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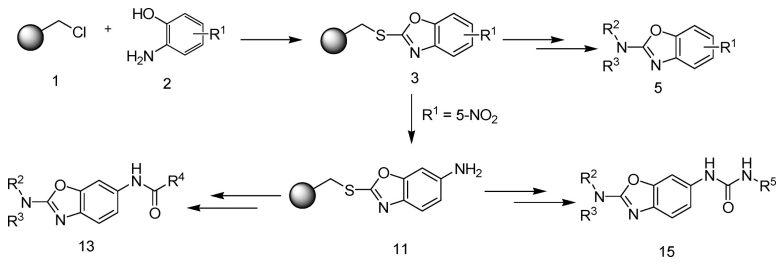

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Articles

Solid-Phase Synthesis of the 2-Aminobenzoxazole Library Using Thioether Linkage as the Safety-Catch Linker

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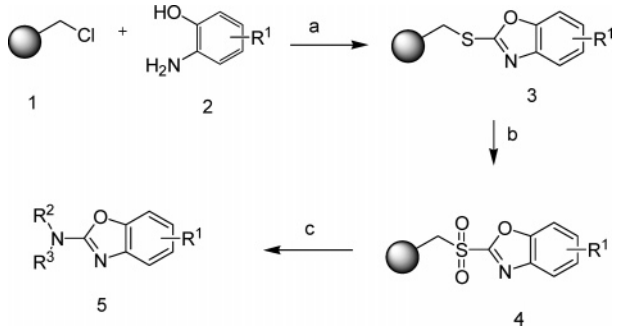
An efficient solid-phase methodology has been developed for the synthesis of 2-aminobenzoxazole derivatives. The key step in this procedure involves preparation of polymer-bound 2-mercaptobenzoxazole resins **3** by reaction of the Merrifield resin with 2-aminophenols and CS_2 in the presence of DIC in MeCN. Oxidation of the resulting resins followed by treatment with amines gives the desired 2-aminobenzoxazole products **5**. Further diversification can be introduced to the key resin **11**, derived from the nitro group containing resin **3c**. This process produces the corresponding amine, which upon reaction with acid chlorides and isocyanates can be used to generate various 6-functionalized 2-aminobenzoxazole analogues **13** and **15**.

Introduction

Combinatorial chemistry has become an extremely powerful technique for the generation of druglike, small, organic molecule libraries in medicinal chemistry programs.[1] Solid-phase organic synthesis (SPOS) is especially useful in creating massive numbers of hit and lead compounds.[2] In these processes, the choice of the linker that serves to attach the library scaffold to the polymer support is critical. As a result, a variety of elegant linking methods have been developed (i.e., safety-catch linkers[3]) that enable introduction of additional diversity into the products during the cleavage reactions. The sulfone linker is an example of a safety-catch linker that can be cleaved from resins by using nucleophilic substitution reactions with amines.[4] We have utilized this general methodology to produce amine-functionalized 1,3,4-oxadiazole, 1,3,4-thiadiazole, and thiazole libraries through consecutive oxidation and amine-promoted cleavage of thioether linkages produced in carbon disulfide-mediated reactions of the Merrifield resin.[5]

As a part of a recent drug discovery effort, we required target libraries that are based on the benzoxazole privileged structure.[6] Benzoxazole derivatives are of particular interest in medicinal chemistry,[7] and consequently, they have been targets of a number of solution- and solid-phase synthetic studies;[8] however, the methods developed to date for preparation of benzoxazole libraries do not have sufficiently high levels of diversity. In a recent investigation aimed at the discovery of a general method for facile and rapid solid-phase parallel synthesis of druglike heterocycles, we have employed a carbon disulfide-mediated thioether linker methodology in a procedure for efficient solid-phase synthesis of 2-aminobenzoxazole derivatives. The results of this effort are presented below.

Scheme 1[a]



[a] Reagents and conditions: (a) CS_2, DIC, TEA, MeCN, rt, 24 h; (b) *m*CPBA, DCM, 0 °C, 3 h; (c) R^2R^3NH, MeCN, 80 °C, 6 h.

Results and Discussion

The sequence used to prepare the target 2-aminobenzoxazole derivatives **5** starts with the Merrifield resin **1** as the polymer support. The benzyl chloride groups in this can be used to produce thioether linkages by reaction with the thiol formed in the cyclization reaction of carbon disulfide and aminophenol (Scheme 1). Specifically, the intermediate benzoxazole resin **3** is generated by treatment of aminophenol **2** with CS_2 and Merrifield resin in the presence of triethylamine (TEA) in MeCN; however, under this condition, **3** is obtained in very low yield. We speculated that the inefficiency of this process is due to rapid release of 2-mercaptobenzoxazole **8** from the intermediate **6** during the cyclization reaction (Scheme 2, path I). We attempted to circumvent this cleavage process by preforming 2-mercaptobenzoxazole

