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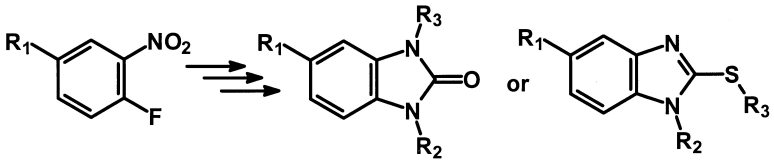

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Solution-Phase Parallel Synthesis of Substituted Benzimidazoles

B. Raju,*[,1] Noel Nguyen, and George W. Holland

Department of Chemistry & Biophysics, Texas Biotechnology Corporation, 7000 Fannin, Suite 1920, Houston Texas 77030

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A solution-phase parallel synthesis of *o*-phenylenediamines is described. These intermediates were then subsequently converted to benzimidazole scaffolds (three-point diversity) in excellent purities and yields. High-throughput purification of this multistep synthetic sequence was accomplished using polymer-bound scavengers and reagents and liquid−liquid extraction protocols.

Automated multiple organic synthesis (AMOS), i.e., automated solution- or solid-phase combinatorial or parallel synthesis, is a new tool at the disposal of the medicinal chemistry practitioner. This technology has undergone a dramatic maturation in a short span of time and appears destined to become a core technology for new lead discovery and optimization. The initial efforts were focused on use of solid-phase organic chemistry[2] (SPOC) to generate small-molecule libraries by taking advantage of simple filtration techniques to wash off the excess reagents and byproducts from the desired polymer-bound product. More recently, a variety of techniques have been developed that enhance the rapid purification of libraries of organic molecules generated using classical solution-phase organic reactions. Some of these techniques include liquid-phase extractive protocols[3] (LPEP), solid-supported liquid−liquid extraction[4] (SLE), fluorous-phase extraction,[5] polymer-supported reagents[6] and catalysts,[7] polymer-supported quench/scavenging reagents[8] (PSQ), and complementary molecular reactivity and molecular recognition[6] (CMR/R). Herein, we disclose our approach to high-throughput organic synthesis of substituted benzimidazoles, which employs a judicious choice of these purification techniques in a multistep solution-phase organic synthesis.

Retrosynthetic analysis of benzimidazolone **1**, 2-thioalkylbenzimidazole **2**, 2-alkylbenzimidazole **5**, and 2-aminobenzimidazole **7** leads to appropriately substituted *o*-phenylenediamine (Figure 1), which can be derived from *o*-fluoronitro intermediates by an aromatic nucleophilic substitution reaction followed by reduction of the nitro group. Hence, a high-throughput synthesis of *o*-phenylenediamines would facilitate the synthesis of benzimidazole and other related heterocyclic scaffolds. Interests in these derivatives stem from our previous work in the development of an elegant route for the synthesis of substituted ureas.[9] In continuation, we desired to build chemical libraries of cyclic ureas and envisioned benzimidazolone as an interesting scaffold.[10] Further, 2-substituted benzimidazoles cover a broad range of biological activities such as antiulcer, antiviral, and antitumor effects.[11] Therefore, a general viable method for high-throughput synthesis of the benzimidazole scaffold is of immense value in a drug discovery process.

As mentioned above, the first step in the synthesis of a benzimidazole scaffold is the aromatic nucleophilic substitution reaction of a halogen atom, preferably a fluorine or chlorine atom, with an amine (Scheme 1). These are generally irreversible reactions and can be driven to completion by using an excess of one of the two substrates. In the present studies, the reactions were driven to completion by employing an excess of *o*-fluoronitro substrates (10−20% excess), and this sets the stage for high-throughput purification. Upon completion of reaction, as judged by thin-layer chromatography (TLC) or by NMR (Figure 3) of an aliquot, the reaction mixture was treated with polymer-bound amine[8a] **9** (Figure 2) to remove excess *o*-fluoronitrobenzene, as evidenced by TLC or NMR (Figure 3). Filtration of the resin and concentration of filtrate gave substituted *o*-nitroanilines **13a**−**f** in excellent purities and yields (Table 1).

A variety of literature reaction conditions[13] are known for reduction of the nitro group. Although one could use either catalytic hydrogenation or chemical reduction of the nitro group to obtain *o*-phenylenediamine, the use catalytic hydrogenation conditions appears preferable because of the ease of workup. However, in the cases of N-benzylated derivatives, a chemical reduction would be needed in order to preclude the possible cleavage of *N*-benzyl groups under catalytic hydrogenation conditions. Hence, one would select the appropriate methodology, chemical reduction vs catalytic hydrogenation conditions, depending on the nature of the functionality at the R_2 diversity point (Figure 1). In the present study, the use of Raney nickel in methanol to reduce a variety of substituted *o*-nitroanilines, **13a**−**f**, to their corresponding *o*-phenylenediamines, **14a**−**f**, was uneventful and gave products in excellent purities and yields (Table 1).

Treatment of *o*-phenylenediamines, **14a**−**f**, with either excess carbonyldiimidazole or thiocarbonyldiimidazole gave complete conversion to their corresponding cyclic analogues **15a**−**f** or **16a**−**f**. The major impurities in this reaction were unreacted carbonyldiimidazole or thiocarbonyldiimidazole and the byproduct imidazole. Upon completion of the reaction, as judged by TLC, the cyclic products **15a**−**f** and

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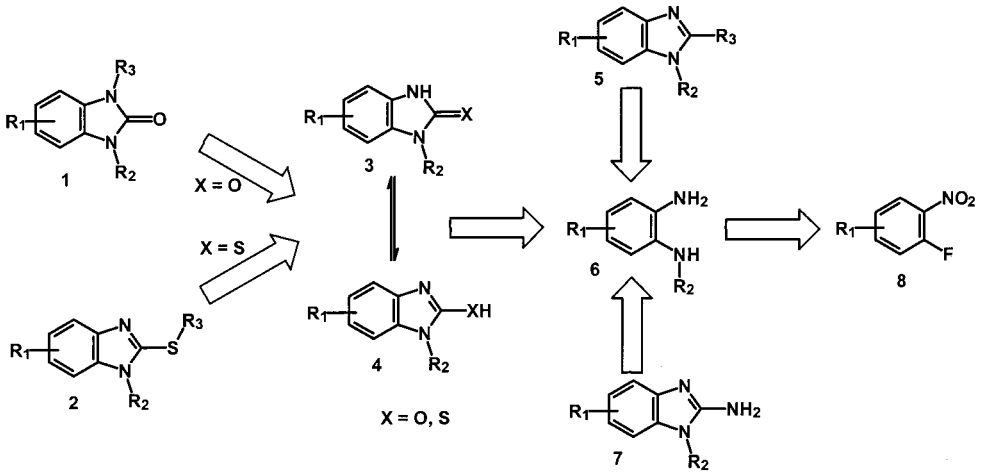
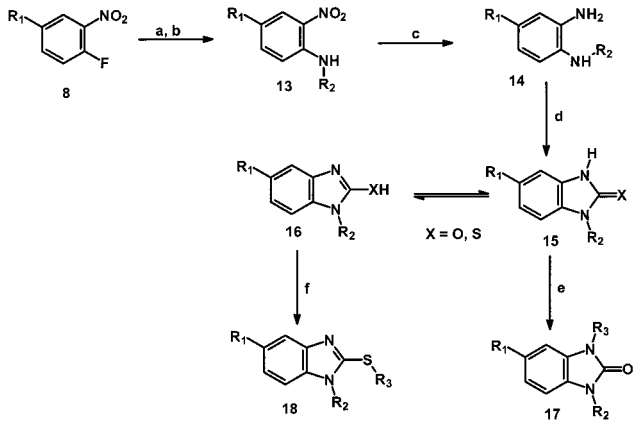


Figure 1. Retrosynthetic analysis of benzimidazole scaffolds.

Scheme 1[a]



[a] Reagents: (a) R_2NH_2, DMF, room temp or 70−80 °C; (b) **9**, 70−80 °C; (c) Raney Ni, MeOH, H_2, 55 psi; (d) CDI or TCDI, THF, room temp; (e) **10**, R_3Br, DMF and then **11**, 50 °C; (f) **12**, R_3Br, CH_3CN.

