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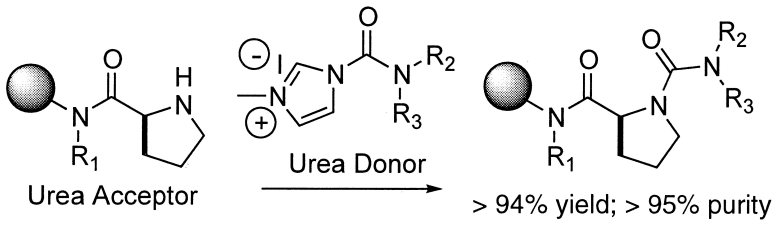

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A General Method for the Solid-Phase Synthesis of Unsymmetrical Tri- and Tetrasubstituted Ureas

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A general method for the preparation of unsymmetrical di, tri-, and tetrasubstituted ureas on polymer supports is presented. Polymer-bound primary and secondary amines react with imidazolium salts (urea donors), which are generated from the reaction of *N*,*N*′-carbonyldiimidazole (CDI) with primary and secondary amines followed by alkylation with MeI to give tri- and tetrasubstituted ureas in excellent yields (76−98%) and purities (80−99%).

Introduction

The efficient functionalization of organic molecules plays an important role in the solid-phase synthesis of large compound libraries for drug discovery. The urea moiety has been found in many biologically active compounds.[1] Formation of ureas on polymer supports has been well documented;[2,3] however, there are only a few solid-phase methods reported for the assembly of unsymmetrical tri- or tetrasubstituted ureas (Scheme 1). Brase et al. reported the synthesis of the trisubstituted ureas by the N-alkylation of the corresponding disubstituted ureas under strong basic conditions on solid phase utilizing the triazene linker.[3b] Scialdone et al. reported the synthesis of trisubstituted ureas by the reaction of secondary amines with isocyanates generated in situ by thermolytic cleavage of polymer-bound oxime carbamates.[4] Wang et al. has reported the reaction of polymer-bound carbamoyl chlorides with primary or secondary amines, affording ureas.[5] In the last two cases, phosgene or triphosgene was needed to prepare the necessary intermediates. The significant drawbacks for these two methods include the lethal toxicity of phosgene and the instability of the carbamoyl chloride intermediates. Therefore, we were motivated to develop a new general method for synthesis of unsymmetrical tri- and tetrasubstituted ureas on polymer supports. Among many methods available for the generation of tetrasubstituted ureas in solution, a method reported by Batey and co-workers was particularly attractive.[6] In this report, carbamoyl imidazolium salts, prepared from the reaction of *N*,*N*′-carbonyldiimidazole (CDI) with a secondary amine followed by alkylation with MeI, reacted with secondary amines to afford tetrasubstituted ureas in good yields. We report herein the successful translation of this solution-phase strategy to the solid-phase synthesis of highly substituted ureas.

Results and Discussion

Urea formation on solid phase could be achieved via two different approaches (Scheme 1). In route A, the urea donor (providing a carbonyl group) is assembled on the solid phase. The polymer-bound urea donors are synthesized as isocyanates,[7] *p*-nitrophenylcarbamates,[8] and carbamoyl chlorides[5] forms. Urea products are produced by coupling the polymer-bound urea donor with an amine (acceptor) in solution. In route B, the urea donor is prepared in solution and coupled to a polymer-bound amine to afford the desired urea products. This strategy is analogous to the preferred C to N method of peptide synthesis, which affords higher yields and purities of the desired peptides than N to C methods. Route B has been widely used in the synthesis of di- or trisubstituted ureas by reacting the polymer-bound primary or secondary amine with the commercially available isocyanates,[3,9] isocyanates prepared in situ,[10] or 4-nitrophenylcarbamates.[11] Unfortunately, these methods are not suitable for the synthesis of tetrasubstituted ureas. We thus explored both routes A and B to synthesize highly substituted ureas on polymer support by use of carbomoyl imadazolium salts as urea donors.

We initially explored the formation of disubstituted ureas, as a model study, using route A (Scheme 2). The polymer-bound amines **6** were obtained by loading *p*-toluidine, 4-methoxybenzylamine, and cyclopentylamine onto 4-(4-formyl-3-methoxyphenoxy)butyryl Nova Gel (FMP Resin) by way of reductive amination. The loading of these amines were determined at 0.50 mmol/g for **6a**, 0.47 mmol/g for **6b**, and 0.53 mmol/g for **6c** by coupling with Fmoc-Gly-OH followed by spectroscopic analysis of the Fmoc chromophore.[12] Conversion of **6** to the polymer-bound urea donor **9** followed the strategy discussed for the solution-phase transformation of amines into carbamoyl imidazolium salts (Scheme 2). Polymer-bound amines reacted with CDI in THF to provide carbamoyl imidazoles **7**. IR spectroscopy was found to be useful for characterizing the formation of the polymer-bound carbamoyl imidazole, which shows a characteristic absorption around 1695 cm^{-1}. Analysis of the IR spectra of **7** showed that **7b** and **7c** were formed, but no **7a** was obtained. The support-bound intermediates were further characterized by cleavage of an analytical amount of each compound from the polymer support and analysis by NMR and MS. The yields of **8b** and **8c** were determined to be 45% and 56%, respectively, based on the recovery of the