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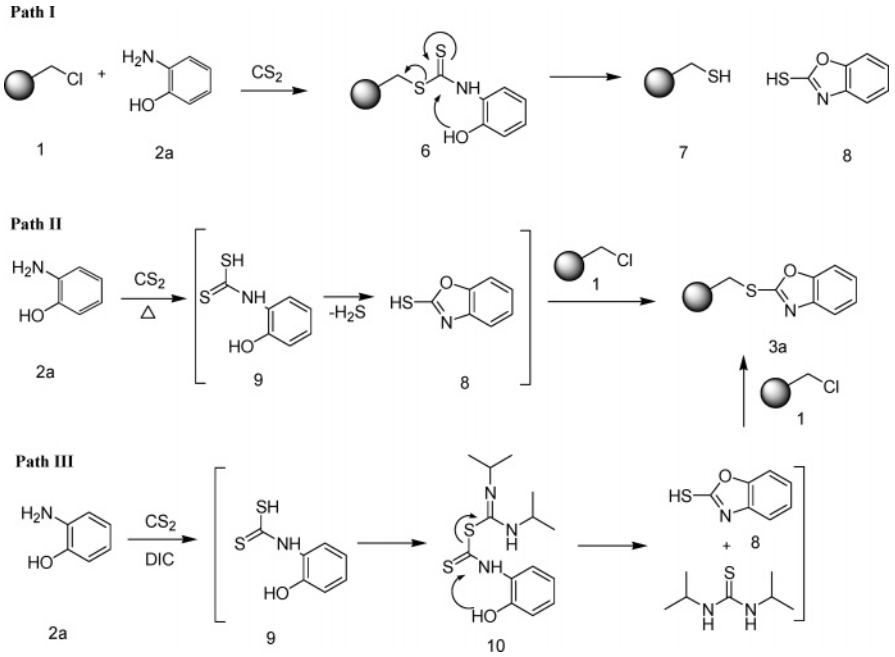
Scheme 2



8; however, reaction of aminophenol with CS_2 for 6 h at 80 °C gave 2-mercaptobenzoxazole **8** in a low yield (Scheme 2, path II). A solution-phase synthesis of 2-mercaptobenzoxazole has been described,[9] but in situ reaction under the reported conditions (CS_2, KOH, EtOH, reflux) did not successfully lead to generation of the desired resin **3**.

We reasoned that a possible solution to this problem would be to accelerate the cyclization reaction. For this purpose, we examined the effects of various additives, including *N*,*N*′-diisopropylcarbodiimide (DIC), *N*,*N*′-dicyclohexylcarbodiimide (DCC), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC), *p*-toluenesulfonyl chloride (*p*-TsCl), and found that the addition of DIC leads to a markedly increased yield of the desired resin **3a**. It appears that in the presence of DIC,[10] the dithiocarbamic acid **9** rapidly reacts to give **10**. This intermediate subsequently cyclizes to yield 2-mercaptobenzoxazole **8**, which combines with the Merrifield resin to give the polymer-bound benzoxazole **3a**. The success of this process is evidenced by the observation of characteristic benzoxazole bands at 1223, 1127, and 1070 cm^{-1} in the attenuated total reflection (ATR)-FTIR spectra and for resin **3c** by nitro bands at 1530 and 1343 cm^{-1} (Figure 1).

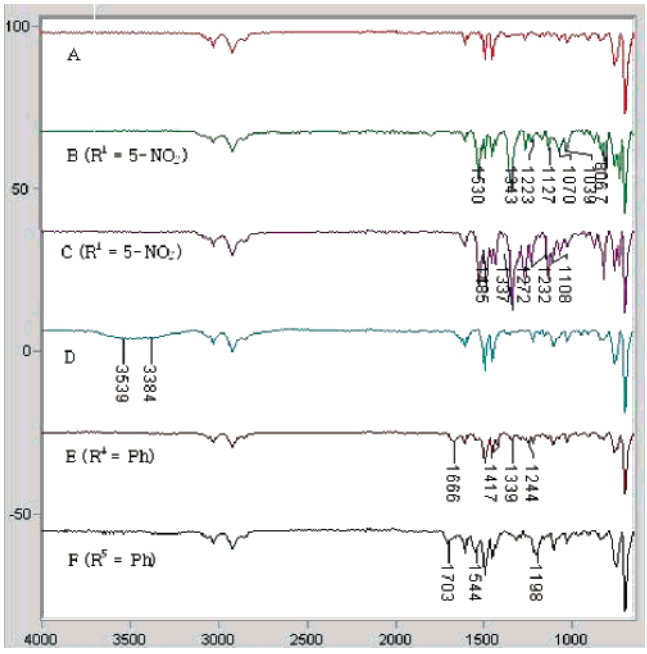


Figure 1. ATR−FTIR spectra on single bead of resins **1** (A), **3** (B), **4** (C), **11** (D), **12** (E), and **14** (F).

The resins **3** are transformed to the respective sulfone derivatives **4** by treatment with *m*-chloroperoxybenzoic acid (*m*CPBA) in DCM at 0 °C. To explore the versatility of this methodology, various amines were reacted with the sulfone containing resins to generate the corresponding benzoxazole derivatives. These cleavage reactions generally proceeded in high yields (Table 1). The LC/MS spectrum of the crude product mixture containing the 2-piperidinobenzoxazole **5a** is shown in Figure 2.To introduce additional diversification

Table 1. Yields of Formation of Benzoxazole Derivatives **5**

Code	R^1	R^2R^3NH	Yield (%)[a]	Purity (%)[b]	Code	R^1	R^2R^3NH	Yield (%)[a]	Purity (%)[b]
5a	H		70	>99	**5k**	5-NO_2		50	89
5b	H		68	>99	**5l**	4-^{t}Bu		73	99
5c	H		53	>99	**5m**	4-^{t}Bu		62	93
5d	H		61	89	**5n**	4-^{t}Bu		60	>99
5e	4-Cl		53	>99	**5o**	5-Me		46	99
5f	4-Cl		49	95	**5p**	5-Me		86	96
5g	4-Cl		47	81	**5q**	5-Me		56	99
5h	4-Cl		75	98	**5r**	5-Me		71	97
5i	5-NO_2		66	74	**5s**	5-Me		79	99
5j	5-NO_2		53	95	**5t**	5-Me		69	>99

[a] Three-step overall yield from the Merrifield resin **1** (loading capacity of the resin **1** is 0.94 mmol/g). [b] Purity of the final products were established by using LC/MS.

