Synthesis and Structural Studies of Aza Analogues of Functionalized Amino Acids: New Anticonvulsant Agents

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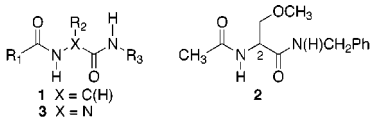
We have reported that functionalized amino acids **1** display potent anticonvulsant activities in mice and rats, and that the activity resides primarily in the D-isomer. In this study we investigated whether selectively replacing the C(2) tetrahedral atom with a trivalent nitrogen provides compounds with comparable activity. Six functionalized N(2)-substituted semicarbazides (**3**) were prepared. X-ray crystallographic analysis of 1-acetyl-4-benzyl-2-(thiazol-2-yl)-semicarbazide (**13**) showed that it lost asymmetry and adopted a configuration midway between the corresponding D- and L-amino acid derivatives. Evaluation of **3** in both mice (ip) and rats (po) showed that the compounds exhibited significant anticonvulsant activities but in most cases at levels lower than their amino acid counterparts. One of the semicarbazides, **13**, displayed excellent activity in mice and rats that compared favorably to that of phenytoin.

Introduction

Peptidomimetics have found increasing use in drug design.[1] Modification of the peptide structure has been accomplished by changing the side chain groups of the amino acid, substituting one amino acid for another, and altering the backbone. Notable backbone modifications include stereochemical inversion of the C(2) site and replacement of a C(2) tetrahedral atom in the peptide with a trivalent nitrogen atom to give the corresponding semicarbazide.[2] Substitution of C(2) with a nitrogen results in asymmetry loss and a configuration midway between the corresponding D- and L-amino acids.

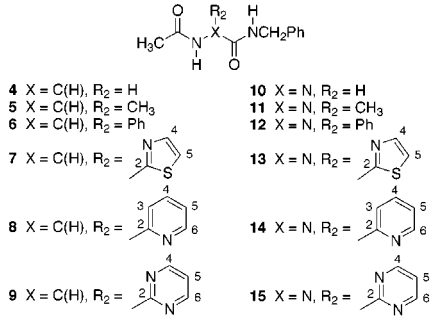


In recent years, we have reported on the anticonvulsant activity of a series of compounds termed functionalized amino acids (FAAs, **1**).[3] These compounds provided excellent protection against maximal electroshock (MES)-induced seizures when the amino terminus was capped with an acetyl moiety ($R_1 = CH_3$) and the carboxy terminus was converted to the *N*-benzylamide ($R_3 = CH_2Ph$). The *distinguishing* feature of FAAs was that the principal anticonvulsant activity resided in the D-isomer.[3a,e] The excellent activity observed for D-**2** has led to its clinical evaluation as an antiepileptic agent. [4]

These findings led us to ask whether the structurally related semicarbazide derivatives **3** displayed comparable anticonvulsant activity. We theorized that replacing the C(2) unit with the corresponding N(2) group might permit the semicarbazides to adopt a conformation similar to that of **1** and provide protection against seizures. In this paper, we report the synthesis, structural characterization, and pharmacological evaluation of a selected series of semicarbazide derivatives **3**. Our findings demonstrate that **3** exhibit significant anticonvulsant activities in the maximal electroshock (MES) seizure test, but most are less potent than their amino acid counterparts. We highlight the structure and bioactivity of the N(2)-thiazole semicarbazide.

Results and Discussion

Choice of Compounds and Synthesis. Our choice of **3** was determined by the findings obtained for FAAs **1**. The FAAs **4**−**9** displayed significant activity in the MES seizure test (mice, ip), and **7**−**9** exhibited activity comparable to that of phenytoin (MES $ED_{50} = 6.5$ mg/kg).[3] Accordingly, we prepared semicarbazides **10**−**15**, the aza analogues of FAAs **4**−**9**, respectively.



