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A Highly Efficient Diversification of 2-Amino/Amido-1,3,4-oxadiazole and 1,3,4-Thiadiazole Derivatives via Reagent-Based Cyclization of Thiosemicarbazide Intermediate on Solid-Phase

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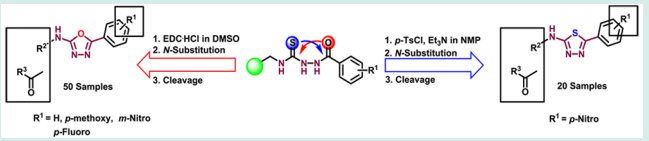
Supporting Information

ABSTRACT: A 2-amino/amido-1,3,4-oxadiazole and 1,3,4-thiadiazole library has been constructed on solid-phase organic synthesis. The key step on this solid-phase synthesis involves the preparation of polymer-bound 2-amino-1,3,4-oxadiazole and 1,3,4-thiadiazole core skeleton resin by cyclization of thiosemicarbazide with EDC·HCl and *p*-TsCl, respectively. The resulting core skeleton undergoes functionalization reaction with various electrophiles such as alkyl halides, and acid chlorides to generate *N*-alkylamino and *N*-acylamino-1,3,4-oxadiazole, and 1,3,4-thiadiazole resin, respectively. Finally, the 2-amino and 2-amido-1,3,4-oxadiazole and 1,3,4-thiadiazole library was then generated in good yields and high purities by cleavage of the respective resin under trifluoroacetic acid(TFA) in dichloromethane(DCM). The constructed library shows reasonable, oral bioavailability drug properties as determine by using the Lipinski's Rule and similar parameters.



KEYWORDS: *solid-phase, BOMBA, thiosemicarbazide, 1,3,4-oxadiazole, 1,3,4-thiadiazole*

INTRODUCTION

Solid-phase organic synthesis (SPOS) is routinely used to prepare drug-like, small organic molecules in medicinal chemistry programs. This procedure enables the generation of massive numbers of hit and lead compounds as part of high-throughput screening techniques.[1] Heterocyclic skeletons serve as ideal scaffolds on which pharmacophores can be appended to yield potent and selective drugs.[2] This is especially true for five-member-ring heterocycles, which are core components of a large number of substances that possess a wide range of interesting biological activities. In this family, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles have been used as "privileged" scaffolds to produce substances of interest in numerous therapeutic areas, such as anti-inflammatory,[3] antimicrobial,[4] anticonvulsant,[5] anticancer,[6] and antihypertensive.[7] Especially, according to our previous research, 1,3,4-oxadiazole analogues show potent biological activity in the canonical Wnt signaling pathway,[8] which has been considered as a key pathway that regulates adipogenesis,[9] osteoporosis,[10] and stem cell differentiation.[11] For this reason, we became interested in the synthesis of 1,3,4-oxadiazole and 1,3,4-thiadiazole analogues.

The synthesis of 1,3,4-oxadiazole with polymer-bound α-selenopropionic acid was reported by Huang.[12] Brill[13] reported 1,3,4-oxadiazole synthesis as a traceless release on the solid support and Lee[14] reported synthesis of 2-amido-1,3,4-oxadiazole derivatives on solid-phase synthesis. Clemens used diisopropylcarbodiimide to afford 1,3,4-oxadiazole from semicarbazide intermediate on solid-phase synthesis.[15] Synthesis of 1,3,4-thiadiazoles on solid-phase was reported by Liu.[16] Kilburn and Lau reported useful synthesis of 1,3,4-oxadiazole and 1,3,4-thiadiazole analogues on the solid-phase synthesis from different kinds of intermediates.[17] In the literature, a reliable and efficient synthetic method for both 1,3,4-oxadiazole and 1,3,4-thiadiazole from one key intermediate on the solid-phase synthesis has not been reported, excepted by our previous methodology.[18] In our previous methodology, we used an acyldithiocarbazate intermediate for both 1,3,4-oxadiazole and 1,3,4-thiadiazole synthesis on the solid-phase. However, our method was limited as we could not efficiently introduce various substituents at the 2-position of 1,3,4-oxadiazole and 1,3,4-thadiazole (Scheme 1a).

Accordingly, we had an interest in developing a useful synthetic method for both 1,3,4-oxadiazoles and 1,3,4-thiadiazoles with a various substituents at the 2-position. Along these lines, in our own research, we developed a synthetic method to afford 1,3,4-oxadiazole and 1,3,4-thiadiazole analogues which were functionalized on the 2-position of 1,3,4-oxadiazole and 1,3,4-thiadiazole with amines, amides, and sulfone amides in the solution-phase organic synthesis[19] and now our interest focuses on the construction of a 1,3,4-oxadiazole and 1,3,4-thadiazole library on the solid-phase organic synthesis. To achieve this, we introduced a thiosemicarbazide intermediate as a key intermediate for 1,3,4-oxadiazole and 1,3,4-thiadiazole on the back bond amide linker (BAL) (Scheme 1b). As can be seen in Scheme 1, our previous methodology used resin as a electrophile and only amine

