Article

Construction of 1,3,4-Oxadiazole and 1,3,4-Thiadiazole Library with a High Level of Skeletal Diversity based on Branching Diversity-oriented Synthesis on Solid-phase

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ACS Comb. Sci., **Just Accepted Manuscript** • DOI: 10.1021/acscombsci.7b00174 • Publication Date (Web): 08 Jan 2018

Graphical Abstract

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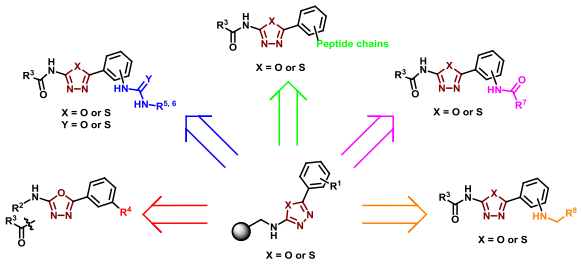
Ji-Eun Ha, Seung-Ju Yang, Young-Dae Gong*

Innovative Drug Library Research Center, Department of Chemistry, College of Science,

Dongguk University, 26, 3-ga, Pil-dong Jung-gu, Seoul 100-715, Korea



* Corresponding author. Tel. : +82-2-2260-3206, Fax : +82-2-2290-1349 ; e-mail: ydgong@dongguk.edu

Construction of 1,3,4-Oxadiazole and 1,3,4-Thiadiazole Library with a High Level of Skeletal Diversity based on Branching Diversity-oriented Synthesis on Solid-phase

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Abstract: An efficient solid-phase synthetic route for the construction of 1,3,4-oxadiazole and 1,3,4-thiadiazole libraries based on branching diversity-oriented synthesis (DOS) has been developed in this study. The core skeleton resins, 1,3,4-oxadiazole and 1,3,4-thiadiazole, were obtained through desulfurative and dehydrative cyclizations of thiosemicarbazide resin, respectively. Various functional groups have been introduced to the core skeleton resins such as aryl, amine, amide, urea, thiourea, and an amino acid. Most of the libraries were purified by simple trituration without extraction or column chromatography after cleavage of the products from the solid-supported resin. As a result, we obtained high yields of pure 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives (total numbers = 128). Finally, we confirmed the drug-like properties of our library by calculation of physicochemical properties, displays of the skeletal diversities of the library in 3D-space, and occupation of a broad range of areas by their functional groups.

KEYWORDS: 1,3,4-Oxadiazole, 1,3,4-Thiadiazole, Solid-phase, Diversity.

Introduction

Construction of a small-molecule library is one of the crucial challenges in the drug discovery process.[1] Of all the small molecules, heterocyclic compounds have played vital roles in the development of potent therapeutic agents.[2] This is because, in chemical biology, heterocyclic modulators facilitate the elucidation of complex biological mechanisms.[3] Along these lines, diversity-oriented synthesis (DOS) emerged as a powerful tool to generate a library of heterocyclic compounds in a time- and cost-efficient manner.[4] As a part of the DOS strategy, the branching DOS strategy has been spotlighted to generate discrete library sets of small heterocyclic compounds.[5] Of these heterocyclic compounds, 5-membered heterocyclic compounds have played pivotal roles; approximately, 23% (n = 250) of the 1086 unique small molecules approved by the U.S. Food and Drug Administration (FDA) belong to the class of 5-membered heterocyclic compounds.[6] As 5-membered heterocyclic compounds, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles have been shown to have numerous biological activities such as anti-inflammatory,[7] antimicrobial,[8] anticonvulsant,[9] anticancer,[10] and antihypertensive properties.[11] Furthermore, 1,3,4-oxadiazole and 1,3,4-thiadiazole core skeletons also have been used in liquid crystal,[12] Organic Light Emitting Diodes (OLED),[13] solar cell,[14] and agricultural chemistry.[15]

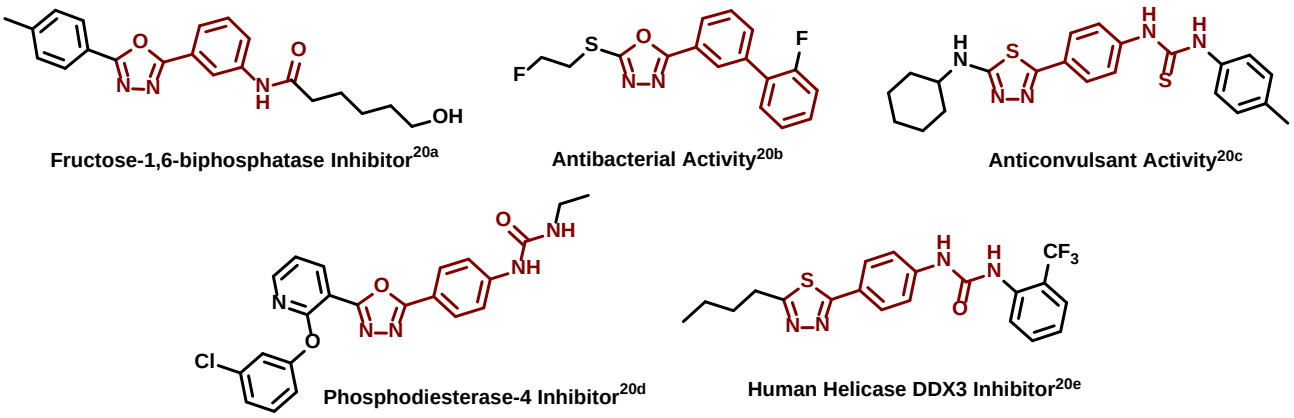


Figure 1. Examples of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles with diverse functional groups and pharmacological activities

In addition, 1,3,4-oxadiazole and 1,3,4-thiadiazole have been used to replace peptide fragments to increase the chemical stability and oral availability of a compound[16a, 16c] since heterocyclic compounds have been considered as alternative structural motifs for peptide bonds, and there are many reports about synthetic methodology and biological activities of peptide analogues equipped with heterocyclic motifs.[16]

For these reasons, these core skeletons have been targeted for synthesis by many organic chemists and medicinal chemists using solution-phase synthesis[17] and solid-phase methods.[18] In this context, we were interested in developing expedient synthesis of 1,3,4-oxadiazole and 1,3,4-thiadiazole via a regioselective way from one versatile intermediate.[19] As an extension of our previous work, we focused on skeletal diversity of substituents of the phenyl group, adjacent to the 1,3,4-oxadiazole and 1,3,4-thiadiazole core skeletons, due to the fact that various kinds of functional groups at this position could result in interesting biological activities (Figure 1).[20] Thus, as a part of our ongoing project aimed at construction of a small-molecule library,[21] we have used solid-phase synthesis based on the branching DOS strategy to construct 1,3,4-oxadiazole and 1,3,4-thiadiazole libraries with a high level of skeletal diversity, containing aryl, amide, urea, thiourea, amine and peptide group as depicted in Figure 2. Herein, we report our recent progress on this project.

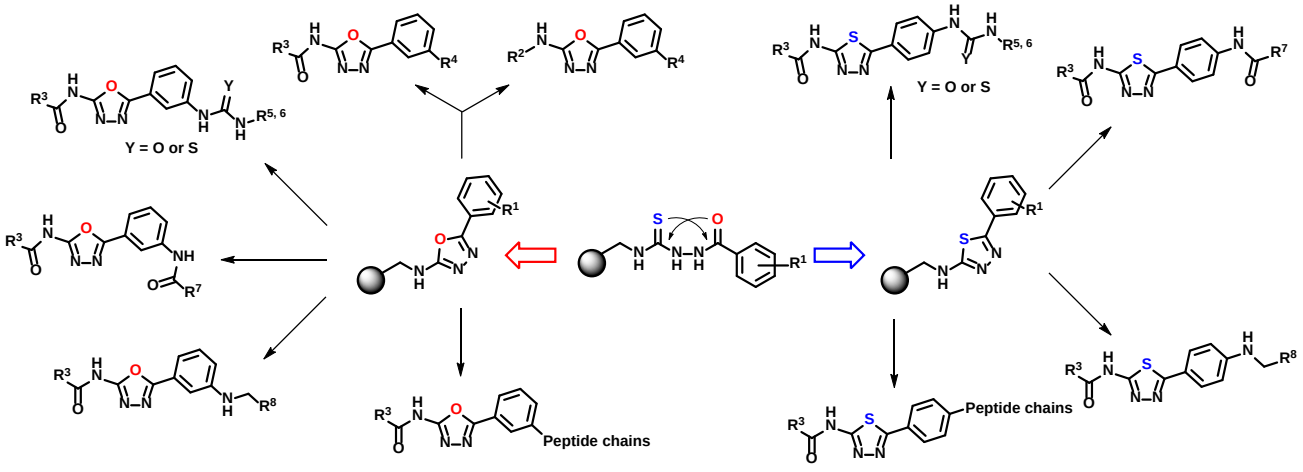
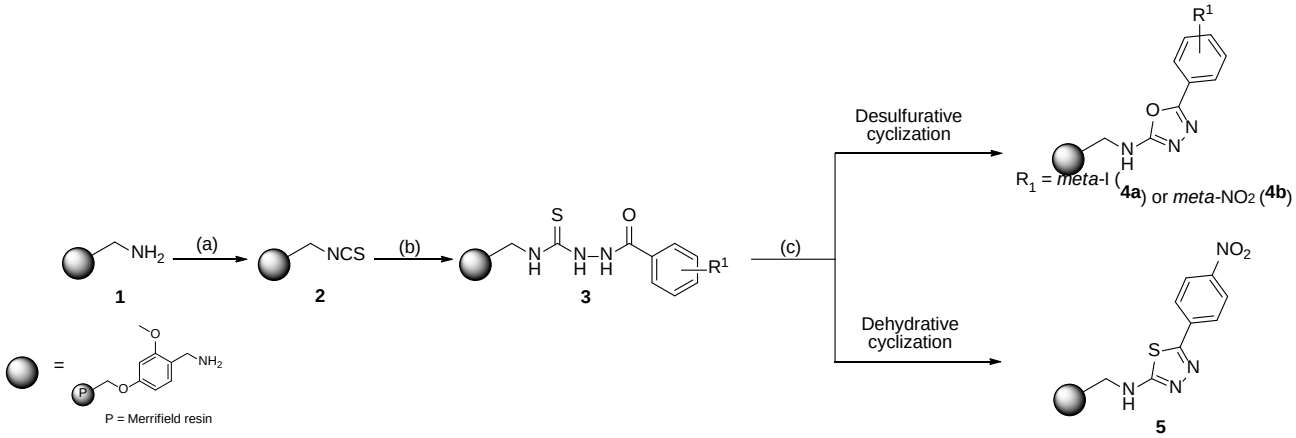


Figure 2. Schematic diagram to yield a myriad of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles based on branching diversity-oriented synthesis

Results and Discussion

We prepared 1,3,4-oxadiazole and 1,3,4-thiadiazole core skeleton resins **4** and **5** using our previous methodology[19a] (Scheme 1) in order to construct a structurally diversified 1,3,4-oxadiazole and 1,3,4-thiadiazole library.

Scheme 1. Synthesis of 1,3,4-oxadiazole and 1,3,4-thiadiazole resin[a]



[a] Reagents and conditions : (a) Et_3N, CS_2, *p*-TsCl, THF, rt, 19 h. (b) Et_3N, THF, rt, 16 h. (c) For desulfurative cyclization, EDC·HCl, DMSO, 60 ºC, 16 h; For dehydrative cyclization, Et_3N, *p*-TsCl, NMP, rt, 12 h.

