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Solid-phase Synthesis of 1,3,4-Thiadiazole Derivatives via Desulfurative Cyclization of Thiosemicarbazide Intermediate Resin

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Abstract A 1,3,4-thiadiazole library was constructed by solid-phase organic synthesis. The key step of this solid-phase synthesis involves the preparation of polymer-bound 2-amido-5-amino-1,3,4-thiadiazole resin by the cyclization of thiosemicarbazide resin using *p*-TsCl as the desulfurative agent, followed by the functionalization of the resin by alkylation, acylation, alkylation/acylation, and Suzuki coupling reactions. Both the alkylation and acylation reactions chemoselectively occurred at the 2-amide position of 2-amido-5-amino-1,3,4-thiadiazole resin and the 5-amine position of 2-amido-5-amino-1,3,4-thiadiazole resin, respectively. Finally, these functionalized 1,3,4-thiadiazole resins were treated with trifluoroacetic acid in dichloromethane, affording diverse 1,3,4-thiadiazole analogs in high yields and purities. The 1,3,4-thiadiazole analogs show a different distribution of physicochemical and biological properties compared to our previously constructed 1,3,4-oxadiazole and 1,3,4-thiadiazole libraries in a range of orally available drug properties.

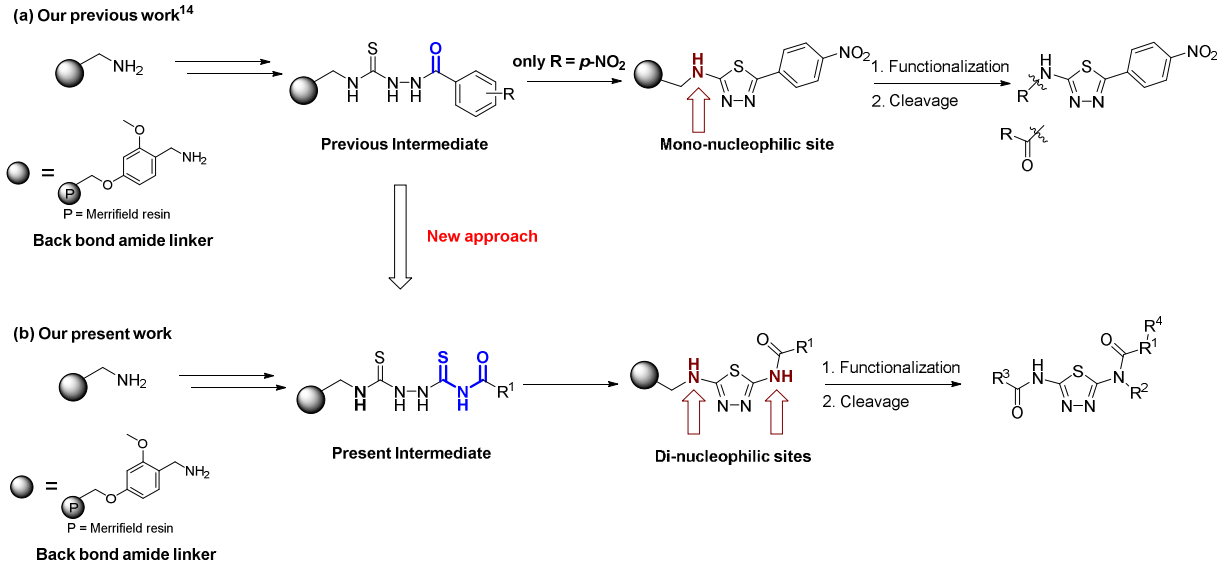
KEYWORDS: Solid-phase, BOMBA, Thiosemicarbazide, 1,3,4-thiadiazole

Introduction

Solid-phase synthesis has emerged as a powerful tool in medicinal chemistry owing to its capability to rapidly generate a massive number of small organic molecules.[1] Among these small molecules, heterocyclic compounds are now used to yield potent and selective drugs having unique pharmacophores.[2] Especially, five-membered ring heterocycles have showed wide range of intriguing biological activities. In this family, 1,3,4-thiadiazole and 1,3,4-oxadiazole derivatives have shown potent biological activity such as anti-inflammatory,[3] antimicrobial,[4] anticonvulsant,[5] anticancer,[6] and antihypertensive[7] in medicinal chemistry areas. The term bioisostere has been used in medicinal chemistry area, because it frequently exhibits enhanced biological activity or physicochemical property without significant changes in the chemical structure.[8] Along these lines, 1,3,4-thiadiazole and 1,3,4-oxadiazole have been considered as a bioisostere for each other in drug design. Lee *et al*. compared the binding affinity of compounds containing 1,3,4-oxadiazole or 1,3,4-thaidiazole in the same chemical structure toward CB_1 receptor in the process of developing an obesity drug.[9] Both 1,3,4-oxadiazoles and 1,3,4-thiadiazoles were also used for the development potent antibacterial agents by Kumar *et al*.[10] Asai *et al.* reported a dramatic difference in the binding affinity between identically substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles toward signal transducers and activators of transcription.[11] Because of these biologically interesting properties of 1,3,4-thiadiazoles and 1,3,4-oxadiazoles, these core skeletons have been targeted for synthesis by organic and medicinal chemists, and as a result, many synthetic methodologies have been reported in the literature.[12] Among these synthetic methodologies, solid-phase synthesis effectively facilitates the rapid generation of various 1,3,4-thiadiazoles and 1,3,4-oxadiazoles.[13] In our previous research, we have also developed solid-phase synthetic methodologies to produce 1,3,4-oxadiazoles and 1,3,4-thiadiazoles.[14] Unfortunately our methodology was limited to the synthesis of *p*-nitro substituted 1,3,4-thiadiazole derivatives (Scheme 1a). To improve over methodology, we attempted to develop a new intermediate to afford various 1,3,4-thiadiazoles. As shown in Scheme 1b, we designed a new thiosemicarbazide key intermediate, and herein, we report our research progress in this area,