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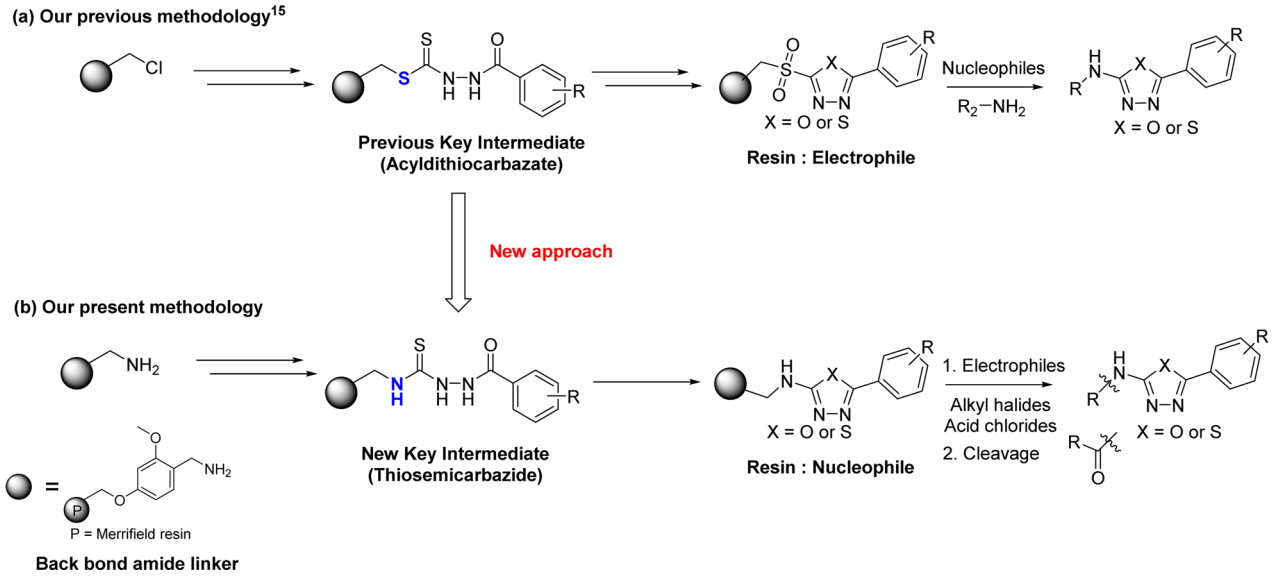
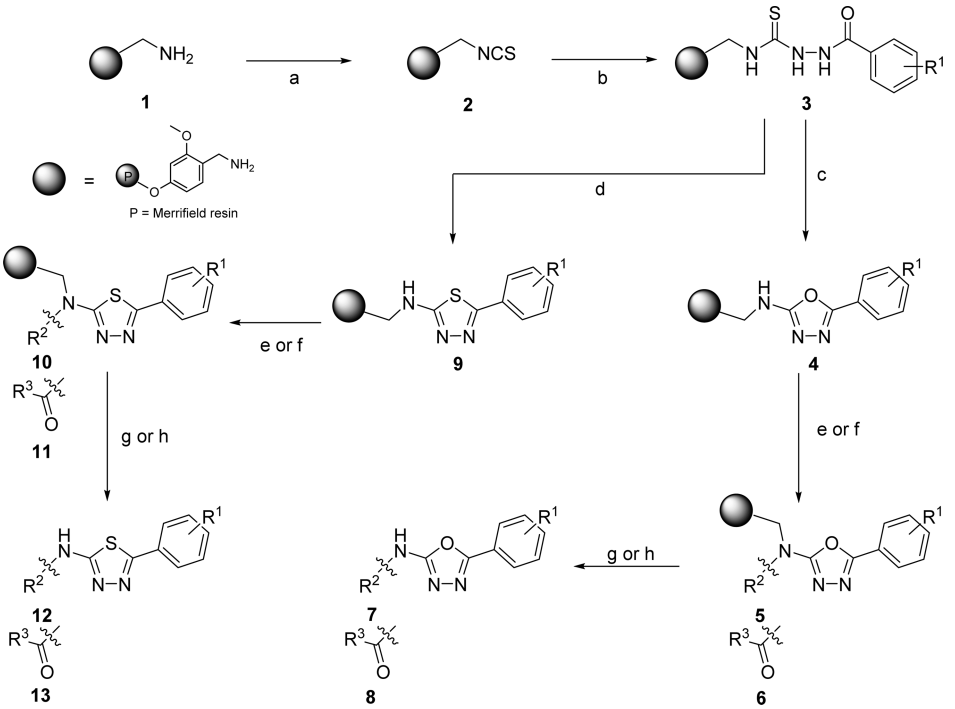
Scheme 1. Strategy Used to Generate Various 2-Amino/Amido-1,3,4-oxadiazoles and 1,3,4-Thiadiazoles



Scheme 2[a]



[a]Reaction condition: (a) CS_2, *p*-TsCl, TEA, THF, room temperature, 18 h; (b) benzhydrazide, TEA, THF, room temperature, 16 h; (c) EDC·HCl, DMSO, 60 °C, 16 h; (d) *p*-TsCl, TEA, rt, 12 h; (e) alkyl halide, *t*-BuOK, DMF, 60 °C, 16 h; (f) acid chloride, pyridine, 60 °C, 12 h; (g) TFA/DCM (1:4, v/v), 40 °C, 8 h; (h) TFA/DCM (1:4, v/v), room temperature, 6 h.

nucleophiles could be introduced at the 2-position of both 1,3,4-oxadiazole and 1,3,4-thiadiazole. On the other hand, in our present methodology, resin was used as a nucleophile and various electrophiles such as alkyl halides and acid chlorides were introduced at the 2-position of both 1,3,4-oxadiazole and 1,3,4-thiadiazole. Herein, we report our recent efforts on this project, which includes the regioselective synthetic protocol for 2-amino/amido-1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives with a thiosemicarbazide intermediate on the solid-phase synthesis.

RESULTS AND DISCUSSION

The sequence used to prepare the thiosemicarbazide intermediate resin **3** uses the 4-benzyloxy-2-methoxybenzylamine(BOMBA) resin **1** as the starting material. Treatment of resin **1** with CS_2, *p*-TsCl, and triethylamine (Et_3N) in tetrahydrofuran (THF) generated the desired isothiocyanate terminated resin **2**.[20] 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 a typical isothiocya-

