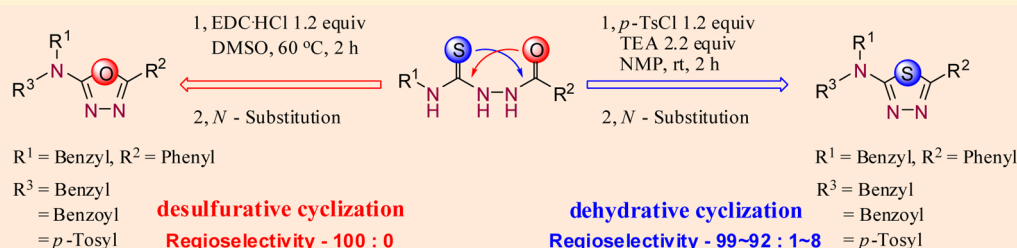


Regioselective Synthesis of 2-Amino-Substituted 1,3,4-Oxadiazole and 1,3,4-Thiadiazole Derivatives via Reagent-Based Cyclization of Thiosemicarbazide Intermediate

Seung-Ju Yang, Seok-Hyeong Lee, Hyun-Jung Kwak, and Young-Dae Gong*

Center for Innovative Drug Library Research, Department of Chemistry, College of Science, Dongguk University, 26, 3-ga, Pil-dong Jung-gu, Seoul 100-715, Korea

Supporting Information



ABSTRACT: A regioselective, reagent-based method for the cyclization reaction of 2-amino-1,3,4-oxadiazole and 2-amino-1,3,4-thiadiazole core skeletons is described. The thiosemicarbazide intermediate **3** was reacted with EDC·HCl in DMSO or *p*-TsCl, triethylamine in *N*-methyl-2-pyrrolidone to give the corresponding 2-amino-1,3,4-oxadiazoles **4** and 2-amino-1,3,4-thiadiazoles **5** through regioselective cyclization processes. The regioselectivity was affected by both R^1 and R^2 in *p*-TsCl mediated cyclization. It is shown in select sets of thiosemicarbazide **3** with R^1 (benzyl) and R^2 (phenyl). 2-Amino-1,3,4-oxadiazole **4** was also shown in the reaction of *p*-TsCl mediated cyclization. The resulting 2-amino-1,3,4-oxadiazole and 2-amino-1,3,4-thiadiazole core skeleton are functionalized with various electrophiles such as alkyl halide, acid halides, and sulfonyl chloride in high yields.