Two procedures were used to prepare the semicarbazides. They differed only in the sequence of the acetylation and benzyl carbamoylation steps (Scheme 1). Method A utilized hydrazines that are either commercially available (**16**) or reported in the literature (**17**,[5] **18**[6]). The hydrazines were treated with acetic anhydride to give *N*-acetylhydrazides[7] and then converted to the semicarbazides by reaction with benzyl

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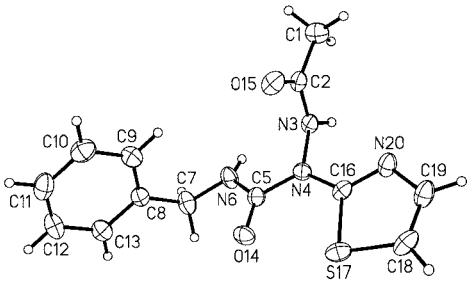
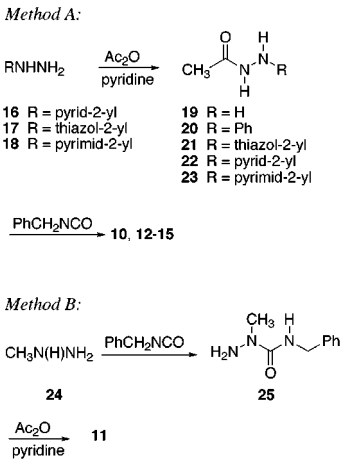


Figure 1. ORTEP drawing of **13** showing the atom numbering scheme. Thermal ellipsoids are 40% equiprobability envelopes, with hydrogens as spheres of arbitrary diameter. Only one orientation of the disordered methyl group (C1) is shown.

Scheme 1. Synthetic Pathways to Semicarbazides **3**



isocyanate. Compounds **10** and **12** were prepared in one step by benzyl carbamoylation of commercially available starting materials. In method B, **24** was first treated with benzyl isocyanate, and the resulting semicarbazide **25** was acetylated to give **11**.

Structural Studies. The ^{1}H and ^{13}C NMR spectroscopy for **10**−**15** indicated that minor amounts of rotamers existed. A variable-temperature NMR study was conducted on **12**, and the ^{1}H NMR in DMSO-d_6 at 90 °C showed coalescence of similar signals. The solid-state structure for thiazole **13** was determined by single-crystal X-ray analysis (Figure 1). Inspection of the ORTEP figure indicated planar sp^2 geometry at N(2) with a 123° C(5)−N(4)−C(16) bond angle and a 120° C(5)−N(4)−N(3) bond angle and the loss of asymmetry.

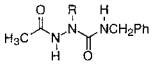
Pharmacological Evaluation. The anticonvulsant activities[8] of **10**−**15** are summarized in Table 1. Listed are activities of **3** in providing protection against MES-induced seizures and against seizures induced by the subcutaneous administration of Metrazole (sc Met). The results are compared with the activities of the proven antiepileptic agents phenytoin,[9] phenobarbital,[10] and valproate.[9] Also included in Table 1 are the median doses for the neurological impairment (TD_{50}) using the rotorod test.[11]

The semicarbazide derivatives **10**−**15** provided moderate-to-excellent protection against MES-induced seizures in mice following ip administration. Compounds **10** and **15** exhibited ED_{50} values between 100 and 300 mg/kg, while **11**, **12**, and **14** showed good activities with estimated ED_{50} values of 30−100 mg/kg. The thiazole **13** displayed the most pronounced anticonvulsant activity with an ED_{50} of 22 mg/kg. Comparison of the anticonvulsant activities of the semicarbazides **10**−**15** (Table 1) to their racemic amino acid counterparts **4**−**9** (MES ED_{50}: **4** ∼ 300 mg/kg;[3b] **5** = 77 mg/kg;[3b] **6** = 20 mg/kg;[3b] **7** = 12 mg/kg;[3c] **8** = 11 mg/kg;[3d] **9** = 8.1 mg/kg[3d]) in the mouse (ip) assay showed that the semicarbazides provided generally lower protection against MES-induced seizures and that the pyrimid-2-yl derivative **15** showed the greatest loss in anticonvulsant potency. We found that compounds **10**−**15** displayed weak activities in the sc Met assay (Table 1). The estimated TD_{50} values for the semicarbazide derivatives **10**−**15** in the rotorod assay for neurologic toxicity were higher than their MES ED_{50} values. Significantly, the protective index (PI = TD_{50}/ED_{50}) for thiazole **13** was 5.4, which was similar to that for phenytoin (PI = 6.6).[9]

Enhanced anticonvulsant activities in the MES seizure assay were observed for **10**−**15** when administered to rats po (Table 1). The estimated ED_{50} values for all compounds was lower than 100 mg/kg with the three heteroaryl derivatives **13**−**15** providing protection at doses of 30 mg/kg or less. The thiazole **13** had excellent activity with an ED_{50} of 6.2 mg/kg. Moreover, no neurological impairment was observed at 250 mg/kg, giving a PI value that exceeded 40.

