Solid-Phase Synthesis of *N*-Acyl-*N*′-Alkyl/Aryl Disubstituted Guanidines

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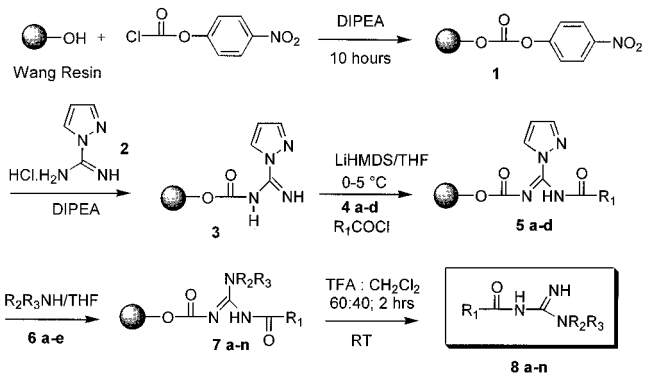
Received September 28, 2000

Combinatorial synthesis plays an increasingly significant role in lead identification. In particular, solid phase combinatorial chemistry has been widely used for the preparation of small molecule libraries.[1] As a result, many standard solution-phase reactions have been adapted to solid-phase chemistry.[2] We recently required an efficient and mild solid-phase method for the generation of *N*-acyl-*N*′-alkyl/aryl disubstituted guanidine libraries. The guanidine moiety is present in many drugs such as cardiovascular, anti-histaminic, anti-influenza, anti-diabetic, and anti-bacterial agents.[3] The synthesis of guanidines usually involves the reaction between electrophilic amidine moieties and amines. Most guanidinylation reagents are derivatives of pyrazole-1-carboxamidine,[4] *N*-trifly guanidine,[5] *S*-alkyl thiourea, and di-Boc activated thioureas.[6] *S*-Alkyl thiourea and di-Boc activated thioureas are two reagents which have been used extensively with $HgCl_2$ or Mukaiyama's reagent.[7]

Scheme 1



A limited number of solid-phase syntheses of guanidines have been reported[8] in the literature, and these methods in general are not suitable for the solid-phase synthesis of *N*-acyl-*N*′-alkyl/aryl disubstituted guanidines. There is a report of the solid-phase synthesis of *N*-acetyl-*N*′-alkyl disubstituted guanidines based on resin-bound acetylthioureas.[9] However, this type of resin-bound guanidinylation agent has a somewhat lower reactivity toward arylamines. Thus, there is a need for more convenient and efficient solid-phase methods for library syntheses of *N*-acyl-*N*′-alky/aryl disubstituted guanidines.[10]

We report here a novel and efficient method for such a library synthesis. In our synthetic strategy (Scheme 1), the Wang resin was first activated with *p*-nitrophenyl chloroformate (the activated carbonate Wang resin is also commercially available). This activated resin **1** is treated with 1-*H*-pyrazole-1-carboxamidine **2** at room temperature to give resin-bound pyrazole carboxamidine **3**. Resin-bound **3** is then deprotonated with lithium hexamethyldisilazide at 0 °C, treated with acylating reagent **4** (for structures see Table 1), and allowed to warm to room

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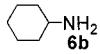
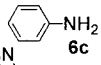
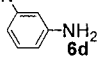
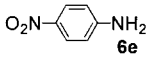
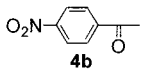
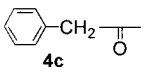
10.1021/jo001420+ CCC: $20.00
Published on Web 03/01/2001

