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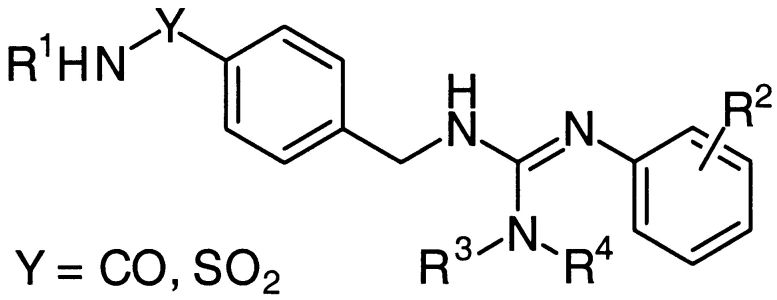

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Solid-Phase Synthesis of Trisubsituted Guanidines

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The solid-phase library synthesis of trisubstituted guanidines was accomplished. Amines were loaded onto the 4-formyl-3,5-dimethoxyphenoxymethyl linker via reductive amination. Subsequent acylation with Fmoc-4-aminomethylbenzoic acid followed by Fmoc deprotection gave solid-supported primary amines. Alternatively, sulfonylation of resin-bound secondary amines with 4-cyanobenzenesulfonyl chloride followed by borane reduction also gave solid-supported primary amines. Both resins were acylated with isocyanates to furnish solid-supported ureas. Dehydration of ureas with *p*-toluenesulfonyl chloride in pyridine gave solid-supported carbodiimides. Nucleophilic addition of amines to the carbodiimide bond followed by cleavage off the solid support gave trisubstituted guanidines.

Introduction

Substituted guanidines are found in many biologically active natural products and drug candidates. In the context of an ongoing combinatorial development program, we were attracted to substituted guanidines for their utility as scaffolds for histamine agonists and antagonists,[2] NMDA receptor antagonists,[3] bradykinin antagonists,[4] and taste receptor ligands[5] (Figure 1). Bethanidine (**1**) is a adrenergic neuron blocker that has been used as an antiarrhythmic agent.[6] Aptiganel (**2**) is a potent NMDA antagonist ($IC_{50} = 36$ nM) that has shown some neuroprotective utility in stroke and head injury. The trisubstituted guanidine **3** is a potent bradykinin antagonist ($IC_{50} = 200$ nM). Several guanidine libraries[7] prepared on solid support have been reported. Many of the synthetic pathways to guanidines use expensive, toxic, or explosive reagents. The synthetic approach presented in this paper converts solid-supported ureas to carbodiimides using *p*-toluenesulfonyl chloride in pyridine. Subsequent addition of amines in DMSO gives solid-supported guanidines. This cost-effective, robust, and general method for the synthesis of trisubstituted guanidines is intended for the preparation of screening libraries.

Results and Discussion

Identification of a Practical Synthetic Route. Our original route was based on a reported solid-supported synthesis of guanidines (Scheme 1).[6a] For safety and health concerns using sodium azide (**7**) in library production, an alternative synthetic route, more suitable for library production, was developed.

We recognized that carbodiimide bond[8] formation on solid support in high purity and in high yield was central to the successful generation of guanidine libraries. We were particularly interested in using *p*-toluenesulfonyl chloride (*p*-TsCl) in the presence of base to dehydrate solid-supported ureas to solid-supported carbodiimides.[9] First, dehydration of ureas to carbodiimides *p*-TsCl in pyridine has been reported in solution.[10] Second, there was precedent for the generation of carbodiimides on solid support by this method.[11] We also needed conditions that were suitable for the manufacture of large libraries (ca. 5000 compounds) by a safe, reliable, and reproducible method.

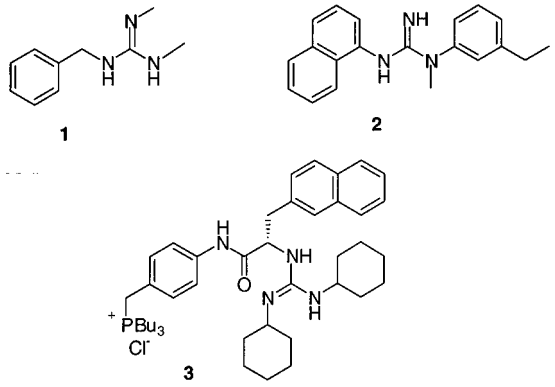

Figure 1. Biologically active substituted guanidines.

We examined several reaction parameters including base, dehydrating agent, solvent, temperature, reaction time, and type of isocyanate (Table 1). Single-bead IR of the intermediate carbodiimide resins **10** was used to monitor the reaction. To evaluate the carbodiimide bond formation process, resins **10** were treated with *N*-methylpiperazine (**11**) and treated with TFA to give guanidines **12**. When ureas **13** on Rink amide resin were treated with methanesulfonyl chloride in pyridine (entry 1, Table 1) or *p*-TsCl in the presence of tertiary amine bases (entries 2−4), the carbodiimide bond stretch was not observed by IR.