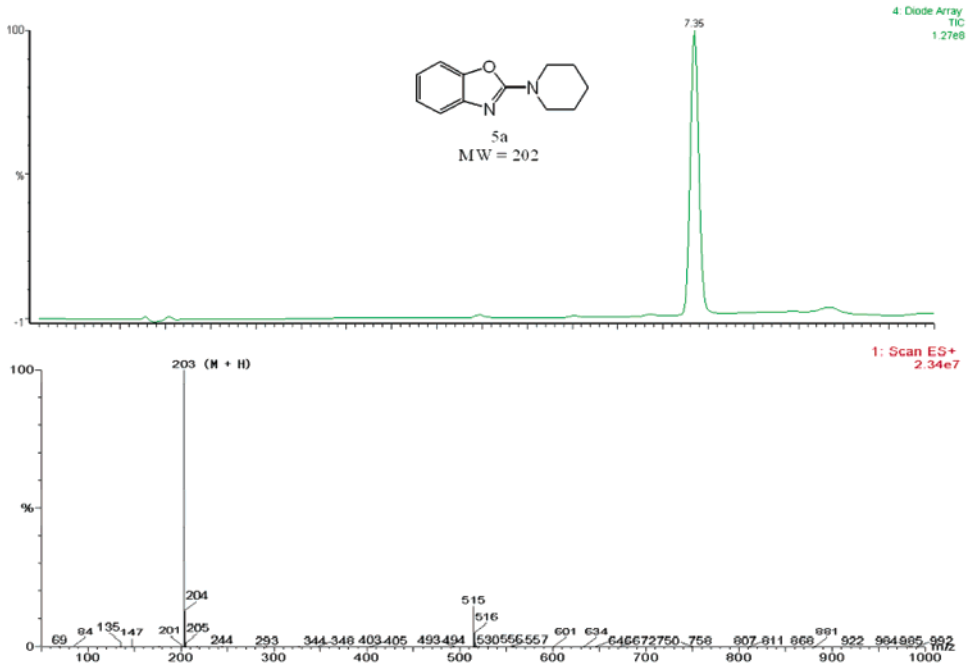
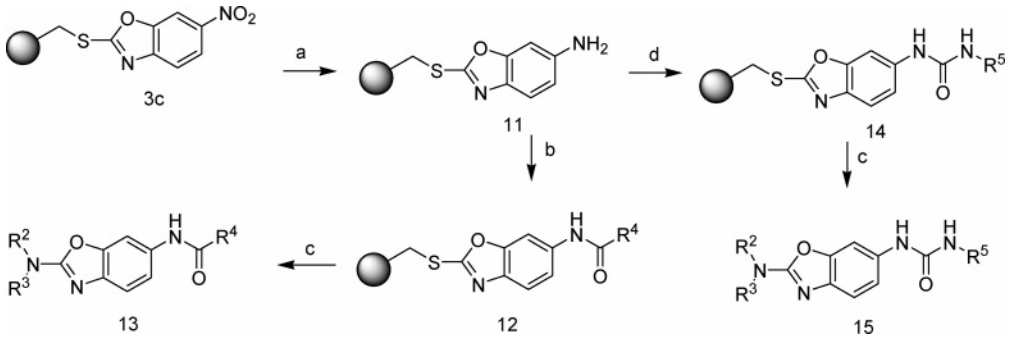


Figure 2. LC/MS spectrum of the crude product mixture containing **5a**.

Scheme 3[a]



[a] Reagents and conditions: (a) $SnCl_2 \cdot 2H_2O$, DMF, rt, 12h; (b) acid chlorides, TEA, DMF, rt, 12 h; (c) (i) *m*CPBA, DCM, 0 °C, 3 h; (ii) R^2R^3NH, MeCN, 80 °C, 6 h; (d) isocyanates, DMF, rt, 12 h.

into this methodology, the nitro group containing resin **3c** was reduced to generate amine resin **11** by treatment with $SnCl_2 \cdot 2H_2O$ in DMF at room temperature for 12 h. The progress of the reaction was monitored by the disappearance of nitro bands (1530 and 1343 cm^{-1}) and the appearance of broad amine bands (3539 and 3384 cm^{-1}) in the ATR-FTIR. Functionalization of the amino group in resin **11** can be promoted by room temperature reactions with acid chlorides or isocyanates in the presence of TEA in DMF to generate corresponding amide resins **12** and urea resins **14**. The progress of these reactions was monitored by ATR-FTIR, which showed the growth of the carbonyl bands for the amide (1666 cm^{-1}) and urea (1703 and 1544 cm^{-1}) groups in **12** and **14**, respectively. In each case, the desired products are cleaved from the resin by sequential treatment with *m*CPBA in DCM at 0 °C (producing the sulfone) and various amines in acetonitrile at 80 °C (Table 2).

In the effort described above, an efficient solid-phase methodology has been developed for the synthesis of 2-aminobenzoxazole-based libraries. The procedure involves generation of polymer-bound 2-mercaptobenzoxazole resins **3** by reaction of the Merrifield resin with 2-aminophenols and CS_2 in the presence of DIC in MeCN. Oxidation of resins **3** followed by treatment with amines gives rise to the desired 2-aminobenzoxazole products **5**. Additional diversification can be introduced into this methodology by reduction of the nitro groups in resin **3c** following treatment with acid chlorides and isocyanates. Sequential oxidation and amine cleavage then gives 6-functionalized 2-aminobenzoxazole derivatives **13** and **15**.