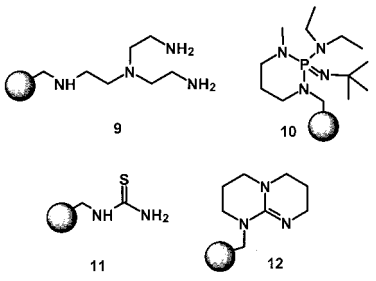


Figure 2. Polymer-bound reagents/scavengers.

16a−**f** were isolated using liquid−liquid extraction techniques in high chemical purities and yields (Table 1).

The high-throughput solution-phase synthesis of benzimidazole scaffolds **15** and **16** on a large scale in excellent purities and yields has set the stage for further derivatization of the functionalities on the benzene and imidazole rings, depending on the nature of substituents. The recently reported polymer-bound organic bases[15] **10** and **12** (Figure 2) were used to perform N- and S-alkylation, respectively, to get **17** and **18** (Scheme 1). The N-alkylation reaction was carried out using excess alkyl bromide, and after completion of the reaction the unreacted alkyl bromide was removed using polymer-bound nucleophile **11.** The purities and yields of the alkylated porducts were excellent (Table 2). The treatment of 2-mercaptobenzimidazole **16** with the polymer-bound base **12** in acetonitrile resulted in formation of an anionic species, which reacted with slightly less than 1 equiv of alkyl bromide. Upon completion of the alkylation reaction, filtration of the resin gave the desired S-alkylated products in good yields and excellent purities (Table 3).

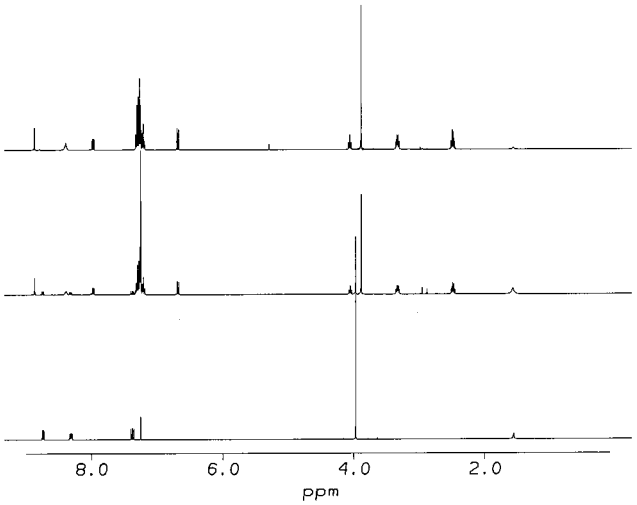


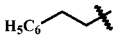
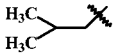
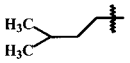
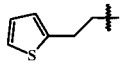
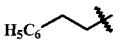
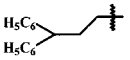
Figure 3. NMR spectra: **13f** (Table 1) after treatment with resin (top); an aliquot of reaction mixture (middle); methyl 4-fluoro-3-nitrobenzoate (bottom, used 20% excess in the reaction).

In summary, a multistep solution-phase synthesis of substituted benzimidazoles has been developed with an elegant choice of purification techniques and is totally devoid of conventional purification methods such as column chromatography and crystallization. This approach provides a practical and complementary solution-phase alternative to several recently reported solid-phase synthesis of benzimidazole and related compounds.[10] Furthermore, the utility of *o*-phenylenediamines in the synthesis of other heterocyclic scaffolds is underway.

Experimental Section

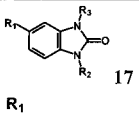
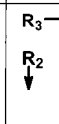
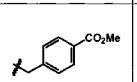
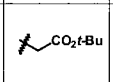
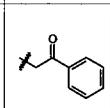
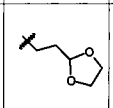
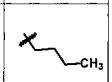
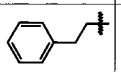
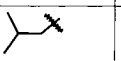
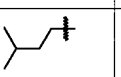
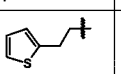
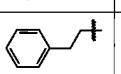
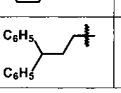
^{1}H NMR spectra were recorded on a JEOL Eclips spectrometer at 400 MHz. Spectra were recorded at ambient temperature unless otherwise noted. Chemical shifts are reported as δ values (ppm). Mass spectra were recorded on an HP 5989 mass spectrometer using atmospheric pressure chemical ionization techniques. Thin-layer chromatography

Table 1. Yields of Intermediates **13**−**16** (Scheme 1)

	R_1	R_2	% Yield 13[a]	14[a]	15 (X = O)[a,11]	16 (X = S)[a,12]
a	-H		95[b]	97[b]	92[b]	99[b]
b	$-CO_2CH_3$		99	95	100	90
c	$-CO_2CH_3$		96	100	95	100
d	$-CO_2CH_3$		100	100	98	95
e	$-CO_2CH_3$		99	78	96	100
f	$-CO_2CH_3$		96	97	90	90

[a] All compounds were baseline pure by proton NMR unless otherwise mentioned. [b] These compounds were >90% pure as determined by proton NMR.

Table 2. Yield, Purity,[14] and Retention Time (HPLC) of N-Alkylated Products **17**[a]

	 17		a 	b 	c 	d 	e 
A	-H		**92** *92* 5.15	**94** *98* 5.183	**75** *97* 5.083	**68** *90* 4.676	**67** *96* 5.233
B	$-CO_2Me$		**100** *98* 5.033	**100** *98* 5.017	**95** *98* 4.917	**87** *90* 4.567	**74** *93* 5.083
C	$-CO_2Me$		**95** *98* 5.267	**100** *98* 5.268	**90** *79* 5.133	**87** *91* 4.867	**74** *99* 5.350
D	$-CO_2Me$		**100** *99* 5.050	**95** *98* 5.083	**93** *77* 4.983	**89** *92* 4.683	**74** *99* 5.117
E	$-CO_2Me$		**100** *98* 5.117	**100** *98* 5.167	**84** *70* 5.083	**93** *98* 4.767	**80** *99* 5.217
F	$-CO_2Me$		**66** *98* 5.721	**100** *98* 5.7	**88** *83* 5.583	**99** *98* 5.383	**88** *94* 5.783

[a] The three numbers for each compound represent the percent yield (bold), HPLC purity (italics), and retention time.

(TLC) was performed using glass plates precoated with silica gel, and the spots were visualized by UV and or 5% phosphomolybidic acid solution followed by heating. All reagents and solvents were of the best grade available from commercial source (Aldrich and Fluka) and used without any further purification. Functionalized ploymers 9, 10, and 12 were purchased from Fluka, and polymer 11 was purchased from Novobiochem.

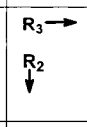
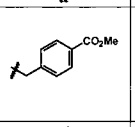
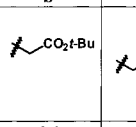
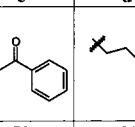
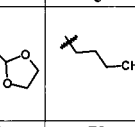
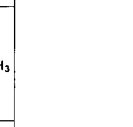
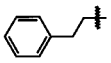
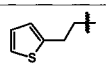
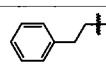
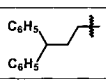
A. General Procedure for Aromatic Nucleophilic Substitution Reaction. To a stirred solution of 2-fluronitrobenzene (3.10 g, 22 mmol) in *N*,*N*-dimethylformamide (25 mL) was added phenethylamine (2.42 g, 20 mmol, slightly exothermic reaction). The reaction mixture was kept at 80 °C with stirring for 14 h. To this was added polymer-bound amine[8a] **9** (3 g, Figure 2), and the mixture continued stirring for 24 h. The reaction mixture was cooled to ambient temperature, and the resin was filtered and then washed with ethyl acetate (50 mL). The combined filtrate was concentrated in vacuo to give product **13a** (4.6 g, 95% yield).