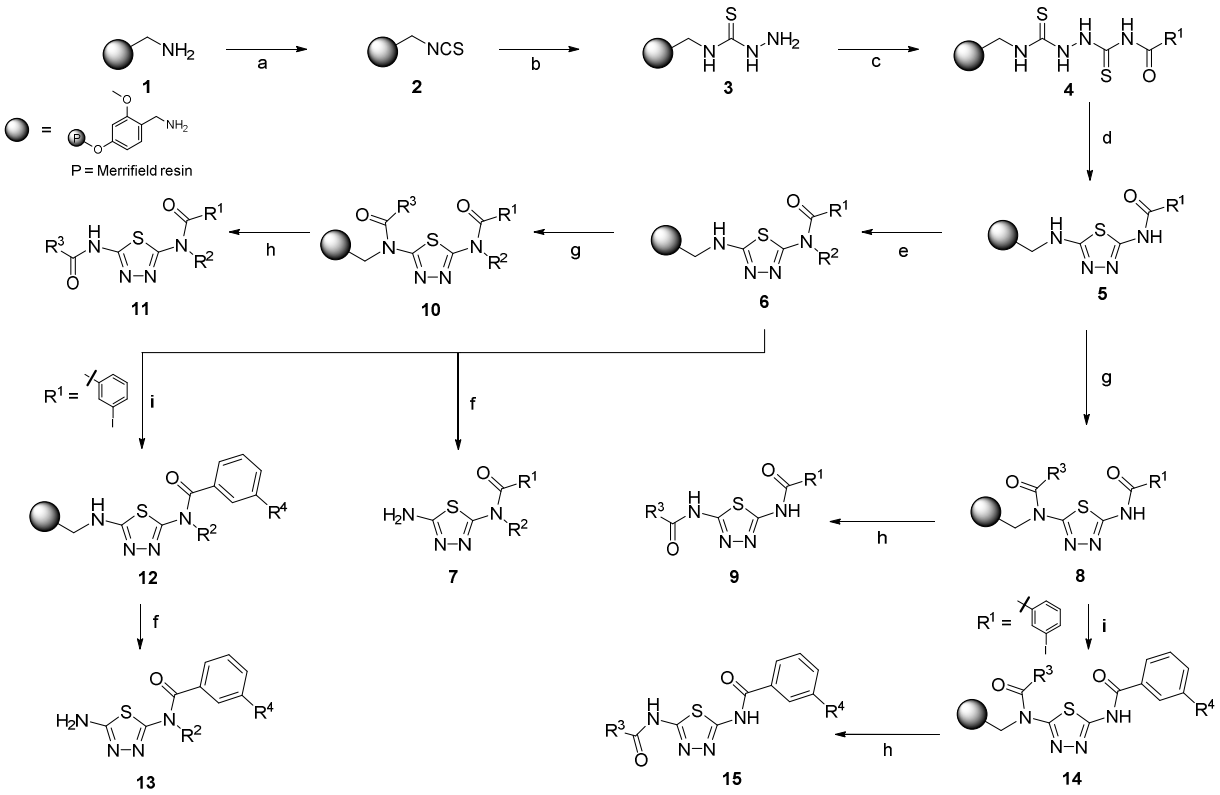
including a desulfurative cyclization process to generate various 1,3,4-thiadiazole derivatives with a high level of diversity via solid-phase synthesis.

Scheme 1 Strategy used to generate various 1,3,4-thiadiazole analogs



Results and Discussion

Scheme 2. Synthesis of 1,3,4-thiadiazole analog by solid-phase synthesis

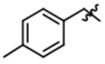
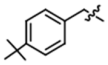
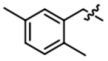
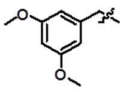
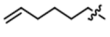
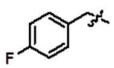
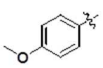
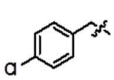
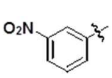