Experimental Section

Representative Procedure for Preparation of Polymer-Bound 2-Mercaptobenzoxazole 3. Preparation of 5-Nitro-2-mercaptobenzoxazole Resin 3c. To a suspension of 4-nitro-2-aminophenol (2.6 g, 16.9 mmol) in MeCN were added successively CS_2 (1.1 mL, 16.9 mmol), DIC (2.6 mL, 16.9 mmol), and TEA (2.4 mL, 16.9 mmol). The mixture was shaken for 1 h at room temperature, Merrifield resin (6.0 g, 5.64 mmol) was added, and the mixture was shaken for 12 h at room temperature. The suspension was filtered, and the precipitate containing the 5-nitro-2-mercaptobenzoxazole resin **3c** was washed with DMF (×2), DCM (×2),

Table 2. Yields of Formation of Benzoxazole Derivatives **13** and **15**

code	R^4	R^2R^3NH	Yield (%)[a]	Purity (%)[b]
13a	Ph		51	95
13b	Ph		48	84
13c	Ph		20	87
13d	cyclopropyl		23	>99
13e	cyclopropyl		59	99
13f	cyclopropyl		32	>99
13g	cyclopropyl		21	>96
13h	4-MeOPh		52	95
13i	4-MeOPh		33	94
13j	2-ClPh		52	95
13k	2-ClPh		48	93
13l	2-ClPh		63	97
13m	2-ClPh		45	95
	R^5			
15a	Ph		46	83
15b	Ph		41	82
15c	Ph		51	87
15d	Ph		38	87
15e	4-MeOPh		45	89
15f	*n*-Bu		37	82
15g	*n*-Bu		29	70

[a] Five-step overall yield from the Merrifield resin **1** (loading capacity of the resin **1** is 0.94 mmol/g). [b] Purity of the final products was established by using LC/MS.

and MeOH (×2) and dried under high vacuum. FTIR (cm^{-1}): 1530, 1343, 1223, 1127, 1070, 1039, 807.

Representative Procedure for Activation of Thioether to Sulfone. To a solution of polymer-bound benzoxazole **3c** (6.0 g, 5.64 mmol) in DCM was added *m*CPBA (4.9 g, 28.2 mmol), and the mixture was shaken for 3 h at 0 °C. The suspension was filtered, and the precipitate containing the resin **4c** was washed with DMF (×2), DCM (×2), and MeOH (×2) and dried under high vacuum. FTIR (cm^{-1}): 1485, 1337, 1272, 1232, 1108, 807.

Representative Procedure for the Thermal Cleavage Step. Formation of 2-Piperidobenzoxzole 5a. To a suspension of the resins **4a** (200 mg, 0.165 mmol) in MeCN (2 mL) was added an excess of piperidine (0.033 mL, 0.330 mmol) at room temperature. The mixture was heated at 80 °C for 6 h to give the desired product. The resin was filtered off and washed with CH_2Cl_2 (5 mL) and MeOH (5 mL). The combined filtrate was concentrated under vacuum to afford a mixture containing the desired product and excess of amine. The excess of amine was removed by short-passed silica gel chromatography to yield the desired product **5a** (23 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, 1H, J = 7.8 Hz), 7.23 (d, 1H, J = 8.0 Hz), 7.16−7.12 (m, 1H), 7.06−6.97 (m, 1H), 3.66 (brs, 4H), 1.68 (brs, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 148.7, 143.4, 123.8, 120.2 116.0, 108.6, 46.6, 25.3, 24.1; LC/MS (ESI) m/z 203 $(M + H)^+$.

2-(4-Phenylpiperazino)benzoxazole 5b. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.24 (m, 5H), 7.20−7.15 (m, 2H), 7.07−7.03 (m, 1H), 6.19−6.09 (m, 1H), 4.64 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.1, 151.1, 148.8, 143.0, 129.3, 124.1, 120.8, 120.7, 116.9, 116.4, 108.8, 49.2, 45.6; LC/MS (ESI) m/z 280 $(M + H)^+$.

2-[4-(2-Chlorophenyl)piperazino]benzoxazole 5c. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.37 (m, 2H), 7.29−7.23 (m, 2H), 7.20−7.16 (m, 1H), 7.06−7.00 (m, 3H), 3.91−3.88 (m, 4H), 3.19−3.16 (m, 4H); LC/MS (ESI) m/z 314 $(M + H)^+$.

2-(4-Methoxyphenethylamino)benzoxazole 5d. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, 1H, J = 7.8 Hz), 7.26−7.22 (m, 1H), 7.19−7.14 (m, 4H), 7.05−7.01 (m, 1H), 6.86 (d, 2H, J = 8.4 Hz), 5.03 (brs, 1H), 3.79 (s, 3H), 3.72 (m, 2H), 2.93 (t, 2H, J = 6.8 Hz); LC/MS (ESI) m/z 314 $(M + H)^+$.

5-Chloro-2-[4-(2-chlorophenyl)piperazino]benzoxazole 5e. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (m, 1H), 7.32 (d, 1H, J = 2.0 Hz), 7.26−7.24 (m, 1H), 7.17 (d, 1H, J = 8.4 Hz), 7.05−7.00 (m, 3H), 3.90−3.87 (m, 4H), 3.18−3.15 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.9, 148.7, 147.4, 144.5, 130.8, 129.4, 129.1, 127.8, 124.5, 120.6, 120.5, 116.4, 109.3, 50.7, 45.9; LC/MS (ESI) m/z 348 $(M + H)^+$.

