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An Efficient Solid-phase Parallel Synthesis of 2-Amino and 2-Amidobenzo[*d*]oxazole Derivatives *via* Cyclization Reactions of 2-Hydroxyphenylthiourea Resin

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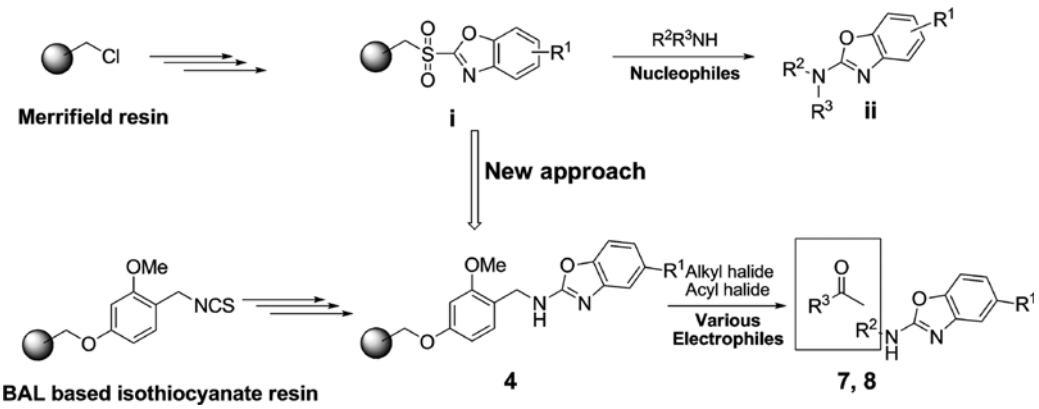
An efficient solid-phase methodology has been developed for the synthesis of 2-amino and 2-amidobenzo[*d*]-oxazole derivatives. The key step in this procedure involves the preparation of polymer-bound 2-aminobenzo-[*d*]oxazole resins **4** by cyclization reaction of 2-hydroxyphenylthiourea resin **3**. The resin-bound 2-hydroxy-phenylthiourea **3** is produced by the addition of 2-aminophenol to the isothiocyanate-terminated resin **2** and serve as a key intermediate for the linker resin. This core skeleton 2-aminobenzo[*d*]oxazole resin **4** undergoes functionalization reaction with various electrophiles, such as alkylhalides and acid chlorides to generate 2-amino and 2-amidobenzo[*d*]oxazole resins **5** and **6** respectively. Finally, 2-amino and 2-amidobenzo[*d*]oxazole derivatives **7** and **8** are then generated in good yields and purities by cleavage of the respective resins **5** and **6** under trifluoroacetic acid (TFA) in dichloromethane (CH_2Cl_2).

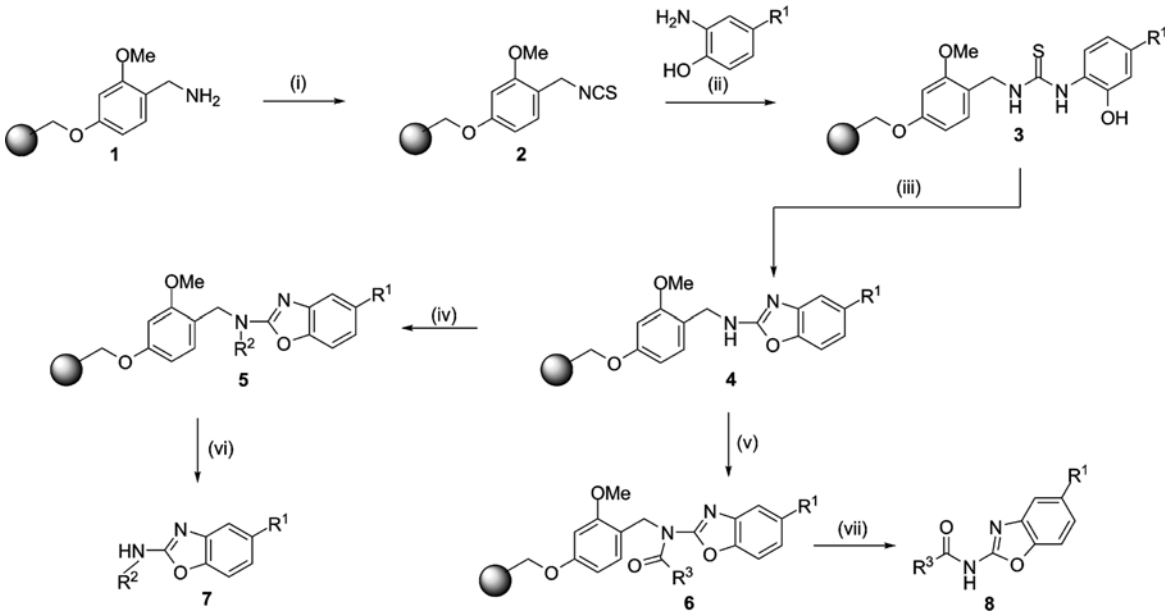
Key Words : Solid-phase parallel synthesis, Heterocycles, Benzo[*d*]oxazole, 2-Hydroxyphenylthiourea linker, BOMBA resin