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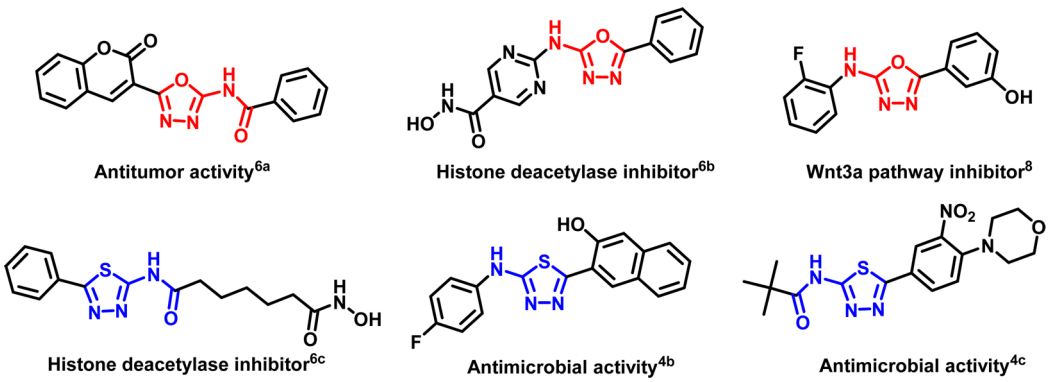
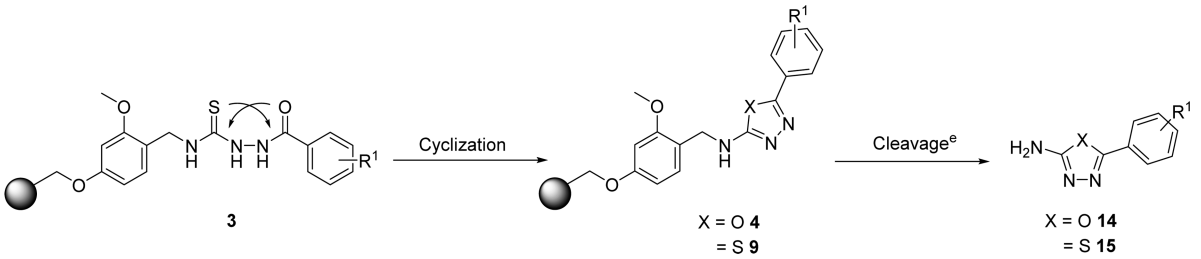


Figure 1. Biologically active compounds containing 1,3,4-oxadiazole, and 1,3,4-thiadiazole core skeleton.

Table 1. Results of Cyclization Condition of Thiosemicarbazide Resin 3



				ratio[d]	
entry	R^1	cyclization	solvent	**14**	**15**
1	H	EDC·HCl	DMSO	100	0
2	*p*-methoxy	EDC·HCl	DMSO	100	0
3	*p*-nitro	EDC·HCl	DMSO	100	0
4	*p*-fluoro	EDC·HCl	DMSO	100	0
5	*m*-nitro	EDC·HCl	DMSO	100	0
6	H	*p*-TsCl/TEA	NMP	41	59
7	*p*-methoxy	*p*-TsCl/TEA	NMP	71	29
8	*p*-nitro	*p*-TsCl/TEA	NMP	12	88
9	*p*-fluoro	*p*-TsCl/TEA	NMP	66	34
10	*m*-nitro	*p*-TsCl/TEA	NMP	38	62
11	*p*-H	*p*-TsCl/TEA	NMP/THF	45	55
12	*p*-nitro	*p*-TsCl/TEA	NMP/THF	12	88

[a]Thiosemicarbazide resin **3** was treated with 3.0 equiv of EDC·HCl in DMSO at 60 °C for 16 h. Thiosemicarbazide resin **3** was treated with 3.0 equiv *p*-TsCl and 3.0 equiv TEA in NMP. [b]NMP/THF(v/v = 1:1). [c]At room temperature for 12 h. [d]Ratio was checked by LC/MS. [e]The mixture of cyclized resin and cleavage cocktail (TFA/DCM = 1:4, v/v) was shaken at 40 °C for 6 h.

nate band at 2070 cm^{-1} (Figure 1b in the Supporting Information). The isothiocyanate terminated resin **2** reacted with substituted benzhydrazide in the presence of Et_3N and THF to obtain thiosemicarbazide intermediate resin **3**, signaled by the absence of the isothiocyanate band at 2070 cm^{-1} and by the appearance of the broad amine peak at 3312 cm^{-1} and amide peak at 1670 cm^{-1} (Figure 1c in the Supporting Information).

From the thiosemicarbazide resin **3**, we tried to synthesize both 1,3,4-oxadiazole resin **4** and 1,3,4-thiadiazole resin **9** via EDC·HCl or *p*-TsCl mediated cyclization. The use of EDC·HCl led to 1,3,4-oxadiazole resin **4** with various substituents at the R^1 position via desulfurative cyclization. (Table 1, entries 1−5) The formation of resin **4** was confirmed by the absence of 3312 and 1670 cm^{-1} of resin **3** and by the appearance of an imine peak at 1604 cm^{-1} (Figure 1d in the Supporting Information (SI)). To determine the exact ratio of regioselectivity, we cleaved the resin after cyclization and confirmed only the 1,3,4-oxadiazole **14** in the LC/MS (SI Figure 2a, 2c, 2e, 2g, and 2i). On the other hand, in the case of *p*-TsCl mediated cyclization, the regioselectivity depended on the substituent at the R^1 position. First, a phenyl thiosemicarbazide showed low regioselectivity (Table 1, entry 6; SI Figure 2b) and thiosemicarbazides substituted with *p*-methoxy or *p*-fluoro which could donate electron pairs showed slight regioselectivity for 1,3,4-oxadiazole (Table 1, entries 7 and 9; SI Figure 2d and 2h). To increase regioselectivity for 1,3,4-thiadiazole, we introduced a nitro group as a strong electron withdrawing group at the para and meta positions of thiosemicarbazide **3**. The *m*-nitro substituted thiosemicarbazide showed slightly increased regioselectivity for 1,3,4-thiadiazole (Table 1, entry 10; SI Figure 2j) and *p*-nitro substituted thiosemicarbazide showed good regioselectivity for 1,3,4-thiadiazole (Table 1, entry 8; SI Figure 2f). The formation of resin **9** was confirmed by the absence of 3291 cm^{-1} (br) and 1683 cm^{-1} (amide) peaks of resin **3** (SI Figure 1g). To know

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Scheme 3. Proposed Mechanism of Cyclization of Thiosemicarbazide Resin 3 Promoted by *p*-TsCl/Et_3N in NMP