5-Chloro-2-(4-pyrimidin-2-ylpiperazino)benzoxazole 5f. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36−8.34 (m, 2H), 7.33 (d, 1H, J = 2.0 Hz), 7.17 (d, 1H, J = 8.5 Hz), 7.01−6.98 (m, 1H), 6.58−6.56 (m, 1H), 4.00−3.98 (m, 4H), 3.79−3.76 (m, 4H); LC/MS (ESI) m/z 316 $(M + H)^+$.

5-Chloro-2-(4-chlorobenzylamino)benzoxazole 5g. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.30 (m, 4H), 7.16−7.10 (m, 2H), 7.03−7.00 (m, 1H), 5.89 (m, 1H), 4.63 (s, 2H); LC/MS (ESI) m/z 293 $(M + H)^+$.

5-Chloro-2-phenylaminobenzoxazole 5h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60−7.58 (m, 3H), 7.45 (d, 1H, J = 2.0 Hz), 7.43−7.39 (m, 2H), 7.26−7.23 (m, 1H), 7.14−7.09 (m, 2H); LC/MS (ESI) m/z 245 $(M + H)^+$.

2-[4-(4-Methoxyphenyl)piperazino]-6-nitrobenzoxazole 5i. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (dd, 1H, J = 8.6, 1.0 Hz), 7.50 (dd, 1H, J = 7.9 Hz, 1.0 Hz), 7.07 (m, 1H), 6.95 (m, 2H), 6.89−6.86 (m, 2H), 4.00−3.98 (m, 4H), 3.79 (s, 3H), 3.22−3.19 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2, 154.8, 150.9, 145.1, 140.0, 136.0, 120.3, 119.4, 119.3, 114.6, 113.7; LC/MS (ESI) m/z 355 $(M + H)^+$.

2-[4-(2-Chlorophenyl)piperazino]-6-nitrobenzoxazole 5j. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02−8.00 (m, 1H), 7.50 (d, 1H, J = 7.8 Hz), 7.42−7.40 (m, 1H), 7.28−7.24 (m, 1H), 7.09−7.03 (m, 3H), 4.04−4.02 (m, 4H), 3.21−3.19 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2, 150.9, 148.5, 140.0, 136.0, 130.8, 129.1, 127.8, 124.6, 120.6, 120.3, 119.3, 113.7; LC/MS (ESI) m/z 359 $(M + H)^+$.

6-Nitro-2-[3-(pyrrolidin-2-one-1-yl)propylamino]benzoxazole 5k. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, 1H, J = 8.5 Hz), 7.48 (d, 1H, J = 7.8 Hz), 7.07−7.03 (m, 1H), 3.60 (br s, 2H), 3.47−3.43 (m, 4H), 2.44 (t, 2H, J = 8.1 Hz), 2.11−2.06 (m, 2H), 1.95−1.90 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.1, 165.2, 150.6, 140.1, 135.6, 120.0,

119.1, 113.8, 47.4, 39.9, 39.6, 30.9, 27.0, 17.9; LC/MS (ESI) *m*/*z* 305 $(M + H)^+$.

5-*tert*-Butyl-2-piperidinobenzoxazole 5l. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, 1H, $J = 1.8$ Hz), 7.14 (d, 1H, $J = 8.4$ Hz), 7.04 (m, 1H), 3.64 (br, 4H), 1.67 (br, 6H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.7, 147.3, 146.7, 143.1, 117.4, 113.2, 107.6, 46.7, 31.8, 25.3, 24.1; LC/MS (ESI) *m*/*z* 259 $(M + H)^+$.

5-*tert*-Butyl-2-[4-(4-methoxyphenyl)piperazino]benzoxazole 5m. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, 1H, $J = 1.9$ Hz), 7.18 (d, 1H, $J = 8.4$ Hz), 7.08 (dd, 1H, $J = 8.4$, 1.9 Hz), 6.95 (m, 2H), 6.86 (m, 2H), 3.86−3.83 (m, 2H), 3.78 (s, 3H), 3.18−3.16 (m, 2H), 1.34 (s, 9H); LC/MS (ESI) *m*/*z* 366 $(M + H)^+$.

5-*tert*-Butyl-2-(phenylamino)benzoxazole 5n. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63−7.61 (m, 2H), 7.56 (d, 1H, $J = 1.8$ Hz), 7.41−7.37 (m, 2H), 7.27−7.25 (m, 1H), 7.19−7.18 (m, 1H), 7.10 (m, 1H), 1.37 (s, 9H); LC/MS (ESI) *m*/*z* 267 $(M + H)^+$.

2-[4-(4-Chlorophenyl)piperazino]-6-methylbenzoxazole 5o. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26−7.22 (m, 3H), 7.09 (s, 1H), 6.99 (m, 1H), 6.88 (dd, 1H, $J = 7.9$, 2.1), 3.84−3.81 (m, 4H), 3.26−3.23 (m, 4H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7, 149.7, 148.9, 140.3, 131.1, 129.1, 125.6, 124.9, 118.1, 115.8, 109.4, 49.1, 45.5, 21.5; LC/MS (ESI) *m*/*z* 328 $(M + H)^+$.

2-[4-(2-Fluorophenyl)piperazino]-6-methylbenzoxazole 5p. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (m, 1H), 7.09−7.03 (m, 2H), 7.01−6.94 (m, 3H), 3.87−3.84 (m, 4H), 3.20−3.17 (m, 4H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.9, 155.8 ($^1J_{CF} = 244.5$ Hz), 149.0, 140.5, 139.7 ($^2J_{CF} = 8.5$ Hz), 130.9, 124.8, 124.5 ($^4J_{CF} = 3.4$ Hz), 123.2 ($^3J_{CF} = 8.0$ Hz), 119.3 ($^3J_{CF} = 3.1$ Hz), 116.3 ($^2J_{CF} = 20.4$ Hz), 115.8, 109.4, 50.1 ($^4J_{CF} = 2.5$ Hz), 45.8, 21.5; LC/MS (ESI) *m*/*z* 312 $(M + H)^+$.