When ureas **13** were treated with *p*-TsCl in pyridine or in 2,6-lutidine, the carbodiimide IR stretch was observed at 2100−2150 cm^{-1} by single-bead IR (entires 5−10, Table 1). Heating at 45 °C in neat pyridine with at least 9 equiv of *p*-TsCl for 30 h completely converted the solid-supported ureas **13** to carbodiimides **10**. At lower temperatures or

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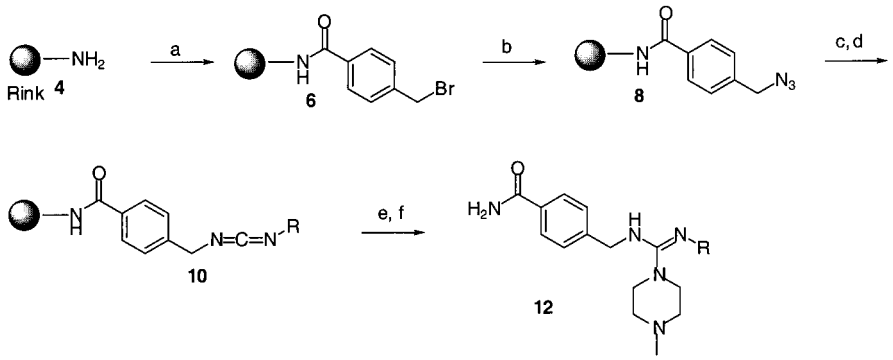
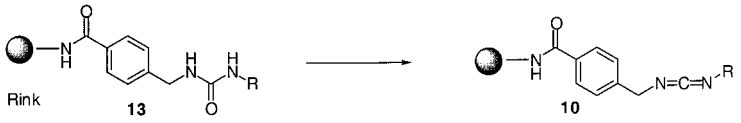
Scheme 1[a]



[a] Reagents and conditions: (a) $BrCH_2C_6H_4CO_2H$ (**5**), DIC, HOBT, DMF, 16 h, 25 °C; (b) NaN_3 (**7**), DMSO, 18 h, 60 °C; (c) PhNCS (**9**), THF; (d) Ph_3P, THF, 4 h, 25 °C; (e) *N*-methylpiperazine (**11**), DMSO, 16 h; (f) 95% CF_3CO_2H/H_2O, 1 h.

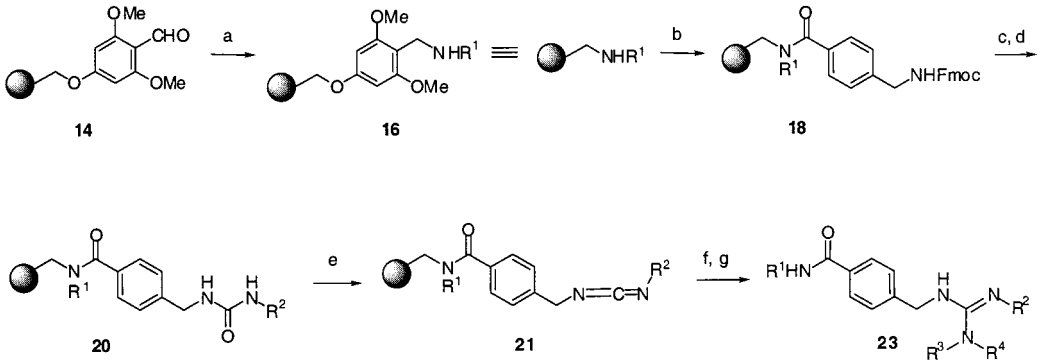
Table 1. Optimization of Carbodiimide Formation on Solid Support



entry	base	dehydrating agent	solvent	temp (°C)	time (h)	R^2	carbodiimide IR stretch (cm^{-1})
1	Pyridine	MsCl (9 equiv)	pyridine	40	27	aryl	not observed
2	Et_3N (8 equiv)	TsCl (2 equiv)	DCE	40	71.5	aryl	not observed
3	DBU (8 equiv)	TsCl (2 equiv)	DCM	25	71.5	aryl	not observed
4	DBU (8 equiv)	TsCl (3 equiv)	DCE	40	48	aryl	not observed
5	2,6-lutidine (8 equiv)	TsCl (2 equiv)	DCE	40	71.5	aryl	2130 (w)
6	2,6-lutidine (8 equiv)	TsCl (3 equiv)	DCE	40	48	aryl	2125 (w)
7	pyridine	TsCl (9 equiv)	pyridine	25	24	aryl	2145 (m)
8	pyridine	TsCl (9 equiv)	pyridine	40−60	2−6	aryl	2145 (s)
9	pyridine	TsCl (9 equiv)	pyridine	40−70	2−6	aliphatic	2122 (w) at ≤2 h and not observed after 4 h.
10[a]	pyridine	TsCl (9 equiv)	pyridine	45	30	aryl	2145 (s)

[a] Optimal conditions.

Scheme 2[a]

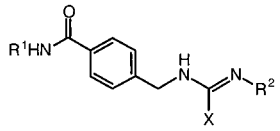


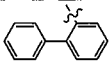
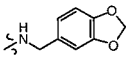
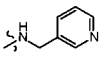
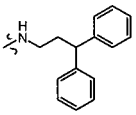
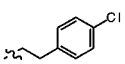
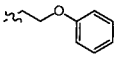
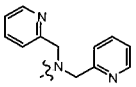
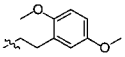
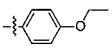
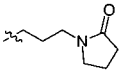
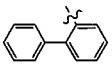
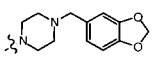
[a] Reagents and conditions: (a) R^1NH_2 (**15**), $NaBH(OAc)_3$, AcOH, THF; (b) Fmoc−NH−CH_2−$C_6H_4CO_2H$ (**17**), DIC, HOBT, DMF; (c) 30% piperidine/DMF; (d) R^2NCO (**19**), *i*-Pr_2NEt, CH_2Cl_2; (e) *p*-TsCl, pyridine, 45 °C, 27−30 h; (f) R^3R^4NH (**22**), DMSO; (g) 10% TFA/CH_2Cl_2.

shorter reaction times, the carbodiimide bond formation was incomplete. At higher temperatures and reaction times greater than 30 h, we also observed significant decomposition of the carbodiimide bond to the urea. Furthermore, both allylic and aliphatic solid-supported ureas showed a very weak IR stretch for the carbodiimide bond at about 2122 cm^{-1} (entry 9, Table 1) and gave guanidine products in low yield and low purity. For the conversion of urea to carbodiimide, aryl groups in the R position were best. The preferred dehydration conditions were use of *p*-TsCl (9 equiv) in anhydrous pyridine at 45 °C for 30 h (entry 10, Table 1) and gave guanidines (ca. 90% by UV area under the curve at 214 nm) with only a small amount of urea (<10% by UV area under the curve at 214 nm).