Introduction

Heterocyclic compounds serve as ideal scaffolds on which pharmacophores can be appended to yield potent and selective drugs.[1] This is especially true for five-member ring heterocyclic compounds, which are core components of a large number of substances that possess a wide range of interesting biological activities. In this respect, the potential of the benzo[*d*]oxazole scaffold to serve as a privileged structure for the generation of drug-like libraries in drug-discovery programs has been plentifully demonstrated in medicinal chemistry.[2] As part of a recent drug discovery effort, we explored target libraries that are based on the five-membered heterocyclic privileged structures.[3] Even though, benzo[*d*]oxazole derivatives are of particular interest in medicinal chemistry and, consequently, have been targets of a number of solution- and solid-phase synthetic studies,[4] the methods developed to date for the preparation of benzo-[*d*]oxazole libraries do not have sufficiently high levels of diversity. Therefore, we have previously concentrated our efforts on describing a facile and rapid solid-phase strategy for the preparation of a small molecule library based on the benzo[*d*]oxazole scaffold. And, we reported a useful method for the solid-phase synthesis of 2-aminobenzo[*d*]oxazole derivatives using thioether linkage as the safety-catch linker.[5] In the processes, the choice of the linker that serves to attach the library scaffold to the polymer support is critical. Thus, a variety of elegant linking methods have been developed (*i.e.*, safety-catch linkers[6]) that enable additional diversity to be introduced 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.[7] We have utilized this general methodology to produce amine-functionalized 2-aminobenzo-[*d*]oxazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, and thiazole libraries through consecutive oxidation and amine-promoted



Scheme 1. Strategy used to make various 2-amino and 2-amidobenzo[*d*]oxazole libraries *via* thiourea linker.



Scheme 2. Solid-phase synthesis route to the various 2-amino and 2-amidobenzo[*d*]oxazole derivatives.
Reagents and conditions: i) CS_2, Et_3N, *p*-TsCl, THF, 0 °C to rt, 18 h; ii) 2-Aminophenol, Et_3N, 1,4-dioxane, 80 °C, 12 h; iii) HgO, 1,4-dioxane, 80 °C, 24 h; iv) Alkyl halides, *t*-BuOK, *N*-methylpyrrolidone (NMP), 60 °C, 24 h; v) Acyl halides, LiHMDS, THF, 60 °C, 12 h; vi) TFA:CH_2Cl_2 (1:4), 40 °C, 12 h; and vii) TFA:CH_2Cl_2 (1:4), rt, 3 h.

cleavage of thiourea linkages produced in carbon disulfide mediated reactions of the Merrifield resin.[5,8] However, our developed method suffered a limitation in that we couldn't efficiently introduce various substitutents such as amine and amides on the 2-position of the benzo[*d*]oxazole core skeleton by nucleophilic substitution reaction at the last cleavage step as shown Scheme 1 (resin **i** → compound **ii**). Moreover the nucleophile substitution reaction of the last cleavage step could only progress with various amine nucleophiles, except for alcohols and thiols. As a result of these limitations, we undertook an investigation aimed at developing efficient and simple parallel synthesis methods to produce various 2-amino and 2-amidobenzo[*d*]oxazole derivatives by a new type of solid-phase linker which can be used to introduce various substituents on the 2-position of benzo[*d*]oxazole at the last cleavage step. Herein we report our recent progress on this project which includes the first solid-phase synthesis protocol for 2-amino and 2-amidobenzo[*d*]oxazole derivatives **7** and **8** (Scheme 1; resin **4** → compound **7**).

Results and Discussion

The overall synthesis strategy used to prepare the target 2-amino and 2-amidobenzo[*d*]oxazole analogues **7** and **8** is outlined in Scheme 2. The initial solid phase synthesis route that we developed to prepare for substances containing the benzo[*d*]oxazole scaffold involved the formation of the intermediate 2-aminobenzo[*d*]oxazole resin **4** from solid-supported 2-hydroxyphenylthiourea linker **3**, which is derived from the isothiocyanate-terminated resin **2**. Next cyclization of thiourea resin **3** in the presence of HgO produced the compound **4** as the key intermediate resin. Subsequently, *N*-alkylation and *N*-acylation reactions respectively furnished a variety of resins **5** and **6**. Finally, the desired 2-amino and 2-amido substituted benzo[*d*]oxazole derivatives **7** and **8** were smoothly obtained by cleavage of linker from the 2-*N*-substituted resins **5** and **6**, respectively under the condition of dilute TFA in good yields and purities (Scheme 2).

For the solid-phase parallel synthesis methodology, we selected the backbone amide linker (BAL) resin **1**, because we have previously developed a facile and very useful method for synthesizing the isothiocyanate-terminated resin **2** using BAL resin **1**. Even though we have previously reported the synthesis of isothiocyanate-terminated resin **2** by reaction with thiophosgene ($CSCl_2$) in the presence of triethylamine in CH_2Cl_2 at 0 °C to room temperature in high yield,[10] the starting reagent of $CSCl_2$ was very difficult to purchase from commercial chemical companies since it was designated a ban material of air-transport. Therefore, the effort was focused on the development of more efficient and convenient method for synthesizing the isothiocyanate-terminated resin **2**. In our results, we achieved a much higher yield and easier synthesis condition of the isothiocyanate-terminated resin **2** compared to the $CSCl_2$ reagent method by reaction with amine resin **1** and carbon disulfide (CS_2) in the presence of triethylamine (Et_3N) in tetrahydrofuran (THF) at 0 °C to room temperature, based on Wong's solution-phase synthesis.[9] The formation of resin **2** was confirmed by inspection of its attenuated total reflection (ATR) single bead Fourier transform infrared (FTIR) spectrum, which showed the presence of the typical isothiocyanate band at 2071 cm^{-1}.