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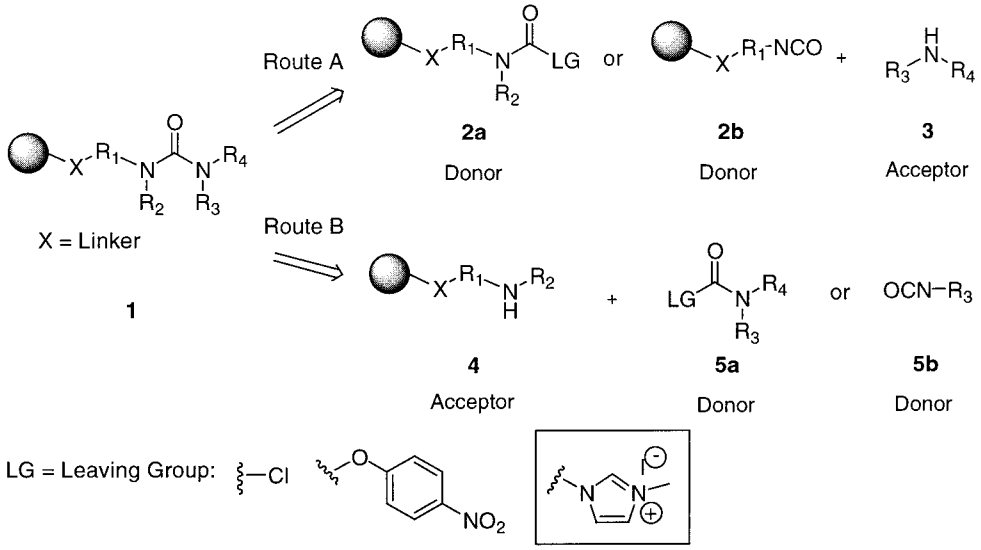
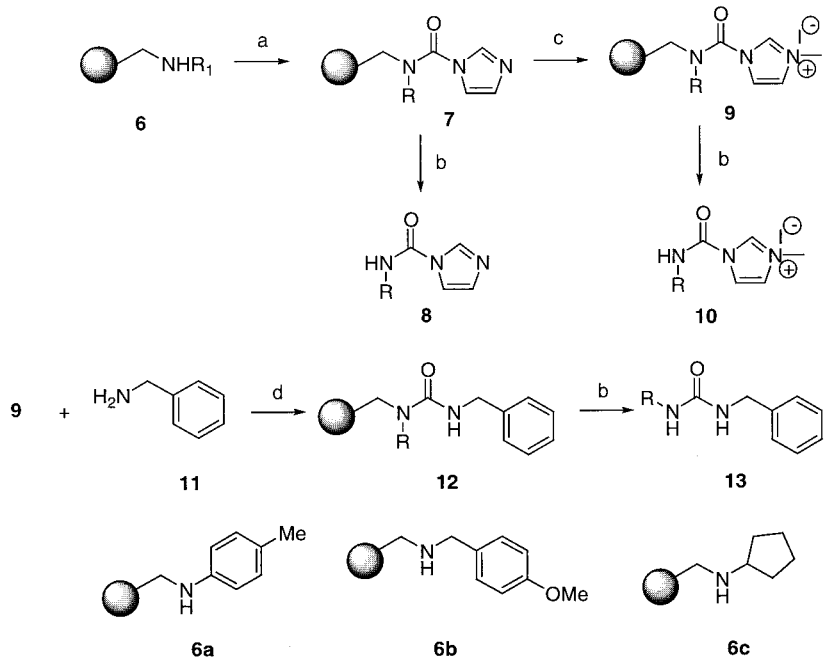
Scheme 1. Solid-Phase Synthesis of Ureas



Scheme 2. Synthesis of Disubstituted Ureas Using Route A[a]



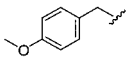
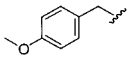
[a] (a) CDI, THF, room temp, 24h; (b) 50% TFA in CH_2Cl_2, room temp, 1 h; (c) MeI, THF, room temp, 24 h; (d) Et_3N, CH_2Cl_2, room temp, 24 h.

products with respect to the loading of FMP resin. The results of MS and NMR analysis of the cleaved products are consistent with IR analysis results in that none of the desired **8a** was formed. N-alkylation of the carbamoyl imidazoles with MeI in acetonitrile produced polymer-bound carbamoyl imidazolium salts **9**. The formation of **9b** and **9c** were confirmed by the cleavage of an analytical amount of each compound from the polymer support and MS and NMR analysis of products **10b** and **10c**. The yield of the transformation from **7** to **9** was greater than 90%. Addition of benzylamine to the suspensions of polymer-bound imidazolium salts **9b** and **9c** in CH_2Cl_2 with triethylamine (TEA), followed by cleavage with TFA, afforded disubstituted ureas **13b** in 10% yield and **13c** in 8% yield, respectively, based on the MS and HPLC analysis (Table 1). The low yields of **13** obtained by route A can be attributed to the poor yields of the resin-bound carbamoyl imidazoles **7**, presumably because of steric hindrance from being close to the polymer backbone. We also observed partial decomposition of imidazolium salts **9** under our coupling conditions. Attempts to further optimize route A are ongoing.