Synthetic Routes. To expand the library size to incorporate various R^1 diversity elements, we switched from the Rink amide linker to the 4-formyl-3,5-dimethoxyphenoxymethyl linker **14** (Scheme 2). Primary amines **15** were coupled to solid-support **14** via reductive amination. Fmoc-4-aminomethylbenzoic acid (**17**) was subsequently coupled to solid-supported secondary amines **16** with DIC/HOBT in DMF to furnish intermediates **18**. The Fmoc protecting group was

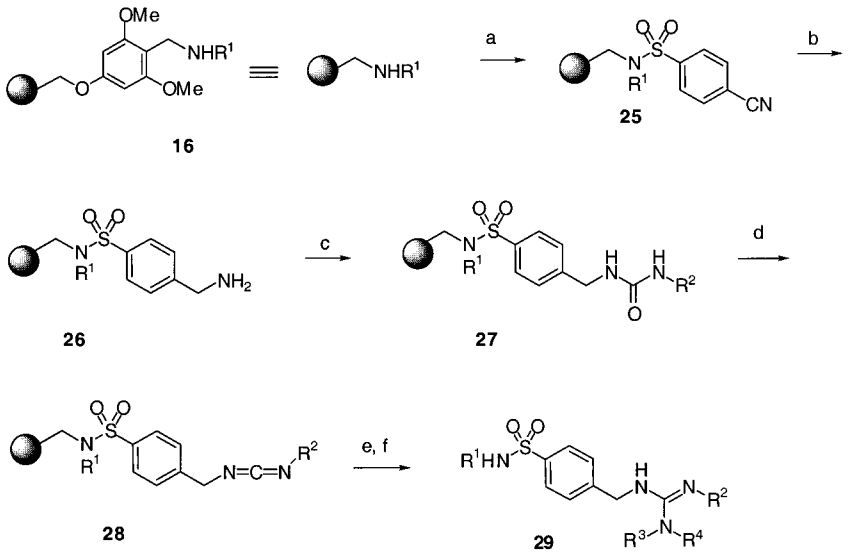
Table 2. Representative Trisubstituted Guanidines **23** Prepared via Solid-Phase Library Syntheses



Compound	R^1	R^2	X	Yield[a] (%)	Purity[b] (%)
23a				73	90
23b				70	81
23c				99	99
23d				99	92
23e				99	90
23f				99	83
23g				90	72

[a] Crude yield. [b] Area under the curve by UV at 214 nm.

Scheme 3[a]

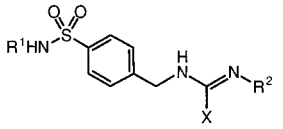


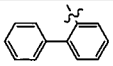
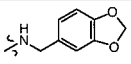
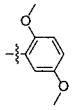
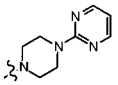
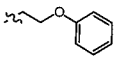
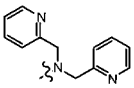
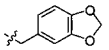
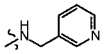
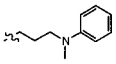
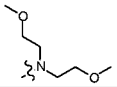
[a] Reagents and conditions: (a) 4-CN−$C_6H_4SO_2Cl$ (**24**), *i*-Pr_2NEt, DMA; (b) BH_3·THF; (c) R^2NCO (**19**), *i*-Pr_2NEt, CH_2Cl_2; (d) *p*-TsCl, pyridine, 45 °C, 27−30 h; (e) R^3R^4NH (**22**), DMSO; (f) 10% TFA/CH_2Cl_2.

removed with 30% piperidine in DMF. After the resins were washed, the primary amine was acylated with aryl isocyanates **19** to furnish ureas **20**. Dehydration of ureas **20** with *p*-TsCl in neat pyridine at 45 °C for 30 h gave solid-supported carbodiimides **21**. Treatment of carbodiimides **21** with various primary and secondary amines **22** in DMSO gave the solid-supported guanidines. Upon treatment of the resins with a 10% solution of trifluoroacetic acid in CH_2Cl_2, the guanidines **23** were generated. We found that α-amino acids gave guanidines in low purity. Representative compounds prepared by these methods are shown in Table 2.

Sulfonylation of secondary amines **16** on the 4-formyl-3,5-dimethoxyphenoxymethyl linker with 4-cyanobenzenesulfonyl chloride yielded benzonitriles **25** (Scheme 3). A practical multigram borane reduction in THF of benzonitriles **25** gave primary amines **26**. Generally, borane as a 1 M solution in THF was added in one portion (Table 4). The reaction was generally complete within 30 min. When we attempted to add the borane·THF solution dropwise over 30 min, the reaction was incomplete after 45 min. At this point, we recognized that either a longer reaction time or heat was required to drive the reaction to completion. We then added the borane solution in THF in one portion to the resin, and

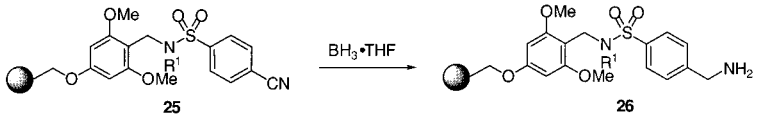
Table 3. Representative Trisubstituted Guanidines **29** Prepared via Solid-Phase Library Syntheses



Compound	R^1	R^2	X	Yield[a] (%)	Purity[b] (%)
29a				92	70
29b				99	69
29c				99	71
29d				99	70
29e				99	81
29f				71	70
29g				91	72

[a] Crude yield. [b] Area under the curve by UV at 214 nm.