The 4-benzyloxy-2-methoxybenzylamine (BOMBA) resin **1** was used as a starting material and reacted with CS_2 and *p*-TsCl in the presence of Et_3N in tetrahydrofuran (THF) for 16 h to yield an isothiocyanate-terminated resin **2**[22] followed by a reaction with hydrazides to obtain a thiosemicarbazide resin **3**. The thiosemicarbazide resin **3** was successfully chemoselectively cyclized to form 1,3,4-oxadiazole resin **4** and 1,3,4-thiadiazole resin **5** under conditions using EDC·HCl and *p*-TsCl / Et_3N, respectively. Next, with 1,3,4-oxadiazole resin **4** and 1,3,4-thiadiazole resin **5** in hand, we synthesized numerous 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives via a branching pathway.

Synthesis of 1,3,4-oxadiazole derivatives 8 and 9

Scheme 2. ***N*-Alkylation / acylation, and Suzuki coupling reaction for synthesis of 1,3,4-oxadiazole derivatives 8 and 9**

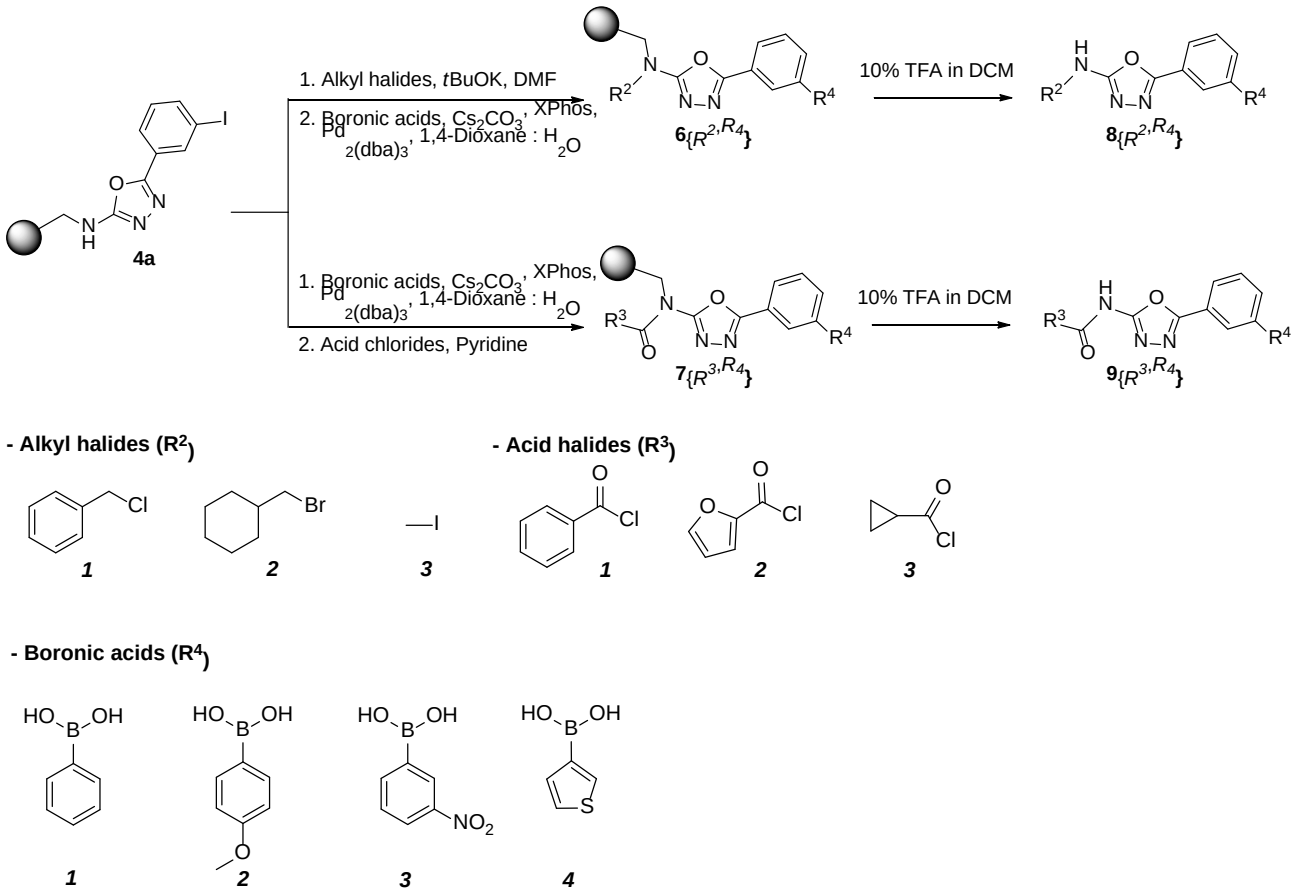


Table 1. Yields and purities of 1,3,4-oxadiazole **8** and **9**[a]

	R4					R4			
	1	*2*	*3*	*4*		*1*	*2*	*3*	*4*
8{*1*,R^4}	17 (98)	17 (96)	13 (95)	13 (95)	**9**{*1*,R^4}	36 (96)	37 (95)	28 (92)	23 (100)
8{*2*,R^4}	19 (97)	10 (97)	10 (100)	12 (97)	**9**{*2*,R^4}	20 (92)	37 (100)	40 (100)	31 (100)
8{*3*,R^4}	13 (95)	11 (91)	58 (96)	8 (96)	**9**{*3*,R^4}	17 (86)	17 (81)	21 (68)	11 (80)

[a] Yield (Purity); Yield is an obtained yield for six steps, and purity is checked by LC-MS at 254 nm.

Before we carried out a Suzuki-coupling reaction on solid-phase, we conducted a model study in solution-phase (Scheme S1 in Supporting Information). As a result, we set *N*-alkylation at an earlier stage than the Suzuki-coupling reaction. Although a quantitative yield was seen in the solution phase, NaH in THF gave a low conversion in the case of performing the *N*-alkylation reaction on solid phase. Thus, we screened several reaction conditions (Entry 1 – 5 of Scheme S2 in Supporting Information). Among these conditions, *t*BuOK in DMF gave good conversion (Entry 5 of Scheme 2 in Supporting Information). After the alkylation reaction, we carried out a Suzuki-coupling reaction with boronic acids in the presence of $Pd_2(dba)_3$, XPhos, and, Cs_2CO_3 in 1,4-dioxane and H_2O (9:1, v/v), followed by a cleavage reaction with 10% trifluoroacetic acid (TFA) in dichloromethane (DCM) to yield *N*-alkyl-Suzuki-coupled 1,3,4-oxadiazole **8**. The liquid chromatography-mass spectrometry (LC-MS) result of the crude product mixture for 1,3,4-oxadiazole **8** is displayed in Figure S3(a) (of Supporting Information), showing that our desired product was the major constituent of the mixture without further purification. To purify the mixture, we used a short plug of silica with hexane/ethyl acetate, then trituration with hexane and diethyl ether. The yields and purities of 1,3,4-oxadiazole **8** are summarized in Table 1. Next, to afford *N*-acyl-Suzuki-coupled 1,3,4-oxadiazole **9**, we introduced an acyl moiety at the 2-amine-position, then Suzuki-coupled it with boronic acid. However, in this synthetic sequence, the major product was obtained in the non-acylated product form (Scheme S3 in Supporting Information). Thus, we first used various boronic acids for the Suzuki-coupling reaction, and then introduced acid chlorides followed by a cleavage reaction with treatment of 10% TFA in DCM at room temperature for 8 h. As a result, we obtained the desired *N*-acylated-Suzuki-coupled 1,3,4-oxadiazole **9** as a major product without further purification (Figure S3(b) in Supporting Information). To purify the 1,3,4-oxadiazole **9**, we triturated the crude product mixture with ethyl acetate / diethyl ether. The yields and purities of 1,3,4-oxadiazole **9** are summarized in Table 1.

Synthesis of 1,3,4-oxadiazole derivatives 12 and 1,3,4-thiadiazole derivatives 13

Scheme 3. *N*-Acylation, and Urea formation for synthesis of 1,3,4-oxadiazole derivatives 12 and 1,3,4-thiadiazole derivatives 13

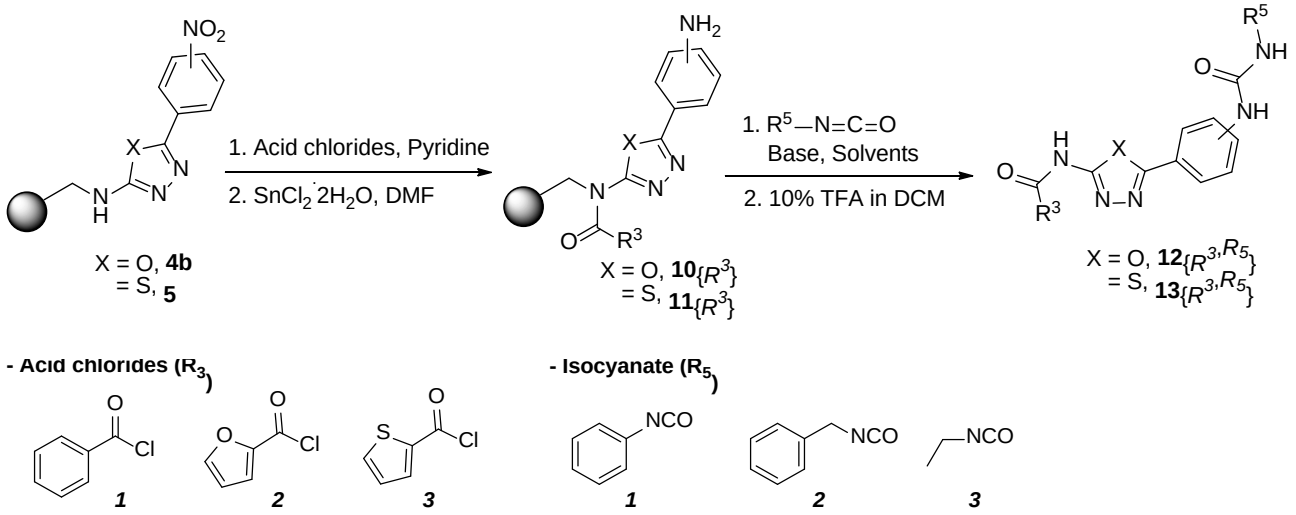
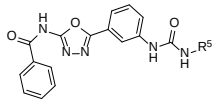
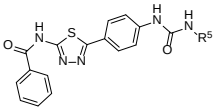
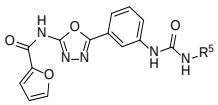
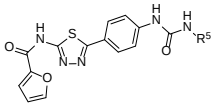
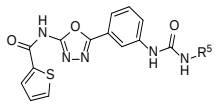
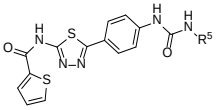


Table 2. Yields and purities of 1,3,4-oxadiazole **12** and 1,3,4-thiadiazole **13** [a]

	R^5				R^5		
	1	*2*	*3*		*1*	*2*	*3*
 **12**{*1*,R^5}	13 (100)	39 (96)	57 (97)	 **13**{*1*,R^5}	12 (94)	20 (100)	19 (100)
 **12**{*2*,R^5}	38 (98)	46 (100)	58 (100)	 **13**{*2*,R^5}	16 (95)	11 (100)	20 (100)
 **12**{*3*,R^5}	34 (100)	33 (100)	18 (100)	 **13**{*3*,R^5}	13 (91)	22 (100)	32 (100)

[a] Yield (Purity); Yield is an obtained yield for seven steps, and purity is checked by LC-MS at 254 nm.