13a: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.02 (t, J = 7.32 Hz, 2H), 3.56 (bt, J = 6.24 Hz, 2H), 6.63 (m, 1H), 6.85 (d, J = 8.76 Hz, 1H), 7.2−7.35 (m, 5H), 7.43 (m, 1H), 8.16 (dd, J = 1.44, 8.4 Hz, 1H). CIMS: m/z 243 $(M + H)^+$.

B. General Procedure for Aromatic Nucleophilic Substitution Reaction. To a stirred solution of 4-carbomethoxy-2-fluronitrobenzene (4.38 g, 22 mmol) in *N*,*N*-dimethylformamide (25 mL) was added isobutylamine (1.47 g, 20 mmol) dropwise over a 15 min period (exothermic reaction), and the mixture continued stirring at room temperature for 8 h. To this was added polymer-bound amine[8a] **9** (3 g, Figure 2), and the mixture continued stirring at 70 °C for 18 h. The reaction mixture was cooled to ambient temperature, and the resin was filtered and washed with ethyl acetate (50 mL). The combined filtrate was concentrated in vacuo to give product **13e** (5.0 g, 99% yield).

13b. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.05 (d, J = 6.6 Hz, 6H), 2.03 (m, 1H), 3.17 (dd, 6.96 Hz, 2H), 3.89 (s, 3H), 6.84 (d, J = 8.8 Hz, 1H), 8.02 (dd, J = 2.2, 8.8 Hz), 8.46 (bs, 1H), 8.87 (d, 2.2 Hz, 1H). CIMS: m/z 253 $(M + H)^+$.

Table 3. Yield, Purity,[14] and Retention Time (HPLC) of S-Alkylated Products **18**[a]

			**a**	**b**	**c**	**d**	**e**
	18						
A	-H		**43** *95* 4.650	**96** *98* 4.717	**53** *93* 4.7	**64** *85* 4.2	**72** *90* 4.583
B	-CO_2Me		**81** *99* 5.217	**100** *98* 5.217	**53** *98* 5.133	**55** *82* 4.517	**67** *93* 4.983
C	-CO_2Me		**97** *99* 5.4	**100** *98* 5.45	**49** *99* 5.35	**80** *84* 4.8	**73** *93* 5.233
D	-CO_2Me		**95** *99* 5.25	**100** *98* 5.233	**43** *90* 5.167	**96** *91* 5.283	**85** *93* 5.083
E	-CO_2Me		**89** *98* 5.3	**100** *98* 5.317	**25** *86* 5.233	**52** *85* 4.717	**78** *93* 5.15
F	-CO_2Me		**91** *98* 5.75	**91** *98* 5.817	**38** *91* 5.717	**51** *84* 4.633	**69** *93* 5.617

[a] The three numbers for each compound represent the percent yield (bold), HPLC purity (italics), and retention time.

13c. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.98 (d, J = 6.6 Hz, 6H), 1.64 (q, J = 6.06 Hz, 2H), 1.75 (m, 1H), 3.35 (m, 2H), 3.89 (s, 3H), 6.86 (d, J = 9.16 Hz, 1H), 8.04 (dd, J = 2.2, 9.16 Hz), 8.32 (bs, 1H), 8.87 (d, 2.2 Hz, 1H). CIMS: m/z 267 $(M + H)^+$.

13d. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.26 (t, J = 6.96 Hz, 2H), 3.65 (q, J = 6.96 Hz, 2H), 3.89 (s, 3H), 6.86 (d, J = 9.16 Hz, 1H), 6.95 (m, 2H), 7.2 (dd, J = 1.08, 5.12 Hz, 1H), 8.05 (dd, J = 1.84 Hz, 8.8 Hz, 1H), 8.44 (bs, 1H), 8.87 (d, J = 2.2 Hz, 1H). CIMS: m/z 307 $(M + H)^+$.

13e. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.04 (t, J = 7.32 Hz, 2H), 3.61 (q, J = 6.96 Hz, 2H), 3.89 (s, 3H), 6.85 (d, J = 9.16 Hz, 1H), 7.25−7.36 (m, 5H), 8.03 (dd, J = 1.84, 9.16 Hz, 1H), 8.39 (bs, 1H), 8.86 (d, J = 1.8 Hz, 1H). CIMS: m/z 301 $(M + H)^+$.

13f. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.47 (q, J = 6.56 Hz, 2H), 3.18 (q, J = 6.24 Hz, 2H), 3.89 (s, 3H), 4.05 (t, J = 8.08 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 7.16−7.32 (m, 10H), 7.97 (dd, J = 2.2, 8.8 Hz, 1H), 8.38 (bs, 1H), 8.86 (d, J = 2.2 Hz, 1H). CIMS: m/z 391 $(M + H)^+$.

C. General Procedure for Nitro Group Reduction. To a solution of nitroaniline **13** (10 mmol) in methanol (100 mL) (THF was used as a cosolvent to get the nitro compounds into solution) was added Raney nickel (0.5 g). This was subjected to hydrogenation at 55 psi for 24 h. The catalyst was filtered off and washed thoroughly with methanol. The combined filtrate was concentrated in vacuo to give product **14**.

14a. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.98 (t, J = 7.36 Hz, 2H), 3.34 (bs, 2H), 3.41 (t, J = 7.32 Hz, 2H), 6.71 (m, 3H), 6.84 (m, 1H), 7.2−7.35 (m, 5H).

14b. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.01 (d, J = 6.6 Hz, 6H), 1.93 (m, 1H), 2.99 (d, J = 7.0 Hz, 2H), 3.83 (s, 3H), 6.57 (d, J = 8.44 Hz, 1H), 7.41 (bs, 1H), 7.57 (bd, J = 7.68 Hz, 1H).

14c. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.95 (d, J = 6.6 Hz, 6H), 1.55 (q, J = 7.68 Hz, 2H), 1.74 (m, 1H), 3.17 (t, J = 7.32 Hz, 2H), 3.84 (s, 3H), 6.58 (d, 8.4 Hz, 1H), 7.4 (d, J = 2.2 Hz, 1H), 7.53 (dd, J = 1.84, 8.44 Hz, 1H).

14d. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.17 (t, J = 6.96 Hz, 2H), 3.47 (bt, J = 6.6 Hz, 2H), 3.79 (s, 2H), 3.83 (s, 3H), 6.63 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 2.56 Hz, 1H), 6.94 (dd, J = 5.12 Hz, 1H), 7.15 (dd, J = 1.12 Hz, 5.16 Hz, 1H), 7.45 (bs, 1H), 7.59 (bd, J = 7.32 Hz, 1H).

14e. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.97 (t, J = 7.32 Hz, 2H), 3.45 (t, J = 7.32 Hz, 2H), 3.85 (s, 3H), 6.67 (d, J = 8.44 Hz, 1H), 7.18−7.32 (m, 5H), 7.5 (d, J = 1.84 Hz, 1H), 7.61 (dd, J = 1.84, 8.4 Hz, 1H).

14f. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.43 (q, J = 6.96 Hz, 2H), 3.18 (t, J = 7.32 Hz, 2H), 3.83 (s, 3H), 4.07 (t, J = 8.04 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 7.17−7.31 (m, 10H), 7.37 (d, J = 1.84 Hz, 1H), 7.52 (dd, J = 1.84, 8.44 Hz, 1H).

D. General Procedure for Cyclization Using Carbonyldiimdazole. To a stirred solution of *o*-phenylenediamine **14** (10 mmol) in THF (80 mL) was added carbonyldiimidazole (15 mmol) in one lot, and the mixture continued stirring at room temperature for 18 h. The solvent was removed in vacuo, and water (75 mL) was added to the residue. This was extracted with ethyl acetate (2 × 75 mL) and then washed with 1 N HCl (2 × 30 mL). The organic layer was dried over $MgSO_4$ and solvent was removed in vacuo to give product **15** (NMR pure).

15a. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.06 (t, J = 8.04 Hz, 2H), 4.1 (t, J = 7.72 Hz, 2H), 6.87 (m, 1H), 7.03−7.30 (m, 8H), 9.42 (bs, 1H). CIMS: m/z 239 $(M + H)^+$.