Table 4. Optimization of Benzonitrile Reduction on Solid Support



25 **26**

entry	resin amount (g)	BH_3·THF addition	solvent	temp (°C)	time (min)	result
1	5	added in one portion to resin	THF	25	30	complete reduction
2	20	added dropwise over 30 min to resin	THF	25	45	incomplete reduction
3	18	added in one portion to resin	THF	25	180	complete reduction
4	20	resin added to a solution of BH_3·THF	THF	25	45	complete reduction 17.5 °C exotherm
5[a]	15.5	added in one portion to resin	THF	25−31	70	complete reduction

[a] Optimal conditions.

the reaction was complete after 3 h with no significant exotherm. Addition of resin to the THF solution of borane also resulted in complete reduction of the nitrile but with a 17.5 °C exotherm. Finally, we found that adding the borane solution in one portion followed by heating the solution to 31 °C (internal temperature) over 30 min, maintaining the temperature at 31 °C for 10 min, then cooling to room temperature over an additional 30 min resulted in complete reduction. In contrast to allowing the reaction to proceed for 3 h, the procedure in which the reaction mixture was heated to 31 °C resulted in complete reduction in higher purity after 1 h. On a larger resin reaction scale (80 g), we successfully applied this final set of reaction conditions and thereby demonstrated that heat (ca. 30 °C) was critical for rapid conversion to primary amines **26**. After complete reduction and resin washing with THF, treatment of the resin with a 0.5 M solution of DBU in NMP/MeOH[11] broke the boron−amine complex, and the borate salts were removed from the resin.[12] Use of the curcumin method for boron analysis enabled the in-process monitoring for the presence of boron.[13]

Subsequent acylation of amines **26** with isocyanates **19** gave the ureas **27**. Dehydration of the ureas **27** to the carbodiimides **28**, addition of amines **22**, and cleavage from solid support gave the sulfonamide guanidines **29**.[14] Representative compounds prepared by these methods are shown in Table 3.

Conclusion

We have developed practical solid-phase methods for the syntheses of trisubstituted guanidines. Central to the synthesis was the optimization of the carbodiimide bond generation on solid support. The methods described above have been successfully applied to the synthesis of several small-molecule libraries composed of about 5000 compounds each.[15,16]

Experimental Section

General. All reactions were performed in standard glassware or suitable materials for parallel library synthesis. At 296 K, ^{1}H NMR and ^{13}C NMR spectra were measured on a JEOL spectrometer at 270 and 67.5 MHz, respectively. EI mass spectra were recorded on a Sciex 150 EX instrument equipped with an HP 1100 HPLC. Elemental analyses were performed by Robertson Microlit Laboratories (Madison, NJ). Flash column chromatography experiments were performed on silica gel 230−400 mesh (flash) from EM Science; thin-layer chromatography experiments (TLC) were performed on glass plates coated with silica gel 60 F_{254} from Merck. Reversed-phase HPLC was performed on an HP1100 system (Hewlett-Packard, Palo Alto, CA) equipped with a vacuum degasser, binary pump, autosample, column compartment, a diode array detector, and a C18 column (3.0 mm × 100 mm, 5 μm, 100 Å) from Phenomenex (Phenomenex, Torrance, CA) at 40 °C with a flow rate of 1.0 mL/min. Two mobile phases (mobile phase A, 99% water, 1% acetonitrile, 0.05% TFA; mobile phase B, 1% water, 99% acetonitrile, 0.05% TFA) were employed to run a gradient condition from 0% B to 100% B in 6.0 min and 100% B for 2.0 min and reequilibrated at 0% B for 2 min. An injection volume of 10 μL was used. All reagents and solvents were purchased reagent grade and were used without further purification.

General Procedure for the Preparation of Library Compounds. Reductive Amination (16). 4-Formyl-3,5-dimethoxyphenoxymethyl resin **14** (25 g, 25 mmol) was suspended in THF (250 mL) to swell the resin. Amine **15** (125 mmol) was added, and the mixture was allowed to stir for 30 min. Glacial acetic acid (14.3 mL, 15 g, 250 mmol) was then added, followed by immediate addition of sodium triacetoxyborohydride (15.9 g, 75 mmol). The suspension was then diluted with THF (75 mL) and agitated for 5 h. The solvent was drained, and the resins were washed with each of the following solvents: MeOH (3×), THF (2×), 15% *i*-Pr_2NEt/CH_2Cl_2 (2×), MeOH (2×), CH_2Cl_2 (2×), Et_2O (2×). Upon treatment with the chloranil reagents, a small portion (ca. 50 mg) of resin turned dark-green and indicated the presence of the secondary amine. An IR spectrum of the resin showed no absorbance at 1680 cm^{-1}. The resin was then immediately carried onto the next step.

Fmoc-4-aminomethylbenzoic Acid Coupling (18). Fmoc-4-aminomethyl benzoic acid (**17**, 125 mmol) and HOBt (8.4 g, 62.5 mmol) was dissolved in anhydrous DMF (300 mL). After all of the solids dissolved, DIC (19.6 mL, 15.8 g, 125 mmol) was added to the solution. The mixture was immediately added to resins (25 mmol). The suspension was agitated for 16 h. The vessels were drained, and the resins were washed with each of the following solvents: DMF (4×), MeOH (3×), CH_2Cl_2 (3×), Et_2O (2×). Upon treatment with the chloranil reagents, a small portion (ca. 50 mg) of resin did not change color and indicated that the coupling was complete. An IR spectrum of the resin showed a stretch at 1726 cm^{-1} corresponding to the carbamate absorbance of the Fmoc group. The resin was dried under high vacuum overnight.

Fmoc Deprotection and Acylation (20). Resins **18** (ca. 100 mg) were washed with CH_2Cl_2 (1×). The resins were treated with 30% piperidine in DMF (1.5 mL/well). After 1 h, the resins were then washed with the following solvents: DMF (4×), CH_2Cl_2 (2×), MeOH (2×), CH_2Cl_2 (2×). Each well was then treated with a 0.375 M solution of an isocyanate (1 mL, 0.375 mmol) dissolved in 0.75 M *i*-Pr_2NEt/CH_2Cl_2. After being shaken for 16 h, the resins were washed using the following solvents: DMF (4×), MeOH (3×), CH_2Cl_2 (3×).