2-(4-Fluorophenylamino)-6-methylbenzoxazole 5q. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (brs, 1H), 7.54−7.51 (m, 2H), 7.30 (d, 1H, $J = 8.0$ Hz), 7.16 (s, 1H), 7.09−7.03 (m, 3H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9 ($^1J_{CF} = 240.6$ Hz), 158.5, 148.1, 139.4, 134.1 ($^4J_{CF} = 2.9$ Hz), 132.0, 125.2, 120.3 ($^3J_{CF} = 8.0$ Hz), 116.1, 116.0 ($^2J_{CF} = 22.5$ Hz), 109.7, 21.5; LC/MS (ESI) *m*/*z* 243 $(M + H)^+$.

2-(4-Methoxybenzylamino)-6-methylbenzoxazole 5r. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, 2, $J = 8.6$ Hz), 7.17−7.15 (m, 1H), 7.04 (s, 1H), 6.95 (d, 1H, $J = 7.9$ Hz), 6.86 (d, 2, $J = 8.6$ Hz), 5.77 (br, 1H), 4.57 (s, 2H), 3.78 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8, 159.2, 148.7, 140.4, 130.9, 129.9, 129.0, 124.6, 115.7, 114.1, 109.3, 55.3, 46.6, 21.4; LC/MS (ESI) *m*/*z* 269 $(M + H)^+$.

2-(4-Methoxyphenethylamino)-6-methylbenzoxazole 5s. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, 1H, $J = 8.0$ Hz), 7.12 (d, 2, $J = 8.3$ Hz), 7.04 (s, 1H), 6.96 (d, 1H, $J = 7.9$ Hz), 6.83 (d, 2, $J = 8.0$ Hz), 5.27 (br, 1H), 3.77 (s, 3H), 3.68 (m, 2H), 2.91 (t, 2H, $J = 4.8$ Hz), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8, 158.4, 148.7, 140.6, 130.8, 130.4, 129.8, 124.6, 115.7, 114.1, 109.3, 55.3, 44.3, 34.9, 21.5; LC/MS (ESI) *m*/*z* 283 $(M + H)^+$.

6-Methyl-2-(4-Methylphenylamino)benzoxazole 5t. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74−8.48 (br, 1H), 7.46 (d, 2, $J = 8.2$ Hz), 7.32 (d, 1H, $J = 8.0$ Hz), 7.19−7.15 (m, 3H), 7.03 (d, 1H, $J = 8.0$ Hz), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 139.7, 135.5, 132.8, 131.6, 129.8, 125.0, 118.7, 116.1, 109.6, 21.5, 20.8; LC/MS (ESI) *m*/*z* 239 $(M + H)^+$.

Procedure for the Reduction of the Nitro Group. To a suspension of the resins **3c** in DMF was added $SnCl_2 \cdot 2H_2O$, and the mixture was shaken for 12 h at room temperature. The suspension was filtered, and the precipitate containing the resin **11** was washed with DMF (×2), DCM (×2), and MeOH (×2) and dried under high vacuum. FTIR (cm^{-1}): 3539, 3384, 1492, 1451, 1220, 1107, 807.

Representative Procedure for the Functionalization of Amino Group. Formation of 6-Benzamidobenzoxazole Resin 12a. To a suspension of the resin **11** (200 mg, 0.154 mmol) was added benzoyl chloride (0.089 mL, 0.771 mmol) and TEA (0.107 mL, 0.771 mmol). The suspension was shaken for 12 h at room temperature. The suspension was filtered, and the precipitate containing resin **12a** was washed with DMF (×2), DCM (×2), and MeOH (×2) and dried under high vacuum. FTIR (cm^{-1}): 1666, 1485, 1450, 1417, 1339, 1244, 1110.

6-Benzamido-2-(4-methoxyphenethylamino)benzoxazole 13a. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (brs, 1H), 8.00 (s, 1H), 7.85 (d, 2H, $J = 7.5$ Hz), 7.54−7.50 (m, 1H), 7.46−7.42 (m, 2H), 7.27−7.24 (m, 1H), 7.13−7.06 (m, 3H), 6.83 (d, 2H, $J = 8.4$ Hz), 5.42 (brs, 1H), 3.77 (s, 3H), 3.67−3.64 (m, 2H), 2.90 (t, 2H, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 162.4, 158.4, 148.6, 139.9, 134.9, 131.8, 131.7, 130.3, 129.8, 129.7, 127.0, 116.5, 115.7, 114.1, 102.9, 55.3, 44.4, 34.7; LC/MS (ESI) *m*/*z* 388 $(M + H)^+$.

6-Benzamido-2-(4-methylphenylamino)benzoxazole 13b. ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 9.93 (s, 1H), 9.86 (s, 1H), 8.14 (d, 1H, $J = 1.4$ Hz), 7.98 (d, 2H, $J = 7.3$ Hz), 7.63−7.61 (m, 2H), 7.53 (d, 1H, $J = 7.3$ Hz), 7.50−7.46 (m, 2H), 7.39−7.34 (m, 2H), 7.13 (d, 1H, $J = 7.9$ Hz), 2.32 (s, 3H); LC/MS (ESI) *m*/*z* 344 $(M + H)^+$.