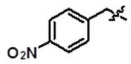
[a]*Reaction conditions*: (a) CS_2, *p*-TsCl, TEA, Tetrahydrofuran, rt, 18 h (b) Hydrazine, DMSO, 50 °C, 4 h (c) Acyl isothiocyanate, Tetrahydrofuran, rt, 3 h (d) *p*-TsCl, Pyridine, DCM, rt, 5 h (e) Alkyl halide, NaH, DMF, 60 °C, 16 h (f) TFA : DCM (1:4, v/v), 40 °C, 4 h (g) Acid chloride, Pyridine, rt, 16 h (h) TFA : DCM (1:4, v/v), rt, 4 h (i) Boronic acid, K_3PO_4, $Pd(PPh_3)_4$, 1,4-Dioxane : H_2O (9:1), 80 °C, 20 h

Based on solid-phase parallel synthesis, the synthetic route used to prepare 2-amido-5-amino-1,3,4-thiadiazole and its derivatives **7**, **9**, **11**, **13** and **15** is outlined in Scheme 2. To synthesize thiosemicarbazide intermediate **4**, 4-benzyloxy-2-methoxybenzylamine (BOMBA) resin **1** was used as the starting material. The reaction of resin **1** with CS_2, *p*-TsCl, and triethylamine (TEA) in tetrahydrofuran (THF) generated isothiocyanate terminated resin **2**,[15] and the formation of resin **2** was confirmed by its attenuated total reflection (ATR) single bead Fourier transform infrared (FTIR) spectrum, showing the presence of a typical isothiocyanate peak at 2071 cm^{-1} (Figure 3b in the Supporting Information). After the treatment of resin **2** with hydrazine in dimethyl sulfoxide (DMSO), the typical isothiocyanate peak at 2071 cm^{-1} disappeared (Figure 3c in the Supporting Information). The following reaction of hydrazinecarbothioamide resin **3** with several acyl isothiocyanates in THF formed thiosemicarbazide resin **4** as the key intermediate, whose ATR-FTIR

spectrum showed the amide peak at 1677 cm^{-1} (Figure 3d in the Supporting Information). As a result, various thiosemicarbazide resins **4** equipped with electron donating groups, electron withdrawing groups, and aliphatic groups at the R^1 position were obtained. Next, thiosemicarbazide resin **4** was reacted with *p*-TsCl and pyridine in dichloromethane (DCM) to afford 2-amido-5-amino-1,3,4-thiadiazole resin **5** via desulfurative cyclization process, and its FTIR spectrum showed a shift of the amide peak from 1677 cm^{-1} to 1664 cm^{-1} (Figure 3e in the Supporting Information). For effective diversification, 2-amido-5-amino-1,3,4-thiadiazole resin **5** was reacted with various alkyl halides in the presence of sodium hydride (NaH) in *N*,*N*-dimethyl formamide (DMF) at 60 °C for 16 h, and various alkyl groups were chemoselectively introduced at the 2-amide position instead of the 5-amine position. The chemoselectivity of the alkylation reaction was investigated by HPLC and COSY analysis (Pages 2–7, the Supporting information). Consequently, alkyl substituted 2-amido-5-amino-1,3,4-thiadiazole resin **6** was successfully generated. To release our desired 2-amido-5-amino-1,3,4-thiadiazole analog **7** from the solid support, the resin **6** was treated with TFA:DCM (1:4, v/v) at 40 °C for 4 h (The LC/MS spectrum of the crude product mixture **7a** is shown in Figure 1 of the Supporting Information). As a result, 2-amido-5-amino-1,3,4-thiadiazole analogs **7** were obtained in good yields and high purities (Table 1).

Table 1. Yields and purities of the 2-*N*-alkylamido-5-amino-1,3,4-thiadiazole derivatives **7**

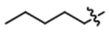
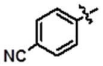
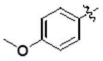
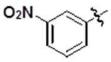
No	R^1	R^2	Yield per step (%)[a]	Purity (%)[b]	No	R^1	R^2	Yield per step (%)[a]	Purity (%)[b]
7a	Ph		81.4	100	**7j**	Ph		75.8	100
7b	Ph		82.3	100	**7k**	Ph		85.1	100
7c	Ph		74.4	96	**7l**	Ph		86.2	100
7d	Ph		78.3	100	**7m**	Ph		71.2	100
7e	Ph		68.1	98	**7n**	Ph		71.2	97
7f	Ph		66.9	100	**7o**			78.8	100
7g	Ph		74.4	100	**7p**			78.3	89

7h	Ph		69.2	100	**7q**			77.7	100
7i	Ph		83.5	100					

[a]Average yield per step calculated over six steps (loading capacity of resin **1** is 1.15 mmol/g). [b]All the purified products were checked by LC/MS.

Next, we tried to synthesize 2-amido-5-amido-1,3,4-thiadiazole resin **8**. Various acid chlorides were used to chemoselectively introduce diverse amide functionality at the amine position of resin **5** at 60 °C for 16 h in neat pyridine (Each ^{1}H NMR spectrum of 2,5-di-amido-1,3,4-thiadiazoles **9** confirmed the chemoselective substitution at the amine position). To obtain 2,5-diamido-1,3,4-thiadiazole analogs **9**, resin **8** was treated with TFA:DCM (1:4, v/v) at room temperature for 4 h. As a result, 2,5-diamido-1,3,4-thiadiazole analogs **9** were obtained in good yields and high purities (Table 2).