Sulfonylation of Secondary Amine (25). Resin **16** (25 mmol) was loaded into a 500 mL Nalgene bottle and treated with a 0.25 M solution of 4-cyanobenzenesulfonyl chloride (250 mL, 62.5 mmol) in 0.5 M *i*-Pr_2NEt/DMA. After being shaken for 24 h, the resin was washed with DMF (3×), MeOH (3×), THF (2×), and CH_2Cl_2 (3×). Upon treatment with the chloranil reagents, a small portion (ca. 50 mg) of the resin did not change color and indicated that the coupling was complete. An IR spectrum of the resin **25** showed a stretch at 2232 cm^{-1} corresponding to the nitrile. The resin was dried under high vacuum.

Borane Reduction of Benzonitrile (26). Resin **25** (15.5 g, 15.5 mmol) was added to a 500 mL four-neck round-bottomed flask equipped with a mechanical stirrer. After addition of anhydrous THF (70 mL), the resin was slowly stirred. A 1 M solution of borane in THF (78 mL, 78 mmol) was added in one portion over 1 min. Anhydrous THF (20 mL) was added to rinse the funnel and the flask. The reaction solution was placed in an oil bath, and the mixture was heated to 31 °C (internal temperature) over 30 min. After an additional 10 min at 31 °C, the oil bath was removed and the reaction mixture was cooled to 19.5 °C (ambient temperature) over 10 min. A small portion of resin (ca. 50−100 mg) was removed 1 h after addition of borane, 1.5 h, and 2 h for analysis (see method description below). After the reaction was judged complete by HPLC analysis (ca. 1 h), the resin was carefully poured into a sintered-glass funnel and washed with THF (6×). The filtrate was segregated and not mixed with any acidic solutions. The filtrate was quenched with acetone (200 mL) followed by addition of water (800 mL). The resin was then washed with MeOH (4×) and THF (3×), soaked in 15% Et_3N/CH_2Cl_2 (2 × 10 min), and finally washed with MeOH (3×) and CH_2Cl_2 (3×). The resin was then transferred into a 500 mL three-neck round-bottomed flask and treated with a cold solution (4 °C) of 0.5 M DBU in 9:1 NMP/MeOH (180 mL, 90 mmol). The suspension was allowed to warm to ambient temperature over 16−24 h and was stirred with a mechanical stirrer. The resin was washed with DMF (4×), MeOH (3×), THF (3×), CH_2Cl_2 (4×), and Et_2O (2×). Upon treament of a small portion (ca. 50 mg) of resin with the curcumin reagent to test for the presence of boron, both the resin and the curcumin solution did not change color. Upon treatment with the Kaiser test reagents, a small portion (ca. 50 mg) of resin turned purple and indicated the presence of primary amine.

For the analysis, a small portion of the resin was quickly washed with THF (6×). The combined THF washes were segregated for the quenching process. The resin was then washed with MeOH (4×) and THF (3×), soaked in 15%

TEA/CH_2Cl_2 (2 × 2 min), and then washed with MeOH (3×) and CH_2Cl_2 (3×). The resin was treated with 50% TFA/CH_2Cl_2 for 10 min. After concentration, the products were diluted with MeOH and injected on an HPLC instrument for analysis.

Acylation (27). Resin **26** (100 mg/well) was treated with a 0.375 M solution of an isocyanate (1 mL, 0.375 mmol) dissolved in 0.75 M *i*-Pr_2NEt/CH_2Cl_2. After being shaken for 16 h, the resins were washed using the following solvents: DMF (4×), MeOH (3×), CH_2Cl_2 (3×).

Carbodiimide Bond Formation (21 or 28). Resins **20** or **27** (100 mg/well) were washed with CH_2Cl_2 (1 mL/well) and then with pyridine (1 mL/well). To each well was added 0.9 M solution of *p*-toluenesulfonyl chloride in anhydrous pyridine (1.2 mL/well). The 96-well deep-well filter plates were placed in a preheated oven at 45 °C (±1 °C). After 27−30 h, the resins were washed with the following solvents: CH_2Cl_2 (4×), water (2×), dioxane (4×), CH_2Cl_2 (3×). After being washed, the resins were immediately carried to the next step.

Guanidine Formation and Cleavage off Solid Support (23 or 29). Each well containing resin **21** or **28** was treated with a 0.5 M solution of amine in DMSO (1 mL/well, 0.5 mmol). After 16−24 h, the resins were then washed with the following solvents: DMF (3×), CH_2Cl_2 (1×), MeOH (1×), CH_2Cl_2 (1×), MeOH (1×), CH_2Cl_2 (1×), MeOH (1×), CH_2Cl_2 (3×). Each well was treated with 10% TFA/CH_2Cl_2 (1 mL). After 30 min, the 96-well deep-well plate was frozen in dry ice. After an additional 60 min, the plate was unclamped and immediately placed on top of a tared 2 mL deep-well plate. The cleavage cocktail was allowed to drain into the 96-well plate for about 5 min. The resins were rinsed three more times with 10% TFA/CH_2Cl_2 (200 μL each), allowing 0.5−2 min between each addition of TFA/CH_2Cl_2. The product **23** or **29** was then concentrated in vacuo. Representative compounds below were purified by reversed-phase preparative HPLC, normal-phase preparative HPLC, or normal-phase flash chromatography.