Next we focused on the synthesis of ureas using route B (Scheme 3). The donor carbomyl imidazolium salt of benzylamine **14** was prepared according to literature methods.[6] The reactions of amines **6a**−**c** with carbamoyl imidazolium salt **14** were carried out in CH_2Cl_2 with TEA at room temperature for 24 h. The resin-bound disubstituted ureas were free of contaminating side products and provided ureas **13a**−**c** in nearly quantitative yields (92−98%) and purities (98−99%) (Table 1).

After establishing a protocol for the efficient coupling of polymer-bound amines with carbamoyl imidazolium salts,

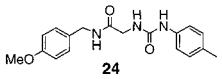
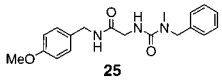
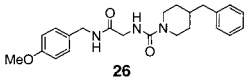
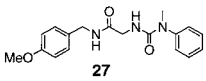
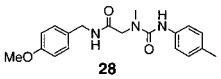
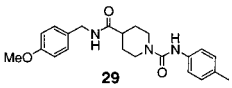
Table 1. Solid-Phase Synthesis of Model Disubstituted Ureas **13**

Product	R	Route	Crude Purity (%)[a]	Yield (%)[b]
13a		A		0
13a		B	99	98
13b		A	80	10
13b		B	98	92
13c		A	56	8
13c		B	99	98

[a] Crude purity based on the HPLC peak area at 220 nm. [b] Yields based on the recovered products cleaved from the polymer supports with respect to loading of amines **6a**−**c**.

we set out to apply this methodology to the synthesis of more highly substituted ureas. Polymer-bound amines **15**−**19**, as urea acceptors, were prepared by coupling amines **6b** and **6c** with Fmoc-Gly-OH, Fmoc-Sar-OH, Fmoc-Isn-OH, Fmoc-Pro-OH, and Fmoc-Nip-OH by HATU and DIEA followed by removal of the Fmoc groups with 20% piperidine in DMF (Figure 1). The urea donors **20**−**23** were synthesized from *p*-toluidine, *N*-benzylmethylamine, 4-benzylpiperidine, and *N*-methylaniline according to the literature procedure.[6] Table 2 showed the results of the synthesis of di- and trisubstituted ureas. The reactions of donors **20**−**23** with primary amine **15** provided disubstituted urea **24** and trisubstituted ureas **25**−**27** in excellent yields (73−98%). Donor **20** was coupled with amines **16** and **17**, affording trisubstituted ureas **28** and **29** in 90% and 98% yields and 95% and 98% purities, respectively (Table 2). Finally, we investigated the synthesis of tetrasubstituted ureas from the coupling reactions of the urea donors derived from secondary amines with polymer-bound secondary amines (Table 3). The coupling of amine **16** with three urea donors **21**−**23** provided the corresponding tetrasubstituted ureas (**30**−**32**) in good yield (76−81%) and

Table 2. Solid-Phase Synthesis of Di- and Trisubstituted Ureas[a]

acceptor	donor	urea	crude purity (%)[b]	yield (%)[c]
15	**20**	 **24**	98	98
15	**21**	 **25**	84	78
15	**22**	 **26**	80	74
15	**23**	 **27**	81	73
16	**20**	 **28**	95	90
17	**20**	 **29**	98	98

[a] Ureas were synthesized using route B. [b] Crude purity based on HPLC peak area at 220 nm. [c] Isolated yield based on initial loading of **6b**.

purities (80−87%). The cyclic secondary amines (**17**−**19**) lead to formation of tetrasubstituted ureas (**33**−**39**) in high yields (85−95%) and excellent purities (90−98%), even for relative sterically hindered proline **18**.

Conclusions

A new general method for the synthesis of highly substituted ureas on polymer support has been developed. This method utilizes carbamoyl imidazolium salt of a primary or a secondary amine as a urea donor that can subsequently react with a polymer-bound primary or a secondary amine to provide the respective di-, tri-, or tetrasubstituted ureas in excellent yields and purities. The use of commercially available CDI to prepare urea donors obviates the need for toxic and unstable phosgene or triphosgene in previous literature methods.

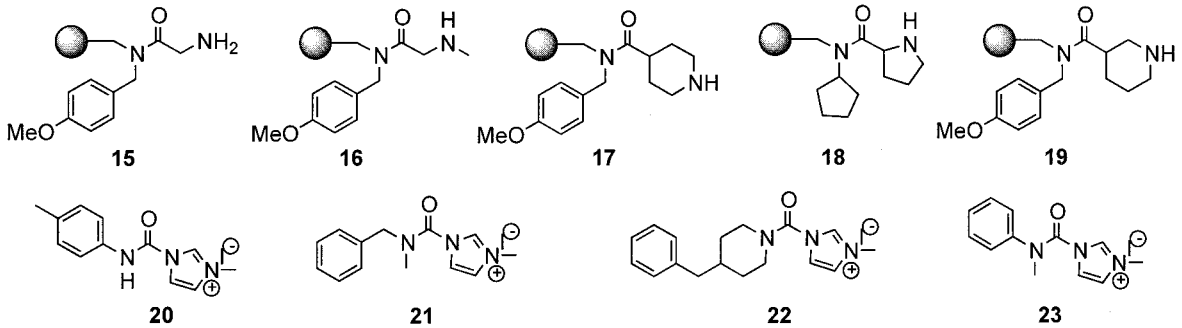
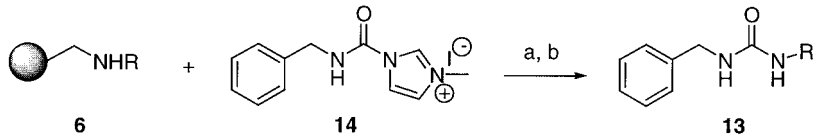