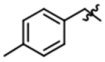
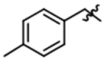
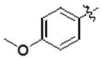
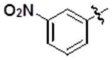
Table 2. Yields and purities of the 2,5-diamido-1,3,4-thiadiazole derivatives **9**

No	R^1	R^3	Yield per step (%)[a]	Purity (%)[b]	No	R^1	R^3	Yield per step (%)[a]	Purity (%)[b]
9a	Ph		75.8	91	**9j**	Ph		68.1	98
9b	Ph		75.1	85	**9k**	Ph		69.2	99
9c	Ph		77.1	95	**9l**	Ph		69.2	98
9d	Ph		74.4	97	**9m**	Ph		68.1	95
9e	Ph		79.9	91	**9n**	Ph		68.1	93
9f	Ph		79.4	94	**9o**			77.7	81
9g	Ph		83.9	91	**9p**			77.7	61
9h	Ph		69.2	92	**9q**			71.2	96
9i	Ph		74.4	96					

[a]Average yield per step calculated over six steps (loading capacity of resin **1** is 1.15 mmol/g). [b]All the purified products were checked by LC/MS.

To maximize the structural diversity of 1,3,4-thiadiazole core skeleton, alkyl and acyl groups were introduced at the amide and amine positions, respectively. First, resin **5** was reacted with alkyl halide in the presence of sodium hydride NaH in DMF at 60 °C for 16 h to afford resin **6,** and subsequently acyl groups were introduced at 60 °C for 16 h in neat pyridine. As a result, 2,5-diamido-1,3,4-thiadiazole resin **10** functionalized at the amide and amine positions were obtained. To afford 2,5-diamido 1,3,4-thiadiazole analog **11**, resin **10** was treated with TFA:DCM (1:4, v/v) at room temperature for 4 h. The yields and purities are summarized in Table 3.

Table 3. Yields and purities of the 2-*N*-alkylamido-5-amido-1,3,4-thiadiazole derivatives **11**

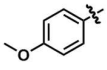
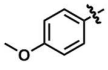
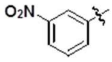
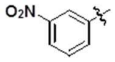
No	R^1	R^2	R^3	Yield per step (%)[a]	Purity (%)[b]
11a	Ph			72	100
11b	Ph			80	98
11c	Ph			66.9	99
11d	Ph			79.5	98
11e	Ph			73.9	99
11f	Ph			68.4	100
11g	Ph			68.4	95
11h	Ph			68.4	97
11i				79.5	100
11j				73.9	99
11k				73	100

[a]Average yield per step calculated over seven steps (loading capacity of resin **1** is 1.15 mmol/g). [b]All the purified products were checked by LC/MS.

For further diversification of the 1,3,4-thiadiazole core skeleton, the R^1 position was functionalized by Suzuki coupling reaction. Resins **6** and **8** equipped with aryl iodine at the R^1 position were reacted with various boronic acids in the presence of K_3PO_4 and $Pd(PPh)_3$ in 1,4-dioxane and water

(9:1, v/v) to produce Suzuki-coupled resins **12** and **14**, respectively, followed by the cleavage reaction in TFA:DCM (1:4, v/v) at 40 °C for 4 h or in TFA:DCM (1:4, v/v) at room temperature for 4 h. As a result, Suzuki-coupled products 2-amido-5-amino-1,3,4-thiadiazoles **13** and 2,5-diamido-1,3,4-thiadiazoles **15** were obtained. The yields and purities are listed in Table 4.

Table 4. Yields and purities of the *N*-(5-amino-1,3,4-thiadiazol-2-yl)-*N*-isopentylbiphenyl-3-carboxamide **13** and *N*-(5-(3-chlorobenzamido)-1,3,4-thiadiazol-2-yl)biphenyl-3-carboxamide **15**

No	R^2	R^4	Yield per step (%)[a]	Purity (%)[b]	No	R^3	R^4	Yield per step (%)[a]	Purity (%)[b]
13a			81.6	98	**15a**			73	52
13b			80	100	**15b**			73.9	91
13c			80	98	**15c**			66.9	65

[a]Average yield per step calculated over seven steps (loading capacity of resin **1** is 1.15 mmol/g). [b]All the purified products were checked by LC/MS.

In the drug discovery process, the development of orally available drug is very important, and Lipinski's Rule[16] and biological parameters have been used as guidelines to determine orally available drug property. In this respect, physicochemical and biological parameters such as molecular weight, ALogP, number of rotatable bonds, polar surface area, and number of hydrogen bond acceptors and donors are displayed and compared to those of our previously constructed 1,3,4-oxadiazole and 1,3,4-thiadiazole library[14] in Figure **1**. As shown in this data, in the case of molecular weight, ALogP, and number of rotatable bonds, our present library (blue) showed a better distribution in a range of those predicted for reasonable orally bioavailable drugs than the previous library (red), whereas it showed a slightly narrower range of distribution in the polar surface area, and both libraries showed a similar distribution in the number of hydrogen bonding acceptors and donors.