6-Benzamido-2-(4-pyrimidin-2-yl-piperazino)benzoxazole 13c. ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 9.15 (s, 1H), 8.35−8.33 (m, 2H), 8.06 (m, 1H), 7.94−7.91 (m, 2H), 7.53−7.49 (m, 1H), 7.46−7.43 (m, 2H), 7.31−7.26 (m, 2H), 6.57−6.55 (m, 1H), 4.10−3.97 (m, 4H), 3.77−3.74 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6): δ 116.1, 162.4, 161.5, 157.8, 148.7, 139.5, 135.2, 132.5, 131.4, 128.4, 127.4, 116.9, 115.6, 110.5, 102.9, 45.4, 43.0; LC/MS (ESI) *m*/*z* 401 $(M + H)^+$.

6-Cyclopropanecarboxamido-2-[4-(4-chlorophenyl)piperazino]benzoxazole 13d. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.56 (s, 1H), 7.26−7.22 (m, 3H), 6.96 (d, 1H, $J = 7.7$ Hz), 6.89−6.86 (m, 2H), 3.84−3.81 (m, 4H), 3.27−3.24 (m, 4H), 1.53−1.49 (m, 1H), 1.11−1.07 (m, 2H), 0.86−0.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 161.8, 149.7, 148.8, 132.3, 129.2, 125.7, 118.2, 115.9, 115.8, 102.5, 49.1, 45.5, 15.7, 7.9; LC/MS (ESI) *m*/*z* 397 $(M + H)^+$.

6-Cyclopropanecarboxamido-2-[4-(2-chlorophenyl)piperazino]benzoxazole 13e. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97−7.91 (m, 2H), 7.40−7.38 (m, 1H), 7.27−7.21 (m, 2H), 7.04−6.97 (m, 3H), 3.86−3.84 (m, 4H), 3.16−3.13 (m, 4H), 1.55−1.51 (m, 1H), 1.10−1.06 (m, 2H), 0.83−0.81 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 162.4, 148.8, 139.3, 132.2, 130.7, 129.0, 127.7, 124.4, 120.6, 116.0, 115.6, 102.6, 50.7, 45.9, 15.6, 7.8; LC/MS (ESI) *m/z* 397 $(M + H)^+$.

6-Cyclopropanecarboxamido-2-(4-chlorobenzylamino)-benzoxazole 13f. ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 9.43 (s, 1H), 7.94 (m, 1H), 7.41−7.40 (m, 1H), 7.35 (d, 2H, J = 8.4 Hz), 7.30−7.28 (m, 2H), 7.18 (d, 1H, J = 8.3 Hz), 7.09−7.06 (m, 1H), 4.57 (d, 1, J = 5.9 Hz), 1.73−1.71 (m, 1H), 1.02−0.98 (m, 2H), 0.81−0.77 (m, 2H); LC/MS (ESI) *m/z* 342 $(M + H)^+$.

6-Cyclopropanecarboxamido-2-(4-fluorophenylamino)-benzoxazole 13g. ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 9.86 (brs, 1H), 9.54 (s, 1H), 8.09 (s, 1H), 7.73−7.70 (m, 2H), 7.31 (d, 1H, J = 8.3 Hz), 7.10 (m, 1H), 7.04−7.00 (m, 2H), 1.74 (m, 1H), 1.26−1.00 (m, 2H), 0.83−0.78 (m, 2H); LC/MS (ESI) *m/z* 312 $(M + H)^+$.

6-(4-Methoxybenzamido)-2-(4-phenylpiperazino)benzoxazole 13h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.87−7.84 (m, 3H), 7.30 (d, 1H, J = 8.4 Hz), 7.09−7.04 (m, 3H), 7.01−6.96 (m, 4H), 3.89−3.86 (m, 7H), 3.22−3.19 (m, 4H); LC/MS (ESI) *m/z* 447 $(M + H)^+$.

6-(4-Methoxybenzamido)-2-(4-fluorobenzylamino)benzoxazole 13i. ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 9.49 (s, 1H), 8.03 (s, 1H), 7.94 (d, 2H, J = 8.6 Hz), 7.48 (s, 1H), 7.39−7.36 (m, 2H), 7.30−7.21 (m, 4H), 7.02−6.93 (m, 4H), 4.58 (d, 2H, J = 4.6 Hz), 3.86 (s, 3H); LC/MS (ESI) *m/z* 392 $(M + H)^+$.

6-(2-Chlorobenzamido)-2-(4-phenylpiperazino)benzoxazole 13j. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.98 (s, 1H), 7.77 (m, 1H), 7.45−7.38 (m, 3H), 7.33−7.26 (m, 3H), 7.09 (m, 1H), 6.98 (d, 2H, J = 7.9 Hz), 6.93 (s, 1H), 3.88−3.85 (m, 4H), 3.33−3.30 (m, 4H); LC/MS (ESI) *m/z* 433 $(M + H)^+$.

6-(2-Chlorobenzamido)-2-(4-methoxybenzylamino)benzoxazole 13k. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.50 (s, 1H), 8.05 (s, 1H), 7.58 (m, 1H), 7.43 (m, 1H), 7.39−7.30 (m, 4H), 7.23 (m, 2H), 6.87−6.84 (m, 3H), 7.55 (d, 2H, J = 5.0 Hz), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 162.7, 159.0, 148.4, 139.8, 136.6, 132.1, 130.9, 130.3, 129.9, 129.4, 129.0, 126.9, 116.1, 115.4, 113.9, 102.3, 55.2, 46.3; LC/MS (ESI) *m/z* 408 $(M + H)^+$.