23a: pale-yellow solid; ^{1}H NMR (270 MHz, CD_3OD/CD_3CN) δ 7.71 (d, J = 8.2 Hz, 2 H), 7.41−7.30 (m, 13 H), 7.19 (t, J = 7.4 Hz, 1 H), 7.05 (dd, J = 7.7, 6.9 Hz, 2 H), 6.66 (d, J = 7.7 Hz, 1 H), 6.47 (d, J = 10.4 Hz, 2 H), 5.86 (s, 2 H), 4.57 (s, 2 H), 4.53 (s, 3 H), 4.29 (s, 2 H), 4.12 (s, 2 H); ^{13}C NMR (67.5 MHz, CD_3OD/CD_3CN) δ 168.2, 152.3, 152.2, 147.8, 146.8, 142.9, 140.1, 139.1, 137.2, 132.9, 132.5, 130.8, 128.9 (2×), 128.5, 128.3 (2×), 127.9 (2×), 127.3 (2×), 127.2 (2×), 127.0, 126.9 (2×), 126.7, 126.4, 124.5, 120.2, 107.8, 107.5, 101.1, 44.5, 44.1, 43.2; MS (ESI) *m*/*z* 569.2 [(M + H)$^+$]. Anal. Calcd for $C_{36}H_{32}N_4O_3 \cdot H_2O$ (586.66): C, 73.70; H, 5.84; N, 9.55. Found: C, 73.41; H, 5.54; N, 9.29.

23b: white solid; ^{1}H NMR (270 MHz, CD_3CN) δ 8.35 (d, J = 2.5 Hz, 2 H), 7.71 (d, J = 8.4 Hz, 3 H), 7.51 (d, J = 7.9 Hz, 1 H), 7.28 (dd, J = 7.7, 7.4 Hz, 1 H), 7.26−6.98 (m, 9 H), 6.81 (dd, J = 7.4, 7.2 Hz, 1 H), 6.65 (d, J = 7.4 Hz, 1 H), 4.9 (s, 1 H), 4.57 (d, J = 5.7 Hz, 2 H), 4.32 (s, 4 H), 1.90 (s, 3 H); ^{13}C NMR (67.5 MHz, CD_3CN) δ 167.1, 162.5, 159.0, 149.3, 148.9, 148.6, 148.0, 144.2, 136.0, 134.8, 133.1, 131.1, 130.4, 129.8, 129.1, 127.0, 126.6, 126.3, 126.1, 124.4, 123.3, 122.8, 121.6, 115.3, 115.0, 44.53, 42.4, 37.0, 17.3; MS (ESI) *m*/*z* 482.1 [(M + H)$^+$]. Anal. Calcd for $C_{29}H_{28}FN_5O$ (481.56): C, 72.33; H, 5.86; F, 3.95; N, 14.54. Found: C, 72.50; H, 5.74; F, 4.04; N, 14.33.

23c: white solid; ^{1}H NMR (270 MHz, CD_3OD) δ 7.80 (d, J = 8.2 Hz, 2 H), 7.60 (d, J = 7.7 Hz, 1 H), 7.46 (dd, J = 7.7, 7.4 Hz, 1 H), 7.39 (d, J = 8.2 Hz, 2 H), 7.24−7.08 (m, 11 H), 6.97 (d, J = 7.9 Hz, 1 H), 4.38 (s, 2 H), 3.82 (t, J = 7.8 Hz, 1 H), 3.54 (s, 4 H), 3.34 (s, 3 H), 3.09 (t, J = 6.8 Hz, 2 H), 2.26−2.18 (m, 2 H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 168.5, 152.6, 152.3, 144.6 (2×), 143.7, 132.9, 132.7, 128.2 (4×), 127.5 (4×), 127.2 (2×), 126.9 (2×), 126.6, 126.5, 126.4, 125.9, 122.0, 70.7, 57.6, 44.3, 39.8 (2×), 39.4 (2×), 34.9; MS (ESI) *m*/*z* 589.2 [(M + H)$^+$]. Anal. Calcd for $C_{34}H_{35}F_3N_4O_2$ (588.66): C, 69.37; H, 5.99; F, 9.68; N, 9.52. Found: C, 69.28; H, 6.11; F, 9.46; N, 9.42.

23d: white solid; ^{1}H NMR (270 MHz, CD_3CN) δ 7.69 (d, J = 1.8 Hz, 1 H), 7.66 (d, J = 2.0 Hz, 1 H), 7.29−7.18 (m, 6 H), 7.04 (d, J = 7.9 Hz, 1 H), 6.74−6.69 (m, 2 H), 4.35 (s, 2 H), 3.71 (s, 2 H), 3.52 (dd, J = 7.4, 6.7 Hz, 2 H), 3.07 (t, J = 7.2 Hz, 2 H), 2.84 (t, J = 7.2, 6.9 Hz, 2 H), 2.17 (s, 3 H), 2.15 (s, 3 H), 1.75 (s, 1 H), 1.46−1.35 (m, 2 H), 1.25−1.11 (m, 2 H), 0.83−0.78 (m, 3 H); ^{13}C NMR (67.5 MHz, CD_3CN/CD_3OD) δ 167.1, 154.4, 141.7, 138.6, 138.3, 138.0, 133.7, 133.2, 131.5, 130.6, 130.5, 128.3, 127.3, 127.1, 125.2, 121.4, 44.8, 41.9, 40.8, 34.6, 31.0, 19.6, 18.9, 18.3, 13.0; MS (ESI) *m*/*z* 491.1 [(M + H)$^+$]. Anal. Calcd for $C_{29}H_{35}ClN_4O$ (491.07): C, 70.93; H, 7.18; N, 11.41. Found: C, 71.06; H, 7.15; N, 11.18.