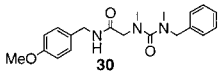
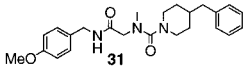
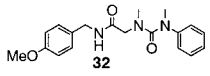
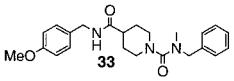
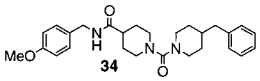
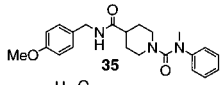
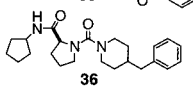
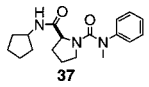
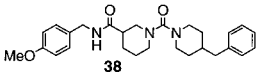
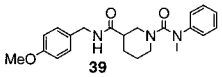
Figure 1. Urea donors and acceptors.

Scheme 3. Solid-Phase Synthesis of Disubstituted Ureas Using Route B[a]



[a] (a) Et_3N, CH_2Cl_2, room temp, 24 h; (b) 1:1 TFA/CH_2Cl_2, room temp, 1 h.

Table 3. Solid-Phase Synthesis of Tetrasubstituted Ureas[a]

acceptor	donor	urea	crude purity (%)[b]	yield (%)[c]
16	21	 **30**	80	76
16	22	 **31**	85	80
16	23	 **32**	87	81
17	21	 **33**	90	87
17	22	 **34**	97	92
17	23	 **35**	91	85
18	22	 **36**	96	94
18	23	 **37**	97	96
19	22	 **38**	95	95
19	23	 **39**	98	95

[a] Ureas were synthesized using route B. [b] Crude purity based on HPLC peak area at 220 nm. [c] Isolated yield based on initial loading of **6b** or **6c**.

Experimental Section

4-(4-Formyl-3-methoxyphenoxy)butyryl NovaGel (Nova-FMP resin, loading of 0.55 mmol/g) was purchased from Novabiochem. Commercially available starting materials and reagents were purchased from Aldrich. Heated reactions were performed in a Quest 210 manufactured by Argonaut Technologies, while all other reactions were performed in bottom-and-top capped polypropylene-fritted tubes manufactured by Bio-Rad Laboratories. Reactions in the polypropylene tubes were shaken using a Labquake tube rotor/rocker manufactured by Thermolyne. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian 300 MHz spectrometer. Chemical shifts are given in ppm with respect to internal TMS. High-resolution mass spectra were recorded using electrospray ionization. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. HPLC analyses were performed on a Hewlett-Packard 1090 liquid chromatography system using a photodiode array detector and ODS-A 5 mm (C18, 4.5 mm × 50 mm) YMC slim-bore column with a gradient of 0% acetonitrile/water containing 0.1% TFA to 100% acetonitrile over 8 min at 3 mL/min flow rate. Peak areas were integrated at 220 and 254 nm. HPLC purification was performed on a Gilson 215 liquid handler using a dual-wavelength UV/vis detector and 10 μm (C18, 250 mm × 22 mm) VYDAC column with a gradient of 0% acetonitrile/water containing 0.1% TFA to 100% acetonitrile over 20 min at 15 mL/min flow rate.

Procedure for the Preparation of Polymer-Bound Amines 6a−c. Nova-FMP resin (100−200 mesh, 1.0 g, loading of 0.55 mmol/g) was mixed with amine (5 equiv) and $NaB(OAc)_3H$ (5 equiv) in 20 mL of CH_2Cl_2. The suspension was shaken at room temperature for 12 h. The resin was washed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×), and dried in vacuo. The loading of these amines were determined to be 0.50 mmol/g for **6a**, 0.47 mmol/g for **6b**, and 0.53 mmol/g for **6c**, based on spectroscopic analysis of the Fmoc chromophore after coupling 50 mg of each polymer-bound amine with Fmoc-Gly-OH (5 equiv) using HATU (5 equiv) and DIEA (10 equiv) in 1 mL of CH_2Cl_2.

General Procedure for the Retrieval of Product from the Solid Support. Polymer-bound urea **12** (route A) (100 mg) was suspended in 2 mL of 1:1 TFA/CH_2Cl_2 and shaken at room temperature for 1 h, and the resin was washed using CH_2Cl_2 (2 × 2 mL). The combined filtrates were evaporated to dryness. Crude purities of all products are based on the HPLC analysis at 220 nm of the crude material. Percent yields of **13**, **24**, **28**, **29**, **34**, and **36**−**39** are based on recovered products in respect to loading of amines **6**. Isolated yields of **25**−**27**, **30**−**33**, and **35** are given after HPLC purification.