Table 1. Solid-Phase Guanidinylation of Amines 6a−e

Entry	$R_1C(=O)-$ **4 a-d**	R_2R_3NH **6a-e**	Conditions Temp/Time	$R_1CON{=}C(NH)NR_2R_3$ **8 a-n**	Isolated yield (%)[a]	HRMS Calc/Obs
1	MeO-C6H4-C(=O)- **4a**	 **6a**	RT, 3 hrs	**8a**	88	262.1555/262.1558
2		 **6b**	RT, 3 hrs	**8b**	83	276.1712/276.1712
3		 **6c**	RT, 3 hrs	**8c**	85	270.1242/270.1240
4		 **6d**	67 °C, 3 hrs	**8d**	77	315.1093/315.1084
5		 **6e**	67 °C, 24 hrs	**8e**	61	315.1093/315.1097
6		**6a**	RT, 3 hrs	**8f**	84	277.1300/277.1301
7	 **4b**	**6b**	RT, 3 hrs	**8g**	75	291.1457/291.1456
8		**6d**	67 °C, 3 hrs	**8h**	71	330.0838/330.0838
9		**6b**	RT, 3 hrs	**8i**	70	260.1762/260.1760
10	 **4c**	**6e**	67 °C, 24 hrs	**8j**	65	299.1144/299.1139
11		**6a**	RT, 3 hrs	**8k**	78	214.1555/214.1556
12	Propyl-O-C(=O)- **4d**	**6b**	RT, 3 hrs	**8l**	74	228.1712/228.1714
13		**6c**	RT, 3 hrs	**8m**	83	222.1242/222.1244
14		**6d**	67 °C, 3 hrs	**8n**	75	267.1093/267.1082

[a] Reported yields are isolated yields after flash chromatography on silica gel, and they are overall yields based on initial loading of the carbonate Wang resin **1**.

temperature to afford resin-bound guanidinylation agent **5**. The amidine moiety in **5a**−**c** is flanked by one amide carbonyl group and one carbamate group, as compared to the two carbamate groups in **5d** and in *N*,*N*′-di-Boc or *N*,*N*′-di-Cbz-pyrazole-1-carboxamidine.[4] Thus, we anticipated that the electrophilic amidine moiety in resin-bound **5a**−**d** would be able to react with an amine **6** to provide resin-bound disubstituted guanidine **7**. Finally, TFA cleavage of **7** could provide disubstituted guanidine compound **8**.

To validate our idea, we chose to test the multistep solid-phase synthesis with a series of structurally and electronically diverse amines **6a**−**e**, and a series of electronically diverse acylating reagents **4a**−**d** (Table 1). In our resin-bound guanidinylation agents, **5a** and **5d**, the electron-donating *p*-methoxy and *n*-propyloxy groups could reduce the electrophilic character of the amidine moiety. On the other hand, the *p*-nitro group in **5b** could increase the electrophilic character of the amidine moiety. Among the amines, we chose piperidine **6a**, cyclohexylamine **6b**, and poorly nucleophilic amines, such as aniline **6c**, *m*-nitroaniline **6d**, and *p*-nitroaniline **6e**. When **6a**, **6b**, and **6c** were reacted with resin-bound **5** (See Table 1), the guanidinylation was completed within 3 h at room temperature in THF irrespective of the electronic character of the amidine moiety in **5**. This indicates that the resin-bound acyl pyrazole-1-carboxamidine moiety is a highly efficient guanidinylation agent, such that the electronic properties of the acyl groups are often not critical to the reaction. This finding is similar to that of the study on resin-bound Boc activated pyrazole-1-carboxamdine.[10] It would then be reasonable to expect that the guanidinylation reaction is more dependent on the nucleophilicity of the amine **6**. Indeed, at room temperature, *m*-nitroaniline **6d** gave partial guanidinylated products, and the reaction was not completed even after 48 h of reaction at room temperature. We found that the reaction was completed within 3 h under reflux in THF (entries 4, 8, and 14 in Table 1). Unlike *m*-nitroaniline **6d**, *p*-nitroaniline **6e** did not undergo complete guanylation after 3 h reflux in THF. A larger excess of *p*-nitroaniline **6e** (typically 10−15 equiv), with 24 h at reflux in THF, was required to drive the reaction close to completion (entries 5 and 10 in Table 1). Diisopropylamine is an example of a highly hindered amine that did not give any product even after 30 h at reflux in THF.

The final products **8a**−**n** were obtained after flash chromatography on silica gel in high yields (70−88%), except for **8e** (61%) and **8j** (65%) (Table 1). The reported yields are the overall yields for all the reaction steps in Scheme 1, based on the initial loading of the carbonate Wang resin. For potential future optimization of this synthetic method, it is worth noting the efficiency for each reaction step. The attachment of **2** to form resin-bound **3** was always quantitative since *p*-nitrophenol was released quantitatively. On the basis of the electrospray mass spectrometry (ES−MS) analysis of products released after each subsequent reaction step upon TFA treatment and the HPLC analysis of the crude final product **8**, it was found that the acylation reactions with **4** were not complete since free pyrazole-1-carboxamidine **2** was always found in the product mixtures of subse-

quent reaction steps. By contrast, the guanidinylation agent **5** was always completely consumed except when it was reacted with *p*-nitroaniline **6e**.