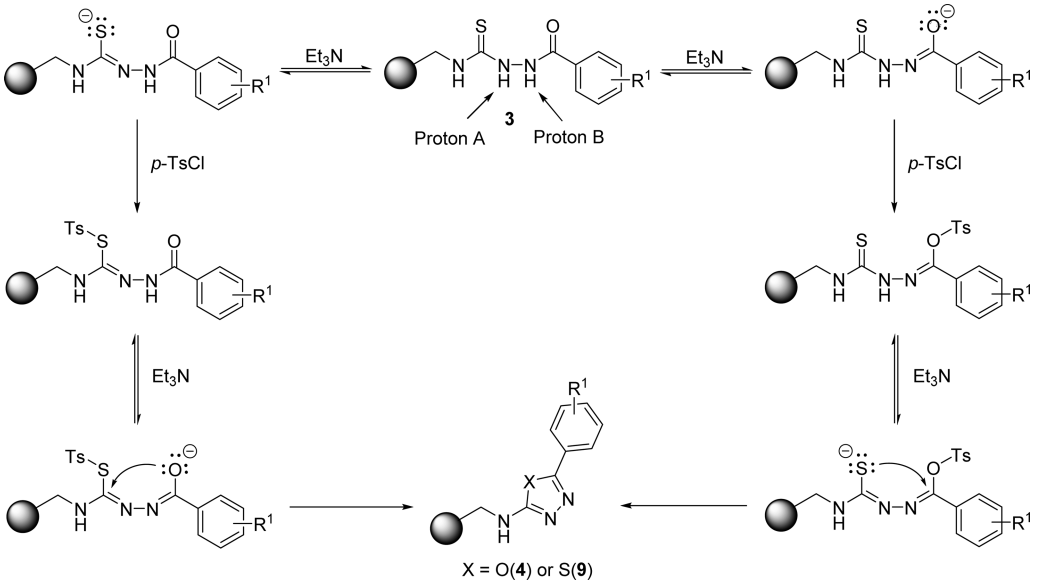
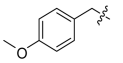
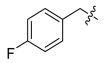
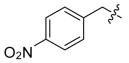
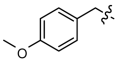
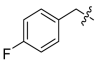
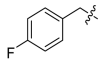
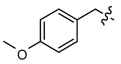
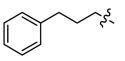
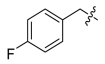
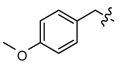


Table 2. Yields and Purities of the 2-Amino-1,3,4-oxadiazole Derivatives 7

No	R^1	R^2	Yield (%)[a]	Purity (%)[b]	No	R^1	R^2	Yield (%)[a]	Purity (%)[b]
7a	H		23	100	**7k**	*p*-Methoxy		29	96
7b	H		16	95	**7l**	*p*-Methoxy		30	100
7c	H		5	89	**7m**	*p*-Methoxy		10	100
7d	H		37	100	**7n**	*p*-Methoxy		23	99
7e	H		40	100	**7o**	*p*-Methoxy		27	100
7f	H		23	100	**7p**	*m*-Nitro		14	99
7g	H		23	99	**7q**	*m*-Nitro		13	97
7h	H		16	100	**7r**	*m*-Nitro		9	100
7i	H		21	98	**7s**	*m*-Nitro		25	98
7j	H		20	93	**7t**	*m*-Nitro		28	96
7u	*p*-Fluoro		30	97	**7v**	*p*-Fluoro		23	100
7w	*p*-Fluoro		23	100	**7x**	*p*-Fluoro		10	98
7y	*p*-Fluoro		27	96					

[a]Five-step overall obtained yields from BAL resin **1** (loading capacity of resin **1** is 1.16 mmol/g). [b]All of purified products were checked by LC/MS.

the exact ratio of regioselectivity, we cleaved the resin after cyclization and then confirmed 1,3,4-thiadiazole **15** as a major product in LC/MS (SI Figure 2f). According to our solution-phase study.[19] the regioselectivity was affected by both electronic and solvent effects in the *p*-TsCl mediated cyclization. Generally, NMP as a solvent and the *p*-nitro group on the R^1 position show good regioselectivity for the 1,3,4-thiadiazole. However, on the solid-phase synthesis, the regioselectivity was not affected by solvent effect, while the electronic effect showed similar regioselectivity with solution-phase synthesis because the resin **3** had not sufficiently swollen in NMP (Table 1, entries 6 and 8). Thus, to increase regioselectivity for the 1,3,4-thiadiazole, we used THF as a cosolvent to enhance the solvent effect which easily swells in

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Table 3. Yields and Purities of the 2-Amido-1,3,4-oxadiazole Derivatives 8

No	R^1	R^3	Yield (%)[a]	Purity (%)[b]	No	R^1	R^3	Yield (%)[a]	Purity (%)[b]
8a	H		63	100	**8k**	*p*-Methoxy		30	94
8b	H		63	100	**8l**	*p*-Methoxy		36	100
8c	H		53	100	**8m**	*p*-Methoxy		28	100
8d	H		54	100	**8n**	*p*-Methoxy		23	90
8e	H		31	100	**8o**	*p*-Methoxy		25	100
8f	H		40	100	**8p**	*m*-Nitro		43	100
8g	H		62	95	**8q**	*m*-Nitro		27	100
8h	H		16	92	**8r**	*m*-Nitro		13	97
8i	H		41	100	**8s**	*m*-Nitro		21	98
8j	H		28	100	**8t**	*m*-Nitro		28	96
8u	*p*-Fluoro		40	100	**8v**	*p*-Fluoro		29	91
8w	*p*-Fluoro		15	100	**8x**	*p*-Fluoro		32	100
8y	*p*-Fluoro		41	91					

[a]Five-step overall obtained yields from BAL resin **1** (loading capacity of resin **1** is 1.16 mmol/g). [b]All of purified products were checked by LC/MS.

the polystyrene resin (Table 1, entry 11 and 12). However, it did not show an increase of regioselectivity for the 1,3,4-thiadiazole (SI Figure 2k and 2l).

The proposed mechanism is described in Scheme 3. According to our experimental results (Table 1, entries 6−10), the regioselectivity in *p*-TsCl mediated cyclization seems to be affected by the pK_a of both proton A and proton B. When we introduced *p*-nitro or *m*-nitro groups at the R^1 position, it caused a decrease of the pK_a of proton B so proton B could be easily deprotonated by Et_3N leading to regioselectivity of the 1,3,4-thiadiazole resin **9** (Table 1, entries 6, 8, and 10). On the other hand, *p*-methoxy and *p*-fluoro groups which could donate an electron pair, caused an increase of the pK_a of proton B that led to regioselectivity of the 1,3,4-oxadiazole resin **4** (Table 1, entries 6, 7, and 9). Next, in other to explore the diversity of our experiment, we tried to synthesize 1,3,4-oxadiazole and 1,3,4-thiadiazole analogues. With the available resin **4**, we focused on the various alkyl and acyl substitution at the 2-*N* position on 2-amino-1,3,4-oxadiazole core skeleton resin **4**.