General Procedure for the Preparation of Urea Donor on Polymer Support. To a suspension of polymer-bound amine **6b** (0.2 g, 0.094 mmol) in THF (5 mL) was added CDI (0.47 mmol). The mixture was refluxed for 24 h. The polymer was filtered, washed with DMF (4×) and CH_2Cl_2 (4×), and dried in vacuo to give **7b** as a slightly yellow resin. IR (KBr): 3058, 3024, 2919, 2869, 1720, 1692 (carbamoyl imidazole), 1671, 1612, 1511, 1492, 1452, 1415, 1248, 1108 cm^{-1}. Compound **7b** was then treated with MeI (0.94 mmol) in acetonitrile (5 mL) at room temperature for 24 h. The polymer was filtered, washed with DMF (3×) and CH_2Cl_2 (3×), and dried in vacuo to give **9b** as a slight yellow resin.

Procedure for the Preparation of Polymer-Bound Amino Amides. Polymer-bound amine **7b** (0.2 g, 0.09 mmol) was suspended in 10 mL of CH_2Cl_2. Fmoc-Gly-OH (5 equiv), HATU (5 equiv), and DIEA (10 equiv) were added. The mixture was shaken at room temperature for 12 h. The polymer was filtered and washed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×). Fmoc deprotection of the resin was accomplished with 20% piperidine in DMF (60 min), followed by washing with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×).

General Procedure for the Formation of Ureas on Solid Supports (Route A). To a suspension of polymer **9b** in 10 mL of CH_2Cl_2 was added benzylamine **11** (0.5 mmol) and triethylamine (0.5 mmol). The mixture was shaken at room temperature for 24 h. The polymer was filtered, washed with MeOH (3×), DMF (2×), and CH_2Cl_2 (3×) and dried in vacuo to give **12b** as a slightly yellow resin.

General Procedure for the Formation of Ureas on Solid Support (Route B). To a suspension of polymer-bound amine **6b** (0.1 mmol) in 10 mL of CH_2Cl_2 (or 10 mL of 1:1 CH_3CN/CH_2Cl_2 if the imidazolium salt was not soluble in CH_2Cl_2) was added the carbamoyl imidazolium salts **14** (0.5 mmol) and triethylamine (0.5 mmol). The mixture was shaken at room temperature for 24 h. The polymer was filtered, washed with MeOH (3×), DMF (3×), and CH_2Cl_2

(2×), and dried in vacuo. The urea product was cleaved from the polymer according to the general procedure described above.

The following compounds were prepared according to the general procedures described above.

***N*-(4-Methoxybenzyl)-1*H*-imidazole-1-carboxamide 8b:** 45% yield; ^{1}H NMR (DMSO-d_6) δ 9.02−8.98 (t, J = 5.5 Hz, 1H), 8.26 (s, 1H), 7.69−7.68 (d, J = 1.4 Hz, 1H), 7.26−6.86 (dd, J = 8.4 Hz, 4H), 7.01 (s, 1H), 4.38−4.36 (d, J = 5.8 Hz, 2H), 3.69 (s, 3H); ESI-MS *m*/*z* 232.2 $[M + H]^+$.

***N*-Cyclopentyl-1*H*-imidazole-1-carboxamide 8c:** 56% yield; ^{1}H NMR ($CDCl_3$) δ 10.07 (s, 1H), 9.27−9.25 (d, J = 6.2 Hz, 1H), 7.86 (s, 1H), 7.28 (s, 1H), 4.28−4.22 (m, 1H), 2.10−1.97 (m, 2H), 1.81−1.59 (m, 6H); ESI-MS *m*/*z* 180.1 $[M + H]^+$.

***N*-Benzyl-*N*′-(4-methylphenyl)urea 13a:** Crude purity 99%; 98% yield; ^{1}H NMR ($CDCl_3$) δ 7.35−7.22 (m, 5H), 7.16−7.10 (d, J = 1.8 Hz, 4H), 6.23 (br, 1H), 5.00 (br, 1H), 4.43−4.45 (d, J = 5.5 Hz, 2H), 2.31 (s, 3H); APCI-MS *m*/*z* 241.1 $[M + H]^+$. HRMS Calcd for $C_{15}H_{17}N_2O$ $[M + H]^+$: 241.1341. Found: 241.1348.

***N*-Benzyl-*N*′-(4-methoxybenzyl)urea 13b:** Crude purity 98%; 92% yield; ^{1}H NMR (CD_3OD) δ 7.20−7.29 (m, 7H), 6.86 (d, J = 8.8 Hz, 2H), 4.33 (s, 2H), 4.26 (s, 2H), 3.76 (s, 3H); ESI-MS *m*/*z* 271.2 $[M + H]^+$. HRMS Calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$: 271.1447. Found: 271.1453.

***N*-Benzyl-*N*′-cyclopentylurea 13c:** Crude purity 99%; 98% yield; ^{1}H NMR ($CDCl_3$) δ 7.21−7.32 (m, 5H), 4.60−5.20 (b, 2H), 4.31 (s, 2H), 3.97−3.89 (m, 1H), 1.93−1.84 (m, 2H), 1.66−1.47 (m, 4H), 1.35−1.28 (m, 2H); APCI-MS *m*/*z* 219.2 $[M + H]^+$. HRMS Calcd for $C_{13}H_{19}N_2O$ $[M + H]^+$: 219.1497. Found: 219.1512.