In conclusion, we have developed a novel and efficient solid-phase method for the generation of *N*-acyl-*N*′-alkyl/aryl disubstituted guanidines. According to our method, one should be able to freely vary the two substituents using commercially available starting materials. Even poorly nucleophilic amines, such as *p*-nitroaniline **6e**, afforded moderate yields of desired products under our solid-phase reaction conditions. Hence, we anticipate that a diverse set of amines and acylating reagents could be used for the solid-phase library synthesis of *N*-acyl-*N*′-alkyl/aryl disubstituted guanidines using this simple procedure.

Experimental Section

General. The ^{1}H NMR spectra were recorded on a Bruker AF 300 MHz spectrometer with TMS as the internal standard. Chemical shifts (δ) are in ppm; multiplicities are indicated by s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants (J) are reported in hertz. Low-resolution mass spectra were obtained using the ESI technique on a Bruker Esquire-LC, while high-resolution mass spectra were obtained using the FAB technique on a JEOL HX 110 spectrometer, resolution 10000. Reversed-phase HPLC analysis was performed using C-18, 10 μm, 4.6 × 250 mm column (gradient from 100% of aqueous 0.1% TFA (eluent A), to 85% eluent A−15% MeCN (eluent B) over 5 min, and then to 50% eluent A−50% eluent B over 35 min). HPLC chromatograms were recorded at λ = 220 nm. Unless otherwise stated, all materials were obtained from commercial suppliers and were used without further purification. Wang resins (1% divinylbenzene polystyrene) were purchased from Novabiochem. THF for acylation reactions was obtained by fresh distillation over sodium/benzophenone. TLC was performed on precoated silica gel plates (Kieselgel 60 F254, E. Merck, Germany) with the solvent system, hexane:ethyl acetate:methanol (50:45:5). Flash chromatography was performed using silica gel 60 (70−230 mesh, E. Merck, Germany).

There are two batches of resin **1** used. Which batch of resin was used is indicated in the preparation details for each compound. The yields of the final compounds, after flash chromatography purification, are calculated on the basis of the initial loading of the starting Wang resin **1** (0.60 mmol/g for Batch 1, 0.78 mmol/g for Batch 2), and are the overall yields of all reaction steps starting from resin **1**.

Preparation of *N*-Immobilized-1-*H*-pyrazole-1-carboxamidine 3. Activated Wang resin **1** (loading 0.6 mmol/g, 2.0 g, Batch 1) was suspended in CH_2Cl_2 (30 mL). Pyrazole-1-carboxamidine hydrochloride **2** (6.0 mmol, 879 mg) was added, followed by the slow addition of DIPEA (12 mmol, 2.2 mL), at room temperature. After the mixture was stirred gently for 10 h, the resin was washed successively with DMA (3 × 25 mL), CH_2Cl_2 (3 × 25 mL), THF (3 × 25 mL), and CH_2Cl_2 (2 × 20 mL) and dried overnight under vacuum over P_2O_5 to a constant weight of resin **3** (1.97 g). In another batch of preparation, 2.0 g of activated Wang resin **1** (0.78 mmol/g, Batch 2) was converted to resin-bound **3** (1.95 g).