For urea formation, we used nitro-substituted 1,3,4-oxadiazole **4b** and 1,3,4-thiadiazole **5**. First, we introduced an acyl group at the 2-amine position, then reduced the nitro group to an amine group using $SnCl_2.2H_2O$ in dimethylformamide (DMF) to yield the 1,3,4-oxadiazole resin **10** and the 1,3,4-thiadiazole resin **11**. To optimize the reaction condition for urea formation, we screened several solvent,

base, and temperature conditions with phenyl isocyanate and 1,3,4-oxadiazole resin **10** (Entries 1 – 5 of Scheme S4 in Supporting Information). Among various conditions, pyridine in THF at 60 ^{o}C gave a quantitative conversion (Entry 5 of Scheme S4 in Supporting Information). However, in the case of benzyl and ethyl isocyanate, the conversion was decreased under this condition. Thus, we studied reaction conditions, and found that 4-(dimethylamino)pyridine (DMAP) in DCM at 60 ^{o}C and room temperature gave excellent conversion with benzyl isocyanate and ethyl isocyanate, respectively (Entries 6 – 11 of Scheme S4 in Supporting Information). Next, we carried out the same reaction with 1,3,4-thiadiazole resin **11**, and the reaction proceeded smoothly. The LC-MS result of the crude product mixture for 1,3,4-oxadiazole **12** and 1,3,4-thiadiazole **13** is displayed in Figure S3(e), and (j) of the Supporting Information. To purify 1,3,4-oxadiazole **12** and 1,3,4-thiadiazole **13**, we triturated the crude product mixture with diethyl ether / ethyl acetate / ethanol. Consequently, we obtained the desired 1,3,4-oxadiazole **12** and 1,3,4-thiadiazole **13** in good yields and high purities (Table 2).

Synthesis of 1,3,4-oxadiazole derivatives 14 and 1,3,4-thiadiazole derivatives 15

Scheme 4. *N*-Acylation, and Thiourea formation for synthesis of 1,3,4-oxadiazole derivatives 14 and 1,3,4-thiadiazole derivatives 15

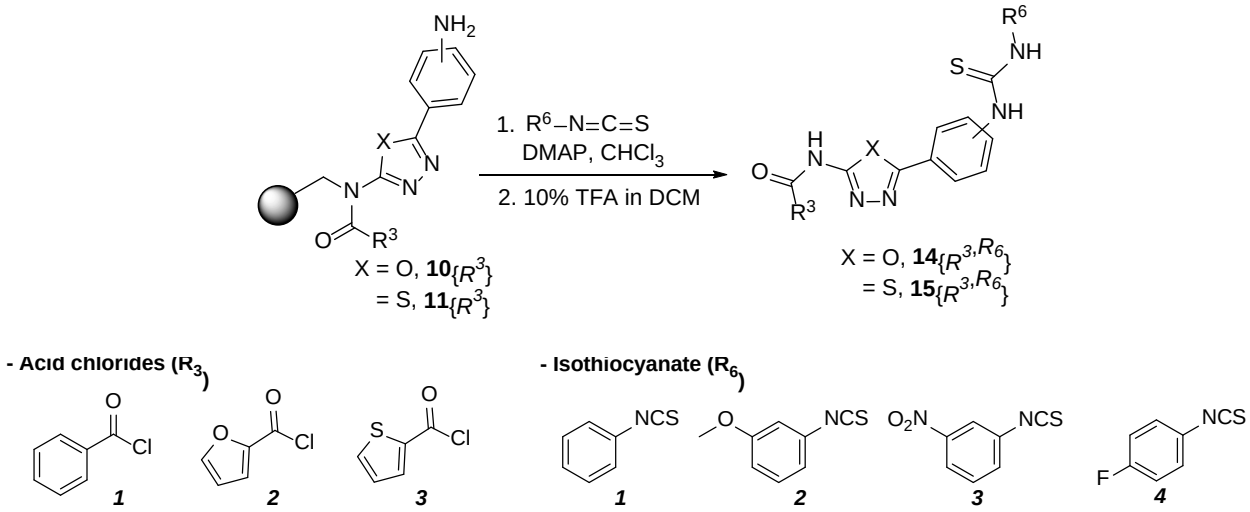
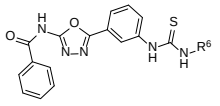
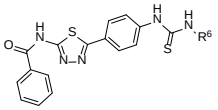
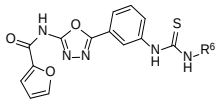
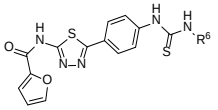
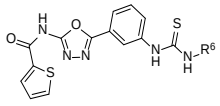
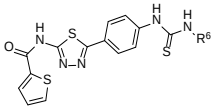


Table 3. Yields and purities of 1,3,4-oxadiazole **14** and 1,3,4-thiadiazole **15** [a]

	R^6					R^6			
	1	*2*	*3*	*4*		*1*	*2*	*3*	*4*
 **14**{*1*,R^6}	17 (100)	22 (94)	32 (100)	27 (100)	 **15**{*1*,R^6}	10 (95)	19 (88)	21 (94)	12 (92)
 **14**{*2*,R^6}	42 (100)	30 (93)	36 (100)	30 (100)	 **15**{*2*,R^6}	15 (100)	15 (100)	17 (100)	13 (91)
 **14**{*3*,R^6}	18 (100)	24 (92)	16 (100)	10 (100)	 **15**{*3*,R^6}	11 (100)	7 (100)	11 (100)	10 (90)

[a] Yield (Purity); Yield is an obtained yield for seven steps, and purity is checked by LC-MS at 254 nm.

For thiourea formation, we used nitro-substituted 1,3,4-oxadiazole **4b** and 1,3,4-thiadiazole **5**. First, we introduced an acyl moiety at the 2-amine position, then reduced the nitro group to an amine group using $SnCl_2.2H_2O$ in DMF to yield the 1,3,4-oxadiazole resin **10** and the 1,3,4-thiadiazole resin **11**. To optimize the reaction conditions, we used diverse solvent and base conditions, with phenyl

isothiocyanate and 1,3,4-oxadiazole resin **10** (Scheme S5 in Supporting Information). Among these conditions, DMAP in $CHCl_3$ at 60 ^oC showed a high conversion (Entries 8 of Scheme S5 in Supporting Information). The optimized reaction conditions also worked well in the case of 1,3,4-thiadiazole resin **11**. The LC-MS spectra of the crude product mixture for 1,3,4-oxadiazole **14** and 1,3,4-thiadiazole **15** is shown in Figure S3 (f), and (k) of the Supporting Information. After thiourea formation, the resin was treated with 10% TFA in DCM at room temperature for 8 h to cleavage 1,3,4-oxadiazole **14** and 1,3,4-thiadiazole **15** from polymer-supported resin, then a crude product mixture was purified by trituration with diethyl ether / ethyl acetate/ ethanol. The yields and purities of 1,3,4-oxadiazole **14** and 1,3,4-thiadiazole **15** are summarized in Table 3.

Synthesis of 1,3,4-oxadiazole derivatives 16 and 1,3,4-thiadiazole derivatives 17

Scheme 5. *N*-Acylation, and Reductive amination for synthesis of 1,3,4-oxadiazole derivatives 16 and 1,3,4-thiadiazole derivatives 17

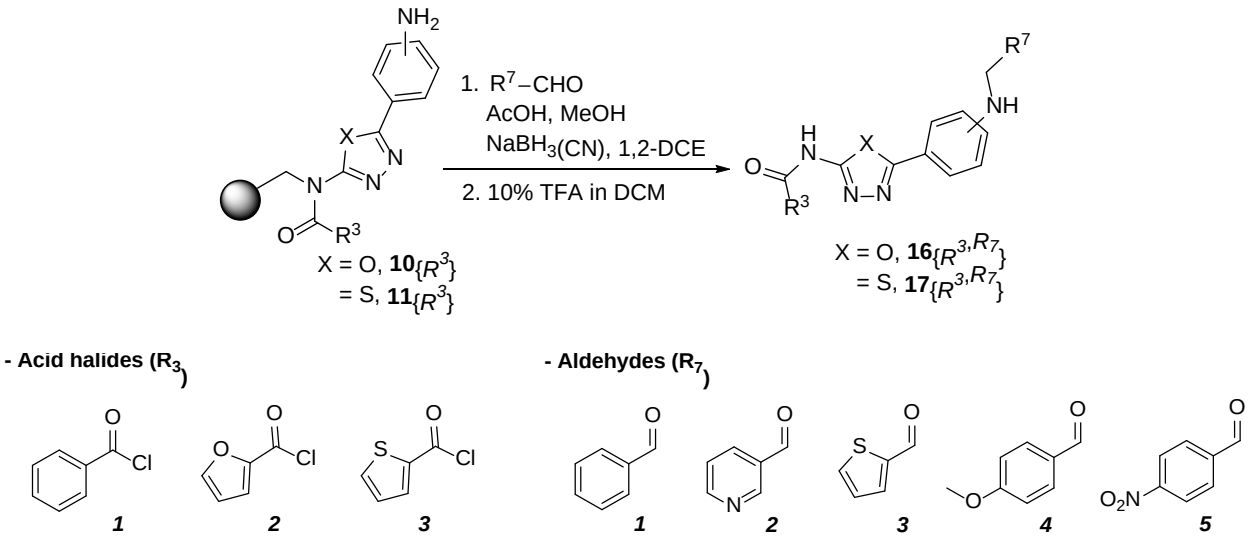


Table 4. Yields and purities of 1,3,4-oxadiazole **16** and 1,3,4-thiadiazole **17** [a]

	R7						R7				
	1	*2*	*3*	*4*	*5*		*1*	*2*	*3*	*4*	*5*
16{*1*,R^7}	57 (90)	28 (100)	27 (100)	41 (80)	40 (73)	**17**{*1*,R^7}	21 (92)	38 (92)	22 (92)	21 (88)	24 (93)
16{*2*,R^7}	54 (90)	24 (93)	28 (100)	41 (100)	47 (100)	**17**{*2*,R^7}	34 (100)	54 (100)	36 (100)	26 (83)	22 (100)
16{*3*,R^7}	19 (98)	18 (100)	15 (100)	32 (100)	11 (100)	**17**{*3*,R^7}	29 (100)	53 (100)	23 (100)	21 (77)	20 (91)

[a] Yield (Purity); Yield is an obtained yield for seven steps, and purity is checked by LC-MS at 254 nm.

Before we conducted reductive amination on solid-phase, we studied reaction conditions in solution-phase (Scheme S6 in Supporting Information). From these studies in solution-phase, we confirmed reaction conditions for reductive amination (benzaldehyde, acetic acid, $NaBH_3(CN)$, MeOH in 1,2-

dichloroethane), and applied these conditions to solid-phase. For reductive amination, we used nitro-substituted 1,3,4-oxadiazole **4b** and 1,3,4-thiadiazole **5**. First, we introduced an acyl moiety at the 2-amine position, then reduced the nitro group to an amine group using $SnCl_2.2H_2O$ in DMF to yield the 1,3,4-oxadiazole resin **10** and the 1,3,4-thiadiazole resin **11**. In case of the solid-phase, the reaction was conducted at 60 ^oC without methanol due to a concern of low swelling of our lipophilic poly-styrene resin in MeOH, resulting in moderate conversion (Entry 1 of Scheme S7 in Supporting Information). Thus, for complete conversion, we used MeOH, and the reaction was mediated at room temperature, resulting in good conversion (Entry 2 of Scheme S7 in Supporting Information). Next, we carried out the same reaction with 1,3,4-thiadiazole resin **11**, and the reaction proceeded well. The LC-MS spectra of the crude product mixture for 1,3,4-oxadiazole **16** and 1,3,4-thiadiazole **17** are shown in Figure S3 (d), and (i) of the Supporting Information. To purify 1,3,4-oxadiazole **16** and 1,3,4-thiadiazole **17**, we triturated the crude product mixture with diethyl ether / ethyl acetate / ethanol. The yields and purities are summarized in Table 4.