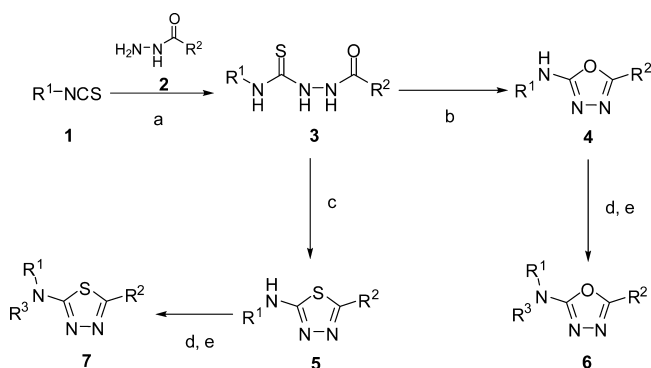
INTRODUCTION

Heterocyclic compounds are commonly used scaffolds on which pharmacophores are arranged to provide potent and selective drugs.¹ This is especially true for five-membered ring heterocyclic compounds, which serve as the core components of many substances that possess a wide range of interesting biological activities. In this family, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles have been used as “privileged” scaffolds to produce substances of interest in numerous therapeutic areas, such as anti-inflammatory,² antimicrobial,³ anticonvulsant,⁴ and anti-hypertensive.⁵ As a result of these applications, 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives have been targets of a number of solution- and solid-phase synthesis studies. 1,3,4-Oxadiazole was synthesized with a Burgess reagent,^{6a} KMnO_4 ,^{6b} and thiosemicarbazide was used to prepare 2-amino-1,3,4-oxadiazole as a starting material with several desulfurating agent such as *p*-TsCl,^{7a} EDC·HCl,^{7b} methyl iodide,^{7c} ethyl bromoacetate,^{7d} and mercury oxide.^{7e} Acidic reagents were generally used to prepare 2-amino-1,3,4-thiadiazole such as POCl_3 ,^{8a} H_3PO_4 ,^{8b} and methanesulfonic acid.^{8c} Recently, Saidi reported synthetic method of 2-amino-1,3,4-thiadiazole with triethylamine in water.⁹ Lau also reported synthetic method to produce both 2-amino-1,3,4-oxadiazole and 2-amino-1,3,4-thiadiazole.^{10a} However, the methods developed thus far lack diversity since they employ different intermediates for the syntheses of the oxygen- and sulfur-containing heterocyclic compounds. The

preparation of 2-aminosulfonamide-1,3,4-oxadiazole and 2-aminosulfonamide-1,3,4-thiadiazole was reported by Ley.^{10b} In this literature, only a sulfonamide group can be introduced on the 2-position of 1,3,4-oxadiazole and 1,3,4-thiadiazole and thus did not correspond our purpose that various substituent are introduced to the 2-position of 1,3,4-oxadiazole and 1,3,4-thiadiazole. Several methods have been tried to develop an efficient synthesis of 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives using the same key intermediate. Zoumpoulakis reported the synthetic method of 2-amino-1,3,4-oxadiazole and 2-amino-1,3,4-thiadiazole by using the I_2/NaOH in ethanol and H_2SO_4 .¹¹ However, protic solvents such as ethanol and water are not suitable for the traditional polystyrene resin in the solid-phase synthesis, and H_2SO_4 cannot be used with some acid sensitive functional group such as *N*-Boc, tetrahydropyranyl, and *tert*-butyldimethylsilyl ether. As a part of our drug discovery program, we developed a facile and a regioselective synthesis of druglike 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives generated by cyclodehydration or cyclodesulfurization reactions via reagent-based cyclization of acyldithiocarbamate intermediate in the previous study.¹² However, the developed method suffered a limitation in which some amine substituents could be introduced since the sulfone leaving group was unaffected by

Received: October 18, 2012

Published: December 7, 2012

Scheme 1. Construction of 2-Amino-Substituted 1,3,4-Oxadiazole and 1,3,4-Thiadiazole^a


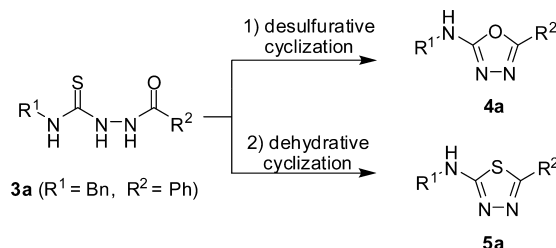
^aReaction conditions: (a) triethylamine, THF, rt, 16 h. (b) EDC·HCl, DMSO, 60 °C, 2 h. (c) *p*-TsCl, TEA, NMP, rt, 2 h. (d) Electrophiles, NaH, NMP, rt, 8 h. (e) Electrophiles, NaH, THF, rt, 1 h.

the various nucleophiles, such as alcohol, thiol, and carboxylic acid groups. Therefore, we undertook an investigation aimed at developing efficient and synthetic methods to produce various 2-amino-substituted 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives, which can be used to introduce various electrophile substituents on the 2-position of 1,3,4-oxadiazole and 1,3,4-thiadiazole rings. Herein we report our recent progress on this project, which includes the first regioselective synthesis protocol for 2-amino-substituted 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives **6** and **7** by cyclodesulfurization or cyclodehydration reactions via reagent-based cyclization of thiosemicarbazide intermediate **3**. We believe our efficient approach is suitable for the construction of druglike 2-amino-

substituted 1,3,4-oxadiazole and 1,3,4-thiadiazole libraries in a high throughput manner (Scheme 1).