Preparation of *N*-Immobilized-*N*′-(4-methoxyphenylcarbonyl)-1-*H*-pyrazole-1-carboxamidine 5a. Dry resin **3** (800 mg, 0.48 mmol, Batch 1) was suspended in dry THF (5 mL) under N_2 for 2 h, and the flask was then cooled to 0−5 °C. A solution of LiHMDS in THF (1.0 M, 0.62 mL, 0.62 mmol) was added dropwise and stirred for 15 min at 0−5 °C. To this reaction mixture a solution of **4a** (106 mg, 0.62 mmol) in THF (1.0 mL) was added slowly (15 min). Without any further addition of ice to the cooling bath, the reaction was allowed to warm to room temperature. The reaction was quenched with aqueous THF. The resin was transferred into polypropylene filter vessels (from BIO-RAD), washed sequentially with DMA (3 × 15 mL), DMA−MeOH 1:1 (3 × 15 mL), CH_2Cl_2 (3 × 20 mL), and THF (3 × 20 mL), and dried under vacuum to a constant weight of resin-bound guanidinylation agent **5a** (870 mg). IR (KBr): 2918, 1739, 1600, 1510, 1488 cm^{-1}. A few resin beads of **5a** were cleaved with TFA:CH_2Cl_2 (60:40, 0.1 mL) at room temperature. ES−MS of this sample showed the desired peak at *m*/*z* 244.99 for the corresponding acyl-1-*H*-pyrazole-1-carboxamidine.

Preparation of *N*-Immobilized-*N*′-(4-nitrophenylcarbonyl)-1-*H*-pyrazole-1-carboxamidine 5b. Resin-bound guanidinylation agent **5b** (868 mg) was prepared from **3** (800 mg, 0.48 mmol, Batch 1), LiHMDS (0.62 mL, 0.62 mmol), and **4b** (115 mg, 0.62 mmol) by following the same procedure as described for **5a**. IR (KBr): 2913, 1644, 1605, 1507, 1488, 1334 cm^{-1}. A few resin beads of **5b** were cleaved with TFA:CH_2Cl_2 (60:40, 0.1 mL) at room temperature. ES−MS of this sample showed the desired peak at *m*/*z* 259.98 for the corresponding acyl-1-*H*-pyrazole-1-carboxamidine.

Preparation of *N*-Immobilized-*N*′-benzylcarbonyl-1-*H*-pyrazole-1-carboxamidine 5c. Resin-bound guanidinylation agent **5c** (868 mg) was prepared from **3** (800 mg, 0.64 mmol, Batch 2), LiHMDS (0.81 mL, 0.81 mmol), and **4c** (0.113 mL, 0.81 mmol) by following the same procedure as described for **5a**. IR (KBr): 2913, 1630 (very broad), 1507, 1488 cm^{-1}. A few resin beads of **5c** were cleaved with TFA:CH_2Cl_2 (60:40, 0.1 mL) at room temperature. ES−MS of this sample showed the desired peak at *m*/*z* 229.04 for the corresponding acyl-1-*H*-pyrazole-1-carboxamidine.

Preparation of *N*-Immobilized-*N*′-(*n*-propyloxycarbonyl)-1-*H*-pyrazole-1-carboxamidine 5d. Resin-bound guanidinylation agent **5d** (438 mg) was prepared from **3** (410 mg, 0.25 mmol, Batch 1), LiHMDS (0.320 mL, 0.32 mmol), and **4d** (0.036 mL, 0.32 mmol) by following the same procedure as described for **5a**. IR (KBr): 2918, 1734, 1655, 1597, 1507, 1488 cm^{-1}. A few resin beads of **5d** were cleaved with TFA:CH_2Cl_2 (60:40, 0.1 mL) at room temperature. ES−MS of this sample showed the desired peak at *m*/*z* 197.05 for the corresponding acyl-1-*H*-pyrazole-1-carboxamidine.

Synthesis of *N*-(4-Methoxyphenylcarbonyl)-*N*′-piperidino-guanidine 8a (Method A). Guanidinylation agent **5a** (100 mg, 0.06 mmol, Batch 1) was placed into a polypropylene filter vessel and suspended in THF (0.5 mL) for 1 h. A solution of piperidine (0.018 mL, 0.18 mmol) in THF (0.5 mL) was added, and the mixture was shaken on a rotator. Reaction was completed in 3 h. The resin was washed sequentially with DMA (3 × 5 mL), DMA−MeOH 1:1 (3 × 5 mL), THF (3 × 20 mL), and CH_2Cl_2 (3 × 10 mL) and cleaved with TFA:CH_2Cl_2 (60:40, 1.0 mL) at room temperature for 2 h. The residue that remained after removal of the solvent under reduced pressure was purified by silica gel column chromatography with hexane:ethyl acetate:methanol (50:48:2) as the eluting solvent to afford **8a** (14 mg, 88%). R_f = 0.45 (hexane:ethyl acetate:methanol = 50:45:5). ^{1}H NMR ($CDCl_3$) δ 1.67 (br s, 6 H), 3.61 (br s, 4 H), 3.85 (s, 3 H), 6.89 (d, J = 8.7 Hz, 2 H), 8.16 (d, J = 8.7 Hz, 2 H). HPLC t_R = 18.05 min, purity 97.4%. ES−MS *m*/*z* 262.15 (M + H)$^+$. HRMS *m*/*z* calcd for ($C_{14}H_{19}N_3O_2$ + H)$^+$, 262.1555; found, 262.1558.