First, to make *N*-alkylamino-1,3,4-oxadiazole resin **5**, we used various alkyl halides in the presence of NaH in NMP at 60 °C for 16 h. In the case of our solution phase synthesis, alkylation was successful in this condition.[19] However, on the solid phase synthesis, it was unsuccessful because of the low solubility of NaH in the organic solvent. We therefore used various bases and solvents such as K_2CO_3, $CsCO_3$, and *t*-BuOK in THF, ACN, and DMF. Among these combinations, *t*-BuOK in DMF showed good reactivity for the alkylation. The progress of this reaction was monitored by ATR-FTIR spectroscopy, which revealed the growth of the band intensity of the C−N bond at 1249 cm^{-1} (SI Figure 1e) and cleavage from resin **5** by treatment of TFA/DCM (1:4, v/v) at 40 °C for 8 h. To purify the crude product mixture of **7**, we used a short plug of silica with hexane/tetrahydrofuran and then triturated this by using the diethyl ether/hexane. Finally, we could obtain various 2-amino-1,3,4-oxadiazole derivatives **7** in good yields and high purities as shown in Table 2. We then used various acid chlorides with NaH in THF to make a *N*-acylamino-1,3,4-oxadiazole resin **6**. However, the solid-phase synthesis was also not successful. We therefore used neat pyridine. In this condition, the acylation reaction proceeded smoothly to give the desired *N*-acylamino-1,3,4-oxadiazole resin **6**. The reaction was monitored by ATR-FTIR spectroscopy, which revealed the growth of the band intensity of the amide bond at 1685 cm^{-1} (SI Figure 1f). This *N*-acylamino-1,3,4-oxadiazole resin **6** could be easily cleaved in TFA/DCM (5:95, v/v) at room temperature for 6 h to afford the corresponding 2-amido-1,3,4-oxadiazole **8**. To purify the crude product mixture **8**, we triturated it with ethyl acetate/diethyl ether to obtain 2-amido-1,3,4-oxadiazole **8** (The LC/MS result of the crude product mixture **8a** is shown in Figure 3 in the Supporting Information). Finally, we obtained 2-amido-1,3,4-oxadiazole derivatives **8** in high yields and purities as shown in Table 3.

Next, to generate 1,3,4-thiadiazole analogues, we used *p*-nitro substituted thiosemicarbazide **3**, which shows regioselectivity for 1,3,4-thiadiazole (Table 1, entry 8). After cyclization of thiosemicarbazide **3** with *p*-TsCl/Et_3N in NMP, we used various alkyl halides in the presence of *t*-BuOK in DMF. The reaction was monitored by ATR-FTIR spectroscopy, which revealed the growth of the bond intensity of C−N bond at

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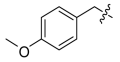
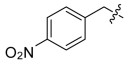
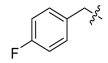
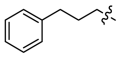
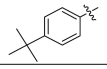
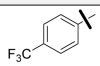
Table 4. Yields and Purities of the 2-Amino-1,3,4-thiadiazole Derivatives 12

No	R^1	R^3	Yield (%)[a]	Purity (%)[b]	No	R^1	R^3	Yield (%)[a]	Purity (%)[b]
12a	*p*-Nitro		11	94	12f	*p*-Nitro		13	100
12b	*p*-Nitro		19	95	12g	*p*-Nitro		7	100
12c	*p*-Nitro		6	90	12h	*p*-Nitro		8	100
12d	*p*-Nitro		14	99	12i	*p*-Nitro		10	92
12e	*p*-Nitro		13	79	12j	*p*-Nitro		8	93

[a]Five-step overall obtained yields from BAL resin **1** (loading capacity of resin **1** is 1.16 mmol/g). [b]All of purified products were checked by LC/MS.

Table 5. Yields and Purities of the 2-Amido-1,3,4-thiadiazole Derivatives 13

No	R^1	R^3	Yield (%)[a]	Purity (%)[b]	No	R^1	R^3	Yield (%)[a]	Purity (%)[b]
13a	*p*-Nitro		40	88	13f	*p*-Nitro		31	63
13b	*p*-Nitro		9	95	13g	*p*-Nitro		13	82
13c	*p*-Nitro		41	73	13h	*p*-Nitro		9	91
13d	*p*-Nitro		34	72	13i	*p*-Nitro		10	94
13e	*p*-Nitro		33	50	13j	*p*-Nitro		21	92

[a]Five-step overall obtained yields from BAL resin **1** (loading capacity of resin **1** is 1.16 mmol/g). [b]All of purified products were checked by LC/MS.

1260 cm^{-1} (SI Figure 1h) and cleavage from resin **10** by treatment of TFA: DCM (1:4, v/v) at 40 °C for 8 h. To purify the crude product mixture of 2-amino-1,3,4-thiadiazole **12**, we used a short plug of silica with hexane/ethyl acetate and then triturated it by using diethyl ether/hexane. As a result, we obtained the desired 2-amino-1,3,4-thiadiazole derivatives in moderate yields and high purities as shown in Table 4.

Next, we tried to synthesize 2-amido-1,3,4-thiadiazole analogues **13**. Various acid chlorides were introduced on the 1,3,4-thiadiazole resin **9** in a neat pyridine condition to afford 2-amido-1,3,4-thiadiazole resin **11**, signaled by the amide peak at 1657 cm^{-1}. (SI Figure 1i) and then cleaved from resin **11** in a TFA/DCM (95:5, v/v) at room temperature for 4 h. To purify crude product mixture **13**, we triturated it with ethyl acetate/ethanol (The LC/MS result of the crude product mixture **13a** is shown in Figure 4 in the Supporting Information). As a result, we obtained the desired 2-amido-1,3,4-thiadiazole **13** in a high yields and purities as shown in Table 5.

Finally, we had an interest to the evaluation of the potential drug properties of the 2-amino/amido-1,3,4-oxadiazole and 1,3,4-thiadiazole library. In the drug development process, it is important to develop orally available drug; Lipinski's Rule[21] and similar parameters could be used as guidelines to an estimation of physicochemical property. The key bioavailability parameters, such as molecular weight, lipophilicity, number of hydrogen bonding donors and acceptors, number of rotatable bond, and polar surface area are displayed in the Figure 2. As can be seen in this data, most of the key parameters of constructed 2-amino/amido-1,3,4-oxadiazole and 1,3,4-thiadiazole library fall within the range of those predicted for reasonable oral bioavailable drugs.