This kind of resin-bound isothiocyanate **2** reacts with 2-aminophenol in the presence of Et_3N in 1,4-dioxane solvent at 80 °C to give 2-hydroxyphenyl thiourea **3** as the key

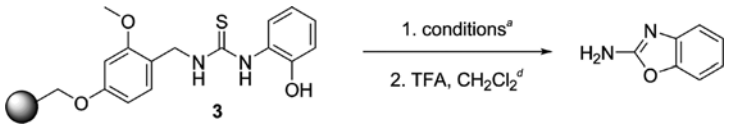


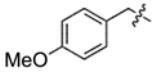
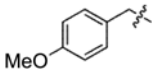
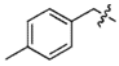
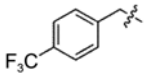
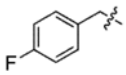
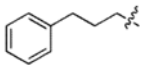
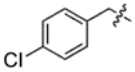
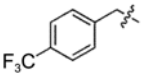
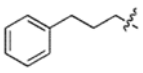
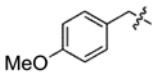
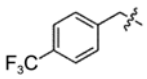
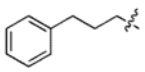
Table 1. Results from an investigation of conditions to promote cyclization of 2-hydroxyphenylthiourea resin **3** to 2-aminobenzo[*d*]oxazole resin **4**

Entry	Reagent[a]	Solvent	Yield[b,c] (%)	Entry	Reagent[a]	Solvent	Yield[b,c] (%)
1	$FeCl_3$	THF	9	**5**	EDC	THF	20
2	CuCl/DIPEA	Toluene:CH_3CN	5	**6**	HgO	CH_3CN	34
3	DIB/Et_3N	CH_3CN	19	**7**	HgO	1,4-Dioxane	71
4	*p*-TsCl/NaOH	THF	20				

[a]5.0 equiv are used. [b]Four-step overall yields from BAL resin **1** (loading capacity of resin **1** is 1.1 mmolg^{-1}) [c]Yield determined by LC/MS. [d]TFA:CH_2Cl_2 (1:1), 40 °C, 12 h.

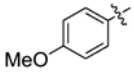
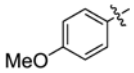
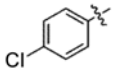
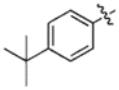
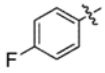
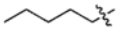
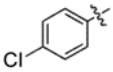
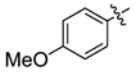
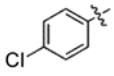
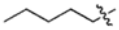
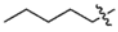
intermediate linker resin, signaled by the absence of the isothiocyanate band at 2071 cm^{-1} and by the appearance of the thiourea peak at 1649 and 1585 cm^{-1} (Figure 1, **3**(c)). We made many attempts to find the suitable solid-phase cyclodesulfurization reaction conditions based on the known benzo[*d*]oxazole cyclization condition, such as $FeCl_3$,[12] CuCl,[13] DIB,[14] *p*-TsCl,[15] EDC[16] and HgO[11] as shown in Table 1. Our results show that 2-aminobenzo[*d*]oxazole resin **4** can be efficiently generated by cyclization of 2-hydroxyphenylthiourea resin **3** in the presence of HgO in 1,4-dioxane at 80 °C for 24 h.[11] (Table 1, entry 7). This effort demonstrated that the proposed procedure is one of the best methods in the solid-phase synthesis of 2-aminobenzo[*d*]oxazole derivatives *via* cyclodesulfurization in the presence of HgO in 1,4-

Table 2. Yields and purities of the *N*-alkylaminobenzo[*d*]oxazole derivatives **7**

Code	R^1	R^2	Yield (%)[a]	Purity (%)[b]	Code	R^1	R^2	Yield (%)[a]	Purity (%)[b]
7a	H		30	99	**7k**	MeO		25	94
7b	H		23	96	**7l**	MeO		20	99
7c	H		29	99	**7m**	MeO		35	93
7d	H		25	99	**7n**	MeO		35	97
7e	H		24	>99	**7o**	MeO		31	>99
7f	H		28	95	**7p**	Cl		38	99
7g	H		31	96	**7q**	Cl		32	98
7h	H		29	98	**7r**	Cl		33	99
7i	H		30	>99	**7s**	Cl		26	>99
7j	H	Me	20	99	**7t**	Cl		35	98

[a]Five-step overall yields from BAL resin **1** (loading capacity of resin **1** is 1.1 mmol/g). [b]All of the purified products were checked by LC/MS.

Table 3. Yields and purities of the *N*-(benzo[*d*]oxazol-2-yl)amide derivatives **8**

Code	R^1	R^2	Yield (%)[a]	Purity (%)[b]	Code	R^1	R^2	Yield (%)[a]	Purity (%)[b]
8a	H		33	>99	**8k**	MeO		32	98
8b	H		27	>99	**8l**	MeO		45	98
8c	H		29	98	**8m**	MeO		24	99
8d	H		25	>99	**8n**	MeO		24	99
8e	H		29	>99	**8o**	MeO		16	99
8f	H		19	96	**8p**	Cl		43	96
8g	H		28	97	**8q**	Cl		46	98
8h	H		31	98	**8r**	Cl		31	98
8i	H		23	>99	**8s**	Cl		31	99
8j	H	Me	42	>99	**8t**	Cl		26	97

[a]Five-step overall yields from BAL resin **1** (loading capacity of resin **1** is 1.1 mmol/g). [b]All of the purified products were checked by LC/MS.

dioxane at 80 °C.

This process led to the formation of the 2-aminobenzo-[*d*]oxazole resin **4**, whose single bead FTIR spectrum contained imine stretching bands at 1606 cm^{-1} (Figure 1, **4**(d)). With the resin **4** in hand, we next turn our attention to the introduction of various alkyl and acyl substitution at the 2-*N* position on 2-aminobenzo[*d*]oxazole core skeleton resin **4**. Alkylation of 2-aminobenzo[*d*]oxazole resin **4** proceeded smoothly to give the desired *N*-alkylamino benzo[*d*]oxazole resin **5** when the resin was reacted with the various alkyl halide in the presence of *t*-BuOK in 1,4-dioxane solvent at 60 °C for 24 h. In this step, the progress of this reaction (R^2 = Bn) was monitored by ATR-FTIR spectroscopy, which have revealed the growth of the band intensity of the C-N bond at 1609 cm^{-1} (Figure 1, **5a**(e)). Final cleavage of linker from the resin **5** was accomplished by treatment of TFA in CH_2Cl_2 to give various *N*-alkylaminobenzo[d]oxazole derivatives. ^1H NMR spectroscopic properties of **7a**, following purified by passing through a short plug of silica, were identical to the corresponding substances produced by using solution-phase synthesis routes.