15b. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.98 (d, J = 6.6 Hz, 6H), 2.29 (m, 1H), 3.78 (d, J = 7.68 Hz, 2H), 3.91 (s, 3H), 7.00 (d, J = 8.04 Hz, 1H), 7.77 (d, J = 1.44 Hz, 1H), 7.85 (dd, J = 1.48, 8.04 Hz, 1H), 8.98 (bs, 1H). CIMS: m/z 249 $(M + H)^+$.

15c. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.99 (d, J = 6.2 Hz, 6H), 1.67 (m, 3H), 3.92 (m, 5H), 6.99 (d, J = 8.04 Hz, 1H), 7.77 (d, J = 1.48 Hz, 1H), 7.85 (dd, J = 1.48, 8.04 Hz, 1H), 8.99 (bs, 1H). CIMS: m/z 263 $(M + H)^+$.

15d. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.3 (t, J = 7.32 Hz, 2H), 3.91 (s, 3H), 4.16 (t, J = 6.96 Hz), 6.81−

6.88 (m, 3H), 7.12 (dd, J = 1.12, 4.04 Hz, 1H), 7.78−7.8 (m, 2H), 9.84 (bs, 1H). CIMS: m/z 303 $(M + H)^+$.

15e. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.06 (t, J = 7.68 Hz, 2H), 3.91 (s, 3H), 4.12 (t, J = 7.32 Hz, 2H), 6.78 (d, J = 8.04 Hz, 1H), 7.18−7.28 (m, 5H), 7.75−7.78 (m, 2H), 8.99 (s, 1H). CIMS: m/z 297 $(M + H)^+$.

15f. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.53 (q, J = 7.32 Hz, 2H), 3.86 (t, J = 7.68 Hz, 2H), 3.91 (s, 3H), 4.02 (t, J = 7.68 Hz, 1H), 6.71 (d, J = 8.44 Hz, 1H), 7.15−7.32 (m, 10H), 7.72 (d, J = 1.48 Hz, 1H), 7.8 (dd, J = 1.48, 8.44 Hz, 1H), 8.55 (s, 1H). CIMS: m/z 387 $(M + H)^+$.

E. General Procedure for Cyclization Using Thiocarbonyldiimdazole. To a stirred solution of *o*-phenylenediamine **14** (10 mmol) in THF (80 mL) was added thiocarbonyldiimidazole (15 mmol) in one lot, and the mixture continued stirring at room temperature for 6 h. The solvent was removed in vacuo, and to the residue was added water (75 mL). This was extracted with ethyl acetate (2 × 75 mL) and then washed with 1 N HCl (2 × 30 mL). The organic layer was dried over $MgSO_4$, and solvent was removed in vacuo to give product **16** (NMR pure).

16a. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.15 (t, J = 8.08 Hz, 2H), 4.48 (t, J = 7.68 Hz, 2H), 6.97 (d, J = 6.96 Hz, 1H), 7.12−7.29 (m, 8H). CIMS: m/z 255 $(M + H)^+$.

16b. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.01 (d, J = 6.24 Hz, 6H), 2.44 (m, 1H, J = 6.6 Hz, 1H), 3.93 (s, 3H), 4.12 (d, J = 7.72 Hz, 2H), 7.2 (d, J = 8.44 Hz, 1H), 7.94 (s, 1H), 7.96 (dd, J = 1.84, 8.44 Hz, 1H,). CIMS: m/z 265 $(M + H)^+$.

16c. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.03 (d, J = 6.24 Hz, 6H), 1.73 (m, 3H), 3.93 (s, 3H), 4.31 (t, J = 7.68 Hz, 2H), 7.18 (d, J = 1.48 Hz, 1H), 7.93 (d, J = 1.12 Hz, 1H), 7.97 (d, J = 7.18 Hz, 1H). CIMS: m/z 279 $(M + H)^+$.

16d. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.39 (t, J = 6.96 Hz, 2H), 3.92 (s, 3H), 4.53 (t, J = 6.96 Hz), 6.78 (bd, J = 3.32 Hz, 1H), 6.85 (dd, J = 5.12 Hz, 1H), 6.91 (d, J = 8.4 Hz), 7.11 (dd, J = 1.12, 5.12 Hz, 1H), 7.86 (dd, J = 1.44, 8.4 Hz, 1H), 7.92 (d, J = 1.44 Hz, 1H). CIMS: m/z 319 $(M + H)^+$.

16e. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.15 (t, J = 7.32 Hz, 2H), 3.92 (s, 3H), 4.51 (t, J = 7.32 Hz, 2H), 6.89 (d, J = 8.44 Hz, 1H), 7.19−7.27 (m, 5H), 7.85 (dd, J = 1.48, 8.44 Hz, 1H), 7.92 (d, J = 1.08 Hz, 1H). CIMS: m/z 313 $(M + H)^+$.

16f. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.61 (q, J = 7.68 Hz, 2H), 3.92 (s, 3H), 4.06 (t, J = 8.04 Hz, 1H), 4.23 (t, J = 7.96 Hz, 2H), 6.8 (d, J = 8.8 Hz, 1H), 7.21 (m, 2H), 7.28 (m, 8H), 7.9 (m, 2H). CIMS: m/z 403 $(M + H)^+$.

F. General Procedure for N-Alkylation of Benzimidazolone. The reactions were conducted in parallel using 5 mL glass vials with screw caps. To a solution of benzimidazalone **15** (0.1 mml) in DMF (2 mL) was added polymer-bound BEMP (**10**, Figure 2, 0.15 g, 0.345 mmol) followed by alkyl halide (0.13 mmol). The reaction mixture was stirred at room temperature for 1 h, during which period there was complete disappearance of starting material as indicated by thin-layer chromatography. To this was added polymer-bound thiourea (**11**, Figure 2, 0.1 g, 0.332 mmol) and DMF (1 mL). The reaction mixture was kept stirring at 50 °C for 18 h. The resin was filtered off and washed with methanol (2 mL) and ethyl acetate (2 mL). Combined filtrate was concentrated in vacuo to give product **17**.

17Aa. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.08 (t, J = 7.68 Hz, 2H), 3.89 (s, 3H), 4.16 (t, J = 7.32 Hz, 2H), 5.09 (s, 2H), 6.78 (d, J = 7.32 Hz, 1H), 6.91−7.04 (m, 3H), 7.2−7.3 (m, 7H), 7.97 (d, J = 8.08 Hz, 2H). CIMS: m/z 387 $(M + H)^+$.

17Ba. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.96 (d, J = 6.60 Hz, 6H), 2.22 (m, 1H), 3.73 d, J = 7.68 Hz, 2H,), 3.86 (s, 3H, $-OCH_3$), 3.88 (s, 3H,), 5.14 (s, 2H), 7.01 (d, J = 8.44 Hz, 1H), 7.35 (d, J = 8.44 Hz, 2H), 7.51 (d, J = 1.48 Hz, 1H), 7.82 (dd, J = 1.84, 8.44 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H). CIMS: m/z 397 $(M + H)^+$.

17Ca. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.99 (d, J = 6.24 Hz, 6H), 1.65 (m, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.95 (t, J = 7.32 Hz), 5.13 (s, 2H), 7.01 (d, J = 8.44 Hz, 1H), 7.35 (d, J = 8.44 Hz, 2H), 7.52 (d, J = 1.48 Hz, 1H), 7.84 (dd, J = 1.48, 8.44 Hz, 1H), 7.98 (d, J = 8.44 Hz, 2H). CIMS: m/z 411 $(M + H)^+$.

17Da. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.31 (t, J = 6.96 Hz, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 4.19 (t, J = 6.96 Hz, 2H), 5.12 (s, 2H), 6.77 (d, J = 1.44 Hz, 1H), 6.83−6.87 (m, 2H), 7.11 (dd, J = 1.12, 5.12 Hz), 7.32 (d, J = 8.40 Hz, 2H), 7.49 (d, J = 1.48 Hz, 1H), 7.77 (dd, J = 1.44, 8.44 Hz), 7.98 (d, J = 8.44 Hz, 2H). CIMS: m/z 451 $(M + H)^+$.