***N*-(4-Methoxybenzyl)-2-[(4-toluidinocarbonyl)amino]-acetamide 24:** Crude purity 98%; 98% yield; ^{1}H NMR (CD_3OD) δ 7.24−7.20 (m, 4H), 7.07−7.05 (d, J = 8.4 Hz, 2H), 6.87−6.84 (d, J = 8.8 Hz, 2H), 4.34 (s, 2H), 3.86 (s, 2H), 3.76 (s, 3H), 2.26 (s, 3H); ESI-MS *m*/*z* 328.2 $[M + H]^+$, 350.2 $[M + Na]^+$. HRMS Calcd for $C_{18}H_{22}N_3O_3$ $[M + H]^+$: 328.1661. Found: 328.1674.

2-({[Benzyl(methyl)amino]carbonyl}amino)-*N*-(4-methoxybenzyl)acetamide 25: Crude purity 84%; 78% yield; ^{1}H NMR (CD_3OD) δ 7.29−7.20 (m, 7H), 6.87−6.84 (d, J = 8.8 Hz, 2H), 4.51 (s, 2H), 4.33 (s, 2H), 3.85 (s, 2H), 3.76 (s, 3H), 2.87 (s, 3H); ESI-MS *m*/*z* 342.2 $[M + H]^+$, 364.2 $[M + Na]^+$. HRMS Calcd for $C_{19}H_{24}N_3O_3$ $[M+H]^+$: 342.1818. Found: 342.1808.

4-Benzyl-*N*-{2-[(4-methoxybenzyl)amino]-2-oxoethyl}-1-piperidinecarboxamide 26: Crude purity 80%; 74% yield; ^{1}H NMR ($CDCl_3$) δ 7.32−7.12 (m, 7H), 6.87−6.84 (d, J = 8.8 Hz, 2H), 4.38 (d, J = 5.8 Hz, 2H), 3.91 (m, 4H), 3.79 (s, 3H), 2.77 (m, 4H), 2.54−2.52 (d, J = 6.9 Hz, 2H), 1.68−1.64 (m, 2H), 1.18−1.13 (m, 2H); ESI-MS *m*/*z* 418.4 $[M + Na]^+$. HRMS Calcd for $C_{23}H_{30}N_3O_3$ $[M + H]^+$: 396.2287. Found: 396.2263.

***N*-(4-Methoxybenzyl)-2-{[(methylanilino)carbonyl]-amino}acetamide 27:** Crude purity 81%; 73% yield; ^{1}H NMR ($CDCl_3$) δ 7.47−7.17 (m, 7H), 6.88−6.85 (d, J = 8.8 Hz, 2H), 6.65 (br, 1H), 5.03 (br, 1H), 4.37−4.35 (d, J = 5.5 Hz, 2H), 3.87−3.85 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.63 (br, 2H), 3.25 (s, 3H); ESI-MS *m*/*z* 328.3 $[M + H]^+$, 350.3 $[M + Na]^+$. HRMS Calcd for $C_{18}H_{22}N_3O_3$ $[M + H]^+$: 328.1661. Found: 328.1634.

***N*-(4-Methoxybenzyl)-2-[methyl(4-toluidinocarbonl)-amino]acetamide 28:** Crude purity 95%; 90% yield; ^{1}H NMR (CD_3OD) δ 7.24−7.20 (m, 4H), 7.09−7.06 (d, J = 8 Hz, 2H), 6.86−6.84 (d, J = 8.8, 2H), 4.34 (s, 2H), 4.05 (s, 2H), 3.76 (s, 3H), 3.07 (s, 3H), 2.28 (s, 3H); ESI-MS *m*/*z* 342.2 $[M + H]^+$, 364.2 $[M + Na]^+$. HRMS Calcd for $C_{19}H_{24}N_3O_3$ $[M + H]^+$: 342.1818. Found: 342.1797.

***N*^{4}-(4-Methoxybenzyl)-*N*^{1}-(4-methylphenyl)-1,4-piperidinedicarboxamide 29:** Crude purity 98%; 98% yield; ^{1}H NMR (CD_3OD) δ 7.21−7.18 (m, 4H), 7.08−7.05 (d, J = 8 Hz, 2H), 6.88−6.84 (d, J = 8.4, 2H), 4.29 (s, 2H), 4.22−4.15 (m, 2H), 3.76 (s, 3H), 2.95−2.85 (m, 2H), 2.50−2.27 (m, 1H), 2.27 (s, 3H), 1.84−1.66 (m, 4H); ESI-MS *m*/*z* 382.2 $[M + H]^+$, 404.4 $[M + Na]^+$. HRMS Calcd for $C_{22}H_{28}N_3O_3$ $[M + H]^+$: 382.2131. Found: 382.2129.