The attenuation of the semicarbazides **10**−**15** anticonvulsant activities compared with their FAA counterparts, **4**−**9**, may be due to several factors. First, aza substitution can alter the physicochemical properties of the test compounds.[12] Second, aza substitution results in increased planarity around N(2) compared with the

Table 1. Anticonvulsant Activities of Substituted Semicarbazide Derivatives[a]



		mice (ip)[b]				rat (po)[g]	
Compound	R	MES[c] ED_{50}	Tox[d] TD_{50}	sc Met[e]	PI[f]	MES[c] ED_{50}	Tox[d] TD_{50}
10	H	>100, <300 [4]	>160 [4]	> 300 [0.5]	-	95 [1] (71-150)	>160 [1]
11	CH_3	89 [2] (69-107)	>500 [2]	>300 [0.5]	>5.6	>30 [4]	>30 [4]
12	Ph	>30, <100 [0.5]	>100, <300 [0.5]	>300 [0.5]	-	>30 [1]	>30 [1]
13		22 [0.25] (19-24)	120 [0.25] (96-134)	>200 [0.25]	5.4	6.2 [0.5] (4.6-8.7)	>250 [0.5]
14		>30, <100 [0.5]	>100, <300 [0.5]	>100, <300 [0.5]	-	<30 [1]	>30[1]
15		>100, <300 [0.5]	>100, <300 [0.5]	>300 [0.5]	-	~30 [0.5]	>30[0.5]
Phenytoin[h]		6.5 [2] (5.7-7.2)	43 [0.5] (36-48)	-[i]	6.6	23 [2] (21-25)	-[i]
Phenobarbital[h]		22 [1] (15-23)	69 [0.5] (63-73)	-[i]	3.1	-[i]	-[i]
Valproate[h]		290 [0.25] (240-360)	480 [0.5] (410-570)	-[i]	1.3	400 [0.5] (330-440)	-[i]

[a] ED_{50} and TD_{50} values are in mg/kg. Numbers in parentheses are 95% confidence intervals. The dose−effect data were obtained at the "time of peak effect" (indicated in hours in brackets). [b] Compounds were administered ip to mice. [c] MES = maximal electroshock seizure test. [d] Tox = neurologic toxicity determined from the rotorod test. [e] sc Met = subcutaneous pentylenetetrazole (Metrazol) seizure test. [f] PI = protective index (TD_{50}/ED_{50}). [g] The compounds were administered orally to rats. [h] Ref 9. [i] Data not available. [j] Ref 10.

corresponding FAA.[2] We suspect that the carbonyl unit adjacent to the N(2) atom in **3** led to a preferred sp^2 geometry at this site and that this hybridization is likely reinforced by an appended aromatic (heteroaromatic) group. In support of this is the solid-state X-ray crystallographic structure for **13** (Figure 1), which showed that this site was nearly planar. Since previous studies have demonstrated the requirement for the D-configuration in **1** for maximal MES seizure protection,[3a,e] the structural factors in functionalized semicarbazides may in some cases hinder these compounds from assuming the conformation optimal for binding to the biological target site. This notion is consistent with two findings. First, among the N(2)-aromatic (heteroaromatic) semicarbazides **12**−**15**, the pyrimid-2-yl compound **15** was the least active followed by the pyrid-2-yl **14** and phenyl **12** derivatives, and the thiazole adduct **13** displayed the most pronounced anticonvulsant activity. Comparison of **12**−**15** with their FAAs **6**−**9** counterparts, we find that the π-deficient pyrimidine ring produced the most dramatic loss of anticonvulsant activity (**15** versus **9**) while the π-excessive thiazole[13] ring caused the least loss of activity (**13** versus **7**). We speculate that the resonance of the N(2) lone pair with the adjacent aromatic ring is less for the π-excessive thiazole ring than for the π-deficient pyrimidyl system, permitting **13** to better mimic the bioactive conformation of **7** when it reaches the target site. The second finding is placement of a hydrogen or a methyl group at the N(2) site in **3** led to compounds **10** and **11**, which displayed anticonvulsant activities comparable to those of their FAA counterparts **4** and **5**, respectively. Both the hydrogen and the methyl group may permit greater conformational flexibility at the N(2) site compared with compounds that contain a π-deficient aromatic (heteroaromatic) N(2) substituent.