As shown by the data given in Table 2, the various desired *N*-substituted alkylamino benzo[*d*]oxazole derivatives **7** can be produced by this five-step route in high overall yields and purities. It was possible to introduce various alkyl building blocks on the 2-amino groups of the benzo[*d*]oxazole core skeleton ring (**7a-7t**).

Next, the acylation reaction of 2-aminobenzo[*d*]oxazole resin **4** produced *N*-substituted amidobenzoxazole resin **6** with various acid chlorides in the condition of LiHMDS in THF solvent at 60 °C for 12 h. This progress of reaction (R^3 = Ph) was also monitored by ATR-FTIR spectroscopy, which revealed the appearance of an amide band at 1643 cm^{-1} (Figure 1, **6a**(f)). This 2-amidobenzo[*d*]oxazole resin **6** could easily be converted to the *N*-substituted amidobenzoxazole derivatives **8** by treatment TFA in CH_2Cl_2. As shown by the data given in Table 2, various *N*-substituted amidobenzoxazole derivatives **8** (**8a-8t**) could be produced by this five-step route in high overall yields and purities.

In this research, an efficient solid-phase methodology has been developed for the synthesis of 2-aminobenzo[*d*]oxazole-based libraries. This solid-phase synthesis route proved much more efficient for generating various 2-aminobenzo[*d*]oxazole-based libraries **7** and **8** than our previously developed solid-phase synthesis method. The key diversification commences with a 2-aminobenzo[*d*]oxazole core skeleton resin **4** and relies on the alkylation or acylation of the 2-*N* position on the 2-aminobenzo[*d*]oxazole ring. This strategy, based on

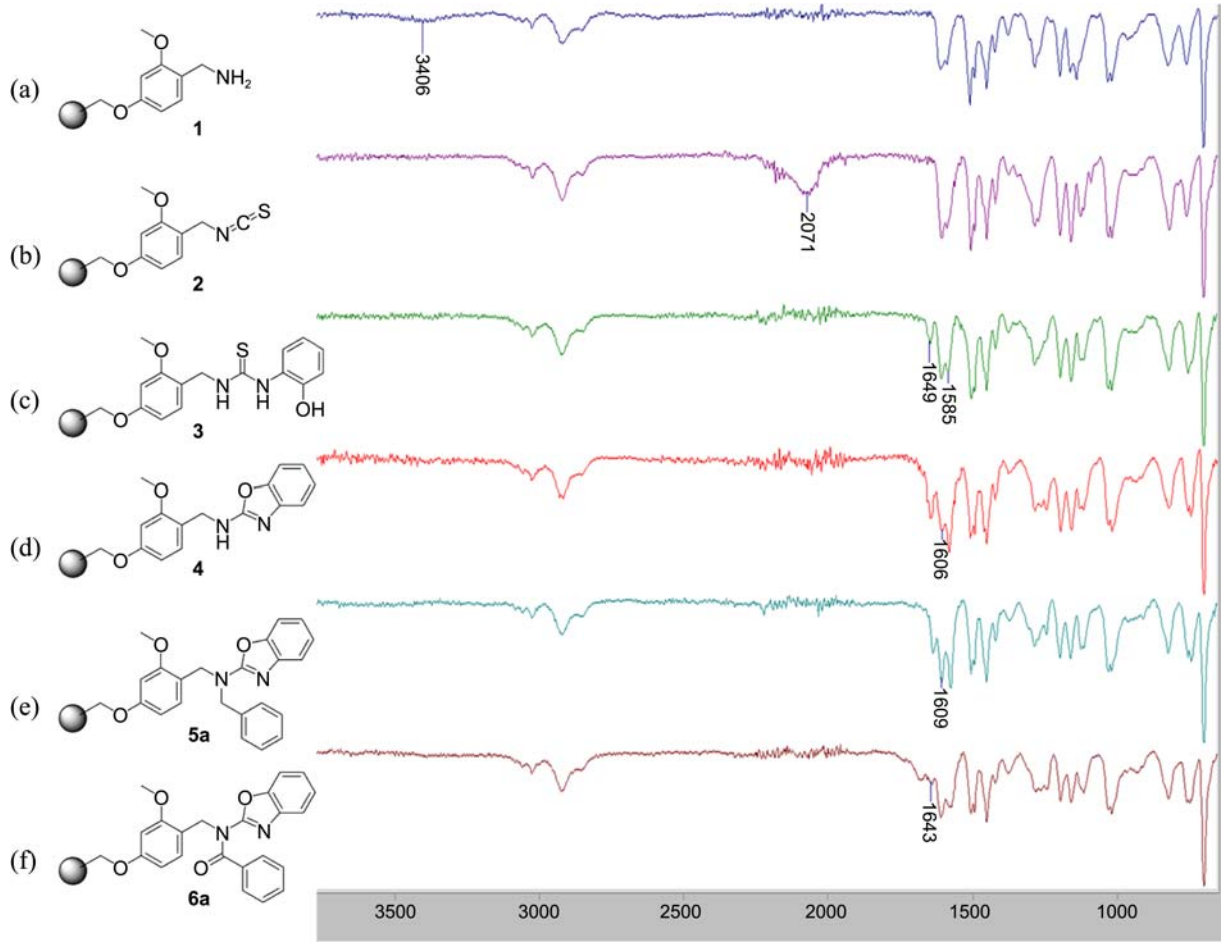


Figure 1. ATR-FTIR spectra on single beads of 2-aminobenzo[*d*]oxazole resins **1** (a), **2** (b), **3**(c), **4** (d), **5a** (e), and **6a** (f).

an efficient solid-phase sequence, enables the construction of a large library and is potentially applicable for the preparation of other drug-like 2-aminobenzo[*d*]oxazole ring systems. Finally, the calculated physicochemical properties of members of the library constructed by using this approach are well distributed within reasonable, orally acceptable, drug-like ranges. Further studies in this area are underway, the results of which will be reported in due course.