RESULTS AND DISCUSSION

The sequence used to prepare the thiosemicarbazide useful intermediate **3** uses the isothiocyanate **1** as the starting material. Treatment of **1** with various acylhydrazides **2** in the presence of triethylamine at room temperature leads to the production of the corresponding thiosemicarbazide intermediate **3**. To investigate suitable methods for reagent-based skeletal diversity-oriented synthesis of 2-amino-substituted 1,3,4-oxadiazoles **4** or 1,3,4-thiadiazoles **5**, cyclization reactions of thiosemicarbazide **3** were investigated by using various reagents, including 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(EDC·HCl), *p*-TsCl, TMSCl, and diphenylchlorophosphate in various conditions. The results of the cyclization reactions of **3a** are summarized in Table 1. Reactions of the thiosemicarbazide intermediate with *p*-TsCl/triethylamine in 1,2-dichloroethane (DCE), which is the desulfurative cyclization condition used in our previous study,¹² gave 2-amino-1,3,4-oxadiazole **4a** and 2-amino-1,3,4-thiadiazole **5a** in low regioselectivity (entry 8 of Table 1). Otherwise, the use of EDC·HCl, which was well-known as a desulfurizing agent,^{7b} leads to 2-amino-1,3,4-oxadiazole **4a** as a major product with regioselectivity (100:0) and a high yield (entry 1 of Table 1). The liquid chromatography mass spectrometry (LC/MS) spectrum of the crude product mixture containing the 2-amino-1,3,4-oxadiazole **4a** formed in the EDC·HCl-initiated process is shown as Figure 1a in the Supporting Information. Next, we tried to make 2-amino-1,3,4-thiadiazole **5a** in various conditions. According to our previous study,¹² we used TMSCl and (PhO)₂P(O)Cl (entries 2 and 3 of Table 1). However, in this condition, thiosemicarbazide **3a** was not

Table 1. Results of the Cyclization of the Thiosemicarbazide Intermediate 3a^a


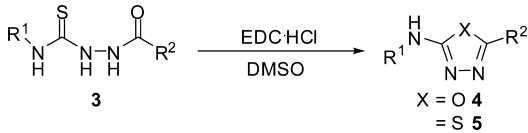
| entry | reagent | solvent | temp (°C) | time (h) | ratio ^b | | yield (%) ^c | |
|-------|--------------------------------|---------|-----------|----------|--------------------|----|------------------------|-----------------|
| | | | | | 4a | 5a | 4a | 5a |
| 1 | EDC·HCl | DMSO | 60 | 2 | 100 | 0 | 99 | |
| 2 | TMSCl | DCE | 60 | 12 | | | | NR ^d |
| 3 | (PhO) ₂ P(O)Cl | DCE | 60 | 12 | | | | NR ^d |
| 4 | <i>p</i> -TsCl/Pyridine | THF | 60 | 16 | 100 | 0 | 87 | |
| 5 | <i>p</i> -TsCl/ <i>t</i> -BuOk | THF | rt | 2 | 85 | 15 | 71 | 11 |
| 6 | <i>p</i> -TsCl/NaOH | THF | rt | 2 | 85 | 15 | 75 | 14 |
| 7 | <i>p</i> -TsCl/TEA | THF | 60 | 2 | 55 | 45 | 50 | 41 |
| 8 | <i>p</i> -TsCl/TEA | DCE | rt | 2 | 40 | 60 | 38 | 56 |
| 9 | <i>p</i> -TsCl/TEA | ACN | rt | 2 | 15 | 85 | 14 | 81 |
| 10 | <i>p</i> -TsCl/TEA | HMPA | rt | 2 | 9 | 91 | 8 | 71 |
| 11 | <i>p</i> -TsCl/TEA | DMF | rt | 2 | 6 | 94 | 3 | 74 |
| 12 | <i>p</i> -TsCl/TEA | NMP | rt | 2 | 4 | 96 | 3 | 92 |