The pronounced activity of **13** in the MES-induced seizure test led us to further evaluate this compound. First, ip administration of **13** provided effective protection of focal seizures in the hippocampal kindled rat test (ED_{50} = 56 mg/kg). The decrease in seizures was accompanied by a reduction in the after discharge duration. Second, **13** provided no significant voltage-dependent blockage of Na^+ channels in NIE-115 neuroblastoma cells (−60 mV, 16%; −90 mV, 1%). By comparison, the two prototypical Na^+ channel blockers, phenytoin and lamotrigne, exhibited 48% and 53% blockage, respectively, at −60 mV. The findings for **13** in these two tests paralleled those observed for **1**.

The anticonvulsant activities seen for semicarbazides **3** in the MES-induced seizure assay can be understood in terms of the SAR previously reported for FAAs **1**. Similarly, both sets of compounds exhibited no appreciable activity in the sc Met assay. These circumstantial findings suggest that these compounds act through similar pathways.

Conclusions

Rapid and efficient procedures have been developed to prepare semicarbazide derivatives **3**. Compounds **3** provided moderate-to-excellent protection against MES-induced seizures in mice (ip) and rats (po). Comparison of a select series of semicarbazides **3** with their FAA counterparts **1** showed that replacement of the tetrahedral C(2) carbon in **1** by a trivalent N led to a reduction in pharmacological activity in most cases upon administration to mice (ip). We found that oral administration of the N(2)-substituted semicarbazides to rats led to improved anticonvulsant activities. Significant protection against MES-induced seizures was observed for N(2)-thiazole **13**. The ED_{50} (rats, po) was 6.2 mg/kg, which exceeded that of phenytoin (ED_{50} = 23 mg/kg).

Experimental Methods

General Methods. See reference 3e.

4-Benzylsemicarbazides. General Procedure. To a stirred pyridine (or indicated solvent) solution of the 2-substituted hydrazine (1 equiv) was slowly added benzyl isocyanate (1 equiv). The solution was concentrated in vacuo and the residue was purified either by trituration with Et_2O or by column chromatography on SiO_2 (using the indicated solvent as the eluent). By use of this procedure, the following compounds were prepared.

1-Acetyl-4-benzylsemicarbazide (10). Pyridine (15 mL), **19** (1.00 g, 13.5 mmol) and benzyl isocyanate (1.98 g, 14.9 mmol) were stirred at room temperature (1 h) to give **10** (2.25 g, 80%): mp 141−142 °C; R_f 0.38 (10% MeOH/$CHCl_3$); IR (KBr) 3354, 3305, 1693, 1653 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.81 (s, 3 H), 4.21 (d, J = 6.0 Hz, 2 H), 6.90−7.00 (m, 1 H), 7.15−7.30 (m, 5 H), 7.78 (s, 1 H), 9.49 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 20.6, 42.6, 126.5, 126.9, 128.1, 140.6, 158.3, 169.2; MS (CI^+) (rel intensity) 208 ($M^+ + 1$, 100), 104 (61); M_r (+CI) 208.108 57 [$M^+ + 1$] (calcd for $C_{10}H_{14}N_3O_2$ 208.10860). Anal. ($C_{10}H_{13}N_3O_2$) C, H, N.

1-Acetyl-4-benzyl-2-phenylsemicarbazide (12). Compound **20** (1.00 g, 6.7 mmol), DMAP (0.005 g), pyridine (5 mL), and benzyl isocyanate (0.98 g, 7.3 mmol) were stirred at 60 °C (3 h) and then at room temperature (18 h). The product was purified by chromatography (10% MeOH/$CHCl_3$) and then crystallized from Et_2O−$CHCl_3$ to afford **12** (1.42 g, 76%): mp 128−131 °C; R_f 0.37 (10% MeOH/$CHCl_3$); IR (KBr) 3359, 3298, 3030, 1723, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (s, 3 H), 4.36 (d, J = 5.7 Hz, 2 H), 5.44 (t, J = 5.7 Hz, 1 H), 7.15−7.45 (m, 10 H), 8.85 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.9, 44.8, 126.0, 127.4, 127.5, 128.8, 129.4, 129.6, 138.8, 141.5, 156.5, 170.6; MS (CI^+) (rel intensity) 284 ($M^+ + 1$, 61), 151 (100), 150 (21); M_r (+CI) 284.13997 [$M^+ + 1$] (calcd for $C_{16}H_{18}N_3O_2$ 284.13990). Anal. ($C_{16}H_{17}N_3O_2$) C, H, N.