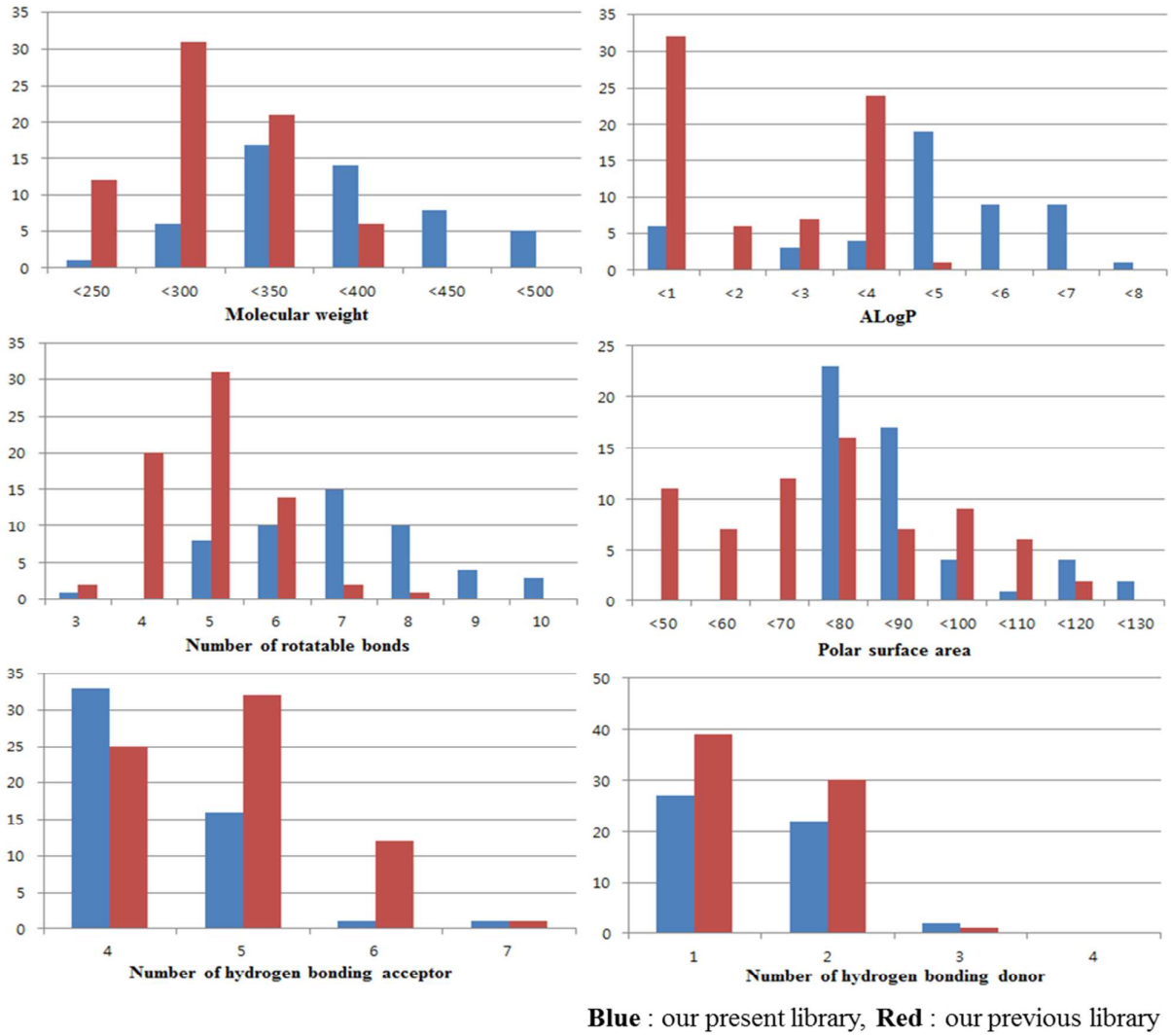


Figure 1. Calculation and comparison of physicochemical and biological properties for our present and previous libraries

In conclusion, we established a solid-phase synthetic method to construct a 1,3,4-thiadiazole library. This method involves a desulfurative cyclization process of thiosemicarbazide resin **4** to afford 1,3,4-thiadiazole core skeleton resin **5** and various functionalization reactions to maximize the structural diversity by reactions such as alkylation, acylation, alkylation/acylation, and Suzuki-coupling reactions. In the functionalization reactions, various alkyl groups were chemoselectively introduced at the 2-amide position of 2-amido-5-amino-1,3,4-thiadiazole resin **5,** and various acyl groups were chemoselectively introduced at the 5-amine position of 2-amido-5-amino-1,3,4-thiadiazole resin **5**. Furthermore, physicochemical and biological properties of 1,3,4-thiadiazole library were calculated and compared to those of our previous library. As a result, our present library showed a different distribution of physicochemical and biological properties compared to that of our

previous library in a range of bioavailable drug property by Lipinski's Rule and parameters.

Experimental

General procedure for synthesis All the 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 the internal reference using a 500 MHz NMR instrument. Liquid chromatography tandem mass spectrometry analysis was performed using an electrospray ionization (ESI) mass spectrometer with photodiode-array detector (PDA) detection. High-resolution mass spectrometry spectra were obtained using a TOF LC/MS system.