^aReaction conditions: Thiosemicarbazide was treated with 1.2 equiv of EDC·HCl in DMSO at 60 °C for 2 h. Thiosemicarbazide was treated with 1.2 equiv of *p*-TsCl and 2.2 equiv of TEA in NMP at room temperature for 2 h. ^bCalculated by using LC/MS. ^cYield is obtained yield. ^dNR = no reaction.

transformed to 2-amino-1,3,4-thiadiazole **5a**. Dolman reported a synthesis method for 2-amino-1,3,4-oxadiazole.^{7a} In this method, *p*-TsCl was used as a desulfurizing agent (entry 4 of Table 1), and we also knew that *p*-TsCl can be used as a dehydrating agent (entry 8 of Table 1). So we investigated using *p*-TsCl as a dehydrating agent in various conditions. First, we used various bases in tetrahydrofuran (THF) (entries 5–7 of Table 1). Among these bases, *t*-BuOK and NaOH showed regioselectivity for 2-amino-1,3,4-oxadiazole **4a**. Therefore, we used triethylamine (TEA) to synthesize 2-amino-1,3,4-thiadiazole **5a**. Second, we used *p*-TsCl and TEA in various solvents. In nonpolar solvent, it showed low regioselectivity (entries 7 and 8 of Table 1). Otherwise, in the polar solvent, it showed regioselectivity for 2-amino-1,3,4-thiadiazole **5a** (entries 9–12 of Table 1). Among these polar solvents, *N*-methyl-2-pyrrolidone (NMP) showed high regioselectivity (96:4) and high yield. Therefore, we used *p*-TsCl/TEA/NMP for the synthesis of 2-amino-1,3,4-thiadiazole **5a**. The LC/MS spectrum of the crude product mixture containing the 2-amino-1,3,4-thiadiazole formed **5a** in the *p*-TsCl/TEA/NMP initiated process is shown as Figure 1b in the Supporting Information.

To explore the various substrates, we used various acylhydrazides and isothiocyanates. The results of the cyclization reactions of thiosemicarbazide **3** are summarized in Tables 2 and 3.

Table 2. Result of Thiosemicarbazide 3 via EDC·HCl-Based Cyclization^a

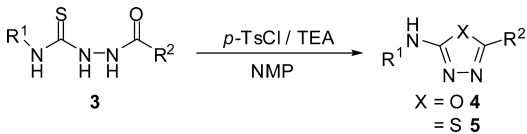


| entry | R ¹ | R ² | ratio ^b | | no. (% yield ^c) |
|-------|-----------------------|-----------------------|--------------------|---|-----------------------------|
| | | | 4 | 5 | |
| 1 | Bn | Ph | 100 | 0 | 4a (99) |
| 2 | Bn | 4-methoxy-Ph | 100 | 0 | 4b (82) |
| 3 | Bn | 4-F-Ph | 100 | 0 | 4c (91) |
| 4 | Bn | 4-NO ₂ -Ph | 100 | 0 | 4d (78) |
| 5 | 4-methoxy-Bn | Ph | 100 | 0 | 4e (69) |
| 6 | 4-CF ₃ -Bn | Ph | 100 | 0 | 4f (51) |
| 7 | ethyl | Ph | 100 | 0 | 4g (99) |
| 8 | 2,4-dimethoxy-Bn | 4-NO ₂ -Ph | 100 | 0 | 4h (80) |
| 9 | Ph | Ph | 100 | 0 | 4i (94) |
| 10 | 4-methoxy-Ph | Ph | 100 | 0 | 4j (72) |
| 11 | 4-F-Ph | Ph | 100 | 0 | 4k (96) |
| 12 | 4-NO ₂ -Ph | Ph | 100 | 0 | 4l (87) |
| 13 | 4-methoxy-Ph | 4-NO ₂ -Ph | 100 | 0 | 4m (74) |

^aReaction condition: Thiosemicarbazide was treated with 1.2 equiv of EDC·HCl in DMSO at 60 °C for 2 h. ^bCalculated by using LC/MS. ^cYield is obtained yield after column chromatography.