2-[{[Benzyl(methyl)amino]carbonyl(methyl)amino]-*N*-(4-methoxybenzyl)acetamide 30: Crude purity 80%; 76% yield; ^{1}H NMR (CD_3OD) δ 7.32−7.25 (m, 5H), 7.21−7.18 (d, J = 8.8 Hz, 2H), 6.86−6.83 (d, J = 8.8 Hz, 2H), 4.40 (s, 2H), 4.30 (s, 2H), 3.86 (s, 2H), 3.76 (s, 3H), 2.92 (s, 3H), 2.76 (s, 3H); ESI-MS *m*/*z* 356.2 $[M + H]^+$, 378.2 $[M + Na]^+$. HRMS Calcd for $C_{20}H_{26}N_3O_3$ $[M + H]^+$: 356.1974. Found: 356.1989.

4-Benzyl-*N*-{2-[(4-methoxybenzyl)amino]-2-oxoethyl}-*N*-methyl-1-piperidinecarboxamide 31: Crude purity 85%; 80% yield; ^{1}H NMR ($CDCl_3$) δ 7.64 (br, 1H), 7.32−7.11 (m, 7H), 6.86−6.84 (d, J = 8.8 Hz, 2H), 4.40−4.38 (d, J = 5.9 Hz, 2H), 4.10−4.01 (br, 2H), 3.85 (s, 2H), 3.79 (s, 3H), 3.70−3.65 (m, 2H), 2.89 (s, 3H), 2.78−2.70 (m, 2H), 2.55−2.53 (d, J = 7 Hz, 2H), 1.71−1.56 (m, 3H), 1.25−1.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 164.5, 159.1, 139.9, 129.9, 129.0, 128.9, 128.3, 126.1, 114.1, 55.3, 54.2, 47.1, 42.95, 42.98, 38.2, 38.1, 31.8; ESI-MS *m*/*z* 410.4 $[M + H]^+$, 432.4 $[M + Na]^+$. HRMS Calcd for $C_{24}H_{32}N_3O_3$ $[M + H]^+$: 410.2443. Found: 410.2433.

***N*-(4-Methoxybenzyl)-2-{methyl[(methylanilino)carbonyl]-amino}acetamide 32:** Crude purity 87%; 81% yield; ^{1}H NMR ($CDCl_3$) δ 7.37−7.07 (m, 7H), 6.89−6.85 (dd, J = 6.6, 2.2 Hz, 2H), 5.64 (br, 1H), 4.37−4.35 (d, J = 5.8 Hz, 2H), 3.89 (s, 2H), 3.81 (s, 3H), 3.22 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 162.5, 159.1, 145.6, 129.9, 129.0, 125.7, 124.7, 114.1, 55.3, 54.3, 43.0, 40.2, 37.8; ESI-MS *m*/*z* 342.3 $[M + H]^+$. HRMS Calcd for $C_{24}H_{32}N_3O_3$ $[M + H]^+$: 342.1817. Found: 342.1806.

***N*^{1}-Benzyl-*N*^{4}-(4-methoxybenzyl)-*N*^{1}-methyl-1,4-piperidinedicarboxamide 33:** Crude purity 90%; 87% yield; ^{1}H NMR (CD_3OD) δ 7.36−7.21 (m, 5H), 7.20−7.17 (d, J = 8.5 Hz, 2H), 6.88−6.84 (d, J = 8.8, 2H), 4.39 (s, 2H), 4.28 (s, 2H), 3.78 (s, 3H), 3.75−3.72 (m, 2H), 2.83−2.79 (m, 2H), 2.76 (s, 3H), 2.42−2.38 (m, 1H), 1.78−1.70 (m, 4H); ESI-MS *m*/*z* 396.2 $[M + H]^+$, 418.2 $[M + Na]^+$. HRMS Calcd for $C_{23}H_{30}N_3O_3$ $[M + H]^+$: 396.2287. Found: 396.2278.

1-[(4-Benzyl-1-piperidinyl)carbonyl]-*N*-(4-methoxybenzyl)-4-piperidinecarboxamide 34: Crude purity 97%; 92% yield; ^{1}H NMR ($CDCl_3$) δ 7.32−7.12 (m, 7H), 6.88−6.85

(d, $J = 8.8$, 2H), 5.91 (t, $J = 5.1$ Hz, 1H), 4.38−4.36 (d, $J = 5.5$ Hz, 2H), 3.80 (s, 3H), 3.72−3.65 (m, 4H), 2.86−2.71 (m, 4H), 2.55−2.53 (d, $J = 6.9$ Hz, 2H), 2.40−2.25 (m, 1H), 1.88−1.64 (m, 7H), 1.23−1.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 164.5, 159.2, 139.9, 129.6, 129.2, 129.1, 128.3, 126.0, 114.2, 55.3, 54.3, 47.3, 46.7, 43.3, 43.0, 38.2, 31.9, 28.5; ESI-MS *m*/*z* 450.4 $[M + H]^+$, 472.4 $[M + Na]^+$. HRMS Calcd for $C_{23}H_{30}N_3O_3$ $[M + H]^+$: 450.2756. Found: 450.2757.