Representative procedure for the preparation of isothiocyanateterminated resin 2

A mixture of BOMBA resin **1** (5.00 g, 5.80 mmol) and Et_3N (5.86 g, 58.0 mmol) in THF (30.0mL) was added to CS_2 (2.65 g, 34.8 mmol) at 0 °C, and then the reaction mixture was stirred at room temperature for 3 h. The mixture was cooled down to 0 °C, followed by adding *p*-TsCl (5.53 g, 29.0 mmol). The reaction mixture was stirred at room temperature for 15 h. The precipitate obtained by the filtration of the mixture was stirred at room temperature, washed with THF, H_2O, MeOH, and CH_2Cl_2, and dried in a vacuum oven, affording resin **2** as a brown solid. Single-Bead ATR-FTIR: 3022, 2920, 2072 (N=C=S), 1604, 1505, 1450, 1266, 1195, 1159, 1122, 1033, 818, 734, and 697 cm^{-1}.

Representative procedure for the preparation of hydrazinecarbothioamide resin 3

A mixture of isothiocyanate resin **2** (5.28 g, 5.80 mmol) and hydrazine (1.86 g, 58.0 mmol) in DMSO (20.0 mL) was stirred at 50 °C for 4 h. The resin was filtered and washed several times with DMSO, THF, H_2O, MeOH, and CH_2Cl_2 and then dried in a vacuum oven. Resin **3** was obtained as a

yellow brown solid. Single-Bead ATR-FTIR: 3025, 2917, 1606, 1503, 1491, 1450, 1419, 1282, 1265, 1194, 1158, 1125, 1028, 818, 733, and 697cm^{-1}.

Representative procedure for the preparation of thiosemicarbazide resins 4a

A mixture of hydrazinecarbothioamide resin **3** (5.47 g, 5.80 mmol) and benzoyl isothiocynate (3.79 g, 23.2 mmol) in THF (20 mL) was stirred at room temperature for 3 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: 3025, 2920, 1684 (C=O), 1600, 1506, 1449, 1419, 1254, 1194, 1159, 1124, 1028, 733, and 697 cm^{-1}.

Representative procedure for the preparation of 2-*N*-alkylamido-5-amino-1,3,4-thiadiazole resin 5a

A mixture of thiosemicarbazide resin **4a** (6.42 g, 5.80 mmol), *p*-TsCl (3.32 g, 17.4 mmol) and pyridine (1.38 g, 17.4 mmol) in CH_2Cl_2 (30.0 mL) was stirred at room temperature for 5 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: 3022, 2925, 1663 (C=O), 1577, 1505, 1450, 1264, 1195, 1160, 1123, 1028, 823, 733, and 697 cm^{-1}.

Representative procedure for the preparation of 2-*N*-alkylamido-5-amino-1,3,4-thiadiazole resin 6a

A mixture of 2,5-amino-1,3,4-thiadiazole resin **5a** (214 mg, 0.2 mmol) in DMF (2.00 mL) was added sodium hydride (32.0 mg, 0.8 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. Benzyl chloride (127 mg, 1.00 mmol) was added to the reaction mixture and 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 a vacuum oven. Resin **6a** was obtained as a brown solid. Single-Bead ATR-FTIR: 3025, 2923, 1673 (C=O), 1601, 1492, 1450, 1381, 1286, 1264, 1196, 1159, 1114, 1020, 818, 733, and 697 cm^{-1}.

Representative procedure for the preparation of *N*-(5-amino-1,3,4-thiadiazol-2-yl)-*N*-

benzylbenzamide 7a

Resin **6a** (232 mg, 0.2 mmol) was treated with a mixture of TFA/CH_2Cl_2 (1:4, v/v) at 40 °C for 4 h. The resin was filtered and then washed several times with CH_2Cl_2 and MeOH. The organic filtrate was neutralized to pH 6–7 with a saturated aqueous $NaHCO_3$ solution and then extracted with CH_2Cl_2 and H_2O. The aqueous layer was back-extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated to obtain the crude product, which was purified diethyl ether/hexane (1:1) to obtain 18.0 mg (81.4%, average yield per step calculated over six steps) of the desired *N*-(5-amino-1,3,4-thiadiazol-2-yl)-*N*-benzylbenzamide **7a**. ^{1}H NMR (500 MHz, DMSO) δ 8.21 (d, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.39–7.33 (m, 4H), 7.33–7.29 (m, 1H), 7.14 (s, 2H), 5.44 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 172.4, 161.8, 159.1, 136.8, 136.7, 132.1, 129.3, 129.1, 128.7, 128.6, 128.3, 53.2, LC-MS (ESI): m/z = 309.1 $[M-H]^-$. HRMS (ESI) calcd for $C_{16}H_{14}N_4OS$ $[M + H]^+$: 311.0961, found: 311.0961.