In the case of EDC·HCl-based cyclization, various thiosemicarbazides **3** showed regioselectivity and high yields. Otherwise, in the case of *p*-TsCl-based cyclization, various thiosemicarbazides **3** showed different regioselectivity depending on the substituent. First, we used benzylisothiocyanate and various acylhydrazides (entries 1–4 of Table 3). Acylhydrazide with an electron-donating group (entry 2 of Table 3) showed decreasing regioselectivity for 2-amino-1,3,4-thiadiazole **5**. Acylhydrazide with an electron-withdrawing group (entries 3

Table 3. Result of the Thiosemicarbazide 3 via *p*-TsCl/TEA-Based Cyclization^a



| entry | R ¹ | R ² | ratio ^b | | no. (% yield ^c) |
|-----------------|-----------------------|-----------------------|--------------------|----|-----------------------------|
| | | | 4 | 5 | |
| 1 | Bn | Ph | 4 | 96 | 5a (92) |
| 2 | Bn | 4-methoxy-Ph | 8 | 92 | 5b (81) |
| 3 | Bn | 4-F-Ph | 1 | 99 | 5c (87) |
| 4 | Bn | 4-NO ₂ -Ph | 1 | 99 | 5d (63) |
| 5 | 4-methoxy-Bn | Ph | 4 | 96 | 5e (73) |
| 6 | 4-CF ₃ -Bn | Ph | 5 | 95 | 5f (67) |
| 7 | ethyl | Ph | 3 | 97 | 5g (94) |
| 8 | 2,4-dimethoxy-Bn | 4-NO ₂ -Ph | 1 | 99 | 5h (87) |
| 9 ^d | Ph | Ph | 53 | 47 | 5i (40) |
| 10 ^d | 4-methoxy-Ph | Ph | 38 | 62 | 5j (53) |
| 11 ^d | 4-F-Ph | Ph | 49 | 51 | 5k (44) |
| 12 ^d | 4-NO ₂ -Ph | Ph | 97 | 3 | 4l (87) |
| 13 ^d | 4-methoxy-Ph | 4-NO ₂ -Ph | 5 | 95 | 5m (84) |

^aThiosemicarbazide was treated with 1.2 equiv of *p*-TsCl and 2.2 equiv of TEA in NMP at room temperature for 2 h. ^bCalculated by using LC/MS. ^cYield is obtained yield after column chromatography. ^dRatio and yield were determined by NMR integration of mixture of 2-amino-1,3,4-oxadiazole and 2-amino-1,3,4-thiadiazole.

and 4 of Table 3) showed increasing regioselectivity for 2-amino-1,3,4-thiadiazole **5**. Second, we used benzoylhydrazide and various benzyl and aliphatic isothiocyanates (entries 5–7 of Table 3). Isothiocyanate with an electron-donating group (entries 5 and 7 of Table 3) showed high regioselectivity and good yields. Otherwise, benzylisothiocyanate with an electron-withdrawing group (entry 6 of Table 3) showed slightly decreasing regioselectivity for 2-amino-1,3,4-thiadiazole **5**. To optimize the regioselectivity for 2-amino-1,3,4-thiadiazole **5**, we used 2,4-dimethoxy-benzylisothiocyanate and 4-nitro-benzoylhydrazide (entry 8 of Table 1). Third, we used benzoylhydrazide and phenyl isothiocyanate (entries 9–12 of Table 3). In the case of phenylisothiocyanate, the regioselectivity for 2-amino-1,3,4-thiadiazole **5** was decreased. Moreover, phenylisothiocyanate with an electron-withdrawing group (entry 12 of