Experimental Section

General Procedure for Synthesis. All chemicals were reagent grade and used as purchased. Reactions were monitored by thin layer chromatography (TLC) analysis using Merck silica gel 60 F-254 thin layer plates or ATR-FTIR analysis using ATR-FTIR spectrometer (Smiths Detection). Flash column chromatography was carried out on Merck silica gel 60 (230-400 mesh). The crude products were purified by parallel chromatography using Isorea One (Biotage). ^{1}H NMR and ^{13}C NMR spectra were recorded in d units relative to deuterated solvent as an internal reference using a Bruker 400 MHz NMR instrument. Liquid chromatography-mass spectrometry (LC-MS/Agilent 6400) analysis was performed on an electrospray ionization (ESI) mass spectrometer with Diode-array detector (DAD) detection. LC-MS area percentage purities of all products were determined by LC peak area analysis (Poroshell 120 EC-C_{18} column, 4.6 mm × 100 mm; PDA detector at 254 nm; 70/30: CH_3CN/5 mM NH_4HCO_2). High-resolution mass spectrometry fast-atom bombardment (HRMS-FAB) spectra were obtained using API 4000Q TRAP LC/MS/MS system (Applied Biosystems).

Representative Procedure for the Preparation of Isothiocyanate-terminated Resin (2). To a mixture of BOMBA resin **1** (5.00 g, 5.5 mmol) in THF (80 mL) was added Et_3N (7.67 mL, 55.0 mmol) and CS_2 (1.98 mL, 33.0 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h, *p*-TsCl (5.24 g, 27.5 mmol) was added at 0 °C, and the mixture was stirred at rt for 15 h. The precipitate obtained by filtration of the mixture was washed with THF, H_2O, MeOH and CH_2Cl_2 and dried in a vacuum oven. This process gave resin **2** (5.02 g) as a dark yellow solid. Single-Bead ATR-FTIR: 2071 (N=C=S), 1607, 1505, 1492, 1450, 1420, 1374, 1284, 1195, 1158, 1125, 1089 cm^{-1}.

Representative Procedure for the Preparation of 2-Hydroxyphenylthiourea Resin (3a). A mixture of isothiocyanate resin **2** (5.02 g, 5.5 mmol), 2-aminophenol (2.40 g, 22.0 mmol) and Et_3N (3.83 mL, 27.5 mmol) in 1,4-dioxane (80 mL) was stirred at 80 °C for 12 h. The resin was filtered and washed several times with H_2O, MeOH and CH_2Cl_2 and then dried in a vacuum oven. Resin **3** was obtained as a light

brown solid (5.29 g). Single-Bead ATR-FTIR: 1649 (C=S), 1607, 1584 (C=S), 1503, 1492, 1450 cm^{-1}.

Representative Procedure for the Preparation of 2-Aminobenzo[*d*]xazole Resin (4a). A mixture of 2-hydroxyphenylthiourea resin **3** (5.29 g, 5.5 mmol) and HgO (5.96 g, 27.5 mmol) in 1,4-dioxane (80 mL) was stirred at 80 °C for 24 h. The resin was filtered and excess HgO was dissolved with 10% HCl. The resin was washed in H_2O the several times with MeOH and CH_2Cl_2, followed by washing with 10% triethylamine in CH_2Cl_2 to neutralize the amine. Following the final wash with MeOH, the resin was dried in a vacuum oven. Resin **4** was black in color (5.20 g). Single-Bead ATR-FTIR: 1643, 1606 (C=N), 1579, 1506, 1491, 1450 cm^{-1}.

Representative Procedure for the Preparation of *N*-Benzylaminobenzo[*d*]xazole Resin (5a). To a mixture of 2-aminobenzo[*d*]xazole resin **4** (150 mg, 0.15 mmol) in NMP (4 mL) was added *t*-BuOK (168 mg, 1.5 mmol) at room temperature. The resulting mixture was stirred for 1 h. Benzyl chloride (86.5 μL, 0.75 mmol) was added, and the resulting mixture was stirred at 60 °C for 24 h. The resin was filtered and washed several times with H_2O, MeOH and CH_2Cl_2, and then the resin was dried in a vacuum oven. Resin **5a** was obtained as a black solid (155 mg). Single-Bead ATR-FTIR: 1635, 1609 (C-N), 1575, 1504, 1493, 1451 cm^{-1}.

Representative Procedure for the Preparation of *N*-(benzo[*d*]oxazol-2-yl)benzamide Resin (6a). To a mixture of 2-aminobenzo[*d*]oxazole resin **4** (150 mg, 0.15 mmol) in anhydrous THF (4 mL) was added lithium bis(trimethylsilyl)-amides (LiHMDS) (126 mg, 0.75 mmol) at room temperature. The resulting mixture was stirred for 1 h. Benzoyl chloride (87.1 μL, 0.75 mmol) was added, and the resulting mixture was stirred at 60 °C for 12 h. The resin was filtered and washed several times with H_2O, MeOH and CH_2Cl_2, and then dried in a vacuum oven. Resin **6a** was obtained as a black solid (160 mg). Single-Bead ATR-FTIR: 3027, 2923, 1643 (C=O), 1609, 1577, 1571, 1504, 1492, 1450 cm^{-1}.