Synthesis of 1,3,4-oxadiazole derivatives 18 and 1,3,4-thiadiazole derivatives 19

Scheme 6. *N*-Acylation, and Amide coupling for synthesis of 1,3,4-oxadiazole derivatives 18 and 1,3,4-thiadiazole derivatives 19

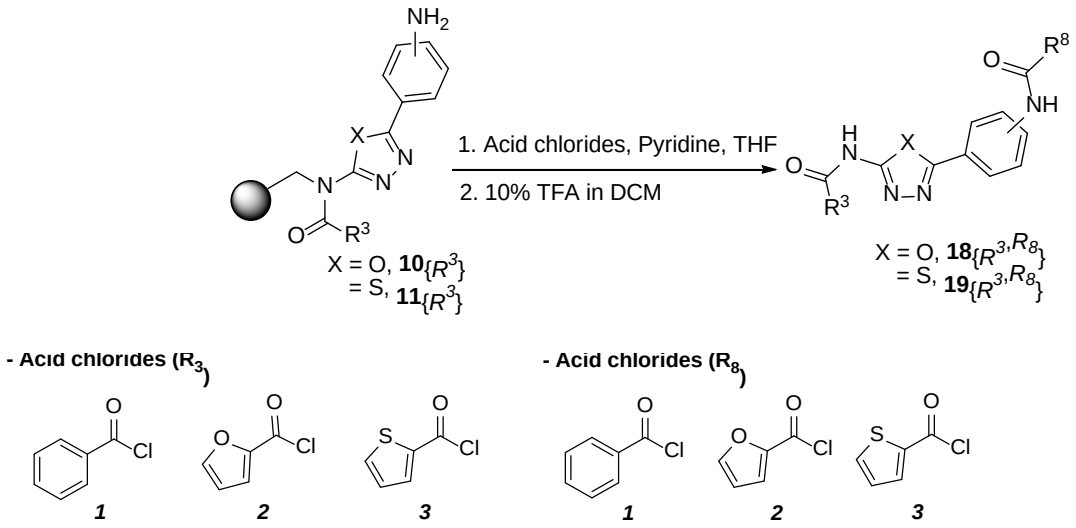
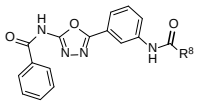
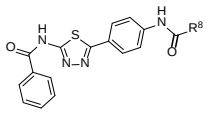
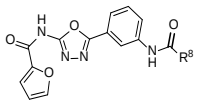
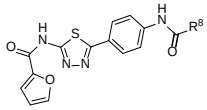
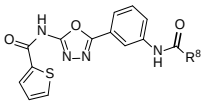
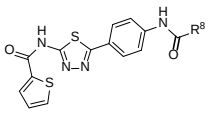


Table 5. Yields and purities of 1,3,4-oxadiazole **18** and 1,3,4-thiadiazole **19** [a]

	R^8				R^8		
	1	*2*	*3*		*1*	*2*	*3*
 **18**{*1*,R^8}	28 (100)	34 (98)	40 (100)	 **19**{*1*,R^8}	21 (98)	19 (97)	16 (92)
 **18**{*2*,R^8}	33 (100)	36 (100)	39 (100)	 **19**{*2*,R^8}	21 (100)	9 (98)	14 (98)
 **18**{*3*,R^8}	15 (98)	14 (98)	10 (98)	 **19**{*3*,R^8}	16 (98)	18 (97)	18 (98)

[a] Yield (Purity); Yield is an obtained yield for seven steps, and purity is checked by LC-MS at 254 nm.

For amide formation, we used nitro-substituted 1,3,4-oxadiazole **4b** and 1,3,4-thiadiazole **5**. First, we introduced an acyl moiety at the 2-amine position, then reduced the nitro group to an amine group using $SnCl_2.2H_2O$ in DMF to yield the 1,3,4-oxadiazole resin **10** and the 1,3,4-thiadiazole resin **11**. 1,3,4-oxadiazole **10** was reacted with benzoyl chloride in pyridine under neat condition (Entry 2 of

Scheme S8 in Supporting Information). However, after the cleavage reaction using 10% TFA in DCM, we obtained the desired 1,3,4-oxadiazole **18** in only moderate yield. Thus, to increase the yield, we used pyridine as base and THF as solvent followed by cleavage with a treatment of 10% TFA in DCM at room temperature for 8 h. As a result, the starting material was almost completely converted to the desired product (Entry 1 of Scheme S8 in Supporting Information). With these reaction conditions in hand, we used 1,3,4-thiadiazole resin **11**, and the reaction proceeded well. The LC-MS spectra of the crude product mixture for 1,3,4-oxadiazole **18** and 1,3,4-thiadiazole **19** showed high purity without further purification (Figure S3 (c), and (h) in Supporting Information) and attenuated total reflection-fourier transform infrared spectroscopy (ATR-FTIR) spectra showing the amide peaks for 1,3,4-oxadiazole resin **10-acylation**, and 1,3,4-thiadiazole resin **11-acylation** are displayed in Figure S1 (d) and S2 (d) of the Supporting information. To obtain our desired product, we triturated the crude product mixture of 1,3,4-oxadiazole **18**, and 1,3,4-thiadiazole **19** with diethyl ether / ethyl acetate / ethanol. The yields and purities of 1,3,4-oxadiazole **18** and 1,3,4-thiadiazole **19** are summarized in the Table 5.

Synthesis of 1,3,4-oxadiazole derivatives 20 and 1,3,4-thiadiazole derivatives 21

Scheme 7. ***N*-Acylation, and peptide coupling for synthesis of 1,3,4-oxadiazole derivatives 20 and 1,3,4-thiadiazole derivatives 21**

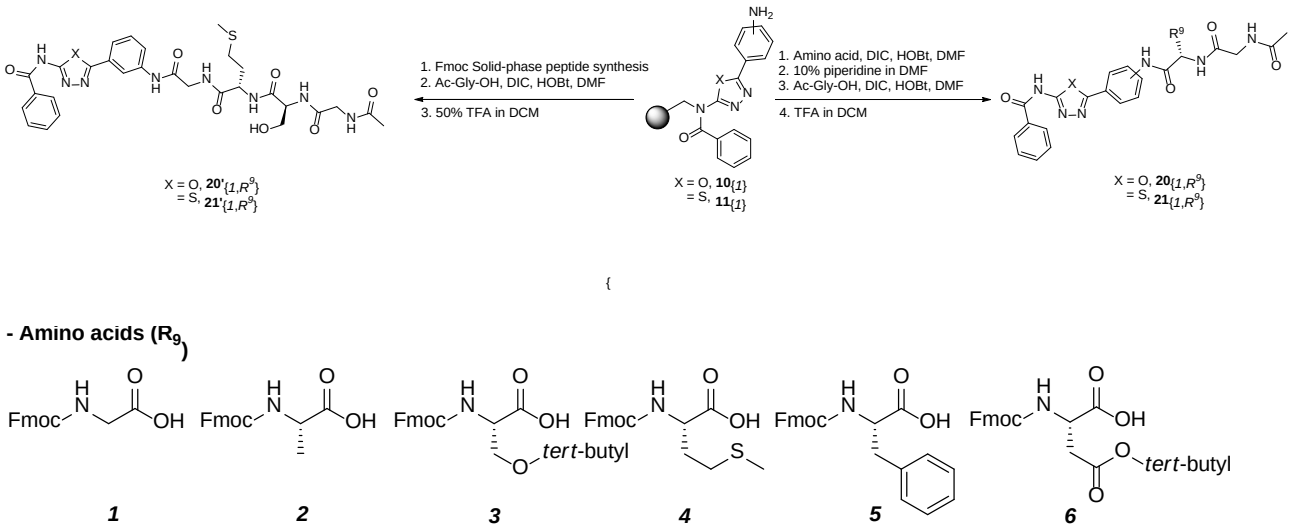
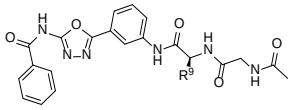
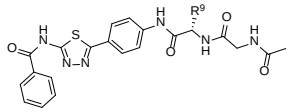
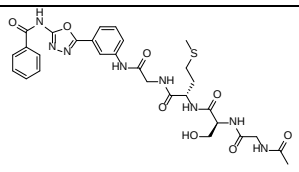
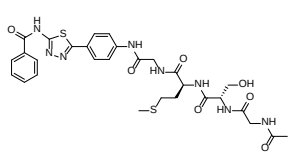


Table 6. Yields and purities of 1,3,4-oxadiazole **20** (**20'**) and 1,3,4-thiadiazole **21** (**21'**)[a]

	R^9					
	1	*2*	*3*	*4*	*5*	*6*
 **20**{*1*,*R*^{9}}	31 (100)	34 (100)	35 (100)	29 (100)	26 (100)	16 (100)
 **21**{*1*,*R*^{9}}	20 (100)	17 (100)	32 (100)	18 (100)	16 (100)	29 (100)
 **20'**{*1*,*1*-*4*-*3*}					28[b] (100)	
 **21'**{*1*,*1*-*4*-*3*}					20[b] (90)	

[a] Yield (Purity); Yield is an obtained yield for nine steps, and purity is checked by LC-MS at 254 nm.

[b] Yield is an obtained yield for thirteen steps.

Finally, we tried to synthesize peptide-like derivatives equipped with 1,3,4-oxadiazole and 1,3,4-thiadiazole motifs. To achieve this, we used nitro-substituted 1,3,4-oxadiazole **4b** and 1,3,4-thiadiazole **5**. We introduced an acyl moiety at the 2-amine position, then reduced the nitro group to an amine group using $SnCl_2.2H_2O$ in DMF to yield the 1,3,4-oxadiazole resin **10** and the 1,3,4-thiadiazole resin **11**. We first introduced six kinds of amino acids at the amine position of 1,3,4-oxadiazole resin **10** and 1,3,4-thiadiazole resin **11** by using DIC, and HOBt in DMF, and then end-capped with acetic glycine followed by treatment with TFA in DCM (the concentration of TFA solution was depend on the nature of the protecting group: see the experimental section) to afford amino acid equipped 1,3,4-oxadiazole **20** and 1,3,4-thiadiazole **21** (Table 6). Most amino acids were introduced in good yields and high purities. However, in the case of methionine (**20**{*1,4*} and **21**{*1,4*}), the yields were low compared to other amino acids (the yields are 6%, and 9% for **20**{*1,4*}, and **21**{*1,4*}, respectively). Thus, to increase the yields, we used EDC·HCl instead of DIC, and obtained **20**{*1,4*} and **21**{*1,4*} in good yields. The LC-MS spectra showed high purity after cleavage without further purification (Figure S3 (g), and (l) in the Supporting Information). Next, we elongated the peptide chains using glycine, methionine, and serine to afford 1,3,4-oxadiazole **20'** and 1,3,4-thiadiazole **21'** followed by treatment with 50% TFA in DCM and purified crude product mixture by trituration with diethyl ether / THF. The yields and purities are summarized in Table 6.