17Ea. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.08 (t, J = 7.36 Hz, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 4.18 (t, J = 7.32 Hz, 2H), 5.13 (s, 2H), 6.85 (d, J = 8.04 Hz, 1H), 7.3−7.1 (m, 7H), 7.48 (d, J = 1.48 Hz, 1H), 7.77 (dd, J = 1.48, 8.4 Hz, 1H), 7.97 (d, J = 8.40 Hz, 2H). CIMS: m/z 445 $(M + H)^+$.

17Fa. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.55 (q, J = 7.32 Hz, 2H), 3.87 (s, 3H), 3.91 (s, 3H, $-OCH_3$), 3.91 (m, 2H), 4.02 (t, J = 7.76 Hz, 1H), 5.09 (s, 2H), 6.75 (d, J = 8.44 Hz, 1H), 7.16−7.20 (m, 2H), 7.24−7.28 (m, 8H), 7.34 d, J = 8.44 Hz, 2H), 7.48 (d, J = 1.48 Hz, 1H), 7.79 (dd, J = 1.44, 8.44 Hz, 1H), 7.98 (d, J = 8.08 Hz, 2H). CIMS: m/z 535 $(M + H)^+$.

17Ab. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.45 (s, 9H), 3.04 (t, J = 7.68 Hz, 2H), 4.10 (t, J = 7.68 Hz, 2H), 4.53 (s, 2H), 6.83−6.90 (m, 2H), 7.01−7.07 (m, 2H), 7.18−7.30 (m, 5H). CIMS: m/z 297 $(M - t\text{Bu})^+$.

17Bb. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.95 (d, J = 6.96 Hz), 1.45 (s, 9H), 2.20 (m, 1H), 3.70 (d, J = 7.72 Hz, 2H), 3.90 (s, 3H), 4.54 (s, 2H), 7.00 (d, J = 8.44 Hz, 1H), 7.55 (d, J = 1.44 Hz, 1H), 7.83 (dd, J = 1.44, 8.4 Hz, 1H). CIMS: m/z 307 $(M - t\text{Bu})^+$.

17Cb. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.97 (d, J = 6.60 Hz, 6H), 1.44 (s, 9H), 1.63 (m, 3H), 3.90 (s, 3H), 3.91 (t, J = 7.32 Hz, 2H), 4.54 (s, 2H), 7.00 (d, J = 8.44 Hz, 1H), 7.56 (d, J = 1.48 Hz, 1H), 7.84 (dd, J = 1.44 Hz, 8.04). CIMS: m/z 321 $(M - t\text{Bu})^+$.

17Db. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.45 (s, 9H), 3.26 (t, J = 7.32 Hz, 2H), 3.89 (s, 3H), 4.14 (t, J = 7.32 Hz, 2H), 4.54 (s, 2H), 6.76−6.81 (m, 2H), 6.85 (dd, J = 5.12, 1.84 Hz, 1H), 7.11 (dd, J = 1.12, 5.16 Hz, 1H), 7.55

(d, J = 1.44 Hz, 1H), 7.77 (dd, J = 1.44, 8.04 Hz, 1H). CIMS: m/z 361 $(M - t\text{Bu})^+$.

17Eb. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.46 (s, 9H), 3.03 (t, J = 7.32 Hz, 2H), 3.89 (s, 3H), 4.11 (t, J = 7.32 Hz, 2H), 4.54 (s, 2H), 6.76 (d, J = 8.44 Hz, 1H), 7.15−7.30 (m, 5H), 7.54 (d, J = 1.44 Hz, 1H), 7.76 (dd, J = 1.48, 8.04 Hz, 1H). CIMS: m/z 355 $(M - t\text{Bu})^+$.

17Fb. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.45 (s, 9H), 2.52 (q, J = 7.68, 7.36 Hz, 2H), 3.87 (t, J = 7.32 Hz, 2H), 3.90 (s, 3H), 4.00 (t, J = 7.68 Hz, 1H), 4.50 (s, 2H), 6.72 (s, J = 8.40 Hz, 1H), 7.15−7.20 (m, 2H), 7.22−7.30 (m, 8H), 7.53 (d, J = 1.44 Hz, 1H), 7.80 (dd, J = 1.44, 8.04 Hz, 1H). CIMS: m/z 445 $(M - t\text{Bu})^+$.

17Ac. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.06 (t, J = 7.68 Hz, 2H), 4.13 (t, J = 7.68 Hz, 2H), 5.26 (s, 2H), 6.80−6.90 (m, 2H), 7.00−7.10 (m, 3H), 7.18−7.31 (m, 4H), 7.52 (t, J = 7.68 Hz, 2H), 7.63 (t, J = 7.68 Hz, 1H), 8.06 (d, J = 7.32 Hz, 2H). CIMS: m/z 357 $(M + H)^+$.

17Bc. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.98 (d, J = 6.96 Hz, 6H), 2.23 (m, 1H), 3.74 (d, J = 7.72 Hz, 2H), 3.85 (s, 3H), 5.35 (s, 2H), 7.03 (d, J = 8.44 Hz, 1H), 7.45−7.52 (m, 3H), 7.64 (t, J = 7.36 Hz, 1H), 7.85 (dd, J = 1.48, 8.4 Hz), 8.04 (d, J = 8.04 Hz, 2H). CIMS: m/z 367 $(M + H)^+$.

17Cc. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.98 (d, J = 6.24, 6H), 1.60−1.70 (m, 3H), 3.85 (s, 3H), 3.94 (t, J = 7.32 Hz, 2H), 5.34 (s, 2H), 7.03 (d, J = 8.44 Hz, 1H), 7.47−7.54 (m, 3H), 7.64 (t, J = 7.32 Hz, 1H), 7.86 (dd, J = 1.48, 8.04 Hz, 1H), 8.04 (d, J = 8.04 Hz, 2H). CIMS: m/z 381 $(M + H)^+$.

17Dc. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.29 (t, J = 7.36 Hz, 2H), 3.85 (s, 3H), 4.17 (t, J = 7.32 Hz, 2H), 5.35 (s, 2H), 6.75−6.90 (m, 3H), 7.12 (dd, J = 1.44, 5.12 Hz, 1H), 7.48 (d, J = 1.48 Hz, 1H), 7.53 (t, J = 7.32 Hz, 2H), 7.65 (t, J = 7.32 Hz, 1H), 7.78 (dd, J = 1.84, 8.4 Hz), 8.04 (dd, J = 1.44, 8.04 Hz, 2H). CIMS: m/z 421 $(M + H)^+$.

17Ec. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.07 (t, J = 7.32 Hz, 2H), 3.85 (s, 3H), 4.15 (t, J = 7.36 Hz, 2H), 5.34 (s, 2H), 6.80 (d, J = 8.04 Hz, 1H), 7.14−7.30 (m, 5H), 7.47 (d, J = 1.48 Hz, 1H), 7.53 (t, J = 8.08 Hz, 2H), 7.65 (t, J = 7.32 Hz, 1H), 7.77 (dd, J = 1.48, 8.44 Hz, 1H), 8.04 (d, J = 8.06 Hz, 2H). CIMS: m/z 415 $(M + H)^+$.

17Fc. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.56 (q, J = 7.32 Hz, 2H), 3.86 (s, 3H), 3.90 (t, J = 7.32 Hz, 2H), 4.03 (t, J = 7.72 Hz, 1H), 5.31 (s, 2H), 6.75 (d, J = 8.44 Hz, 1H), 7.15−7.31 (m, 10H), 7.47 (d, J = 1.48 Hz, 1H), 7.52 (t, J = 7.36 Hz, 2H), 7.64 (t, J = 7.32 Hz, 1H), 7.81 (dd, J = 1.44, 8.04 Hz, 1H), 8.04 (d, J = 7.32 Hz, 2H). CIMS: m/z 505 $(M + H)^+$.