Representative procedure for the preparation of 2,5-diamido-1,3,4-thiadiazole resin 8a

A mixture of 2,5-amino-1,3,4-thiadiazole resin **5a** (214 mg, 0.2 mmol) in Pyridine (2.00 mL) was added Benzoyl chloride(140 mg, 1.0 mmol) The resulting mixture was stirred at 60 ^{o}C 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 8a was obtained as a brown solid. Single-Bead ATR-FTIR : 3023, 2919, 1671, 1600, 1506, 1449, 1373, 1262, 1195, 1158, 1114, 1024, 817, 749 and 696cm $^{-1}$.

Representative procedure for the preparation of *N*,*N*'-(1,3,4- thiadiazole-2,5-diyl)dibenzamide 9a

A resin **8a** (235 mg, 0.2 mmol) was treated with a mixture of TFA/CH_2Cl_2 (1:4, v/v) at rt for 4 h. The resin was filtered and then washed several times with CH_2Cl_2 and MeOH. The organic filtrate was neutralized to pH 6-7 with a saturated $NaHCO_3$ aqueous solution and then extracted with CH_2Cl_2 and H_2O. 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) to afford 12.0 mg (75.8%, average yield per step calculated over six step) of desired *N*,*N*'- (1,3,4-thiadiazole-2,5-diyl)dibenzamide **9a**. ^{1}H NMR (500 MHz, DMSO) δ 12.75 (s, 2H), 8.12 (d, *J* = 7.4 Hz, 4H), 7.67 (t, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 4H). ^{13}C NMR (126 MHz, DMSO) δ 165.5, 156.4, 133.3, 132.2, 129.1, 128.8. LC-MS (ESI): m/z = 323.1 [M-H] - . HRMS (ESI) calcd for $C_{16}H_{12}N_4O_2S$ $[M + Na]^+$: 347.0573, found :347.0574.

Representative procedure for the preparation of 2-*N*-alkylamido-5-amido-1,3,4-thiadiazole resin 10a A mixture of 2-*N*-alkylamido-5-lamino-1,3,4-thiadiazole resin **6a** (232 mg, 0.2 mmol) in Pyridine (2.00 mL) was added Benzoyl chloride (140 mg, 1.0 mmol) The resulting mixture was stirred at 60 ^{o}C 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 **10a** was obtained as a brown solid. Single-Bead ATR-FTIR : 3021, 2924, 1664(C=O), 1600, 1493, 1449, 1371, 1269, 1194, 1159, 1110, 1026, 823, 761 and 696 cm -1 .

Representative procedure for the preparation of *N*-(5-benzamido-1,3,4-thiadiazol-2-yl)-*N*-benzylbenzamide 11a A resin **10a** (253 mg, 0.2 mmol) was treated with a mixture of TFA/CH_2Cl_2 (1:4, v/v) at rt for 4 h. The resin was filtered and then washed several times with CH_2Cl_2 and MeOH. The organic filtrate was neutralized to pH 6-7 with a saturated $NaHCO_3$ aqueous solution and then extracted with CH_2Cl_2 and H_2O. 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) to afford 8.28 mg (72%, average yield per step calculated over seven steps) of desired *N*-(5-benzamido-1,3,4-thiadiazol-2-yl)-*N*-benzylbenzamide **11a**. ^{1}H NMR (500 MHz, DMSO) δ 12.76 (s, 1H), 8.28 (d, *J* = 7.2 Hz, 2H), 8.08 (d, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.61 – 7.54 (m, 3H), 7.53 (d, *J* = 4.9 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.1 Hz, 1H), 5.66 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 173.3, 166.4, 163.7, 152.3, 136.5, 136.4, 133.6, 132.5, 131.8, 129.5, 129.2, 129.1, 128.9, 128.8, 128.5, 128.5, 53.5. LC-MS (ESI): m/z = 413.2 $[M-H]^-$. HRMS

(ESI) calcd for $C_{23}H_{18}N_4O_2S$ $[M + Na]^+$: 437.1043, found :437.1044.

Representative procedure for the preparation of *N*-(5-(ethylamino)-1,3,4-thiadiazol-2-yl)-*N*-isopentylbiphenyl-3-carboxamide resin 12a

A resin **6r** (127 mg, 0.1 mmol) was added successively K_3PO_4 (106.14 mg, 0.5 mmol), Phenylboronic acid (60.9 mg, 0.5 mmol) in 1,4-Dioxane : H_2O(9:1), and $Pd(PPh_3)_4$ (23.1 mg, 0.02 mmol) was added under nitrogen atmosphere. The mixture was shaken for 20 h at 80 ^oC. *N*-(5-amino-1,3,4-thiadiazol-2-yl)-*N*-isopentylbiphenyl-3-carboxamide resin **12a** was filtered and washed with H_2O, MeOH, and CH_2Cl_2 and dried in a vacuum oven. This process made resin **12a** as a dark brown solid. Single-Bead ATRFTIR :3023, 2926, 2864, 1669(C=O), 1588, 1491, 1449, 1419, 1387, 1313, 1258, 1193, 1157, 1115, 1026, 818, 744 and 695cm -1 .