23e: white solid; ^{1}H NMR (270 MHz, CD_3CN) δ 8.42 (d, J = 4.4 Hz, 2 H), 7.69 (d, J = 7.9 Hz, 2 H), 7.57−7.52 (m, 2 H), 7.29−7.24 (m, 5 H), 7.16−7.11 (m, 3 H), 7.08 (s, 1 H), 6.94−6.81 (m, 5 H), 6.66−6.61 (m, 2 H), 4.46 (s, 4 H), 4.20 (s, 2 H), 4.11 (t, J = 5.7 Hz, 2 H), 3.70 (q, J = 5.7 Hz, 2 H), 2.22 (s, 1 H); ^{13}C NMR (67.5 MHz, CD_3CN) δ 167.0, 158.9, 158.8, 158.7, 155.2, 154.0, 149.0, 144.9, 143.8, 136.6, 129.6, 127.4, 127.2, 122.4, 122.2, 120.8, 117.4, 115.2, 114.8, 114.6, 66.3, 54.7, 39.2; MS (ESI) *m*/*z* 589.1 [(M + H)$^+$]. Anal. Calcd for $C_{35}H_{33}FN_6O_2$ (588.67): C, 71.41; H, 5.65; F, 3.23; N, 14.28. Found: C, 71.13; H, 5.64; F, 3.22; N, 14.14.

23f: colorless oil; ^{1}H NMR (270 MHz, CD_3CN) δ 7.66 (t, J = 2.0 Hz, 1 H), 7.63 (t, J = 2.0 Hz, 1 H), 7.25 (d, J = 8.4 Hz, 2 H), 7.14 (dd, J = 5.7, 5.4 Hz, 1 H), 6.84 (d, J = 8.9 Hz, 1 H), 6.75−6.68 (m, 4 H), 6.54 (dd, J = 3.2, 2.5 Hz, 1 H), 6.50 (dd, J = 3.8, 2.2 Hz, 1 H), 4.18 (s, 2 H), 3.92 (q, J = 7.2 Hz, 2 H), 3.74 (s, 3 H), 3.67 (s, 3 H), 3.53 (q, 2 H), 3.12−3.09 (m, 4 H), 2.84 (t, J = 6.9 Hz, 2 H), 2.31 (t, J = 4.9 Hz, 4 H), 2.19 (s, 3 H), 1.30 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (67.5 MHz, CD_3CN) δ 166.6, 155.4, 153.7, 153.6, 151.9, 143.7, 142.8, 133.7, 129.0, 127.5, 127.0, 122.6, 116.7, 115.0, 111.7, 63.5, 55.7, 55.2, 54.7, 47.6 (2×), 45.5, 39.9, 30.0, 14.4; MS (ESI) *m*/*z* 560.2 [(M + H)$^+$]. Anal. Calcd for $C_{32}H_{41}N_5O_4$ (559.70): C, 68.67; H, 7.38; N, 12.51. Found: C, 68.66; H, 7.17; N, 12.53.

23g: white solid; ^{1}H NMR (270 MHz, CD_3CN) δ 7.74−7.67 (m, 3 H), 7.42−7.10 (m, 9 H), 6.95 (ddd, J = 7.4, 7.4, 1.0 Hz, 1 H), 6.78−6.65 (m, 4 H), 5.90 (s, 2 H), 4.11 (s, 2 H), 3.40−3.26 (m, 8 H), 2.96 (t, J = 4.7 Hz, 4 H), 2.36−

2.21 (m, 6 H), 2.01−1.90 (m, 3 H), 1.75−1.65 (m, 2 H); ^{13}C NMR (67.5 MHz, CD_3CN) δ 198.3, 198.0, 176.8, 167.5, 155.4, 148.9, 148.8, 147.8, 144.8, 142.1, 134.84, 134.78, 131.5, 130.5, 129.4, 129.0, 128.7, 28.2, 127.6, 124.3, 123.4, 122.9, 110.4, 108.9, 102.4, 63.4, 53.6, 51.8, 50.8, 48.6, 48.1, 48.0, 40.6, 37.1, 31.8, 27.6,19.0; MS (ESI) *m/z* 673 [(M + H)$^+$]. Anal. Calcd for $C_{40}H_{44}N_6O_4$ (672.82): C, 71.41; H, 6.59; N, 12.49. Found: C, 71.13; H, 6.64; N, 12.30.

29a: white solid; ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.09 (br s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.41−7.15 (m, 14H), 6.94 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 6.79−6.73 (m, 3H), 6.60 (dd, J = 8.2, 1.5 Hz, 1 H), 5.96 (s, 2H), 5.88 (br s, 1H), 5.56 (br s, 1H), 4.31 (s, 2H), 4.13 (s, 2H), 3.93 (s, 2H); ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 149.3, 148.0, 147.0, 145.8, 140.7, 138.4, 137.7, 134.5, 134.2, 130.0, 128.8, 128.2, 128.0, 127.53, 127.47, 127.4, 127.1, 126.2, 126.0, 124.1, 121.0, 120.1, 107.8, 100.7, 46.1, 44.2, 43.7; MS (ESI) *m/z* 605 [(M + H)$^+$]. Anal. Calcd for $C_{35}H_{32}N_4O_4S$: C, 69.52; H, 5.33; N, 9.26; S, 5.30. Found: C, 69.27; H, 5.31; N, 9.03; S, 5.34.

29b: white solid; ^{1}H NMR (270 MHz, CD_3CN) δ 8.30−8.29 (m, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.19−7.12 (m, 2 H), 6.82−6.76 (m, 3 H), 6.56−6.32 (m, 3H), 4.32 (s, 2H), 4.02 (s, 2H), 3.78−3.71 (br m, 4H), 3.67 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 3.27−3.19 (m, 4H); ^{13}C NMR (67.5 MHz, CD_3CN) δ 162.9, 158.8, 158.2, 156.0, 155.3, 146.4, 146.2, 139.9, 130.4, 130.1, 128.8, 127.8, 125.7, 125.7, 121.2, 113.8, 111.4, 111.2, 109.5, 107.2, 56.9, 56.1, 55.9, 48.3, 44.4, 43.6; MS (ESI) *m/z* 632 [(M + H)$^+$]. Anal. Calcd for $C_{32}H_{37}N_7O_5S$: C, 60.84; H, 5.90; N, 15.52; S, 5.08. Found: C, 60.57; H, 5.82; N, 15.37; S, 4.81.