Displayed 3D structure, Polar surface area, and Physicochemical property of 1,3,4-oxadiazole and 1,3,4-thiadiazole library

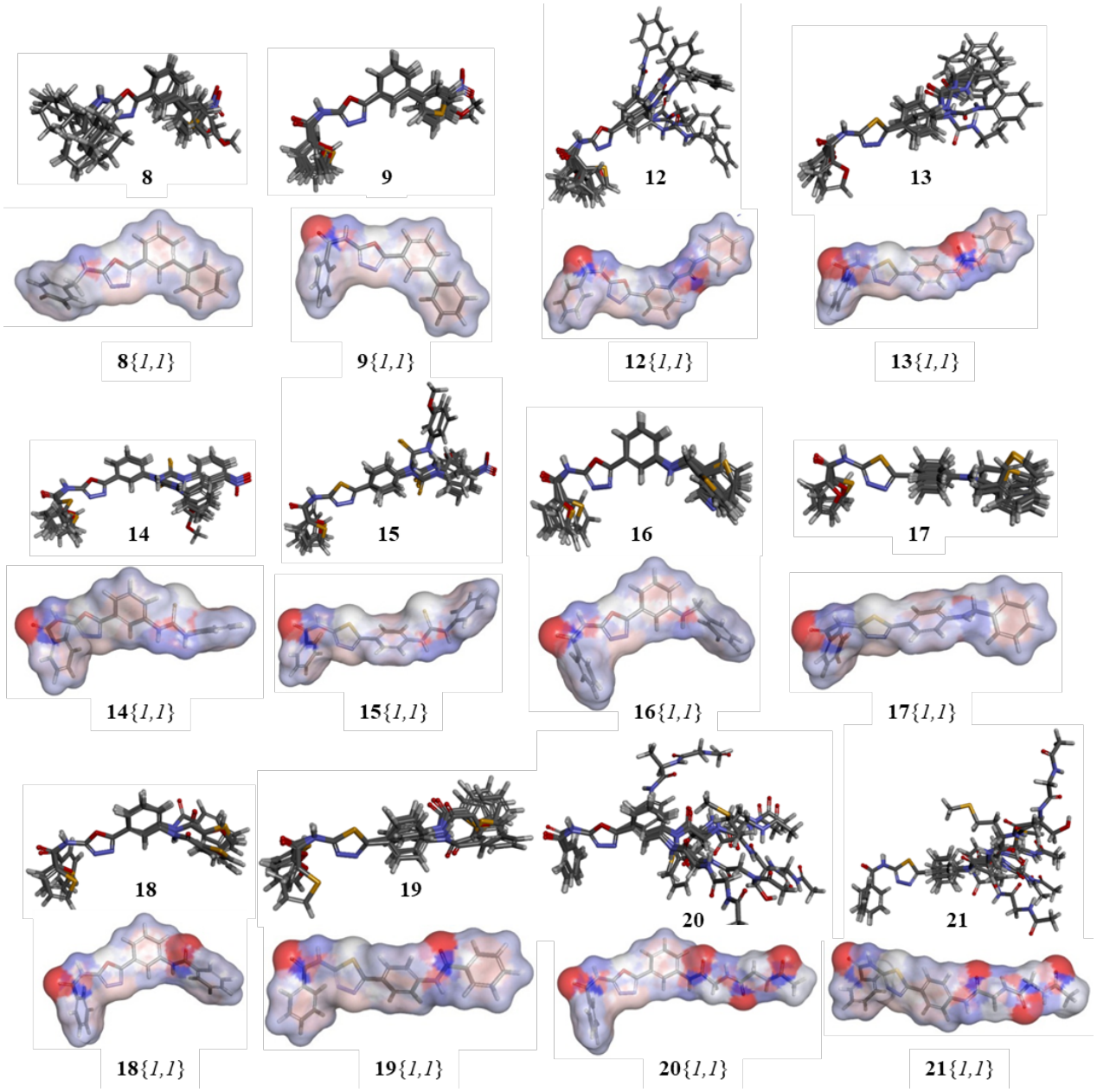


Figure 3. Displayed 3D structure, and Polar surface area of 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives

To measure structural diversity, we display each library aligned at the 1,3,4-oxadiazole or 1,3,4-thiadiazole (Figure 3) and show polar surface area of representative 1,3,4-oxadiazole and 1,3,4-thiadiazole analogues. As can be seen in Figure 3, the 12 kinds of libraries occupy distinct 3D spaces with respect to their specific functional groups. In addition, these functional groups bring different polar surface areas, which has been consider one of the key factors to interact with target proteins by

non-covalent interaction, promising that each library set could have distinct biological activities.

Table 7. Physicochemical property of representative 1,3,4-oxadiazole and 1,3,4-thiadiazole[a]

No	ALogP	MW	HBA	HBD	PSA (Å^2)	Rotatable bond
8{*1,1*}	4.581	327.37	3	1	50.95	5
9{*1,1*}	3.973	341.36	3	1	68.02	4
12{*1,1*}	3.148	399.40	4	3	109.15	5
13{*1,1*}	3.706	415.46	4	3	124.25	5
14{*1,1*}	4.992	415.46	4	3	124.17	7
15{*1,1*}	5.55	431.53	4	3	139.27	7
16{*1,1*}	3.847	370.40	4	2	80.05	6
17{*1,1*}	4.405	386.47	4	2	95.15	6
18{*1,1*}**}**	3.24	384.38	4	2	97.12	5
19{*1,1*}	3.798	400.45	4	2	112.22	5
20{*1,1*}	-0.305	436.42	6	4	155.32	8
21{*1,1*}	0.253	452.48	6	4	170.42	8

MW: Molecular Weight; **HBA**: Hydrogen Bonding Acceptor; **HBD**: Hydrogen Bonding Donor; **PSA**: Polar Surface Area
[a] is calculated by Drug Discovery Studio 2016.

Next, to measure the orally available drug properties, we calculated the physicochemical properties of representative 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives (Table 7). Lipinski's Rule[23] and similar parameters have been used as a guide to achieve the ultimate goal of isolating an orally bioavailable drug during the drug discovery process. In this context, most of the key parameters of our 12 kinds of 1,3,4-oxadiazole and 1,3,4-thiadiazole analogues fall within a range of those typically predicted for orally bioavailable drugs. Compared with other analogues, the ALogP and PSA values are very low and high, respectively, for 1.3.4-oxadiazole **20**{*1,1*} and 1,3,4-thiadiazole **21**{*1,1*}. This is probably due to the hydrophilicity of the peptide moiety.

Conclusion

In conclusion, we have synthesized 128 1,3,4-oxadiazole and 1,3,4-thiadiazole analogues classified to 12 kinds of distinct library sets having aryl, urea, thiourea, amine, amide, and peptide chains on solid-phase. In this synthetic procedure, most of the 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives are purified by simple trituration after cleavage from the polymer supported resin - our protocols do not require complex processes for purification such as extraction, and column chromatography facilitating rapid library construction. Each library set occupies specific positions in 3D space based on their functional groups and have distinct polar surface areas. Finally, we calculated the physicochemical properties of representative analogues to probe their orally available drug properties. As a result, most of the key parameters of the analogues fall within the acceptable range for oral drugs, thus enabling us to explore and biologically evaluate each library set. We will use these libraries to evaluate biological activities of these compounds in our future work.

Experimental section

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

A mixture of BOMBA resin **1** (5.00 g, 5.80 mmol), and Et_3N (5.86 g, 58.0 mmol) in THF (30.0 mL) was added CS_2 (2.65 g, 34.8 mmol) at 0 °C and then the mixture was shaken at room temperature for 3 h. The mixture was cooled down to 0 °C and then added *p*-TsCl (5.53 g, 29.0 mmol). The mixture was shaken at room temperature for 15 h. The precipitate obtained by filteration of the mixture was washed with THF, H_2O, MeOH, and DCM and dried in a vacuum oven. This process made **resin 2** as a brown solid. Single-Bead ATR-FTIR : 2918, 2061(N=C=S), 1610, 1504, 1451, 1286, 1195, 1159, 1028, 817, 757 and 697 cm^{-1}.

Representative procedure for the preparation of thiosemicarbazide resin 3-I

A mixture of isothiocyanate resin **2** (3 g, 3.18 mmol), and Et_3N (0.97 g, 9.54 mmol) in THF (20 mL) was added 3-iodobenzhydrazide (2.5 g, 9.54 mmol) and then the mixture was shaken at room temperature for 16 h. The resin was filtered and washed several times with MeOH and DCM and then dried in a vacuum oven. **Resin 3-I** was obtained as a yellow brown solid. Single-Bead ATR-FTIR : Single-Bead ATR-FTIR: 3310(br), 2916, 1670(C═O), 1610, 1450, 1194, 1157, 818, 733, 697 cm^{-1}.

Representative procedure for the preparation of thiosemicarbazide resin 3-*m*-NO_2

A mixture of isothiocyanate resin **2** (3 g, 3.18 mmol), and Et_3N (0.97 g, 9.54 mmol) in THF (20 mL) was added 3-nitrobenzahydrazide (1.73 g, 9.54 mmol) and then the mixture was shaken at room temperature for 16 h. The resin was filtered and washed several times with MeOH and DCM and then dried in a vacuum oven. **Resin 3-*m*-NO_2** was obtained as a yellow brown solid. Single-Bead ATR-FTIR : 3310(br), 2918, 1670(C═O), 1612, 1530, 1450, 1194, 1157, 816, 732, 697 cm^{-1}.

Representative procedure for the preparation of 1,3,4-oxadiazole resin 4a

A mixture of thiosemicarbazide resin **3-I** (3 g, 3.18 mmol) and EDC·HCl (3.03 g, 15.9 mmol) in DMSO (20 mL) was stirred at 60 ^oC for 16 h. The resin was filtered and washed several times with MeOH, H_2O and DCM and then dried in a vacuum oven. **Resin 4a** was obtained as a dark gold solid. Single-Bead ATR-FTIR: 2918, 1610(C═N), 1492, 1450, 1194, 1159, 817, 733, and 697 cm^{-1}.

Representative procedure for the preparation of 1,3,4-oxadiazole resin 4b

A mixture of thiosemicarbazide **resin 3-*m*-NO_2** (3 g, 3.18 mmol) and EDC·HCl (3.03 g, 15.9 mmol) in DMSO (20 mL) was stirred at 60 ^oC for 16 h. The resin was filtered and washed several times with MeOH, H_2O and DCM and then dried in a vacuum oven. **Resin 4b** was obtained as a brown solid. Single-Bead ATR-FTIR: 3023, 2919, 1612(C═N), 1529, 1504, 1493, 1451, 1348, 1194, 1158, 817, 756, 730, and 698 cm^{-1}.

Representative Procedure for 1,3,4-oxadiazole resin 6{*1,1*}

To a mixture of cyclized **resin 4a** (0.2 g, 0.21 mmol) in DMF (3 mL), t-BuOK (0.112 g, 1.1 mmol) was added, and the reaction mixture was shaken for 1 h at room temperature. After 1 h benzyl chloride (0.134 g, 1.1 mmol) was added, and the temperature was increased to 60 ^oC. The reaction mixture was shaken for 16 h. The resin was filtered and washed successively with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 4a-alkylation** was obtained as a dark orange solid. Single-bead ATR-FTIR: 3022, 2019, 1600, 1490, 1449, 1280, 1250(C−N), 1196, 1159, and 895

cm^{-1}.

Suzuki coupling reaction was carried out under inert atmosphere. To a suspension of resin **4a-alkylation** (200 mg, 0.21 mmol) in 1,4-dioxane (1.8 mL), $Pd_2(dba)_3$ (39 mg, 0.04 mmol), XPhos (41 mg, 0.08 mmol), phenylboronic acid (78 mg, 0.06 mmol), and Cs_2CO_3 (0.35 g, 1.06 mmol) dissolved in H_2O (0.2 mL) were added. The reaction mixture was shaken for 14 h at 110 ^oC and cooled to room temperature. The resin was filtered and washed several times with MeOH, H_2O and DCM, and dried under high vacuum. **Resin 6**{*1,1*} was obtained as a dark black solid.