Representative procedure for the preparation of *N*-(5-amino-1,3,4-thiadiazol-2-yl)-*N*-isopentylbiphenyl-3-carboxamide 13a A resin **12a** (122 mg, 0.1 mmol) was treated with a mixture of TFA/CH_2Cl_2 (1:4, v/v) at 40 ^oC for 4 h. The resin was filtered and then washed several times with CH_2Cl_2 and MeOH. The organic filtrate was neutralized to pH 6-7 with a saturated $NaHCO_3$ aqueous solution and then extracted with CH_2Cl_2 and H_2O. 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) to afford 8.8 mg (81.6%, average yield per step calculated over seven steps) of desired *N*-(5- amino-1,3,4-thiadiazol-2-yl)-*N*-isopentylbiphenyl-3- carboxamide **13a**. ^1H NMR (500 MHz, DMSO) δ 8.46 (s, 1H), 8.16 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.14 (s, 2H), 4.29 (t, *J* = 7.0 Hz, 2H), 1.71 (dd, *J* = 13.9, 6.9 Hz, 2H), 1.57 (dt, *J* = 13.1, 6.5 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, DMSO) δ 171.9, 161.2, 159.2, 140.6, 140.3, 137.7, 130.3, 129.5, 129.4, 129.1, 128.2, 127.3, 127.2, 48.3, 37.0, 25.4, 22.7. MS (ESI): m/z = 365.2 $[M-H]^-$. HRMS (ESI) calcd for $C_{20}H_{22}N_4OS$ $[M + H]^+$: 367.1587, found :367.1587.

Representative procedure for the preparation of *N*-(5-(3-chloroN-ethylbenzamido)-1,3,4-thiadiazol-2-yl)biphenyl-3- carboxamide resin 14a

A resin **8r** (267.3 mg, 0.2 mmol) was added successively K_3PO_4 (212.3 mg, 1.0 mmol), Phenylboronic acid (121.9 mg, 1.0 mmol) in 1,4-Dioxane : H_2O (9:1), and $Pd(PPh_3)_4$ (46.2 mg, 0.04 mmol) was added under nitrogen atmosphere. The mixture was shaken for 20 h at 80 ^oC. *N*-(5-(3-chloro-*N*-ethylbenzamido)-1,3,4-thiadiazol-2-yl)biphenyl-3-carboxamide resin **14a** was filtered and washed with H_2O, MeOH, and CH_2Cl_2 and dried in a vacuum oven. This process made resin **14a** as a dark brown solid. Single-Bead ATR-FTIR :3026, 2924, 2852, 1664(C=O), 1600, 1506, 1449, 1419, 1364, 1285, 1260, 1194, 1157, 1115, 1024, 899, 816, 747 and 696 cm^{-1}.

Representative procedure for the preparation of *N*-(5-(3- chlorobenzamido)-1,3,4-thiadiazol-2-yl)biphenyl-3-carboxamide 15a

A resin **14a** (257 mg, 0.2 mmol) was treated with a mixture of TFA/CH_2Cl_2 (1:4, v/v) at rt for 4 h. The resin was filtered and then washed several times with CH_2Cl_2 and MeOH. The organic filtrate was neutralized to pH 6-7 with a saturated $NaHCO_3$ aqueous solution and then extracted with CH_2Cl_2 and H_2O. 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) to afford 9.6 mg (73%, average yield per step over seven steps) of desired *N*-(5-(3- chlorobenzamido)-1,3,4-thiadiazol-2-yl)biphenyl-3-carboxamide **15a**. ^1H NMR (500 MHz, DMSO) δ 12.89 (s, 2H), 8.48 (s, 1H), 8.19 (s, 1H), 8.09 (dd, *J* = 19.2, 7.7 Hz, 2H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 7.1 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.1 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 141.7, 140.9, 139.7, 137.1, 134.2, 133.9, 133.1, 131.2, 131.1, 129.9, 129.5, 129.1, 128.8, 128.6, 128.5, 128.2, 128.0, 127.6, 127.4, 126.8. MS (ESI): m/z = 433.2$[M-H]^-$. HRMS (ESI) calcd for $C_{23}H_{17}ClN_4OS$ $[M + H]^+$: 435.0677, found :435.0676.

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Supporting Information Available: Full analytical data of compounds, along with the copies of ^{1}H NMR, ^{13}C NMR, LC/MS, and HRMS spectra of all the synthesized compounds; analytical data of chemoselective alkylation reactions; the LC/MS spectra of the crude product mixture **7a** and **9a**. the representative ATR-FTIR spectrum of the corresponding resins; this material is available free of charge via the Internet at http://pubs.acs.org.

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Graphical Abstract

Solid-phase Synthesis of 1,3,4-Thiadiazole Derivatives via Desulfurative Cyclization of Thiosemicarbazide Intermediate Resin

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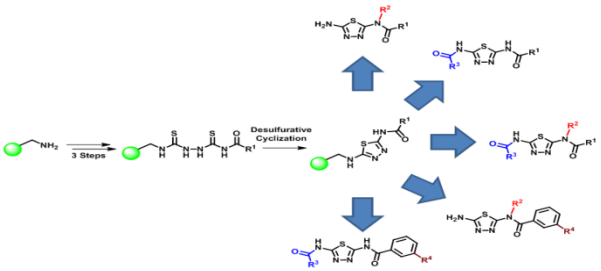

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