Representative Procedure for the First Generation Alkylation Reaction Step v, Preparation of *N*-Benzylbenzo[*d*]-oxazol-2-amine (7a) from Resin (5a). A mixture of *N*-benzylaminobenzo[*d*]xazole resin **5a** (155 mg, 0.15 mmol) and 2 mL of cleavage cocktail (TFA-CH_2Cl_2 = 1:4, v/v) was shaken at 40 °C for 8 h. Filtration followed by washing the precipitate with CH_2Cl_2 afforded a filtrate that was neutralized by saturated K_2CO_3 solution. The filtrate was washed with water and dried over $MgSO_4$. The solution was concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) to afford *N*-benzylbenzo[*d*]oxazol-2-amine **7a**. Yield (10 mg, 30%, five-step overall yield from BAL resin, loading capacity 1.1 mmol/g) as a white solid. mp 116.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.27 (m, 6H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.16 (td, *J* = 7.7, 0.8 Hz, 1H), 7.04 (td, *J* = 7.8, 1.0 Hz, 1H), 5.59 (s, 1H), 4.68 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.98, 148.62, 142.93, 137.71, 128.84, 127.86, 127.62, 123.96, 120.97, 116.51, 108.81, 47.16 cm^{-1}; LC-MS (ESI): *m/z* = 225 $[M+1]^+$; HRMS (EI): *m/z* = $[M + 1]^+$ calcd for $C_{14}H_{13}N_2O$: 225.2658; found: 225.096.

***N*-(4-methoxybenzyl)benzo[*d*]oxazol-2-amine (7b):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 9.3 Hz, 1H), 7.17 (td, *J* = 7.7, 1.0 Hz, 1H), 7.04 (td, *J* = 7.9, 1.1 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.32 (bs, 1H), 4.60 (s, 2H), 3.80 (s, *J* = 5.9 Hz, 3H); LC-MS (ESI): *m/z* = 255 $[M+1]^+$.

***N*-(4-methylbenzyl)benzo[*d*]oxazol-2-amine (7c):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.8 Hz, 1H), 7.26 (dd, *J* = 13.3, 8.4 Hz, 3H), 7.20-7.13 (m, 3H), 7.04 (td, *J* = 7.8, 1.1 Hz, 1H), 5.23 (bs, 1H), 4.64 (s, 2H), 2.35 (s, 3H), 1.61 (s, 3H); LC-MS (ESI): *m/z* = 239 $[M+1]^+$.

***N*-(4-fluorobenzyl)benzo[*d*]oxazol-2-amine (7d):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.32 (m, 3H), 7.25 (d, *J* = 6.4 Hz, 1H), 7.17 (td, *J* = 7.7, 0.9 Hz, 1H), 7.09-7.00 (m, 3H), 5.45 (s, 1H), 4.65 (s, 2H); LC-MS (ESI): *m/z* = 243 $[M+1]^+$.

***N*-(4-chlorobenzyl)benzo[*d*]oxazol-2-amine (7e):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H), 7.28-7.23 (m, 2H), 7.18 (td, *J* = 7.7, 1.1 Hz, 1H), 7.05 (td, *J* = 7.8, 1.2 Hz, 1H), 5.42 (s, 1H), 4.65 (s, 2H); LC-MS (ESI): *m/z* = 259 $[M+1]^+$.

***N*-(4-(trifluoromethyl)benzyl)benzo[*d*]oxazol-2-amine (7f).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 40.9, 8.1 Hz, 4H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 5.7 Hz, 1H), 7.18 (td, *J* = 7.7, 1.0 Hz, 1H), 7.06 (td, *J* = 7.9, 1.1 Hz, 1H), 5.65-5.48 (bs, 1H), 4.75 (s, 2H); LC-MS (ESI): *m/z* = 293 $[M+1]^+$.

***N*-(3-phenylpropyl)benzo[*d*]oxazol-2-amine (7g):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.32-7.24 (m, 3H), 7.23-7.13 (m, 4H), 7.03 (dd, *J* = 11.2, 4.3 Hz, 1H), 5.08 (s, 1H), 3.52 (t, *J* = 6.9 Hz, 2H), 2.83-2.65 (m, 2H), 2.09-1.97 (m, 2H); LC-MS (ESI): *m/z* = 253 $[M+1]^+$.

***N*-(cyclopropylmethyl)benzo[*d*]oxazol-2-amine (7h):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.16 (td, *J* = 7.7, 1.0 Hz, 1H), 7.03 (td, *J* = 7.8, 1.1 Hz, 1H), 5.08 (s, 1H), 3.35 (dd, *J* = 6.7, 5.0 Hz, 2H), 1.23-1.08 (m, 1H), 0.67-0.47 (m, 2H), 0.39-0.22 (m, 2H); LC-MS (ESI): *m/z* = 189 $[M+1]^+$.

***N*-(cyclohexylmethyl)benzo[*d*]oxazol-2-amine (7i):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 5.27 (s, 1H), 3.33 (d, *J* = 2.9 Hz, 2H), 1.87-1.57 (m, 5H), 1.35-1.11 (m, 3H), 1.08-0.78 (m, 2H); LC-MS (ESI): *m/z* = 231 $[M+1]^+$.

***N*-methylbenzo[*d*]oxazol-2-amine (7j):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.20-7.13 (m, 1H), 7.03 (td, *J* = 7.9, 0.9 Hz, 1H), 4.98 (s, 1H), 3.13 (s, 3H); LC-MS (ESI): *m/z* = 149 $[M+1]^+$.

***N*-benzyl-5-methoxybenzo[*d*]oxazol-2-amine (7k):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.25 (m, 5H), 7.12 (d, *J* = 8.7 Hz, 1H), 6.91 (d, *J* = 2.5 Hz, 1H), 6.60 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.47 (s, 1H), 4.66 (s, 2H), 3.81 (d, *J* = 5.4 Hz, 3H); LC-MS (ESI): *m/z* = 255 $[M+1]^+$.