***N*-(4-Methoxyphenylcarbonyl)-*N*′-cyclohexyl-guanidine (8b).** Following method A, 100 mg (0.06 mmol, Batch 1) of **5a** and 0.021 mL (0.18 mmol) of cyclohexylamine were reacted to yield 13.8 mg (83%) of **8b**. R_f = 0.70. ^{1}HNMR ($CDCl_3$) δ 1.25−1.45 (m, 5 H), 1.50−2.17 (m, 5 H), 3.6 (brs, 1 H), 3.86 (s, 3 H), 6.93 (d, J = 8.7 Hz, 2 H), 8.09 (d, J = 8.7 Hz, 2 H). HPLC t_R = 27.08 min, purity 97.6%. ES−MS *m*/*z* 276.17 (M + H)$^+$. HRMS *m*/*z* calcd for ($C_{15}H_{21}N_3O_2$ + H)$^+$, 276.1712; found, 276.1712.

***N*-(4-Methoxyphenylcarbonyl)-*N*′-phenyl-guanidine (8c).** Following method A, 100 mg (0.06 mmol, Batch 1) of **5a** and 0.017 mL (0.18 mmol) of aniline were reacted to yield 13 mg (85%) of **8c**. R_f = 0.39. ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3 H), 6.92 (d, J = 8.7 Hz, 2 H), 7.41 (m, 5 H), 8.07 (d, J = 8.7 Hz, 2 H). HPLC t_R = 22.10 min, purity 96%. ES−MS *m*/*z* 270.10 (M + H)$^+$. HRMS *m*/*z* calcd for ($C_{15}H_{15}N_3O_2$ + H)$^+$, 270.1242; found, 270.1240.

***N*-(4-Methoxyphenylcarbonyl)-*N*′-(3-nitrophenyl)-guanidine (8d) (Method B).** Guanidinylation agent **5a** (100 mg, 0.06 mmol, Batch 1) was placed into a flask fitted with N_2 and suspended in THF (4 mL) for 1 h. A solution of 3-nitro-aniline (83 mg, 0.6 mmol) in THF (2 mL) was added, and the reaction mixture was refluxed for 3 h. The reaction mixture was then cooled to room temperature. The resin was transferred into a polypropylene tube and then treated according to method A to

yield 14 mg (74%) of **8d**. $R_f = 0.47$. ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 6.91 (d, $J = 8.7$ Hz, 2 H), 7.41−7.49 (m, 3 H), 7.94 (d, $J = 8.7$ Hz, 2 H), 8.06 (s, 1 H). HPLC $t_R = 22.63$ min, purity 98.5%. ES−MS m/z 315.09 $(M + H)^+$. HRMS m/z calcd for $(C_{15}H_{15}N_4O_4 + H)^+$, 315.1093; found, 315.1084.

***N*-(4-Methoxyphenyl-carbonyl)-*N′*-(4-nitrophenyl)-guanidine (8e).** Following method B, **5a** (150 mg, 0.09 mmol, Batch 1) and 4-nitroaniline (124 mg, 0.9 mmol) were refluxed for 24 h to provide 17 mg (61%) of **8e**. $R_f = 0.50$. ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3 H), 6.91 (d, $J = 8.7$ Hz, 2 H), 7.11 (d, $J = 8.7$ Hz, 2 H), 7.87 (d, $J = 8.7$ Hz, 2 H), 8.16 (d, $J = 8.7$ Hz, 2 H). HPLC $t_R = 23.21$ min, purity 98%. ES−MS m/z 315.12 $(M + H)^+$. HRMS m/z calcd for $(C_{15}H_{15}N_4O_4 + H)^+$, 315.1093; found, 315.1097.