1-Acetyl-4-benzyl-2-(thiazol-2-yl)semicarbazide (13). Compound **21** (1.30 g, 8.3 mmol), DMAP (0.005 g), pyridine (10 mL) and benzyl isocyanate (1.10 g, 8.3 mmol) were stirred at 40 °C (18 h) and gave an oily residue, which was triturated with Et_2O (75 mL) and then purified by chromatography (10% MeOH/$CHCl_3$) to afford 1.70 g (72%) of **13**: mp 149−151 °C; R_f 0.43 (10% MeOH/$CHCl_3$); IR (KBr) 3347, 3255, 1695, 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3 H), 4.54 (d, J = 5.7 Hz, 2 H), 6.85 (d, J = 3.3 Hz, 1 H), 7.20−7.40 (m, 6 H), 8.84 (br s, 1 H), 9.10−9.20 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.0, 44.8, 113.3, 127.5, 127.8, 128.9, 138.3, 138.7, 153.5, 166.6, 171.3; MS (CI^+) (rel intensity) 291 ($M^+ + 1$, 34), 158 (100); M_r (+CI) 291.09071 [$M^+ + 1$] (calcd for $C_{13}H_{15}N_4O_2S$ 291.09157). Anal. ($C_{13}H_{14}N_4O_2S \cdot 0.66H_2O$) C, H, N.

1-Acetyl-4-benzyl-2-(pyrid-2-yl)semicarbazide (14). Benzyl isocyanate (0.99 g, 7.4 mmol), pyridine (5 mL), **22**[7] (1.12 g, 7.4 mmol) and DMAP (0.005 g) were stirred at 50 °C (3 h) and then at room temperature (18 h). The oily residue was purified by chromatography (5% MeOH/$CHCl_3$) to obtain **14** as an oil (1.62 g, 84%): R_f 0.40 (10% MeOH/$CHCl_3$); IR (neat, NaCl) 3413, 1699, 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3 H), 4.56 (d, J = 5.4 Hz, 2 H), 6.95 (dd, J = 5.3, 7.1 Hz, 1 H), 7.16 (d, J = 8.4 Hz, 1 H), 7.20−7.40 (m, 5 H), 7.60−7.70 (m, 1 H), 8.16−8.25 (m, 1 H), 9.12 (s, 1 H), 10.63 (t, J = 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.0, 44.7, 111.4, 118.1, 127.2, 127.3, 128.7, 138.9, 139.2, 145.6, 155.7, 155.8, 171.4; MS (CI^+) (rel intensity) 285 ($M^+ + 1$, 100), 152 (56); M_r (+CI) 285.135 14 [$M^+ + 1$] (calcd for $C_{15}H_{17}N_4O_2$ 285.13515). Anal. ($C_{15}H_{16}N_4O_2 \cdot 0.45H_2O$) C, H, N.

1-Acetyl-4-benzyl-2-(pyrimid-2-yl)semicarbazide (15). Benzyl isocyanate (2.88 g, 21.4 mmol), **23** (2.73 g, 17.8 mmol), DMAP (0.005 g), pyridine (1.69 g, 21.4 mmol) and anhydrous 1,4-dioxane (100 mL) were stirred at 65 °C (18 h). The resulting residue was purified by chromatography (20% acetone/ethyl acetate) to afford **15** (1.70 g, 33%): mp 139−140 °C; R_f 0.31 (20% acetone/ethyl acetate); IR (KBr) 3447, 3418, 1695, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H), 4.56−4.64 (m, 2 H), 6.96 (t, J = 4.8 Hz, 1 H), 7.20−7.40 (m, 5 H), 8.45 (s, 1 H), 8.53 (d, J = 4.8 Hz, 2 H), 10.19 (t, J = 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.1, 45.1, 115.6, 127.4, 127.6, 128.8, 138.7, 154.6, 157.9, 159.9, 170.0; MS (CI^+) (rel intensity) 286 ($M^+ + 1$, 3), 153 (100); M_r (+CI) 286.13038 [$M^+ + 1$] (calcd for $C_{14}H_{16}N_5O_2$ 286.13040). Anal. ($C_{14}H_{15}N_5O_2 \cdot 0.33H_2O$) C, H, N.