6-(2-Chlorobenzamido)-2-(phenylamino)benzoxazole 13l. ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 9.92 (s, 1H), 9.82 (s, 1H), 8.22 (d, 1H, J = 2.1 Hz), 7.73 (d, 2H, J = 7.7 Hz), 7.58 (d, 1H, J = 1.8 Hz), 7.45 (d, 1H, J = 1.3 Hz), 7.39−7.32 (m, 6H), 7.02 (d, 1H, J = 7.4 Hz); LC/MS (ESI) *m/z* 364 $(M + H)^+$.

6-(2-Chlorobenzamido)-2-(2-pyrrolidin-1-yl-ethylamino)benzoxazole 13m. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.91 (d, 1H, J = 1.9 Hz), 7.70−7.67 (m, 1H), 7.41−7.24 (m, 4H), 7.18−7.15 (m, 1H), 6.40 (t, 1H, 1.3 Hz), 3.43−3.36 (m, 6H), 2.40−2.36 (m, 2H), 2.06−1.99 (m, 2H), 1.87−1.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.0, 164.7, 162.6, 148.5, 140.2, 135.5, 131.4, 131.3, 130.7, 130.2, 130.0, 127.1, 116.37, 115.5, 102.7, 47.4, 39.6, 30.8, 26.4, 17.9; LC/MS (ESI) *m/z* 413 $(M + H)^+$.

2-[4-(4-Methoxyphenyl)piperazino]-6-phenylureidobenzoxazole 15a. ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 8.16 (s, 1H), 7.07 (s, 1H), 7.85 (s, 1H), 7.45 (d, 2H, J = 7.6 Hz), 7.29−7.25 (m, 2H), 7.22 (d, 1H, J = 7.8 Hz), 6.99−6.94 (m, 3H), 6.90 (d, 1H, J = 8.4 Hz), 6.87−6.85 (m, 2H), 3.84−3.81 (m, 4H), 3.78 (s, 3H), 3.19−3.16 (m, 4H); LC/MS (ESI) *m/z* 444 $(M + H)^+$.

2-[4-(4-Chlorophenyl)piperazino]-6-phenylureidobenzoxazole 15b. ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 8.16 (s, 1H), 8.06 (s, 1H), 7.88 (s, 1H), 7.46−7.44 (m, 2H), 7.30−7.26 (m, 2H), 7.25−7.22 (m, 3H), 7.00 (m, 1H), 6.91−6.89 (m, 3H), 3.83−3.81 (m, 4H), 3.28−3.25 (m, 4H); LC/MS (ESI) *m/z* 448 $(M + H)^+$.

2-[4-(2-Chlorophenyl)piperazino]-6-phenylureidobenzoxazole 15c. ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 8.15 (s, 1H), 8.06 (s, 1H), 7.84 (s, 1H), 7.44 (d, 2H, J = 7.7 Hz), 7.40−7.38 (m, 1H), 7.29−7.22 (m, 4H), 7.07−7.02 (m, 3H), 6.80 (m, 1H), 3.86−3.84 (m, 4H), 3.17−3.15 (m, 4H); LC/MS (ESI) *m/z* 448 $(M + H)^+$.

2-(4-Methoxybenzylamino)-6-phenylureidobenzoxazole 15d. ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 8.70 (s, 1H), 8.68 (s, 1H), 8.35 (m, 1H), 7.70 (s, 1H), 7.45 (d, 2H, J = 8.0 Hz), 7.32−7.25 (m, 4H), 7.15 (d, 1H, J = 8.4 Hz), 6.99−6.95 (m, 2H), 6.90 (d, 2H, J = 8.4 Hz), 4.42 (d, 2H, J = 6.0 Hz), 3.87 (s, 3H); LC/MS (ESI) *m/z* 389 $(M + H)^+$.

2-(4-Phenylpiperazino)-6-(4-methoxyphenylureido)benzoxazole 15e. ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 8.04 (s, 1H), 7.85−7.83 (m, 2H), 7.34−7.28 (m, 3H), 7.22 (d, 1H, J = 8.3 Hz), 6.98 (d, 2H, J = 8.0 Hz), 6.92−6.89 (m, 3H), 6.83 (d, 2H, J = 8.9 Hz), 3.85−3.81 (m, 4H), 3.72 (s, 3H), 3.31−3.29 (m, 4H); LC/MS (ESI) *m/z* 444 $(M + H)^+$.

6-*n*-Butyl-ureido-2-[4-(4-chlorophenyl)piperazino] benzoxazole 15f. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.26−7.23 (m, 3H), 6.90−6.86 (m, 3H), 6.69 (s, 1H), 4.90 (m, 1H), 3.82−3.80 (m, 4H), 3.25−3.21 (m, 6H), 1.49−1.45 (m, 2H), 1.35−1.30 (m, 2H), 0.90 (t, 3H, J = 7.4 Hz); LC/MS (ESI) *m/z* 428 $(M + H)^+$.

6-*n*-Butyl-ureido-2-[4-(2-chlorophenyl)piperazino]benzoxazole 15g. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.40−7.38 (m, 1H), 7.26−7.23 (m, 2H), 7.04−7.01 (m, 3H), 6.91−6.89 (m, 1H), 6.83 (s, 1H), 5.01 (m, 1H), 3.86−3.84 (m, 4H), 3.25−3.21 (m, 2H), 3.17−3.13 (m, 4H), 1.48−1.45 (m, 2H), 1.34−1.29 (m, 2H), 0.90 (t, 3H, J = 7.3 Hz); LC/MS (ESI) *m/z* 428 $(M + H)^+$.

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Supporting Information Available. Analytical data (^{1}H NMR, ^{13}C NMR, LC/MS) are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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