***N*-(4-Nitrophenylcarbonyl)-*N′*-piperidino-guanidine (8f).** Following method A, 100 mg (0.06 mmol, Batch 1) of **5b** and 0.018 mL (0.18 mmol) of piperidine were reacted to yield 14 mg of **8f** (84%). $R_f = 0.5$. ^{1}H NMR ($CDCl_3$) δ 1.70 (brs, 6 H), 3.64 (brs, 4 H), 8.22 (d, $J = 8.7$, Hz, 2 H), 8.33 (d, $J = 8.7$, Hz, 2 H). HPLC t_R =18.24 min, purity 98.9%. ES−MS m/z 277.15 $(M + H)^+$. HRMS m/z calcd for $(C_{13}H_{16}N_4O_3 + H)^+$, 277.1300; found, 277.1301.

***N*-(4-Nitrophenylcarbonyl)-*N′*-cyclohexyl-guanidine (8g).** Following method A, 100 mg (0.06 mmol, Batch 1) of **5b** and 0.021 mL (0.18 mmol) of cyclohexylamine were reacted to yield 12.6 mg (73%) of **8g**. $R_f = 0.47$. ^{1}H NMR ($CDCl_3$) δ 1.25−1.40 (m, 5 H), 1.42−2.05 (m, 5 H), 3.20 (br s, 1 H), 8.22 (dt, $J = 8.7$, 2.1 Hz, 2 H), 8.30 (dt, $J = 8.7$, 2.1 Hz, 2 H). HPLC t_R =25.55 min, purity 91%. ES−MS m/z 291.17 $(M + H)^+$. HRMS m/z calcd for $(C_{14}H_{18}N_4O_3 + H)^+$, 291.1457; found, 291.1456. Anal. Calcd for $C_{14}H_{18}N_4O_3 \cdot (1/3H_2O)$: C, 56.75; H, 6.35; N, 18.91. Found: C, 56.65; H, 6.23; N, 18.89.

***N*-(4-Nitrophenylcarbonyl)-*N′*-(3-nitrophenyl)-guanidine (8h).** Following method B, **5b** (100 mg, 0.06 mmol, Batch 1) and 3-nitroaniline (83 mg, 0.6 mmol) were refluxed to yield 14 mg (71%) of **8h**. $R_f = 0.39$. ^{1}H NMR (acetone-d_6) δ 9.04 (s, 1 H), 8.50 (d, 2 H, $J = 4.8$ Hz), 8.33 (d, 2 H, $J = 4.8$ Hz), 8.03 (d, 1 H, $J = 4.8$ Hz), 7.91 (d, 1 H, $J = 4.8$ Hz), 7.70 (m, 1 H), 7.64 (brs, 1 H). HPLC $t_R = 24.53$ min, purity 99%. ES−MS m/z 330.14 $(M + H)^+$. HRMS m/z calcd for $(C_{14}H_{11}N_5O_5 + H)^+$, 330.0838; found, 330.0838.

***N*-Benzylcarbonyl-*N′*-cyclohexyl-guanidine (8i).** Following method A, **5c** (100 mg, 0.078 mmol, Batch 2) and cyclohexylamine (0.027 mL 0.23 mmol) were reacted to yield 14 mg (70%) of **8i**. ^{1}H NMR ($CDCl_3$) δ 1.25−1.38 (m, 5 H), 1.40−2.03 (m, 5 H), 3.20 (br s, 1 H), 3.64 (brs, 2 H), 7.21−7.31 (m, 5 H). HPLC t_R = 26.96 min, purity 96.3%. ES−MS m/z 260.17 $(M + H)^+$. HRMS m/z calcd for $(C_{15}H_{21}N_3O + H)^+$, 260.1762; found, 260.1760.