In conclusion, we established a solid-phase synthetic method to construct a 2-amino/amido-1,3,4-oxadiazole and 1,3,4-thiadiazole library. The isothiocyanate terminated resin **2** was prepared from BOMBA resin **1** by using the CS_2, *p*-TsCl, and Et_3N in THF and was then reacted with various benzhydrazides to give the thiosemicarbazide resin **3**. Cyclization of resin **3** was promoted by EDC·HCl in DMSO and *p*-TsCl/Et_3N in NMP to generate 2-amino-1,3,4-oxadiazole and 1,3,4-thiadiazole core skeleton resin **4** and **9** respectively. In the case of *p*-TsCl mediated cyclization, the regioselectivity for 1,3,4-thiadiazole was shown with *p*-nitro substituted thiosemicarbazide while the cyclization mediated in EDC·HCl showed regioselectivity for 1,3,4-oxadiazole with various substituent such as *p*-methoxy, *p*-nitro, *m*-nitro, and *p*-F. To functionalize both 2-amino-1,3,4-oxadiazole resin **4** and 1,3,4-thiadiazole resin **9**, various alkyl halides and acid chlorides were used to generate corresponding 2-amino/amido-1,3,4-oxadiazole resin **5** and **7** as well as 2-amino/amido-1,3,4-thiadiazole resin **10** and **11**. Finally, we obtained the desired 2-amino/amido-1,3,4-oxadiazole and 1,3,4-thiadiazole analogues **7**, **8**, **12**, and **13** after cleavage with TFA/DCM in high yields and purities. The yields of 2-amino/amido-1,3,4-oxadiazole analogues **7** and **8** are slightly higher than the yields of 2-amino/amido-1,3,4-thiadiazole analogues **12** and **13** because EDC·HCl mediated cyclization for 1,3,4-oxadiazole resin **4** is a regiospecific reaction while *p*-TsCl mediated cyclization for 1,3,4-thiadiazole resin **9** is a regioselective reaction. To know the potential of bioavailable drug properties of our constructed library, we used Lipinski's

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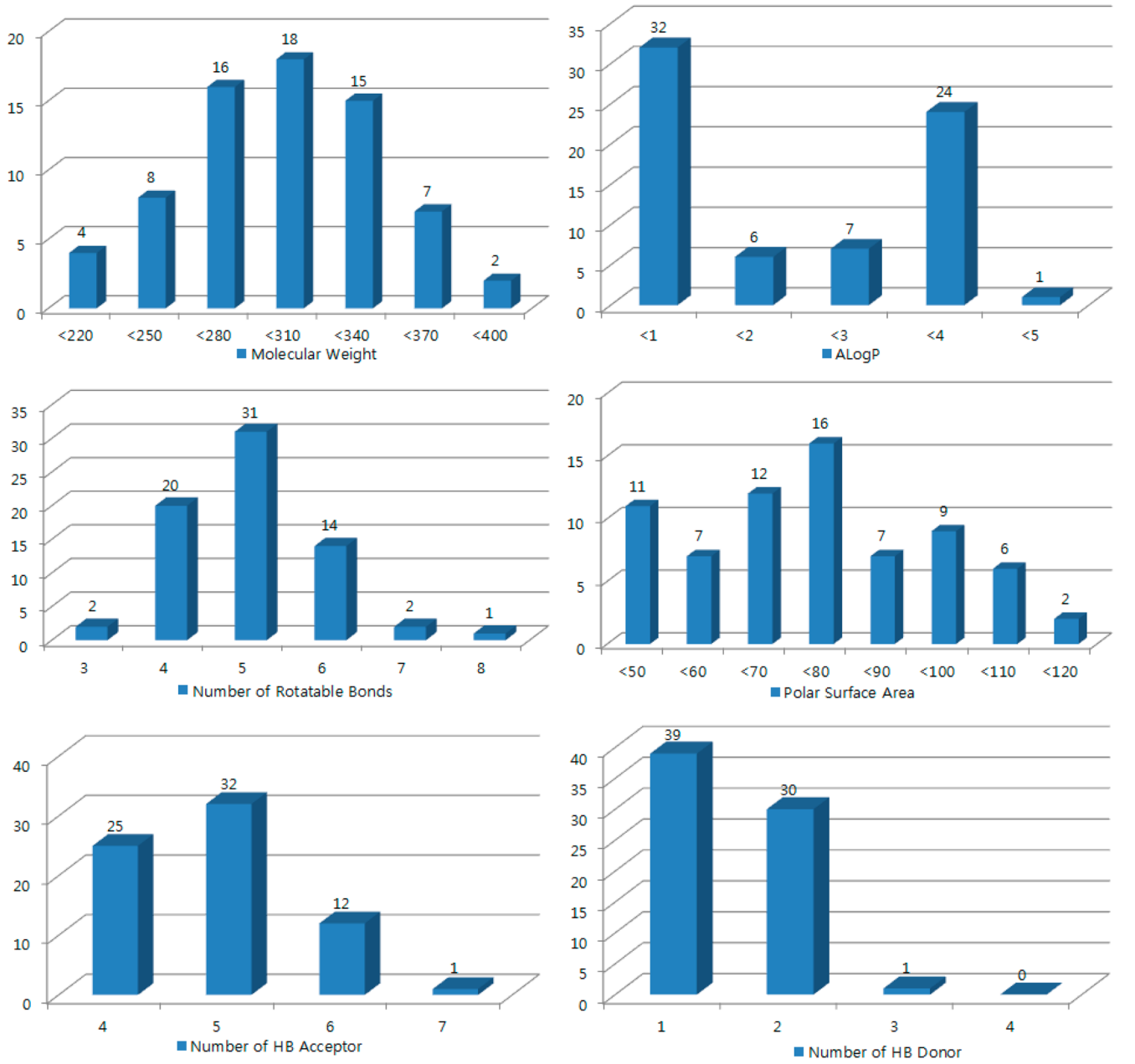

Figure 2. Calculated physicochemical properties of constructed 1,3,4-oxadiazole and 1,3,4-thiadiazole library.