5-Methoxy-*N*-(4-methoxybenzyl)benzo[*d*]oxazol-2-amine (7l): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.91-6.86 (m, 2H), 6.60 (dd, *J* = 8.7, 2.6 Hz, 1H), 5.21 (s, 1H), 4.58 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H); LC-MS (ESI): *m/z* = 285 $[M+1]^+$.

5-Methoxy-*N*-(4-(trifluoromethyl)benzyl)benzo[*d*]oxazol-2-amine (7m): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd,

J = 42.8, 8.1 Hz, 4H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.90 (d, *J* = 2.5 Hz, 1H), 6.62 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.66 (s, 1H), 4.73 (s, 2H), 3.80 (s, 3H); LC-MS (ESI): *m/z* = 323 $[M+1]^+$.

5-Methoxy-*N*-(3-phenylpropyl)benzo[*d*]oxazol-2-amine (7n): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 2H), 7.23-7.16 (m, 3H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.59 (dd, *J* = 8.7, 2.6 Hz, 1H), 4.96 (s, 1H), 3.80 (s, 3H), 3.55-3.46 (m, 2H), 2.74 (m, 2H), 2.07-1.96 (m, 2H); LC-MS (ESI): *m/z* = 283 $[M+1]^+$.

***N*-(cyclohexylmethyl)-5-methoxybenzo[*d*]oxazol-2-amine (7o):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.58 (dd, *J* = 8.7, 2.6 Hz, 1H), 5.01 (s, 1H), 3.80 (s, 3H), 3.31 (t, *J* = 6.4 Hz, 2H), 1.87-1.56 (m, 6H), 1.33-1.10 (m, 3H), 1.00 (qd, *J* = 12.0, 2.9 Hz, 2H); LC-MS (ESI): *m/z* = 261 $[M+1]^+$.

***N*-benzyl-5-chlorobenzo[*d*]oxazol-2-amine (7p):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.29 (m, 5H), 7.22 (d, *J* = 2.1 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.75 (s, 1H), 4.66 (d, *J* = 3.3 Hz, 2H); LC-MS (ESI): *m/z* = 259 $[M+1]^+$.

5-Chloro-*N*-(4-methoxybenzyl)benzo[*d*]oxazol-2-amine (7q): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 2H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.99 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.93-6.85 (m, 2H), 5.48 (s, 1H), 4.59 (d, *J* = 5.2 Hz, 2H), 3.81 (s, 3H); LC-MS (ESI): *m/z* = 289 $[M+1]^+$.

5-Chloro-*N*-(4-(trifluoromethyl)benzyl)benzo[*d*]oxazol-2-amine (7r): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.02 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.61 (s, 1H), 4.74 (s, 2H); LC-MS (ESI): *m/z* = 327 $[M+1]^+$.

5-Chloro-*N*-(3-phenylpropyl)benzo[*d*]oxazol-2-amine (7s): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 3H), 7.24-7.16 (m, 3H), 7.12 (d, *J* = 8.3 Hz, 1H), 6.99 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.04 (s, 1H), 3.50 (dt, *J* = 7.0, 5.9 Hz, 2H), 2.74 (m, 2H), 2.12-1.94 (m, 2H); LC-MS (ESI): *m/z* = 287 $[M+1]^+$.

5-Chloro-*N*-(cyclohexylmethyl)benzo[*d*]oxazol-2-amine (7t): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 2.0 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.17 (s, 1H), 3.32 (t, *J* = 6.4 Hz, 2H), 1.87-1.54 (m, 6H), 1.34-1.11 (m, 3H), 1.06-0.94 (m, 2H); LC-MS (ESI): *m/z* = 265 $[M+1]^+$.

Representative Procedure for the Second-generation Acylation Reaction Step vi, the Preparation of *N*-(benzo-[*d*]oxazol-2-yl)benzamide (8a) from Resin (6a). Resin **6a** (160 mg) was treated with a mixture of (TFA-CH_2Cl_2 = 1:4, v/v) for 3 h at room temperature, and then, washed with CH_2Cl_2 several times. The organic filtrates were neutralized by saturated K_2CO_3 solution. The filtrate was washed with water and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was washed with diethyl ether to afford *N*-(benzo[*d*]oxazol-2-yl)benzamide **8a** (12 mg, 33%, five-step overall yield from BAL resin, loading capacity 1.1 mmol/g) as a white solid. mp 327.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 6.65 (d, *J* = 7.5 Hz, 2H), 6.28-6.21 (m, 2H), 6.19 (d, *J* = 7.1 Hz, 1H), 6.14 (t, *J* = 7.6 Hz, 2H), 5.97-5.85 (m, 2H); LC-MS (ESI): *m/z* = 239 $[M+1]^+$; HRMS (EI): *m/z* = $[M + 1]^+$ calcd for $C_{14}H_{11}N_2O_2$: 239.0821; found: 239.126.

***N*-(benzo[*d*]oxazol-2-yl)-4-methoxybenzamide (8b):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.04 (m, 2H), 7.47 (d, *J* = 7.0 Hz, 1H), 7.39-7.20 (m, 4H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H); LC-MS (ESI): *m/z* = 269 $[M+1]^+$.

***N*-(benzo[*d*]oxazol-2-yl)-4-methylbenzamide (8c):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 2H), 7.53-7.44 (m, 1H), 7.38-7.22 (m, 5H), 2.42 (s, 3H); LC-MS (ESI): *m/z* = 253 $[M+1]^+$.

***N*-(benzo[*d*]oxazol-2-yl)-4-tert-butylbenzamide (8d):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 2H), 7.49 (d, *J* = 8.3 Hz, 3H), 7.34-7.20 (m, 3H), 1.35 (s, 9H); LC-MS (ESI): *m/z* = 295 $[M+1]^+$.

***N*-(benzo[*d*]oxazol-2-yl)-4-fluorobenzamide (8e):** ^{1}H NMR (400 MHz, DMSO) δ 12.42 (s, 1H), 8.15 (dd, *J* = 8.5, 5.7 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.46-7.24 (m, 4H); LC-MS (ESI): *m/z* = 257 $[M+1]^+$.