Scheme 2. Proposed Mechanism of Cyclization 3 Promoted by *p*-TsCl/TEA in NMP

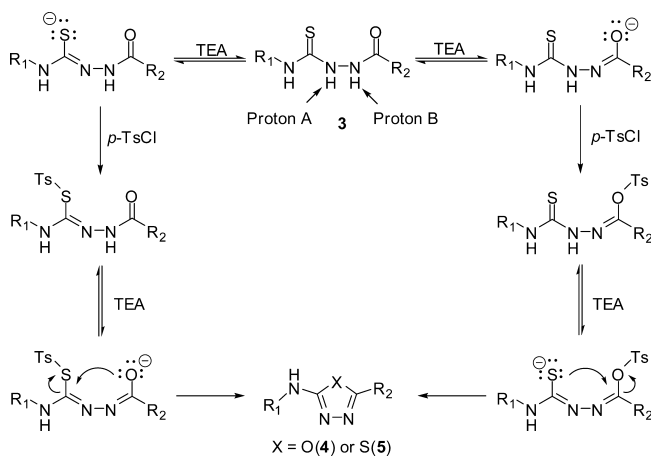
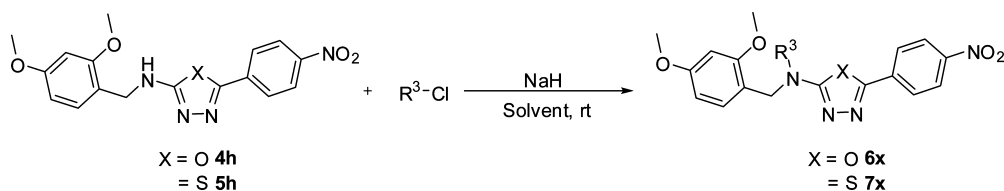


Table 4. *N*-Substitution of 1,3,4-Oxadiazole **4h** and 1,3,4-Thiadiazole **5h**^a

| no. | R ³ | time (h) | yield ^b (%) | no. | R ³ | time (h) | yield ^b (%) |
|------------------------|-----------------|----------|------------------------|------------------------|-----------------|----------|------------------------|
| 6a ^c | benzyl | 8 | 87 | 7a ^c | benzyl | 8 | 80 |
| 6b ^d | benzoyl | 1 | 41 | 7b ^d | benzoyl | 1 | 82 |
| 6c ^d | <i>p</i> -tosyl | 1 | 60 | 7c ^d | <i>p</i> -tosyl | 1 | 97 |

^aReaction condition: 2-amino-1,3,4-oxadiazole **4h** was treated with 1.2 equiv of electrophiles and 1.2 equiv of NaH (60% dispersion in mineral oil) in solvent. ^bYield is obtained yield after column chromatography. ^cReaction was mediated in NMP. ^dReaction was mediated in THF.

Table 3) showed high regioselectivity for 2-amino-1,3,4-oxadiazole **4l**. To increase the regioselectivity for 2-amino-1,3,4-thiadiazole **5** with phenylisothiocyanate, we introduced an electron-withdrawing group to acylhydrazide and an electron-donating group to phenylisothiocyanate (entry 13 of Table 3). In this case, we generated 2-amino-1,3,4-thiadiazole **5m** in high regioselectivity and high yields. The proposed mechanism is shown in Scheme 2. According to our study, the regioselectivity depends on the pK_a of amine which can be affected by R₁ and R₂. At entry 9 in Table 3, the phenyl group on the R₁ position acted as an electron-withdrawing group and decreased the pK_a of proton A as you can see in Scheme 2. It caused increasing of regioselectivity for 2-amino-1,3,4-oxadiazole **4** (entries 9–12 of Table 3).

Next, to explore the diversity of this methodology, various electrophiles were used to generate 2-amino-substituted 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives from 2-amino-1,3,4-oxadiazole **4h** and 2-amino-1,3,4-thiadiazole **5h** core skeletons (Table 4). Alkylation reactions with benzylchloride gave high yields (Table 4, nos. **6a** and **7a**). We then introduced various electrophiles to the 2-amino-1,3,4-oxadiazole **4h** and 2-amino-1,3,4-thiadiazole **5h** with acid chlorides and sulfonyl chlorides. Generally, *N*-acylation and sulfonylation reaction can occur with simple organic bases such as TEA and pyridine. However, in the case of our experiment, it was not going well because of its low nucleophilicity. So we used NaH, which is a strong inorganic base, and then we obtained the desired substituted products **6b**, **6c**, **7b**, and **7c**, respectively, in good yields, as shown in Table 4.