Rule and similar parameters. As a result, we know that the constructed library has the potential to be used as an orally bioavailable drug. We envision that these libraries will be used in the drug discovery process as well as for the exploration of biological areas.

EXPERIMENTAL PROCEDURES

General Procedure for Synthesis. All chemicals were reagent grade and used as purchased. Reactions were monitored by ATR-FTIR. Flash column chromatography was carried out on silica gel (230−400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded in δ units relative to deuterated solvent as an internal reference using a 500 MHz NMR instrument. Liquid chromatography tandem mass spectrometry analysis was performed on an electro spray ionization (ESI) mass spectrometer with photodiode-array detector (PDA) detection. High-resolution mass spectrometry spectra were obtained using TOF LC/MS system.

Representative Procedure for the Preparation of Isothiocyanate-Terminated Resin ***2****.* Et_3N (5.87 g, 58.0 mmol) and CS_2 (2.65 g, 34.8 mmol) was added to a mixture of BOMBA resin **1** (5 g, 5.8 mmol) in THF (30 mL) at 0 °C. The mixture was stirred at room temperature for 3 h. *p*-TsCl (5.52 g, 29.0 mmol) was added at 0 °C and the mixture was stirred at room temperature for 15 h. The precipitate obtained by filteration of the mixture was washed with THF, H_2O, MeOH, and CH_2Cl_2 and dried in a vacuum oven. This process made resin **2** a brown solid. Single-Bead ATR-FTIR: 3026, 2920, 2070 (N═C═S), 1607, 1587, 1504, 1449, 1284, 1194, 1157, 1028, and 816 cm $^{-1}$.

Representative Procedure for the Preparation of Thiosemicarbazide Resin ***3a****.* A mixture of isothiocyanate resin **2** (5.23 g. 5.8 mmol), benzhydrazide (2.37 g, 17.4 mmol), and Et_3N (2.43 g, 17.4 mmol) in THF (30 mL) was stirred at room temperature for 16 h. The resin was filtered and washed several times with MeOH and CH_2Cl_2 and then dried in a vacuum oven. Resin **3a** was obtained as a brown solid. Single-Bead ATR-FTIR: 3312(br), 2923, 1670(C═O), 1606, 1504, 1449, 1280, 1193, 1156, 1016, and 818 cm $^{-1}$.

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*Representative Procedure for the Preparation of 2-Amino-1,3,4-oxadiazole Resin **4a**.* A mixture of thiosemicarbazide resin **3a** (6.00 g, 5.8 mmol) and EDC·HCl (3.34 g, 17.4 mmol) in DMSO (30 mL) was stirred at 60 °C for 16 h. The resin was filtered and washed several times with MeOH, H_2O, and CH_2Cl_2 and then dried in a vacuum oven. Resin **4a** was obtained as a brown solid. Single-Bead ATR-FTIR: 3023, 2922, 1604(C═N), 1503, 1448, 1418, 1269, 1194, 1157, 1015, and 818 cm^{-1}.

*Representative Procedure for the Preparation of N-Benzylamino-1,3,4-oxadiazole Resin **5a**.* A 2-amino-1,3,4-oxadiazole resin **4a** (200 mg, 0.2 mmol) in DMF (3 mL) was added *t*-BuOK (112 mg, 1.0 mmol) at room temperature. The resulting mixture was stirred at room temperature for 15 min. Benzyl chloride(127 mg, 1.0 mmol) was added to a mixture and then stirred at 60 °C for 16 h. The resin was filtered and washed several times with MeOH, H_2O, and CH_2Cl_2 and then dried in a vacuum oven. Resin **5a** was obtained as a brown solid. Single-bead ATR-FTIR: 3023, 2019, 1606, 1491, 1448, 1285, 1249(C−N), 1196, 1160, 1025, and 902 cm^{-1}.

*Representative Procedure for the Preparation of N-Benzyl-5-phenyl-1,3,4-oxadiazol-2-amine **7a**.* A resin **5a** (200 mg, 0.2 mmol) was treated with a mixture of TFA/CH_2Cl_2 (1:4, v/v) at 40 °C for 8 h. The resin was filtered and then washed several times with CH_2Cl_2 and MeOH. The organic filtrate was evaporated and then extracted with CH_2Cl_2 and H_2O followed by neutralized to pH 7 by using saturated $NaHCO_3$ aqueous solution. The aqueous layer was back-extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to obtain the crude product, which was purified by column chromatography on silica gel (hexane/THF) and triturated with diethyl ether/hexane(1:1) to obtain 11.9 mg (23.3%, 5 steps overall yield) of desired *N*-benzyl-5-phenyl-1,3,4-oxadiazol-2-amine **7a**. ^1H NMR (500 MHz, DMSO): δ 8.38 (s, 1H), 7.87−7.77 (m, 2H), 7.53 (d, J = 1.8 Hz, 3H), 7.38 (d, J = 17.5 Hz, 4H), 7.28 (s, 1H), 4.46 (d, J = 2.1 Hz, 2H). ^{13}C NMR (126 MHz, DMSO): δ 164.1, 158.2, 139.2, 131.0, 129.7, 128.9, 127.9, 127.6, 125.6, 124.7, 46.5. LC-MS (ESI): m/z = 250.2 $[M - H]^-$. HRMS (ESI) calcd for $C_{14}H_{10}FN_3O$ $[M + H]^+$: 252.1131, found: 252.1137.

*Representative Procedure for the Preparation of N-Benzoylamino-1,3,4-oxadiazole Resin **6a**.* A 2-amino-1,3,4-oxadiazole resin **4a** (200 mg, 0.2 mmol) in pyridine (3 mL) was added benzoyl chloride (140 mg, 1.0 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 12 h. The resin was filtered and washed several times with MeOH, H_2O, and CH_2Cl_2 and then dried in vacuum oven. Resin **6a** was obtained as a brown solid. Single-bead ATR-FTIR: 3023, 2923, 1685(amide), 1607, 1576, 1504, 1448, 1265, 1195, 1025, 820 cm^{-1}.