***N*-Benzylcarbonyl-*N′*-(4-nitrophenyl)-guanidine (8j).** Following method B, **5c** (100 mg, 0.078 mmol, Batch 2) and 4-nitroaniline (107 mg, 0.78 mmol) were refluxed for 24 h to yield 15 mg (65%) of **8j**. ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 2 H), 6.96 (d, $J = 8.7$, Hz, 2 H), 7.25−7.36 (m, 5 H), 8.14 (d, $J = 8.7$, Hz, 2 H). HPLC $t_R = 22.91$ min, purity 93.3%. ES−MS m/z 299.12 $(M + H)^+$. HRMS m/z calcd for $(C_{15}H_{14}N_4O_3 + H)^+$, 299.1144; found, 299.1139.

***N*-(*n*-Propyloxycarbonyl)-*N′*-piperidino-guanidine (8k).** Following method A, **5d** (100 mg, 0.06 mmol, Batch 1) and piperidine (0.018 mL, 0.18 mmol) were reacted to yield 10 mg (78%) of **8k**. ^{1}H NMR ($CDCl_3$) δ 0.95 (t, $J = 7.2$ Hz, 3 H), 1.62 (br s, 6 H), 1.70 (m, 2 H), 3.49 (m, 4 H), 4.0 (t, $J = 6.8$ Hz, 2 H). HPLC $t_R = 13.94$ min, purity 97.2%. ES−MS m/z 214.14 $(M + H)^+$. HRMS m/z calcd for $(C_{10}H_{19}N_3O_2 + H)^+$, 214.1555; found, 214.1556.

***N*-(*n*-Propyloxycarbonyl)-*N′*-cyclohexyl-guanidine (8l).** Following method A, **5d** (100 mg, 0.06 mmol, Batch 1) and cyclohexylamine (0.021 mL, 0.18 mmol) were reacted to yield 10 mg (74%) of **8l**. ^{1}H NMR ($CDCl_3$) δ 0.95 (t, $J = 7.2$ Hz, 3 H), 1.15−1.35 (m, 5 H), 1.52−1.92 (m, 7 H), 3.2 (br s, 1 H), 4.0 (t, $J = 6.8$ Hz, 2 H). HPLC $t_R = 22.78$ min, purity 98%. ES−MS m/z 228.14 $(M + H)^+$. HRMS m/z calcd for $(C_{11}H_{21}N_3O_2 + H)^+$, 228.1712; found, 228.1714.

***N*-(*n*-Propyloxycarbonyl)-*N′*-phenyl-guanidine (8m).** Following method A, **5d** (100 mg, 0.06 mmol, Batch 1) and aniline (0.017 mL, 0.18 mmol) were reacted to yield 11 mg (83%) of **8m**. $R_f = 0.34$. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 7.2$ Hz, 3 H), 1.42−1.59 (m, 2 H), 3.95 (t, $J = 6.8$ Hz, 2 H), 7.12−7.20 (m, 3 H), 7.38−7.43 (m, 2 H). HPLC $t_R = 16.45$ min, purity 99.4%. ES−MS m/z 222.10 $(M + H)^+$. HRMS m/z calcd for $(C_{11}H_{15}N_3O_2 + H)^+$, 222.1242; found, 222.1244.

***N*-(*n*-Propyloxycarbonyl)-*N′*-(3-nitrophenyl)-guanidine (8n).** Following method B, **5d** (100 mg, 0.06 mmol, Batch 1) and 3-nitroaniline (83 mg, 0.6 mmol) were refluxed to yield 12 mg (75%) of **8n**. $R_f = 0.50$. ^{1}H NMR ($CDCl_3$) δ 0.80 (t, $J = 7.2$ Hz, 3 H), 1.30−1.42 (m, 2 H), 3.9 (t, $J = 6.8$ Hz, 2 H), 7.36 (m, 1 H), 7.50 (m, 1 H), 7.90 (m, 1 H), 7.95 (m, 1 H). HPLC t_R = 17.39 min, purity 97.1%. ES−MS m/z 267.07 $(M + H)^+$. HRMS m/z calcd for $(C_{11}H_{14}N_4O_4 + H)^+$, 267.1093; found, 267.1082. Anal. Calcd for $C_{11}H_{14}N_4O_4 \cdot (1/2H_2O)$: C, 48.00; H, 5.49; N, 20.35. Found: C, 48.39; H, 5.25; N, 20.17.

Acknowledgment. This work was supported by the School of Medicine, University of Washington, and NIH Grant AI34501.

JO001420+