In summary, an efficient regioselective synthesis method has been developed for the synthesis of 2-amino-substituted 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives. The thiosemicarbazides **3**, which serve as useful intermediates in this process, are generated by reaction of the isothiocyanate starting material with acylhydrazides. Regioselective cyclization reactions of the resulting intermediate successfully give the 2-amino-1,3,4-oxadiazole and 1,3,4-thiadiazole core skeletons as the key step, culminating in reagent-based, skeletal diversity-oriented synthesis. The resulting 2-amino-1,3,4-oxadiazole and 1,3,4-thiadiazole core skeletons are subjected to various substitution reactions with alkyl halides, acid chlorides, and sulfonyl chlorides to afford various druglike 2-amino-substituted 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives. In further work, we will carry out this methodology on the solid-phase with a backbone amide linker (BAL) to construct a 1,3,4-oxadiazole and 1,3,4-thiadiazole library.

EXPERIMENTAL SECTION

General Procedure for Synthesis. All chemicals were reagent grade and used as purchased. Reactions were monitored by thin-layer chromatography (TLC). Flash column chromatography was carried out on silica gel (230–400 mesh). ¹H NMR and ¹³C NMR spectra were recorded in δ units relative to deuterated solvent as an internal reference using a 400-MHz NMR instrument. LC/MS analysis was performed on an electrospray ionization (ESI) mass spectrometer with photodiode-array detector (PDA) detection. High-resolution MS spectra were obtained using a time-of-flight LC/MS system.

Representative Procedure for the Preparation of Thiosemicarbazide (3a–3h). Benzyl-isothiocyanate **1a** (358 mg, 2.40 mmol) was added to a stirred solution of benzoylhydrazide **2a** (272 mg, 2.00 mmol) and triethylamine (202 mg, 2.00 mmol) in 10 mL of THF. The reaction mixture was stirred at room temperature for 16 h, and then the solvents were removed via a rotary evaporator. The residue was triturated with diethyl ether/ethyl acetate (95:5) to afford 543 mg (95% yield, white solid) of the desired thiosemicarbazide **3a**. ¹H NMR (400 MHz, DMSO) δ 10.64–10.29 (s, 1H), 9.62–9.22 (s, 1H), 8.86–8.45 (s, 1H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.63–7.54 (m, 1H), 7.50 (d, *J* = 7.7 Hz, 2H), 7.36–7.27 (m, 4H), 7.26–7.14 (m, 1H), 4.75 (d, *J* = 5.9 Hz, 2H). Mp 193–195 °C. LC/MS (ESI): *m/z* = 284.0 [M–1][–].

Representative Procedure for the Preparation of Thiosemicarbazide (3i–3m). Phenyl-isothiocyanate **1i** (324 mg, 2.40 mmol) was added to a stirred solution of benzoylhydrazide **2i** (272 mg, 2.00 mmol) in 1 mL of DMSO. The reaction mixture was stirred at room temperature for 4 h. Distilled water (2 mL) was added to a reaction mixture at 0 °C and then filtered to afford a white solid. The solid was triturated with diethyl ether/ethyl acetate (95:5) to afford 504 mg (93% yield, white solid) of the desired thiosemicarbazide **3i**. ¹H NMR (400 MHz, DMSO) δ 10.55 (s, 1H), 9.83 (s, 1H), 9.74 (s, 1H), 7.97–7.94 (d, *J* = 6 Hz, 2H), 7.59–7.11 (m, 8H). Mp 166–168 °C. LC/MS (ESI): *m/z* = 270.0 [M–1][–].