***N*-(benzo[*d*]oxazol-2-yl)-4-chlorobenzamide (8f):** ^{1}H NMR (400 MHz, DMSO) δ 12.45 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 2H), 7.69-7.54 (m, 4H), 7.40-7.26 (m, 2H); LC-MS (ESI): *m/z* = 273 $[M+1]^+$.

***N*-(benzo[*d*]oxazol-2-yl)thiophene-2-carboxamide (8g):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 3.1 Hz, 1H), 7.57 (d, *J* = 4.2 Hz, 1H), 7.48-7.41 (m, 1H), 7.37-7.24 (m, 3H), 7.13 (dd, *J* = 4.8, 3.9 Hz, 1H); LC-MS (ESI): *m/z* = 245 $[M+1]^+$.

***N*-(benzo[*d*]oxazol-2-yl)cyclopropanecarboxamide (8h):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.36-7.22 (m, 2H), 2.40-2.15 (m, 1H), 1.31-1.19 (m, 2H), 1.09-0.97 (m, 2H); LC-MS (ESI): *m/z* = 203 $[M+1]^+$.

***N*-(benzo[*d*]oxazol-2-yl)hexanamide (8i):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32-9.03 (m, 1H), 7.78-7.54 (m, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.34-7.23 (m, 1H), 2.83-2.58 (m, 2H), 1.85-1.70 (m, 2H), 1.47-1.29 (m, 4H), 0.93 (d, *J* = 7.0 Hz, 3H); LC-MS (ESI): *m/z* = 233 $[M+1]^+$.

***N*-(benzo[*d*]oxazol-2-yl)acetamide (8j):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.94 (s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.40-7.23 (m, 2H), 2.52 (s, 3H); LC-MS (ESI): *m/z* = 177 $[M+1]^+$.

***N*-(5-methoxybenzo[*d*]oxazol-2-yl)benzamide (8k):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1H), 8.04 (s, 2H), 7.65 (s, 2H), 7.61-7.47 (m, 3H), 7.20 (s, 1H), 6.88 (dd, *J* = 8.8, 2.1 Hz, 1H), 3.81 (s, 3H); LC-MS (ESI): *m/z* = 269 $[M+1]^+$.

4-Methoxy-*N*-(5-methoxybenzo[*d*]oxazol-2-yl)benzamide (8l): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 8.5 Hz, 3H), 6.96 (d, *J* = 8.6 Hz, 3H), 3.80 (s, *J* = 10.0 Hz, 6H); LC-MS (ESI): *m/z* = 299 $[M+1]^+$.

4-Chloro-*N*-(5-methoxybenzo[*d*]oxazol-2-yl)benzamide (8m): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (s, 1H), 8.08 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.9 Hz, 1H), 7.14 (s, 1H), 6.88 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.80 (s, 3H); LC-MS (ESI): *m/z* = 303 $[M+1]^+$.

***N*-(5-methoxybenzo[*d*]oxazol-2-yl)cyclopropanecarboxamide (8n):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 7.07 (s, 1H), 6.83 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.84 (s, 3H), 2.36-2.12 (m, 1H), 1.28-1.20 (m, 2H), 1.03 (td, *J* = 7.2, 3.9 Hz, 2H); LC-MS (ESI): *m/z* = 233

$[M+1]^+$.

***N*-(5-methoxybenzo[*d*]oxazol-2-yl)hexanamide (8o):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.10 (s, 1H), 6.83 (dd, J = 8.9, 2.2 Hz, 1H), 3.85 (s, 3H), 2.81-2.63 (m, 2H), 1.84-1.72 (m, 2H), 1.48-1.28 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); LC-MS (ESI): m/z = 263 $[M+1]^+$.

***N*-(5-chlorobenzo[*d*]oxazol-2-yl)benzamide (8p):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.42 (d, J = 8.6 Hz, 1H), 7.24 (dd, J = 8.6, 2.0 Hz, 1H), 7.14 (s, 1H); LC-MS (ESI): m/z = 273 $[M+1]^+$.

***N*-(5-chlorobenzo[*d*]oxazol-2-yl)-4-methoxybenzamide (8q):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.04 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 7.34 (dd, J = 8.6, 2.1 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); LC-MS (ESI): m/z = 303 $[M+1]^+$.

4-Chloro-*N*-(5-chlorobenzo[*d*]oxazol-2-yl)benzamide (8r): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1H), 8.05 (s, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H), 7.35 (dd, J = 8.6, 2.2 Hz, 1H); LC-MS (ESI): m/z = 307 $[M+1]^+$.

***N*-(5-chlorobenzo[*d*]oxazol-2-yl)cyclopropanecarboxamide (8s):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.59 (d, J = 1.9 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 7.24 (dd, J = 8.6, 2.1 Hz, 1H), 2.74 (s, 2H), 1.85-1.72 (m, 2H), 1.45-1.33 (m, 4H), 0.92 (t, J = 7.1 Hz, 3H); LC-MS (ESI): m/z = 237 $[M+1]^+$.

***N*-(5-chlorobenzo[*d*]oxazol-2-yl)hexanamide (8t):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 7.57 (d, J = 1.8 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 7.23 (dd, J = 8.6, 2.1 Hz, 1H), 2.29 (s, 1H), 1.31-1.20 (m, 2H), 1.10-1.00 (m, 2H); LC-MS (ESI): m/z = 267 $[M+1]^+$.

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Supporting Information Available. Full analytical data of compounds, copies of ^{1}H NMR, ^{13}C NMR, LC-MS, and High Resolution-MS spectra of compounds **7a** and **8a** and the ^{1}H NMR, and MS spectra of compounds **7b-7t** and **8b-8t**.

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