Representative Procedure for the Preparation of 8{*1,1*}

A resin **6**{*1,1*} (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (1:4, v/v, 2 mL) and shaken for 8 h at 40 ^oC. The resin was filtered and then washed several times with DCM and MeOH, and organic filtrate was collected and evaporated. The residue was dissolved in ethyl acetate, washed with H_2O, and neutralized to pH 7 with saturated aqueous $NaHCO_3$ solution. The organic layer was dried with anhydrous $NaSO_4$ and evaporated. The crude mixture was purified by column chromatography on silica gel (hexane/ethyl acetate) and triturated with hexane and diethyl ether (7:3, v/v) affording **8**{*1,1*} (17%, six-step overall yield). ^1H NMR (500 MHz, DMSO-d6) δ 8.42 (t, *J* = 6.2 Hz, 1H), 8.02 (s, 1H), 7.81 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 7.3 Hz, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 4.48 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (126 MHz, Chloroform-d) δ 163.30, 159.20, 141.93, 140.04, 137.37, 129.34, 129.28, 128.89, 128.86, 128.02, 127.82, 127.80, 127.14, 124.89, 124.58, 124.47, 47.74; m.p. 153-158 ^oC; LC-MS (ESI): m/z = 328.2 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{17}N_3O$ $[M + H]^+$: 328.1444, found : 328.1439.

Representative procedure for the Preparation of 1,3,4-oxadiazole resin 7{*1,1*}

Suzuki coupling reaction was carried out under inert atmosphere. To a suspension of resin **4a** (200 mg, 0.21 mmol) in 1,4-dioxane (1.8 mL), $Pd_2(dba)_3$ (39 mg, 0.04 mmol), XPhos (41 mg, 0.08 mmol), phenylboronic acid (78 mg, 0.06 mmol), and Cs_2CO_3 (0.35 g, 1.06 mmol) dissolved in H_2O (0.2 mL)

were added. The reaction mixture was shaken for 14 h at 110 °C and cooled to room temperature. The resin was filtered and washed several times with MeOH, H_2O and DCM, and dried under high vacuum. **Resin 4a-Suzuki coupling** was obtained as a dark black solid.

To a suspension of **resin 4a-Suzuki coupling** (0.2 g, 0.21 mmol) in pyridine (2 mL), benzoyl chloride (0.149 g, 1.06 mmol), and DMAP (cat. amount) were added successively. The reaction mixture was shaken for 12 h at 60 °C. **Resin 7**{*1,1*} was filtered and washed successively with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 7**{*1,1*} was obtained as a dark brown solid. Single-bead ATR-FTIR: 3022, 2921, 1680(amide), 1600, 1575, 1504, 1449, 1265, 1195, 1022, 825 cm^{-1}.

Representative Procedure for the Preparation of 9{*1,1*}

A **resin 7**{*1,1*} (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (1:9, v/v, 2 mL) and shaken for 6 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with diethyl ether and ethyl acetate (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was beige color solid (36%, six-step overall yield). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.24 (s, 1H), 8.09 (d, *J* = 7.7 Hz, 2H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.77 (t, *J* = 7.3 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 9.3 Hz, 4H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.46 – 7.42 (m, 1H); ^{13}C NMR (126 MHz, Chloroform-d) δ 166.57, 161.40, 157.10, 143.27, 138.99, 135.80, 133.09, 130.41, 129.73, 129.31, 129.24, 128.92, 128.67, 127.23, 126.02, 125.86, 120.62; m.p. 180-190 °C; LC-MS (ESI): m/z = 342.2 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{15}N_3O_2$ $[M + H]^+$: 342.1237, found : 342.1227.

Representative Procedure for the Preparation of resin 10{*1*}

To a suspension of **resin 4b** (0.2 g, 0.21 mmol) in pyridine (2 mL), benzoyl chloride (0.149 g, 1.06 mmol), and DMAP (cat. Amount) were added successively. The reaction mixture was shaken for 12 h

at 60 °C. The resin was filtered and washed several times with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 4b-Acylation** was obtained as a brown solid. Single-bead ATR-FTIR: 2919, 1680(amide), 1529, 1506, 1492, 1450, 1348, 1195, 1159, 1113, 817, 735, 690 cm^{-1}.

And then, to a suspension of **resin 4b-Acylation** (0.2 g, 0.21 mmol) in DMF (2 mL), $SnCl_2 \cdot 2H_2O$ (0.24 g, 1.06 mmol) was added successively. The reaction mixture was shaken for 12 h at room temperature. The resin was filtered and washed several times with DMF, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 10**{*1*} was obtained as a brown solid. Single-bead ATR-FTIR: 3220(br), 1680(amide), 1449, 1194, 1159, 1115, 818, 732, 697 cm^{-1}.

Representative Procedure for the Preparation of resin 10-Urea

(1) **In case of Phenyl isocyanate** : A mixture of **resin 10**{*1*} (0.2 g, 0.21 mmol), and Pyridine (83 mg, 1.06 mmol) in THF (2 mL) was added phenyl isocyanate (126 mg, 1.06 mmol) and then the mixture was shaken at 60 °C for 12 h. The resin was filtered and washed several times with THF, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 10**{*1,1*}-**Urea** was obtained as a brown solid.

(2) **In case of Benzyl isocyanate** : A mixture of **resin 10**{*1*} (0.2 g, 0.21 mmol), and DMAP (14 mg, 0.12 mmol) in DCM (2 mL) was added benzyl isocyanate (158 mg, 1.06 mmol) and then the mixture was shaken at 60 °C for 12 h. The resin was filtered and washed several times with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 10**{*1,2*}**-Urea** was obtained as a brown solid.

(3) **In case of Ethyl isocyanate** : A mixture of **resin 10**{*1*} (0.2 g, 0.21 mmol), and DMAP (14 mg, 0.12 mmol) in DCM (2 mL) was added ethyl isocyanate (75 mg, 1.06 mmol) and then the mixture was shaken at room temperature for 12 h. The resin was filtered and washed several times with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 10**{*1,3*}**-Urea** was obtained as a brown solid.

Representative Procedure for the Preparation of 12{*1,1*}

A **resin 10**{*1,1*}**-Urea** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (1:9, v/v, 2 mL) and shaken for 6 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with diethyl ether and ethyl acetate (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was beige color solid (12%, seven-step overall yield). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.06 (d, *J* = 7.4 Hz, 2H), 7.94 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 4H); ^{13}C NMR (126 MHz, Chloroform-d) δ 166.45, 156.87, 138.13, 136.02, 131.40, 131.02, 130.29, 129.80, 129.59, 129.51, 128.88, 127.84, 127.27, 126.82, 124.82, 123.11, 120.93, 120.12; m.p. 245-250 ^{o}C; LC-MS (ESI): m/z = 400.2 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{17}N_5O_3$ $[M + H]^+$: 400.1404, found : 400.1391.

Representative Procedure for the Preparation of resin 10{*1,1*}**-Thiourea**

A mixture of **resin 10**{*1*} (0.2 g, 0.21 mmol), and DMAP (14 mg, 0.12 mmol) in $CHCl_3$ (2 mL) was added phenyl isothiocyanate (143 mg, 1.06 mmol) and then the mixture was shaken at 60 ^{o}C for 12 h. The resin was filtered and washed several times with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 10**{*1,1*}**-Thiourea** was obtained as a brown solid.

Representative Procedure for the Preparation of 14{*1,1*}

A **resin 10**{*1,1*}**-Thiourea** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (1:9, v/v, 2 mL) and shaken for 6 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with diethyl ether and ethyl acetate (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was beige color solid (17%, seven-step overall yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 12.19 (s, 1H), 10.07 (d, *J* = 17.7 Hz, 1H), 8.20 (s, 1H), 8.05 (d, *J* = 6.8 Hz, 3H), 7.76 – 7.70 (m, 2H), 7.70 – 7.64 (m, 2H), 7.60 – 7.55 (m, 4H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.8 Hz,

2H), 7.16 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 180.24, 170.80, 141.11, 140.84, 139.67, 133.41, 130.07, 129.26, 129.13, 129.03, 128.80, 127.06, 125.17, 124.25, 123.85, 122.18, 121.31, 118.87; m.p. 130-140 ^{o}C; LC-MS (ESI): m/z = 416.1 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{17}N_5O_2S$ $[M + H]^+$: 416.1176, found : 416.1164.

Representative Procedure for the Preparation of resin 10{*1,1*}**-Reductive amination**

To a suspension of **resin 10**{*1*} (0.2 g, 0.21 mmol) in 1,2-Dichloroethane (1.2 mL), Benzaldehyde (112 mg, 1.06 mmol) was added successively. The mixture was shaken at room temperature for 3 h. An acetic acid (38 mg, 0.64 mmol), MeOH (0.8 mL), $NaBH_3(CN)$ (67 mg, 1.06 mmol) was added, and then the mixture was shaken at room temperature for 12 h. The resin was filtered and washed several times with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. Resin **10**{*1,1*}**-Reductive amination** was obtained as an orange solid.

Representative Procedure for the Preparation of 16{*1,1*}

A **resin 10**{*1,1*}**-Reductive amination** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (1:9, v/v, 2 mL) and shaken for 6 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with diethyl ether and ethyl acetate (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was beige color solid (57%, seven-step overall yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 12.16 (s, 1H), 8.79 (s, 1H), 8.68 (d, *J* = 5.1 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.78 – 7.74 (m, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 3H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.24 (s, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.51 (s, 2H); ^{13}C NMR (126 MHz, Chloroform-d) δ 167.42, 159.56, 157.67, 149.89, 144.25, 143.30, 136.88, 133.11, 132.21, 130.30, 129.33, 129.28, 128.77, 128.67, 127.72, 123.38, 121.06, 52.61; m.p. 170-176 ^{o}C; LC-MS (ESI): m/z = 371.2 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{18}N_4O_2$ $[M + H]^+$: 371.1503, found : 371.1497.

Representative Procedure for the Preparation of resin 10{*1,1*}-Acylation.

A mixture of **resin 10**{*1*} (0.2 g, 0.21 mmol), and Pyridine (83 mg, 1.06 mmol) in THF (2 mL) was added benzoyl chloride (149 mg, 1.06 mmol) and then the mixture was shaken at 60 ^{o}C for 12 h. The resin was filtered and washed several times with THF, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. Single-bead ATR-FTIR: 2919, 1685(amide), 1680(amide), 1530, 1507, 1495, 1451, 1345, 1195, 1159, 1113, 818, 636 cm^{-1}. **Resin 10**{*1,1*}**-Acylation** was obtained as a brown solid.

Representative Procedure for the Preparation of 18{*1,1*}

A **resin 10**{*1,1*}**-Acylation** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (1:9, v/v, 2 mL) and shaken for 6 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with diethyl ether and ethyl acetate (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was beige color solid (28%, seven-step overall yield). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.71 (s, 1H), 8.33 (s, 1H), 8.08 (dd, *J* = 16.3, 7.8 Hz, 3H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 2H), 7.77 (t, *J* = 7.4 Hz, 1H), 7.64 (dq, *J* = 15.2, 7.4 Hz, 4H), 7.55 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (126 MHz, Chloroform-d) δ 170.02, 166.38, 160.56, 157.05, 138.17, 135.90, 133.73, 132.49, 131.06, 129.79, 129.45, 128.93, 128.82, 127.46, 126.89, 124.40, 121.15, 120.16; m.p. 275-280 ^{o}C; LC-MS (ESI): m/z = 385.1 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{16}N_4O_3$ $[M + H]^+$: 385.1295, found : 385.1285.