17Ad. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.02−2.18 (m, 2H), 3.00−3.10 (m, 2H), 3.80−4.18 (m, 8H), 4.92 (t, J = 4.40 Hz, 1H), 6.85−6.90 (m, 1H), 7.00−7.10 (m, 3H), 7.18−7.32 (m, 5H). CIMS: m/z 339 $(M + H)^+$.

17Bd. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.94 (d, J = 6.60 Hz, 6H), 2.10−2.26 (m, 3H), 3.68 (d, J = 7.68 Hz, 2H), 3.78−4.00 (m, 7H), 4.06 (t, J = 6.96 Hz, 2H), 4.93 (t, J = 4.40 H, 1H), 6.97 (d, J = 8.07 Hz, 1H), 7.72 (d, J = 1.48 Hz, 1H), 7.81 (dd, J = 1.48, 8.08 Hz, 1H). CIMS: m/z 349 $(M + H)^+$.

17Cd. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.96 (d, J = 6.24 Hz, 6H), 1.62 (m, 3H), 2.12 (m, 2H), 3.80−3.95 (m, 9H, $-OCH_3$), 4.05 (t, J = 6.96 Hz, 1H), 4.93 (t, J = 4.40 Hz, 1H), 6.97 (d, J = 8.44 Hz, 1H), 7.72 (d, J = 1.48 Hz, 1H), 7.83 (dd, J = 1.48, 8.08 Hz, 1H). CIMS: m/z 363 $(M + H)^+$.

17Dd. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.12 (m, 2H), 3.25 (t, J = 7.32 Hz, 2H), 3.80−4.00 (m, 7H), 4.06 (t, J = 7.32 Hz, 2H), 4.13 (t, J = 7.36 Hz, 2H), 4.93 (t, J = 4.40 Hz, 1H), 6.74−6.82 (m, 2H), 6.85 (dd, J = 5.12, 1.84 Hz, 1H), 7.11 (dd, J = 1.12, 5.16 Hz, 1H), 7.71 (d, J = 1.48 Hz, 1H), 7.76 (dd, J = 1.44, 8.44 Hz, 1H). CIMS: m/z 403 $(M + H)^+$.

17Ed. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.08−2.18 (m, 2H), 3.02 (t, J = 7.36 Hz, 2H), 3.80−4.00 (m, 7H), 4.05 (t, J = 6.96 Hz, 2H), 4.08 (t, J = 7.72, Hz, 2H), 4.92 (t, J = 4.40 Hz, 1H), 6.77 (d, J = 8.44 Hz, 1H), 7.10−7.30 (m, 5H), 7.71 (d, J = 1.48 Hz, 1H), 7.75 (dd, J = 1.84, 8.44 Hz, 1H). CIMS: m/z 397 $(M + H)^+$.

17Fd. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.11 (m, 2H), 2.51 (q, J = 7.32 Hz, 2H), 3.80−4.05 (m, 11H), 4.92 (t, J = 4.40 Hz, 1H), 6.71 (d, J = 8.08, 1H), 7.14−7.20 (m, 2H), 7.20−7.30 (m, 8H), 7.69 (d, J = 1.08 Hz, 1H), 7.78 (dd, J = 1.48, 8.4 Hz, 1H). CIMS: m/z 487 $(M + H)^+$.

17Ae. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.95 (t, J = 7.72 Hz, 3H), 1.30−1.40 (m, 2H), 1.69−1.73 (m, 2H), 3.04 (m, 2H), 3.87 (t, J = 7.32 Hz, 2H), 4.07−4.15 (t, J = 7.32 Hz, 2H), 6.85−6.92 (m, 1H), 6.98−7.10 (m, 3H), 7.18−7.34 (m, 5H). CIMS: m/z 295 $(M + H)^+$.

17Be. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.90−1.00 (m, 9H), 1.32−1.42 (m, 2H), 1.69−1.76 (m, 2H), 2.13−2.24 (m, 1H), 3.69 (d, J = 7.36 Hz, 2H), 3.86−3.92 (m, 5H), 6.98 (d, J = 8.08 Hz, 1H), 7.65 (d, J = 1.48 Hz, 1H), 7.82 (dd, J = 1.84, 8.04 Hz, 1H). CIMS: m/z 305 $(M + H)^+$.

17Ce. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.90−1.00 (m, 9H), 1.34−1.44 (m, 2H), 1.58−1.68 (m, 3H), 1.73 (m, 2H), 3.86−3.94 (m, 7H), 6.98 (d, J = 8.40 Hz, 1H), 7.65 (d, J = 1.48 Hz, 1H), 7.83 (dd, J = 1.44, 8.04 Hz, 1H). CIMS: m/z 319 $(M + H)^+$.

17De. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.95 (t, J = 7.32 Hz, 3H), 1.33−1.41 (m, 2H), 1.69−1.74 (m, 2H), 3.26 (t, J = 7.32 Hz, 2H), 3.90 (t, J = 7.32 Hz, 2H), 3.91 (s, 3H), 4.14 (t, J = 7.32 Hz, 2H), 6.77 (dd, J = 1.12, 3.98 Hz, 1H), 6.81 (d, J = 8.40, 1H), 6.86 (q, J = 3.64, 1.48 Hz, 1H), 7.11 (dd, J = 1.12, 5.12 Hz, 1H), 7.64 (d, J = 1.48 Hz, 1H), 7.77 (dd, J = 1.48, 8.04 Hz, 1H). CIMS: m/z 359 $(M + H)^+$.

17Ee. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.95 (t, J = 7.32 Hz, 3H), 1.31−1.39 (m, 2H), 1.69−1.73 (m, 2H), 3.03 (t, J = 7.36 Hz, 2H), 3.89 (t, J = 7.32 Hz, 2H), 3.91 (s, 3H), 4.11 (t, J = 7.36 Hz, 2H), 6.80 (d, J = 8.04 Hz, 1H), 7.14−7.28 (m, 5H), 7.64 (d, J = 1.48 Hz, 1H), 7.76 (dd, J = 1.48, 8.04 Hz, 1H). CIMS: m/z 353 $(M + H)^+$.

17Fe. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.95 (t, J = 7.32 Hz, 3H), 1.32−1.44 (m, 2H), 1.69−1.76 (m, 2H), 2.52 (q, J = 7.32 Hz, 2H), 3.86 (t, J = 7.32 Hz, 2H), 3.92 (s, 3H), 4.01 (t, J = 7.68 Hz, 1H), 6.72 (d, J = 8.08 Hz, 1H),

7.15−7.20 (m, 2H), 7.22−7.30 (m, 8H), 7.62 (d, J = 1.48 Hz, 1H), 7.79 (dd, J = 1.48, 8.4 Hz, 1H). CIMS: m/z 443 $(M + H)^+$.

G. General Procedure for S-Alkylation of 2-Mercaptobenzimidazole. These reactions were conducted in parallel using 5 mL glass vials with screw caps and magnetic stir bars. To a solution of 2-mercaptobenzimidazole (0.12 mmol) in acetonitrile (2 mL) was added polymer-bound TBD (**12**, Figure 2, 0.15 g, 0.345 mmol) followed by alkyl halide (0.1 mmol). The reaction mixture was stirred at room temperature for 12 h, during which period there was complete disappearance of starting material as indicated by thin-layer chromatography. The resin was filtered off and washed with acetonitrile (4 mL), and unreacted 2-mercaptobenzimidazole is resin-bound through ionic interactions. Combined filtrate was concentrated in vacuo to give product **18**.

18Aa. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.98 (t, J = 7.32 Hz, 2H), 3.88 (s, 3H), 4.24 (t, J = 7.32 Hz, 2H), 4.60 (s, 2H), 7.04 (dd, J = 2.20, 8.44, 2H), 7.15−7.28 (m, 6H), 7.45 (d, J = 8.40 Hz, 2H), 7.72 (d, J = 8.40 Hz, 1H), 7.95 (d, J = 8.44 Hz, 2H). CIMS: m/z 403 $(M + H)^+$.