4-Benzyl-2-methylsemicarbazide (25). $CHCl_3$ (5 mL), **24** (0.43 g, 9.4 mmol), and benzyl isocyanate (1.25 g, 9.4 mmol) were stirred at 0 °C (2 h). The residue was dissolved in 10% aqueous HCl (100 mL) and the solution was washed with $CHCl_3$ (3 × 50 mL). The aqueous layer was adjusted to pH 12 (saturated aqueous NaOH) and then extracted with $CHCl_3$ (3 × 50 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and evaporated in vacuo to obtain 1.20 g (71%) of **25**: mp 83−84 °C; R_f 0.64 (10% MeOH/$CHCl_3$); IR (KBr) 3394, 3311, 3192, 1654, 1625 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.95 (s, 3 H), 4.19 (d, J = 6.3 Hz, 2 H), 4.47 (s, 2 H), 7.10−7.40 (m, 6 H); ^{13}C NMR (DMSO-d_6) δ 38.2, 43.5, 126.8, 127.4, 128.5, 141.6, 159.7; MS (CI^+) (rel intensity) 180 ($M^+ + 1$); M_r (+CI) 180.11264 [$M^+ + 1$] (calcd for $C_9H_{14}N_3O$ 180.11369). Anal. ($C_9H_{13}N_3O$) C, H, N.

1-Acetyl-4-benzyl-2-methylsemicarbazide (11). Ac_2O (0.77 g, 7.5 mmol) was slowly added to a pyridine solution (5 mL) of **25** (1.35 g, 7.5 mmol) and the solution was stirred at room temperature (10 h). The solution was concentrated in vacuo and the residue was purified by chromatography (SiO_2, EtOAc) to obtain **11** as a pale yellow oil (1.36 g, 81%): HPLC analyses using two different gradients showed a single peak; R_f 0.44 (10% MeOH/$CHCl_3$); IR (neat, NaCl) 3344, 1688, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (s, 3 H), 2.99 (s, 3 H), 4.25 (d, J = 5.7 Hz, 2 H), 6.09 (t, J = 5.7 Hz, 1 H), 7.10−7.30 (m, 5 H), 9.21 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.7, 35.8, 44.2, 127.0, 127.1, 128.5, 139.1, 158.6, 170.5; MS (CI^+) (rel intensity) 222 ($M^+ + 1$, 100), 179 (16); M_r (+CI) 222.12428 [$M^+ + 1$] (calcd for $C_{11}H_{15}N_3O_2$ 222.12425).

1-Acetyl-2-(thiazol-2-yl)hydrazine (21). To a pyridine (15 mL) solution of **17**[5] (2.80 g, 24.4 mmol) was added Ac_2O (2.50 g, 24.4 mmol) and the solution was stirred at room temperature (2 h). The pyridine was evaporated in vacuo and the residue was triturated with absolute EtOH (75 mL) to afford 1.43 g (37%) of **21**: mp 177−179 °C dec; R_f 0.35 (10% MeOH/$CHCl_3$); IR (KBr) 3216, 2866, 1682, 1669 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (s, 3 H), 6.76 (d, J = 3.6 Hz, 1 H), 7.09 (d, J = 3.6 Hz, 1 H), 9.16−9.40 (m, 1 H), 10.00−10.20 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 20.6, 108.4, 139.2, 169.1, 172.9; MS (CI^+) (rel intensity) 158 ($M^+ + 1$); M_r (+CI) 158.03816 [$M^+ + 1$] (calcd for $C_5H_7N_3OS$ 158.03881). Anal. ($C_5H_6N_3OS$) C, H, N.

1-Acetyl-2-(pyrimid-2-yl)hydrazine (22). To an acetonitrile (100 mL) solution of **18**[6] (1.98 g, 25 mmol) were added successively pyridine (1.98 g, 25 mmol) and Ac_2O (2.55 g, 25 mmol) and the solution was allowed to stir at room temperature (2 h). The solution was concentrated in vacuo and the residue was triturated with Et_2O (150 mL) to afford **22** (2.72 g, 79%): mp 164−165 °C; R_f 0.16 (10% MeOH/$CHCl_3$); IR (KBr) 3333, 3281, 1685, 1648 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (s, 3 H), 6.75 (t, J = 4.8 Hz, 1 H), 8.35 (d, J = 4.8 Hz, 2 H), 8.80 (s, 1 H), 9.70 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 20.6, 112.3, 158.0 (2 C), 163.0, 168.8; MS (CI^+) (rel intensity) 153 ($M^+ + 1$); M_r (+CI) 153.07683 [$M^+ + 1$] (calcd for $C_6H_9N_4O$ 153.07764). Anal. ($C_6H_8N_4O$) C, H, N.

Pharmacology. See references 3a,e.

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Supporting Information Available: X-ray crystallographic information (data collection, final atomic positional parameters, H atom coordinates, isotropic displacement parameters, bond distances, angles) for **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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