***N*^{4}-(4-Methoxybenzyl)-*N*^{1}-methyl-*N*^{1}-phenyl-1,4-piperidinedicarboxamide 35:** Crude purity 91%; 85% yield; ^{1}H NMR ($CDCl_3$) δ 7.37−7.08 (m, 7H), 6.86−6.83 (d, $J = 8.8$, 2H), 5.80 (t, $J = 4.8$ Hz, 1H), 4.33−4.32 (d, $J = 5.5$ Hz, 2H), 3.85−3.80 (m, 1H), 3.79 (s, 3H), 3.22 (s, 3H), 2.65−2.56 (m, 2H), 2.19−2.14 (m, 1H), 1.69−1.64 (m, 2H), 1.54−1.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 161.6, 159.2, 146.3, 129.8, 129.6, 125.2, 124.0, 114.2, 55.3, 45.5, 43.2, 43.1, 39.7, 28.1; ESI-MS *m*/*z* 382.3 $[M + H]^+$. HRMS Calcd for $C_{22}H_{28}N_3O_3$ $[M + H]^+$: 382.2130. Found: 382.2153.

1-[(4-Benzyl-1-piperidinyl)carbonyl]-*N*-cyclopentyl-2-pyrrolidinecarboxamide 36: Crude purity 96%; 94% yield; ^{1}H NMR ($CDCl_3$) δ 7.31−7.11 (m, 5H), 6.71−6.69 (d, $J = 7.0$ Hz, 1H), 4.49−4.44 (m, 1H), 4.25−4.10 (m, 2H), 3.85−3.70 (m, 2H), 3.47−3.38 (m, 2H), 2.84−2.65 (m, 2H), 2.55−2.53 (d, $J = 7$ Hz, 2H), 2.18−1.13 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 162.8, 139.8, 129.0, 128.3, 126.0, 61.5, 51.5, 51.3, 46.6, 46.4, 43.0, 38.1, 32.83, 32.78, 32.3, 31.6, 28.9, 25.6, 23.7; ESI-MS *m*/*z* 384.4 $[M + H]^+$, 406.4 $[M + Na]^+$. HRMS Calcd for $C_{23}H_{34}N_3O_2$ $[M + H]^+$: 384.2651. Found: 384.2669.

***N*^{2}-Cyclopentyl-*N*^{1}-methyl-*N*^{1}-phenyl-1,2-pyrrolidinedicarboxamide 37:** Crude purity 97%; 96% yield; ^{1}H NMR ($CDCl_3$) δ 7.40−7.17 (m, 5H), 6.54 (br, 1H), 4.47−4.42 (t, $J = 7.5$ Hz, 1H), 4.22−4.15 (m, 1H), 3.24 (s, 3H), 3.06−2.98 (m, 1H), 2.63−2.54 (m, 1H), 2.04−1.85 (m, 3H), 1.78−1.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 160.4, 145.2, 129.7, 125.8, 125.5, 61.6, 51.4, 49.9, 40.0, 32.9, 28.7, 25.3, 23.74, 23.72; ESI-MS *m*/*z* 316.3 $[M + H]^+$, 338.3 $[M + Na]^+$. HRMS Calcd for $C_{18}H_{26}N_3O_2$ $[M + H]^+$: 316.2025. Found: 316.2047.

1-[(4-Benzyl-1-piperidinyl)carbonyl]-*N*-(4-methoxybenzyl)-3-piperidinecarboxamide 38: Crude purity 95%; 95% yield; ^{1}H NMR ($CDCl_3$) δ 7.31−7.11 (m, 7H), 6.86−6.83 (d, $J = 8.8$ Hz, 2H), 4.41−4.30 (m, 2H), 3.78 (s, 3H), 3.61−3.17 (m, 6H), 2.77−2.52 (m, 5H), 2.10−1.51 (m, 7H), 1.20−1.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 160.0, 159.1, 139.8, 129.6, 129.3, 129.0, 128.3, 126.1, 114.0, 55.3, 48.4, 47.3, 47.2, 43.4, 42.9, 41.8, 38.1, 31.9, 31.8, 27.2, 23.9; ESI-MS *m*/*z* 450.4 $[M + H]^+$, 472.4 $[M + Na]^+$. HRMS Calcd for $C_{27}H_{36}N_3O_3$ $[M + H]^+$: 450.2756. Found: 450.2734.

***N*^{3}-(4-Methoxybenzyl)-*N*^{1}-methyl-*N*^{1}-phenyl-1,3-piperidinedicarboxamide 39:** Crude purity 98%; 95% yield; ^{1}H NMR ($CDCl_3$) δ 7.33−7.02 (m, 7H), 6.90−6.86 (d, $J = 8.8$ Hz, 2H), 4.38−4.27 (m, 2H), 3.81 (s, 3H), 3.49−3.45 (m, 2H), 3.17 (s, 3H), 3.15−3.08 (m, 1H), 2.85−2.75 (m, 1H), 2.27−1.20 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 161.4, 159.1, 146.1, 130.0, 129.7, 129.3, 125.1, 124.1, 114.0, 55.3, 47.5, 46.8, 43.3, 42.0, 39.6, 27.1, 23.7; ESI-MS *m*/*z* 382.3 $[M + H]^+$, 404.3 $[M + Na]^+$. HRMS Calcd for $C_{22}H_{28}N_3O_3$ $[M + H]^+$: 382.2130. Found: 382.2135.

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Supporting Information Available. Characterization (IR) of the resins **6** and **7**, ^{1}H NMR spectra for compounds **8b**, **8c**, **13a**−**c**, **24**−**39**, and ^{13}C NMR spectra for compounds **31**−**39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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