), 1.94 (s, 3 H), 2.49–2.72 (m, 2 H), 4.28–4.39 (m, 2 H), 5.71 (d, J = 9.9 Hz, 1 H), 7.21–7.34 (m, 5 H), 8.83 (d, J = 9.9 Hz, 1 H), 8.98 (t, J = 5.6 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 6.47, 22.43, 41.53, 42.55, 67.90, 126.98, 127.36 (2 C), 128.33 (2 C), 138.39, 164.43, 169.82 ppm.

Synthesis of 2-Acetamido-*N*-benzyl-2-(ethanesulfonyl)acetamide (3z). An aqueous solution (20 mL) of $NaIO_4$ (3.00 g, 14.02 mmol) was added to a MeOH solution (20 mL) of **3w** (0.95 g, 3.57 mmol). The initial homogeneous solution rapidly became turbid. H_2O (~10 mL) was then added dropwise until the system became homogeneous. The solution was stirred (18 h) at 50–60 °C. MeOH (50 mL) was added to the reaction solution, and the precipitated salt was filtered and washed with MeOH (10 mL). The filtrate was concentrated, and the remaining solution was extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on SiO_2 gel (1% MeOH/$CHCl_3$) to give 0.34 g (32%) of the desired product. Compound **3z** was further purified by recrystallization from EtOH: mp 161–163 °C; R_f 0.34 (3% MeOH/$CHCl_3$); IR (KBr) 3300, 2940, 1660, 1520, 1310, 1230, 1120, 900 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.22 (t, J = 7.4 Hz, 3 H), 1.99 (s, 3 H), 3.04–3.24 (m, 2 H), 4.31 (dd, J = 5.7, 15.3 Hz, 1 H), 4.41 (dd, J = 5.7, 15.3 Hz, 1 H), 5.93 (d, J = 9.8 Hz, 1 H), 7.22–7.35 (m, 5 H), 9.13 (t, J = 5.7 Hz, 1 H), 9.17 (d, J = 9.8 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 5.72, 22.27, 42.63, 45.43, 69.14, 127.02, 127.28 (2 C), 128.33 (2 C), 138.16, 161.88, 169.83 ppm; mass spectrum (FD) 298 (M^+). Anal. ($C_{13}H_{18}N_2O_4S$) C, H, N.

Pharmacology. Initial anticonvulsant evaluation of **3** was conducted with at least three dose levels (30, 100, and 300 mg/kg) administered intraperitoneally. All tests were performed with male CF-1 mice from Charles River Breeding Laboratories (Portage, MI). Test solutions of all compounds were dissolved in 30% poly(ethylene glycol) 400. Four mice at each dose level were tested at 0.5, 1, and 4 h after administration to determine if there was protection agsinst MES seizures.

MES 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 the 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.

After the time of peak activity and the approximate dose range were determined, a dose–response curve was generated 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 to protect 50%

of the mice in the MES test. Neurological impairment was measured in mice using the horizontal screen (tox) text.[14] 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 ED_{50} values, a dose–response curve was determined at the time of peak anticonvulsant activity with at least three to four doses and 12 mice per dose. The TD_{50} is the estimated dose that impaired 50% of the mice.

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Arocalciferols: Synthesis and Biological Evaluation of Aromatic Side-Chain Analogues of 1α,25-Dihydroxyvitamin D_3[1a]

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Aromatic side-chain analogues (arocalciferols **6–9**) of the steroid hormone 1α,25-dihydroxyvitamin D_3 (**1**) were synthesized and biologically evaluated. The analogues were prepared by coupling the vitamin D A-ring enyne **14** with the appropriate enol triflate of a modified CD steroid fragment of the type **22**. The resulting dienyne **23** was then transformed in three steps to the vitamin D analogues **6–9**. Biological evaluation of these analogues have provided information concerning side-chain topographical effects on in vivo and in vitro activity.

Introduction

The steroid hormone 1α,25-dihydroxyvitamin D_3 [**1**, $1,25(OH)_2D_3$], the physiologically active form of vitamin D (calciferol), is considered to be one of the most potent stimulators of calcitropic effects (intestinal calcium absorption, ICA, and bone calcium mobilization, BCM).[2] Besides its traditional role as a hormone in calcium homeostasis,[3] $1,25(OH)_2D_3$ induces differentiation and affects cellular proliferation, indicating its possible use in the treatment of certain cancers and skin disorders.[4-6] There has accordingly been an increased interest in the further development of $1,25(OH)_2D_3$ analogues for these new therapeutic purposes.

The clinical utility of $1,25(OH)_2D_3$ is limited because therapeutically effective doses induce hypercalcemia.[7] This has led investigators toward the development of an analogue with a more useful therapeutic index, specifically directed toward analogues with high cell differentiating ability and low calcitropic action. A series of remarkably diverse side-chain analogues of $1,25(OH)_2D_3$ exhibiting promising therapeutic indices have in fact been reported

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