Representative Procedure for the Preparation of resin 10{*1,1*}-Amino acid

Resin 10{*1*} (0.2 g, 0.21 mmol) was swollen in DMF (2 mL) for 10 min. Amino acid (glycine) was pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment of Fmoc-protected amino acids (4.0 eq.) in DMF. In each case, the mixture was added to the resin and the syringe tumbled on a shaker for 2 h at room temperature and 160 rpm. The resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). Removal of Fmoc groups was achieved by treatment of the resin with 20 vol% piperidine in DMF (2 × 10 min). Washings between

deprotection and coupling steps were performed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). After Fmoc cleavage, free amine group was end-capped with acetic glycine. To achieve this, the resin was swollen in DMF for 10 min. Acetic glycine (99 mg, 0.85 mmol) were pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment in DMF (2 mL). The mixture was added to the resin and the syringe tumbled on a shaker for 2 h at room temperature and 160 rpm. Following the final coupling, the resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and dried under high vacuum. **Resin 10**{*1,1*}**-Amino acid** was obtained as a brown solid.

In case of methionine, to increase the yields, we used EDC·HCl instead of DIC. Resin **10**{*1*} (0.2 g, 0.21 mmol) was swollen in DMF (2 mL) for 10 min. Amino acids were pre-activated for 2 min by HOBt (97 mg, 0.64 mmol) and EDC·HCl (121 mg, 0.64 mmol) treatment of Fmoc-protected methionine (315 mg, 0.64 mmol) in DMF. The mixture was added to the resin and the syringe tumbled on a shaker for 1 day at room temperature and 160 rpm. The resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). Removal of Fmoc groups was achieved by treatment of the resin with 20 vol% piperidine in DMF (2 × 10 min). After Fmoc cleavage, free amine group was end-capped with acetic glycine. To achieve this, the resin was swollen in DMF (2 mL) for 10 min. Acetic glycine (74 mg, 0.64 mmol) were pre-activated for 2 min by HOBt (97 mg, 0.64 mmol) and EDC·HCl (121 mg, 0.64 mmol) treatment in DMF. The mixture was added to the resin and the syringe tumbled on a shaker for 1 day at room temperature and 160 rpm. Following the final coupling, the resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and dried under high vacuum. **Resin 10**{*1,4*}**-Amino acid** was obtained as a brown solid.

Representative Procedure for the Preparation of 20{*1,1*}

A **resin 10**{*1,1*}**-Amino acid** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (1:9, v/v, 2 mL) and shaken for 6 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with diethyl ether and tetrahydrofuran (9:1, v/v) solvent mixture and dried under high

vacuum. The resulting product was beige color solid (31%, nine-step overall yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 12.21 (s, 1H), 10.15 (s, 1H), 8.40 (s, 1H), 8.31 (t, *J* = 5.4 Hz, 1H), 8.27 (t, *J* = 4.9 Hz, 1H), 8.05 (d, *J* = 7.0 Hz, 2H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.58 (t, *J* = 8.4 Hz, 3H), 3.92 (d, *J* = 5.6 Hz, 2H), 3.74 (d, *J* = 5.5 Hz, 2H), 1.89 (s, 3H), 1.22 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 169.46, 169.20, 169.03, 167.80, 167.55, 139.17, 139.06, 132.38, 129.45, 128.06, 127.71, 123.19, 121.45, 120.26, 120.14, 115.74, 42.14, 41.66, 21.91; m.p. 190-195 ^{o}C; LC-MS (ESI): m/z = 437.2 $[M + H]^{+}$; HRMS (ESI) calcd for $C_{21}H_{20}N_6O_5$ $[M + H]^{+}$: 437.1568, found : 437.1560.

Representative Procedure for the Preparation of Resin 10{*1,1-4-3*}**-Amino acid**

Resin 10{*1*} (0.2 g, 0.21 mmol) was swollen in DMF (2 mL) for 10 min. Glycine was pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment of Fmoc-protected glycine (252 mg, 0.85 mmol) in DMF. In each case, the mixture was added to the resin and the syringe tumbled on a shaker for 2 h at room temperature and 160 rpm. The resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). Removal of Fmoc groups was achieved by treatment of the resin with 20 vol% piperidine in DMF (2 × 10 min). Washings between deprotection and coupling steps were performed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). **Resin 10**{*1,1*}**-Amino acid** (0.2 g, 0.21 mmol) was swollen in DMF (2 mL) for 10 min. Methionine was pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment of Fmoc-protected methionine (315 mg, 0.85 mmol) in DMF. The mixture was added to the resin and the syringe tumbled on a shaker for 2 h at room temperature and 160 rpm. The resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). Removal of Fmoc groups was achieved by treatment of the resin with 20 vol% piperidine in DMF (2 × 10 min). Washings between deprotection and coupling steps were performed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). **Resin 10**{*1,1-4*}**-Amino acid** (0.2 g, 0.21 mmol) was swollen in DMF (2 mL) for 10 min. Serine was pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment of Fmoc-protected serine (325 mg, 0.85 mmol) in DMF. The mixture was added to the resin and the syringe

tumbled on a shaker for 2 h at room temperature and 160 rpm. The resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). Removal of Fmoc groups was achieved by treatment of the resin with 20 vol% piperidine in DMF (2 × 10 min). Washings between deprotection and coupling steps were performed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). After Fmoc cleavage, free amine group was end-capped with acetic glycine. To achieve this, the resin was swollen in DMF for 10 min. Acetic glycine (99 mg, 0.85 mmol) were pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment in DMF (2 mL). The mixture was added to the resin and the syringe tumbled on a shaker for 2 h at room temperature and 160 rpm. Following the final coupling, the resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and dried under high vacuum. **Resin 10**{*1,1-4-3*}**-Amino acid** was obtained as a brown solid.

Representative Procedure for the Preparation of 20'{*1,1-4-3*}

A **resin 10**{*1,1-4-3*}**-Amino acid** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (1:1, v/v, 2 mL) and shaken for 6 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with diethyl ether and tetrahydrofuran (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was beige color solid (28%, thirteen-step overall yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 12.24 (s, 1H), 10.18 (s, 1H), 8.38 (d, *J* = 13.7 Hz, 1H), 8.21 (d, *J* = 31.4 Hz, 3H), 8.09 – 8.02 (m, 2H), 7.78 (d, *J* = 6.9 Hz, 1H), 7.68 (s, 2H), 7.58 (s, 3H), 4.36 (s, 1H), 3.93 (s, 2H), 3.80 (s, 2H), 3.74 (s, 2H), 3.65 (s, 1H), 3.60 (s, 3H), 2.05 (s, 2H), 1.86 (s, 3H), 1.76 (s, 2H), 1.49 (s, 1H); ^{13}C NMR (126 MHz, DMSO) δ 172.05, 170.94, 170.32, 169.84, 165.97, 154.10, 140.15, 133.51, 133.42, 130.58, 129.14, 129.07, 128.80, 128.78, 124.27, 122.49, 121.34, 116.72, 67.49, 62.06, 55.52, 52.70, 31.77, 29.98, 25.60, 22.88, 15.04; m.p. 105-110 ^{o}C; LC-MS (ESI): m/z = 655.3 $[M + H]^{+}$; HRMS (ESI) calcd for $C_{29}H_{34}N_8O_8S$ $[M + H]^{+}$: 655.2293, found : 655.2276.

Representative procedure for the preparation of 1,3,4-thiadiazole resin 5

A mixture of *p*-nitro-substituted thiosemicarbazide resin **3-*p*-NO$_2$** (3.00 g, 3.18 mmol), TEA (965 mg,

9.54 mmol) and *p*-TsCl (1.82 g, 9.54 mmol) in NMP (20 mL) was stirred at room temperature for 12 h. The resin was filtered and washed several times with MeOH, H_2O, and DCM and then dried in a vacuum oven. Resin **5** was obtained as a dark brown solid. Single-bead ATR-FTIR: 3022, 2925, 1602, 1521(NO_2), 1507, 1449, 1342(NO_2), 1195, 1161, and 851 cm^{-1}.

Representative Procedure for the Preparation of resin 11{*1*}

To a suspension of **resin 5** (0.2 g, 0.21 mmol) in pyridine (2 mL), benzoyl chloride (0.149 g, 1.06 mmol), and DMAP (cat. Amount) were added successively. The reaction mixture was shaken for 12 h at 60 °C. The resin was filtered and washed several times with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 5-Acylation** was obtained as a brown solid. Single-bead ATR-FTIR: 2919, 1654(amide), 1521, 1507, 1449, 1449, 1342, 1195, 1161, 1110, 851, 697 cm^{-1}. Next, to a suspension of **resin 5-Acylation** (0.2 g, 0.21 mmol) in DMF (2 mL), $SnCl_2 \cdot 2H_2O$ (0.24 g, 1.06 mmol) was added successively. The reaction mixture was shaken for 12 h at room temperature. The resin was filtered and washed several times with DMF, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 11**{*1*} was obtained as a brown solid. Single-bead ATR-FTIR: 3410(br), 1654(amide), 1449, 1195, 1160, 1113, 822, 756, 697 cm^{-1}.

Representative Procedure for the Preparation of resin 11-Urea

(1) **In case of Phenyl isocyanate** : A mixture of resin **11**{*1*} (0.2 g, 0.21 mmol), and Pyridine (83 mg, 1.06 mmol) in THF (2 mL) was added phenyl isocyanate (126 mg, 1.06 mmol) and then the mixture was shaken at 60 °C for 12 h. The resin was filtered and washed several times with THF, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 11**{*1,1*}-**Urea** was obtained as a brown solid.

(2) **In case of Benzyl isocyanate** : A mixture of **resin 11**{*1*} (0.2 g, 0.21 mmol), and DMAP (14 mg, 0.12 mmol) in DCM (2 mL) was added benzyl isocyanate (158 mg, 1.06 mmol) and then the mixture was shaken at 60 °C for 12 h. The resin was filtered and washed several times with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin**

11{*1,2*}**-Urea** was obtained as a brown solid.

(3) **In case of Ethyl isocyanate** : A mixture of resin **11**{*1*} (0.2 g, 0.21 mmol), and DMAP (14 mg, 0.12 mmol) in DCM (2 mL) was added ethyl isocyanate (75 mg, 1.06 mmol) and then the mixture was shaken at room temperature for 12 h. The resin was filtered and washed several times with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 11**{*1,3*}**-Urea** was obtained as a brown solid.

Representative Procedure for the Preparation of 13{*1,1*}

A **resin 11**{*1,1*}**-Urea** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (5:95, v/v, 2 mL) and shaken for 4 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with ethyl acetate and ethanol (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was brown color solid (12%, seven-step overall yield). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.11 (d, *J* = 7.7 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.76 (t, *J* = 7.2 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.42 – 7.37 (m, 1H), 7.35 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (126 MHz, DMSO) δ 206.94, 152.76, 142.53, 139.91, 133.46, 131.98, 129.29, 129.13, 128.88, 128.23, 127.60, 127.60, 123.93, 122.55, 118.83, 118.77; m.p. 330-340 ºC; LC-MS (ESI): m/z = 416.1 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{17}N_5O_2S$ $[M + H]^+$: 416.1176, found : 416.1159.

Representative Procedure for the Preparation of resin 11{*1,1*}**-Thiourea**

A mixture of **resin 11**{*1*} (0.2 g, 0.21 mmol), and DMAP (14 mg, 0.12 mmol) in $CHCl_3$ (2 mL) was added phenyl isothiocyanate (143 mg, 1.06 mmol) and then the mixture was shaken at 60 ºC for 12 h. The resin was filtered and washed several times with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 11**{*1,1*}**-Thiourea** was obtained as a brown solid.