*Representative Procedure for the Preparation of N-(5-Phenyl-1,3,4-oxadiazol-2-yl)benzamide **8a**.* A resin **6a** (200 mg, 0.2 mmol) was treated with a mixture of TFA/CH_2Cl_2 (5:95, v/v) at room temperature for 6 h. The resin was filtered and then washed with several times CH_2Cl_2, and MeOH. The organic filtrate was evaporated and then extracted with ethyl acetate and H_2O followed by neutralized to pH 4 by saturated $NaHCO_3$ aqueous solution. The aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated to afford the crude product, which was triturated by ethyl acetate/diethyl ether to afford 33.4 mg (63%, 5 steps overall yield) of desired *N*-(5-phenyl-1,3,4-oxadiazol-2-yl)benzamide **8a**. ^1H NMR (500 MHz, DMSO): δ 12.19 (s, 1H), 8.16−7.89 (m, 4H), 7.75−7.44 (m, 6H). ^{13}C NMR (126 MHz, DMSO): δ 165.5, 161.7, 158.4, 133.4, 132.7, 132.3, 123.0, 129.2, 128.8, 126.6, 123.8. LC-MS (ESI): m/z = 263.9 $[M - H]^-$. HRMS (ESI) calcd for $NaC_{15}H_{12}N_3O_2$ $[M + Na]^+$: 288.0743, found 288.0750.

*Representative Procedure for the Preparation of 2-Amino-1,3,4-thiadiazole Resin **9**.* A mixture of *p*-nitro-substituted thiosemicarbazide resin **3** (6.00 g, 5.8 mmol) and *p*-TsCl (3.32 g, 17.4 mmol) in NMP (30 mL) was stirred at room temperature for 12 h. The resin was filtered and washed several times with MeOH, H_2O, and CH_2Cl_2 and then dried in a vacuum oven. Resin **9** was obtained as a brown solid. Single-bead ATR-FTIR: 3026, 2924, 2850, 1600, 1521(NO_2), 1505, 1489, 1341(NO_2), 1190, 1156, and 853 cm^{-1}.

*Representative Procedure for the Preparation of N-Benzylamino-1,3,4-thiadiazole Resin **10a**.* A 2-amino-1,3,4-thiadiazole resin **9** (213 mg, 0.2 mmol) in DMF (3 mL) was added *t*-BuOK (112 mg, 1.0 mmol) at room temperature. The resulting mixture was stirred at room temperature for 15 min. Benzyl chloride(127 mg, 1.0 mmol) was added to a mixture and then stirred at 60 °C for 16 h. The resin was filtered and washed several times with MeOH, H_2O, and CH_2Cl_2 and then dried in a vacuum oven. Resin **10a** was obtained as a brown solid. Single-bead ATR-FTIR: 3023, 2915, 2852, 1597, 1520(NO_2), 1505, 1489, 1447, 1339(NO_2) 1260(C−N), 1193, 1160, and 846 cm^{-1}.

*Representative Procedure for the Preparation of N-Benzyl-5-phenyl-1,3,4-thiadiazol-2-amine **12a**.* A resin **10a** (213 mg, 0.2 mmol) was treated with a mixture of TFA/CH_2Cl_2 (1:4, v/v) at 40 °C for 8 h. The resin was filtered and then washed several times with CH_2Cl_2 and MeOH. The organic filtrate was evaporated and then extracted with ethyl acetate and H_2O followed by neutralized to pH 7 by using saturated $NaHCO_3$ aqueous solution. The aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated to obtain the crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate) and triturated with diethyl ether/hexane(1:1) to obtain 6.6 mg (11%, 5 steps overall yield) of desired *N*-benzyl-5-phenyl-1,3,4-thiadiazol-2-amine **12a**. ^1H NMR (500 MHz, DMSO) δ 8.77 (t, J = 5.6 Hz, 1H), 8.30 (d, J = 8.6 Hz, 2H), 8.02 (d, J = 8.7 Hz, 2H), 7.43−7.35 (m, J = 15.1, 7.5 Hz, 4H), 7.30 (t, J = 6.9 Hz, 1H), 4.59 (d, J = 5.6 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 169.7, 154.0, 147.5, 138.2, 136.6, 128.5, 127.6, 127.3, 127.2, 124.5, 48.1. LC-MS (ESI): m/z = 313.2 $[M + H]^+$. HRMS (ESI) calcd for $C_{15}H_{13}N_4O_2S$ $[M + H]^+$: 313.0754; found 313.0755.

*Representative Procedure for the Preparation of N-Benzoylamino-1,3,4-thiadiazole Resin **11a**.* A 2-amino-1,3,4-oxadiazole resin **9a** (213 mg, 0.2 mmol) in pyridine (3 mL) was added benzoyl chloride (140 mg, 1.0 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 12 h. The resin was filtered and washed several times with MeOH, H_2O, and CH_2Cl_2 and then dried in vacuum oven. Resin **11a** was obtained as a brown solid. Single-bead ATR-FTIR: 3023, 2921, 2852, 1657(amide), 1600, 1581, 1521(NO_2), 1503, 1489, 1449, 1343(NO_2), 1193, 1156, 1017, and 851 cm^{-1}.

*Representative Procedure for the Preparation of N-(5-Phenyl-1,3,4-oxadiazol-2-yl)benzamide **13a**.* A resin **11a** (213 mg, 0.2 mmol) was treated with a mixture of TFA/CH_2Cl_2 (5:95, v/v) at room temperature for 4 h. The resin was filtered and then washed with several times CH_2Cl_2, and MeOH. The organic filtrate was evaporated and then extracted with ethyl acetate and H_2O. The aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated to afford the crude product, which was triturated by ethyl acetate/ethanol to afford 31.5 mg (48%, 5 steps overall yield) of desired *N*-(5-phenyl-1,3,4-oxadiazol-2-yl)benzamide **13a**. ^1H NMR (500 MHz, DMSO): δ 13.31 (s, 1H), 8.37 (d, J = 8.4 Hz, 2H), 8.28 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 8.0 Hz, 2H), 7.69 (t, J = 7.1 Hz, 1H), 7.59 (t, J = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, DMSO): δ 165.3, 160.6, 160.0, 148.2, 135.9, 133.1, 131.2, 128.6, 128.4, 128.0, 124.5. LC-MS (ESI): m/z = 327.1 $[M + H]^+$. HRMS (ESI) calcd for $C_{15}H_{11}N_4O_3S$ $[M + H]^+$: 327.0546; found 327.0539.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00140.

Full analytical data of compounds, along with copies of ^1H NMR, ^{13}C NMR, LC/MS, and HRMS spectra of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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