18Ba. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.89 (d, J = 6.0 Hz, 6H), 2.17 (m, 1H), 3.82 (d, J = 7.32 Hz, 2H), 3.88 (s, 3H), 3.93 (s, 3H), 4.66 (s, 2H), 7.23 (d, J = 8.40 Hz, 1H), 7.50 (d, J = 8.04 Hz), 7.90−7.99 (m, 3H), 8.39 (d, J = 1.12 Hz, 1H). CIMS: m/z 413 $(M + H)^+$.

18Ca. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.94 (d, J = 6.24 Hz, 6H), 1.54−1.63 (m, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 4.02 (t, J = 7.32 Hz, 2H), 4.67 (s, 2H), 7.23 (d, J = 8.40 Hz, 1H), 7.50 (d, J = 8.08 Hz, 2H), 7.93−7.97 (m, 3H), 8.40 (d, J =1.08 Hz, 1H). CIMS: m/z 427 $(M + H)^+$.

18Da. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.19 (t, J = 7.32 Hz, 2H), 3.87 (s, 3H), 3.92 (s, 3H), 4.25 (t, J = 7.36 Hz, 2H), 4.61 (s, 2H), 6.58 (d, J = 2.6 Hz, 1H), 6.82 (m, 1H), 7.05−7.13 (m, 2H), 7.47 (d, J = 8.40 Hz, 2H), 7.88 (dd, J = 1.48, 8.4 Hz, 1H), 7.95 (d, J = 8.40 Hz, 2H), 8.38 (d, J = 1.48 Hz, 1H). CIMS: m/z 467 $(M + H)^+$.

18Ea. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.98 (t, J = 7.32 Hz, 2H), 3.88 (s, 3H), 3.93 (s, 3H), 4.24 (t, J = 7.68 Hz, 2H), 4.61 (s, 2H), 6.97−7.09 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 7.17−7.24 (m, 3H), 7.47 (d, J = 8.44 Hz, 2H), 7.87 (dd, J = 1.48, 8.4, Hz, 1H), 7.96 (d, J = 7.96 Hz, 2H), 8.38 (d, J = 1.08 Hz, 1H). CIMS: m/z 461 $(M + H)^+$.

18Fa. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.19 (q, J = 7.32 Hz, 2H), 3.87 (s, 3H), 3.92 (s, 3H), 4.25 (t, J = 7.36 Hz, 2H), 4.64 (s, 2H), 6.90 (d, J = 8.44 Hz), 7.20 (m, 2H), 7.05−7.13 (m, 2H), 7.47 (d, J = 8.40 Hz, 2H), 7.88 (dd, J = 1.48, 8.40 Hz, 1H), 7.95 (d, J = 8.40 Hz, 2H), 8.38 (d, J = 1.48 Hz, 1H). CIMS: m/z 551 $(M + H)^+$.

18Ab. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.44 (s, 9H), 3.08 (t, J = 7.32 Hz, 2H), 4.11 (s, 2H), 4.34 (t, J = 7.32 Hz, 2H), 7.10−7.30 (m, 8H), 7.62−7.67 (m, 1H). CIMS: m/z 369 $(M + H)^+$.

18Bb. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.95 (d, J = 6.96 Hz, 6H), 1.44 (s, 9H), 2.25 (m, 1H), 3.85−3.93 (m, 3H), 4.14 (s, 2H), 7.23 (d, J = 8.44 Hz, 1H), 7.91 (dd, J = 1.44, 8.44 Hz, 1H), 8.31 (d, J = 1.12 Hz, 1H). CIMS: m/z 379 $(M + H)^+$.

18Cb. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.99 (d, J = 6.56 Hz, 6H), 1.45 (s, 9H), 1.64−1.71 (m, 3H), 3.89 (s, 3H), 4.10 (t, J = 7.32 Hz, 2H), 4.15 (s, 2H), 7.24 (d, J = 8.04 Hz, 1H), 7.92 (dd, J = 1.48, 8.4 Hz, 1H), 8.32 (d, J = 1.08 Hz, 1H). CIMS: m/z 393 $(M + H)^+$.

18Db. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.44 (s, 9H, −OtBu), 3.03 (t, J = 7.32 Hz, 2H), 3.91 (s, 3H), 4.11 (s, 2H), 4.35 (t, J = 7.32 Hz, 2H), 6.67 (dd, J = 1.08, 2.60 Hz, 1H), 6.85 (q, J = 3.64, 1.52 Hz, 1H), 7.09 (d, J = 8.40 Hz, 1H), 7.13 (dd, J = 1.48, 3.64 Hz, 1H), 7.87 (dd, J = 1.84, 8.4 Hz, 1H), 8.31 (d, J = 1.48 Hz, 1H). CIMS: m/z 434 $(M + H)^+$.

18Eb. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.46 (s, 9H), 3.08 (t, J = 7.32 Hz, 2H), 3.91 (s, 3H), 4.11 (s, 2H), 4.33 (t, J = 7.32 Hz, 2H), 7.03−7.10 (m, 3H), 7.18−7.28 (m, 3H), 7.86 (dd, J = 1.48, 8.4 Hz), 8.31 (d, J = 1.48 Hz, 1H). CIMS: m/z 427 $(M + H)^+$.

18Fb. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.45 (s, 9H), 2.57 (q, J = 7.68 Hz, 2H), 3.92 (s, 3H), 3.98 (t, J = 8.04 Hz, 1H), 4.06 (t, J = 7.68 Hz, 2H), 4.12 (s, 2H), 6.92 (d, J = 8.40 Hz, 1H), 7.18−7.34 (m, 10H), 7.87 (dd, J = 1.48, 8.4 Hz, 1H), 8.31 (d, J = 1.48 Hz, 1H). CIMS: m/z 518 $(M + H)^+$.

18Ac. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.09 (t, J = 7.32 Hz, 2H), 4.37 (t, J = 7.32 Hz, 2H), 4.99 (s, 2H), 7.10−7.30 (m, 10H), 7.48 (t, J = 8.04 Hz, 2H), 7.58−7.68 (m, 1H), 8.06 (d, J = 8.44 Hz, 2H). CIMS: m/z 373 $(M + H)^+$.

18Bc. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.96 (d, J = 6.24 Hz, 6H), 2.28 (m, 1H), 3.86−3.96 (m, 5H, OCH_3), 5.06 (s, 2H), 7.25 (d, J = 8.80 Hz, 1H), 7.49 (t, J = 7.72 Hz, 2H), 7.61 (t, J = 7.68 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 7.32 Hz, 2H), 8.33 (s, 1H). CIMS: m/z 383 $(M + H)^+$.

18Cc. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.00 (d, J = 6.24 Hz, 6H), 1.66−1.70 (m, 3H), 3.92 (s, 3H), 4.13 (t, J = 7.32 Hz, 2H), 5.06 (s, 2H), 7.25 (d, J = 8.40 Hz, 1H), 7.50 (t, J = 7.32 Hz, 2H), 7.62 (t, J = 7.32 Hz, 1H), 7.93 (dd, J = 1.48 Hz, 8.44 Hz, 1H), 8.09 (dd, J = 1.48, 8.8 Hz, 2H), 8.32 (d, J = 1.48 Hz, 1H). CIMS: m/z 397 $(M + H)^+$.

18Dc. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.33 (t, J = 7.32 Hz, 2H), 3.91 (s, 3H), 4.40 (t, J = 7.32 Hz, 2H), 5.03 (s, 2H), 6.68 (dd, J = 1.12, 3.68 Hz, 1H), 6.85 (q, J = 1.12, 5.16 Hz, 1H), 7.08−7.14 (m, 2H), 7.50 (t, J = 7.72 Hz, 2H), 7.62 (t, J = 7.32 Hz, 1H), 7.89 (dd, J = 1.44, 8.44 Hz, 1H), 8.07 (d, J = 7.70 Hz, 2H), 8.32 (s, 1H). CIMS: m/z 437 $(M + H)^+$.