Representative Procedure for the Preparation of 15{*1,1*}

A **resin 11**{*1,1*}**-Thiourea** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (5:95, v/v, 2 mL) and shaken for 4 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with ethyl acetate and ethanol (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was brown color solid (10%, seven-step overall yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 13.13 (s, 1H), 10.15 (s, 1H), 10.08 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.70 – 7.66 (m, 1H), 7.59 (t, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 179.82, 142.27, 139.78, 139.55, 133.51, 132.02, 129.15, 128.97, 128.89, 127.66, 126.05, 125.10, 124.17, 123.72, 114.67, 107.40; m.p. 303-314 ºC; LC-MS (ESI): m/z = 432.1 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{17}N_5OS_2$ $[M + H]^+$: 432.0947, found : 432.0932.

Representative Procedure for the Preparation of resin 11{*1,1*}**-Reductive amination**

To a suspension of **resin 11**{*1*} (0.2 g, 0.21 mmol) in 1,2-Dichloroethane (1.2 mL), Benzaldehyde (112 mg, 1.06 mmol) was added successively. The mixture was shaken at room temperature for 3 h. A mixture and acetic acid (38 mg, 0.64 mmol), MeOH (0.8 mL), $NaBH_3(CN)$ (67 mg, 1.06 mmol) was added and then the mixture was shaken at room temperature for 12 h. The resin was filtered and washed several times with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 11**{*1,1*}**-Reductive amination** was obtained as a brown solid.

Representative Procedure for the Preparation of 17{*1,1*}

A **resin 11**{*1,1*}**-Reductive amination** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (5:95, v/v, 2 mL) and shaken for 4 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with ethyl acetate and ethanol (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was brown color solid (21%, seven-step overall yield). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.13 (d, *J* = 7.5 Hz, 2H), 8.05 (d, *J* = 8.6 Hz, 2H), 7.75 (d, *J* = 7.4 Hz, 1H),

7.63 (t, *J* = 7.8 Hz, 3H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 2.8 Hz, 2H), 4.68 (s, 2H); ^{13}C NMR (126 MHz, Chloroform-d) δ 165.81, 162.95, 161.42, 136.97, 135.20, 130.93, 130.29, 129.92, 129.61, 129.44, 128.98, 128.64, 128.10, 124.40, 57.99; m.p. decomposed above ~ 250 ^{o}C; LC-MS (ESI): m/z = 387.2 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{18}N_4OS$ $[M + H]^+$: 387.1274, found : 387.1263.

Representative Procedure for the Preparation of resin 11{*1,1*}**-Acylation**

A mixture of resin **11**{*1*} (0.2 g, 0.21 mmol), and Pyridine (83 mg, 1.06 mmol) in THF (2 mL) was added benzoyl chloride (149 mg, 1.06 mmol) and then the mixture was shaken at 60 ^{o}C for 12 h. The resin was filtered and washed several times with THF, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum. **Resin 11**{*1,1*}**-Acylation** was obtained as a brown solid. Single-bead ATR-FTIR: 2919, 1675(amide), 1654(amide), 1600, 1508, 1449, 1195, 1161, 754, 697 cm^{-1}.

Representative Procedure for the Preparation of 19{*1,1*}

A **resin 11**{*1,1*}**-Acylation** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (5:95, v/v, 2 mL) and shaken for 4 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with ethyl acetate and ethanol (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was brown color solid (21%, seven-step overall yield). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.39 (s, 1H), 8.11 (d, *J* = 7.5 Hz, 2H), 7.99 (d, *J* = 8.6 Hz, 2H), 7.86 (d, *J* = 7.5 Hz, 4H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 2H), 7.57 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (126 MHz, Chloroform-d) δ 171.11, 167.14, 165.19, 142.26, 136.26, 134.44, 132.93, 130.22, 129.95, 129.70, 129.12, 128.92, 128.30, 127.89, 123.09, 122.90; m.p. decomposed above ~ 250 ^{o}C; LC-MS (ESI): m/z = 401.1 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{16}N_4O_2S$ $[M + H]^+$: 401.1067, found : 401.1053.

Representative Procedure for the Preparation of resin 11{*1,1*}**-Amino acid**

Resin 11{*1*} (0.2 g, 0.21 mmol) was swollen in DMF (2 mL) for 10 min. Amino acid (glycine) was pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment of

Fmoc-protected amino acids (4.0 eq.) in DMF. In each case, the mixture was added to the resin and the syringe tumbled on a shaker for 2 h at room temperature and 160 rpm. The resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). Removal of Fmoc groups was achieved by treatment of the resin with 20 vol% piperidine in DMF (2 × 10 min). Washings between deprotection and coupling steps were performed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). After Fmoc cleavage, free amine group was end-capped with acetic glycine. The resin was swollen in DMF for 10 min. Acetic glycine (99 mg, 0.85 mmol) were pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment in DMF (2 mL). The mixture was added to the resin and the syringe tumbled on a shaker for 2 h at room temperature and 160 rpm. Following the final coupling, the resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and dried under high vacuum. **Resin 11**{*1,1*}**-Amino acid** was obtained as a brown solid.

In case of methionine, to increase the yields, we used EDC·HCl instead of DIC. Resin **11**{*1*} (0.2 g, 0.21 mmol) was swollen in DMF (2 mL) for 10 min. Methionine was pre-activated for 2 min by HOBt (97 mg, 0.64 mmol) and EDC·HCl (121 mg, 0.64 mmol) treatment of Fmoc-protected methionine (315 mg, 0.64 mmol) in DMF. The mixture was added to the resin and the syringe tumbled on a shaker for 1 day at room temperature and 160 rpm. The resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). Removal of Fmoc groups was achieved by treatment of the resin with 20 vol% piperidine in DMF (2 × 10 min). After Fmoc cleavage, free amine group was end-capped with acetic glycine. The resin was swollen in DMF (2 mL) for 10 min. Acetic glycine (74 mg, 0.64 mmol) were pre-activated for 2 min by HOBt (97 mg, 0.64 mmol) and EDC·HCl (121 mg, 0.64 mmol) treatment in DMF. The mixture was added to the resin and the syringe tumbled on a shaker for 1 day at room temperature and 160 rpm. Following the final coupling, the resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and dried under high vacuum. **Resin 11**{*1,4*}**-Amino acid** was obtained as a brown solid.

Representative Procedure for the Preparation of 21{*1,1*}**-Amino acid**

A **resin 11**{*1,1*}**-Amino acid** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (5:95, v/v, 2 mL) and shaken for 4 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with diethyl ether and tetrahydrofuran (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was brown color solid (20%, nine-step overall yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 13.13 (s, 1H), 10.19 (d, *J* = 81.9 Hz, 1H), 8.30 (d, *J* = 19.1 Hz, 2H), 8.14 (d, *J* = 6.8 Hz, 2H), 7.95 (d, *J* = 6.6 Hz, 2H), 7.83 – 7.75 (m, 2H), 7.71 – 7.66 (m, 1H), 7.58 (s, 2H), 3.93 (s, 2H), 3.74 (s, 2H), 1.90 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 170.57, 170.27, 170.09, 168.82, 168.58, 141.49, 141.37, 133.52, 129.16, 128.88, 128.17, 125.45, 119.90, 119.87, 67.49, 25.60, 22.90; m.p. 250-260 ºC; LC-MS (ESI): m/z = 453.2 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{20}N_6O_4S$ $[M + H]^+$: 453.1340, found : 453.1334.

Representative Procedure for the Preparation of resin 11{*1,1-4-3*}**-Amino acid**

Resin 11{*1*} (0.2 g, 0.21 mmol) was swollen in DMF (2 mL) for 10 min. Glycine was pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment of Fmoc-protected glycine (252 mg, 0.85 mmol) in DMF. In each case, the mixture was added to the resin and the syringe tumbled on a shaker for 2 h at room temperature and 160 rpm. The resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). Removal of Fmoc groups was achieved by treatment of the resin with 20 vol% piperidine in DMF (2 × 10 min). Washings between deprotection and coupling steps were performed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). **Resin 11**{*1,1*}**-Amino acid** (0.2 g, 0.21 mmol) was swollen in DMF (2 mL) for 10 min. Methionine was pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment of Fmoc-protected methionine (315 mg, 0.85 mmol) in DMF. The mixture was added to the resin and the syringe tumbled on a shaker for 2 h at room temperature and 160 rpm. The resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). Removal of Fmoc groups was achieved by treatment of the resin with 20 vol% piperidine in DMF (2 × 10 min). Washings between deprotection and coupling steps were performed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). **Resin**

11{*1,1-4*}-**Amino acid** (0.2 g, 0.21 mmol) was swollen in DMF (2 mL) for 10 min. Serine was pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment of Fmoc-protected serine (325 mg, 0.85 mmol) in DMF. The mixture was added to the resin and the syringe tumbled on a shaker for 2 h at room temperature and 160 rpm. The resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). Removal of Fmoc groups was achieved by treatment of the resin with 20 vol% piperidine in DMF (2 × 10 min). Washings between deprotection and coupling steps were performed with DMF (5 × 1 min), DCM (5 × 1 min), and DMF (5 × 1 min). After Fmoc cleavage, free amine group was end-capped with acetic glycine. To achieve this, the resin was swollen in DMF for 10 min. Acetic glycine (99 mg, 0.85 mmol) were pre-activated for 2 min by HOBt (130 mg, 0.85 mmol) and DIC (107 mg, 0.85 mmol) treatment in DMF (2 mL). The mixture was added to the resin and the syringe tumbled on a shaker for 2 h at room temperature and 160 rpm. Following the final coupling, the resin was washed with DMF (5 × 1 min), DCM (5 × 1 min), and dried under high vacuum. **Resin 11**{*1,1-4-3*}-**Amino acid** was obtained as a brown solid.

Representative Procedure for the Preparation of 21'{*1,1-4-3*}

A **resin 11**{*1,1-4-3*}-**Amino acid** (200 mg, 0.21 mmol) was treated with a mixture of TFA and DCM (1:1, v/v, 2 mL) and shaken for 4 h at room temperature. The resin was filtered and washed with DCM and MeOH (×3), and organic filtrate was collected and evaporated. The crude mixture was purified by trituration with diethyl ether and tetrahydrofuran (9:1, v/v) solvent mixture and dried under high vacuum. The resulting product was beige color solid (20%, thirteen-step overall yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 13.14 (s, 1H), 8.25 (s, 1H), 8.21 (d, *J* = 7.1 Hz, 1H), 8.19 – 8.10 (m, 3H), 8.06 (d, *J* = 5.8 Hz, 1H), 8.00 – 7.92 (m, 2H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.74 – 7.64 (m, 2H), 7.59 (s, 2H), 4.46 – 4.24 (m, 2H), 3.93 (s, 2H), 3.77 – 3.73 (m, 3H), 3.61 (s, 1H), 2.06 (s, 3H), 1.91 (s, 1H), 1.87 (s, 2H); ^{13}C NMR (126 MHz, DMSO) δ 172.04, 170.96, 170.33, 169.83, 168.31, 141.49, 141.36, 133.51, 129.15, 129.11, 128.88, 128.82, 128.72, 128.19, 125.43, 119.88, 114.73, 62.04, 55.53, 52.75, 43.29, 42.64, 31.76, 29.98, 22.89, 15.05; m.p. 205-218 °C; LC-MS (ESI): m/z = 671.3 $[M + H]^+$; HRMS (ESI) calcd for $C_{29}H_{34}N_8O_7S_2$ $[M + H]^+$: 671.2065, found : 671.2049.

Supporting Information

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, and complete description of the studies for the reactions

Acknowledgements

All authors were supported from the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (No. 2016R1D1A1B04932654) and by the Bio & Medical Technology Development Program of the National Research Foundation funded by the Ministry of Science, ICT & Future Planning (No. 2014M3A9A9073847) in Korea.

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