29c: white solid; ^{1}H NMR (270 MHz, CD_3CN) δ 7.74 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.16 (t, J = 7.7 Hz, 2H), 6.85 (t, J = 7.4 Hz, 1H), 6.64 (d, J = 7.7 Hz, 2H), 4.27 (s, 2H), 3.59 (t, J = 4.7 Hz, 4H), 3.12 (t, J = 4.7, 4H), 2.80 (t, J = 6.9 Hz, 2H), 1.43−1.18 (m, 4H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (67.5 MHz, CD_3CN) δ 155.5, 150.6, 146.4, 139.8, 123.0, 129.1, 127.9, 122.4, 121.9, 67.2, 49.1, 48.3, 43.7, 32.3, 20.5, 13.9; MS (ESI) *m/z* 431 [(M + H)$^+$]. Anal. Calcd for $C_{22}H_{30}N_4O_3S$: C, 61.37; H, 7.02; N, 13.01; S, 7.45. Found: C,61.20; H, 6.99; N, 12.79; S, 7.56.

29d: colorless oil; ^{1}H NMR (270 MHz, CD_3CN/CD_3OD) δ 8.44 (d, J = 4.4 Hz, 2 H), 7.74 (d, J = 8.2 Hz, 2 H), 7.58 (t, J = 7.7 Hz, 2 H), 7.37 (d, J = 8.2 Hz, 2 H), 7.25−7.11 (m, 6 H), 6.93−6.63 (m, 7 H), 4.48 (s, 4 H), 4.26 (s, 2 H), 3.92 (t, J = 5.4 Hz, 2 H), 3.21 (t, J = 5.4 Hz, 2 H), 2.51 (br s, 1 H); ^{13}C NMR (67.5 MHz, CD_3CN/CD_3OD) δ 160.1, 159.4, 156.6, 155.3, 150.0, 147.2, 146.5, 139.8, 137.8, 130.5, 129.0, 127.9, 123.54, 123.38, 122.0, 116.2, 116.0, 115.5, 67.2, 55.7, 47.8, 43.5; MS (ESI) *m/z* 625 [(M + H)$^+$]. Anal. Calcd for $C_{34}H_{33}FN_6O_3S$: C, 65.37; H, 5.32; F, 3.04; N, 13.45; S, 5.13. Found: C, 65.16; H, 5.35; F, 3.23; N, 13.19; S, 5.15.

29e: white solid; ^{1}H NMR (270 MHz, CD_3CN) δ 7.74 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.18−6.62 (m, 5H), 4.27 (s, 2H), 3.84−3.55 (m, 3H), 3.16−3.12 (m, 4H), 2.96−2.75 (m, 2H), 2.32−2.29 (br t, 3H), 2.19 (s, 3H), 1.91−1.72 (m, 2H), 1.56−1.44 (m, 1H); ^{13}C NMR (67.5 MHz, CD_3CN) δ 156.0, 150.7, 146.8, 140.2, 130.3, 129.4, 128.2, 122.8, 122.2, 78.5, 69.0, 55.9, 48.7, 48.6, 48.3, 46.7, 29.7, 26.7; MS (ESI) *m/z* 472 [(M + H)$^+$]. Anal. Calcd for $C_{24}H_{33}N_5O_3S\cdot H_2O$: C, 58.87; H, 7.20; N, 14.30; S, 6.55. Found: C, 58.66; H, 6.82; N, 13.97; S, 6.60.

29f: white solid; ^{1}H NMR (270 MHz, CD_3CN) δ 8.38−8.32 (m, 2H), 7.68 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 7.7 Hz, 1H), 7.30 (d, J = 8.2 Hz, 3H), 6.86−6.82 (m, 4H), 6.68−6.61 (m, 3H), 5.86 (s, 2H), 4.37 (s, 2H), 4.35 (s, 2H), 1.34−1.23 (m, 3H); ^{13}C NMR (67.5 MHz, CD_3CN) δ 159.7, 154.9, 152.6, 148.1, 147.7, 147.6, 146.9, 144.7, 138.8, 135.7, 135.5, 131.1, 127.6, 127.0, 125.1, 123.9, 121.5, 115.5, 108.3, 108.0, 101.3, 63.8, 46.4, 44.2, 42.2, 14.3; MS (ESI) *m/z* 573.9 [(M + H)$^+$]. Anal. Calcd for $C_{30}H_{31}N_5O_5S\cdot H_2O$: C, 60.90; H, 5.62; N, 11.84. Found: C, 60.89; H, 5.35; N, 11.71.

29g: pale-yellow solid; ^{1}H NMR (270 MHz, CD_3CN) δ 7.70 (d, J = 8.4 Hz, 2H), 7.35 (s, J = 8.2 Hz, 2H), 7.15 (dd, J = 8.9, 7.2 Hz, 2H), 6.89−6.82 (m, 2H), 6.66−6.59 (m, 5H), 5.83 (br s, 1H), 4.14 (s, 2H), 3.50−3.42 (m, 4H), 3.34−3.22 (m, 6H), 3.28 (s, 6H), 2.85 (t, J = 6.9 Hz, 2H), 2.80 (s, 3H), 1.68−1.57 (m, 2H); ^{13}C NMR (67.5 MHz, CD_3CN) δ 149.3, 138.4, 129.0, 127.8, 126.8, 122.1, 116.0, 115.1, 114.8, 112.3, 70.9, 58.1, 49.5, 49.3, 41.0, 37.6, 26.2; MS (ESI) *m/z* 586 [(M + H)$^+$]. Anal. Calcd for $C_{30}H_{40}FN_5O_4S$: C, 61.52; H, 6.88; F, 3.24; N, 11.96; S, 5.47. Found: C, 61.50; H, 6.81; F, 3.38; N, 11.93; S, 5.64.

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References and Notes

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