18Ec. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.10 (t, J = 7.32 Hz, 2H), 3.91 (s, 3H), 4.37 (t, J = 7.32 Hz, 2H), 5.00 (s, 2H), 7.08 (t, J = 8.44 Hz, 3H), 7.17−7.29 (m, 3H), 7.50 (t, J = 8.08 Hz, 2H), 7.62 (t, J = 8.04 Hz, 1H), 7.87 (dd, J = 1.48, 8.04 Hz, 1H), 8.08 (d, J = 8.04 Hz, 2H), 8.32 (d, J = 1.44 Hz, 1H). CIMS: m/z 431 $(M + H)^+$.

18Fc. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.53−2.62 (m, 2H), 3.92 (s, 3H), 3.99 (t, J = 7.68 Hz, 1H), 4.09 (t, J = 7.68 Hz, 2H), 5.03 (s, 2H), 6.92 (d. J = 8.44 Hz, 1H), 7.18−7.33 (m, 10H), 7.50 (t, J = 8.04 Hz, 2H), 7.61 (t, J = 7.36 Hz, 1H), 7.87 (dd, J = 1.48, 8.4 Hz, 1H), 8.08 (dd, J = 1.08, 7.36 Hz, 2H), 8.31 (d, J = 0.76 Hz, 1H). CIMS: m/z 521 $(M + H)^+$.

18Ad. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.10−2.20 (m, 2H), 3.05 (t, J = 7.68 Hz, 2H), 3.44 (t, J = 7.32 Hz, 2H), 3.82−4.04 (m, 4H), 4.29 (t, J = 7.32 Hz, 2H), 5.02 (t, J = 4.80 Hz, 1H), 7.10−7.30 (m, 8H), 7.65−7.69 (m, 1H). CIMS: m/z 355 $(M + H)^+$.

18Bd. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.93 (d, J = 6.60 Hz, 6H), 2.16−2.28 (m, 3H), 3.49 (t, J = 7.32 Hz, 2H), 3.84−4.00 (m, 9H), 5.04 (t, J = 4.40 Hz, 1H, −C*H*), 7.22 (d, J = 8.44 Hz, 1H), 7.90 (dd, J = 1.84, 8.04 Hz, 1H), 8.35 (d, J = 1.08 Hz, 1H). CIMS: m/z 365 $(M + H)^+$.

18Cd. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.92−1.02 (d, J = 6.7 Hz, 6H), 1.60−1.70 (m, 3H), 2.16−2.22 (m, 2H), 3.49 (t, J = 7.36 Hz, 2H), 3.86−4.10 (m, 9H), 5.04 (t, J = 4.40 Hz, 1H), 7.22 (t, J = 8.40 Hz, 1H), 7.91 (dd, J = 1.44 Hz, 8.04 Hz, 1H), 8.35 (d, J = 1.48 Hz, 1H). CIMS: m/z 379 $(M + H)^+$.

18Dd. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.17 (m, 2H), 3.27 (t, J = 7.32 Hz, 2H), 3.47 (t, J = 7.32 Hz, 2H), 3.84−4.02 (m, 5H), 4.31 (t, J = 7.68 Hz, 2H), 5.02 (t, J = 4.40 Hz, 1H), 6.66 (d, J = 3.10 Hz, 1H), 6.85 (dd, J = 3.28, 1.88 Hz, 1H), 7.09 (d, J = 8.44 Hz, 1H), 7.13 (dd, J = 1.12, 4.00 Hz, 1H), 7.87 (dd, J = 1.48, 8.04 Hz, 1H), 8.35 (d, J = 1.48 Hz, 1H). CIMS: m/z 419 $(M + H)^+$.

18Ed. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.16 (m, 2H), 3.04 (t, J = 7.68 Hz, 2H), 3.46 (t, J = 7.36 Hz, 2H), 3.84−4.00 (m, 7H, $-OCH_2$), 4.28 (t, J = 7.32 Hz, 2H), 5.02 (t, J = 4.40 Hz, 1H), 7.04−7.08 (m, 3H), 7.18−7.28 (m, 3H), 7.85 (dd, J = 1.84, 8.04 Hz, 1H), 8.34 (d, J = 1.08 Hz, 1H). CIMS: m/z 413 $(M + H)^+$.

18Fd. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.19 (m, 2H), 2.53 (m, 2H), 3.48 (t, J = 7.32 Hz, 2H), 3.84−4.08 (m, 12H), 5.03 (t, J = 4.40 Hz, 1H), 6.90 (d, J = 8.80 Hz, 1H), 7.18−7.34 (m, 10H), 7.86 (dd, J = 1.44, 8.04 Hz, 1H), 8.34 (d, J = 1.08 Hz, 1H). CIMS: m/z 503 $(M + H)^+$.

18Ae. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.95 (t, J = 7.32 Hz, 3H), 1.48 (m, 2H), 1.74 (m, 2H), 3.05 (t, J = 7.68 Hz, 2H), 3.36 (t, J = 7.32 Hz, 2H), 4.29 (t, J = 7.72 Hz, 2H), 7.13−7.33 (m, 8H), 7.66−7.77 (m, 1H). CIMS: m/z 311 $(M + H)^+$.

18Be. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.90−1.00 (m, 9H), 1.49 (m, 2H), 1.77 (m, 2H), 2.25 (m, 1H), 3.41 (m, 2H), 3.87 (d, J = 7.72 Hz, 2H), 3.91 (s, 3H), 7.23 (d, J = 8.44 Hz, 1H), 7.91 (dd, J = 1.48, 8.44 Hz, 1H), 8.37 (d, J = 1.44 Hz, 1H). CIMS: m/z (CI) 321 $(M + H)^+$.

18Ce. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.97 (t, J = 7.32 Hz, 3H), 0.99 (d, J = 6.24 Hz, 6H), 1.50 (m, 2H), 1.64−1.67 (m, 3H, $-CH_2$), 1.78 (m, 2H), 3.41 (t, J = 7.32 Hz, 2H), 3.91 (s, 3H), 4.07 (t, J = 7.32 Hz, 2H), 7.22 (d, J = 8.44 Hz, 1H), 7.92 (dd, J = 1.44, 8.44 Hz, 1H), 8.36 (d, J = 1.08 Hz, 1H). CIMS: m/z 335 $(M + H)^+$.

18De. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.95 (t, J = 7.36 Hz, 3H), 1.49 (m, 2H), 1.76 (m, 2H), 3.28 (t, J = 7.32 Hz, 2H), 3.39 (t, J = 7.32 Hz, 2H), 3.91 (s, 3H), 4.32 (t, J = 7.32 Hz, 2H), 6.68 (dd, J = 1.08, 4.00 Hz, 1H), 6.86 (dd, J = 5.12 Hz, 1H), 7.09 (d, J = 8.44 Hz, 1H), 7.14 (dd, J = 1.08, 5.16 Hz, 1H), 7.87 (dd, J = 1.80, 8.76 Hz, 1H), 8.36 (d, J = 1.08 Hz, 1H). CIMS: m/z 375 $(M + H)^+$.

18Ee. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.95 (t, J = 7.36 Hz, 3H), 1.46 (m, 2H), 1.76 (m, 2H), 3.05 (t, J = 7.32 Hz, 2H), 3.38 (t, J = 7.36 Hz, 2H), 3.91 (s, 3H), 4.29 (t, J = 7.32 Hz, 2H), 7.05−7.28 (m, 3H), 7.18−7.28 (m, 3H), 7.86 (dd, J = 1.48, 8.44 Hz, 1H), 8.36 (d, J = 1.48 Hz, 1H). CIMS: m/z 369 $(M + H)^+$.

18Fe. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.96 (t, J = 7.36 Hz, 3H), 1.49 (m, 2H), 1.78 (m, 2H), 2.54 (q, J = 7.68 Hz, 2H), 3.39 (t, J = 7.32 Hz, 2H), 3.92 (s, 3H), 3.94−4.05 (m, 3H), 6.90 (d, J = 8.44 Hz, 1H), 7.20−7.36 (m, 10H), 7.86 (dd, J = 1.48, 8.44 Hz, 1H), 8.36 (d, J = 1.12 Hz, 1H). CIMS: m/z 459 $(M + H)^+$.

References and Notes

(1) Current address: Versicor, Inc., 34790 Ardentech Court, Fremont, CA 93555. E-mail: braju@versicor.com.

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