Representative Procedure for the Preparation of 2-Amino-1,3,4-oxadiazole (4a–4m). EDC·HCl (115 mg, 0.6 mmol) was added to a stirred solution of thiosemicarbazide **3a** (143 mg, 0.50 mmol) in 1 mL of DMSO. The reaction mixture was stirred at 60 °C for 2 h and extracted with dichloromethane (DCM, 15 mL) and distilled water (10 mL), after which the aqueous layer was removed. The aqueous layer was back-extracted with DCM (3 × 10 mL). The combined organic layers were dried over MgSO₄ and evaporated to afford the crude product, which was purified by column chromatography on silica gel (hexane/THF) to afford 124 mg (99% yield, white solid) of the desired 2-amino-1,3,4-oxadiazole **4a**. ¹H NMR (400 MHz, CDCl₃) δ 7.94–7.86 (m, 2H), 7.51–7.28 (m, 8H), 5.05 (s, 1H), 4.62 (d, *J* = 5.7 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 163.3, 159.3, 137.4, 130.6, 128.9, 128.9, 128.1, 127.8, 125.9, 124.5, 47.8. Mp 177–179 °C. LC/MS (ESI): *m/z* = 250.0 [M–1][–].

***N*-Benzyl-5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine (4b).** Yield, 82% (115 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 8.23 (s, 1H), 7.74 (d, *J* = 8.9 Hz, 2H), 7.44–7.23 (m, 5H), 7.08 (d, *J* = 8.9 Hz, 2H), 4.44 (d, *J* = 6.2 Hz, 2H), 3.82 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 163.8, 161.4, 158.2, 139.3, 128.9, 127.9, 127.6, 127.4,

117.2, 115.2, 55.9, 46.6. Mp 166–167 °C. LC/MS (ESI): $m/z = 280.0$ [M–1][–]. HRMS (ESI): m/z [M+1]⁺ calcd for C₁₆H₁₅N₃O₂, 282.1243; found, 282.1245.

N-Benzyl-5-(4-fluorophenyl)-1,3,4-oxadiazol-2-amine (4c). Yield, 91% (122 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 8.34 (t, *J* = 6.1 Hz, 1H), 7.91–7.81 (m, 2H), 7.47–7.21 (m, 7H), 4.46 (d, *J* = 6.1 Hz, 2H). ¹³C NMR (101 MHz, DMSO) δ 169.0, 163.2 (d, ¹J_{CF} = 248.5 Hz), 155.6, 139.0, 129.0 (d, ³J_{CF} = 9.1 Hz), 128.9, 128.0, 127.9 (d, ⁴J_{CF} = 3.0 Hz), 127.6, 116.7 (d, ²J_{CF} = 22.2 Hz), 48.52. Mp 170–173 °C. LC/MS (ESI): $m/z = 268.0$ [M–1][–].

N-Benzyl-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (4d). Yield, 78% (115 mg, yellow solid). ¹H NMR (400 MHz, DMSO) δ 8.62 (t, *J* = 6.2 Hz, 1H), 8.37 (d, *J* = 9.0 Hz, 2H), 8.05 (d, *J* = 9.0 Hz, 2H), 7.43–7.25 (m, 5H), 4.50 (d, *J* = 6.2 Hz, 2H). ¹³C NMR (101 MHz, DMSO) δ 164.8, 157.0, 148.5, 139.0, 130.1, 128.9, 127.9, 127.7, 126.6, 125.1, 46.6. Mp 190–193 °C. LC/MS (ESI): $m/z = 295.0$ [M–1][–].

N-(4-Methoxybenzyl)-5-phenyl-1,3,4-oxadiazol-2-amine (4e). Yield, 69% (97 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 8.25 (t, *J* = 6.1 Hz, 1H), 7.86–7.77 (m, 2H), 7.57–7.49 (m, 3H), 7.32 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.38 (d, *J* = 6.1 Hz, 2H), 3.74 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 164.1, 159.0, 158.1, 131.2, 130.9, 129.7, 129.3, 125.6, 124.7, 114.2, 55.6, 46.1. Mp 182–185 °C. LC/MS (ESI): $m/z = 280.0$ [M–1][–]. HRMS (ESI): m/z [M+1]⁺ calcd for C₁₆H₁₅N₃O₂, 282.1243; found, 282.1252.

5-Phenyl-N-(4-(trifluoromethyl)benzyl)-1,3,4-oxadiazol-2-amine (4f). Yield, 51% (81 mg, white solid). ¹H NMR (400 MHz, CDCl₃) δ 7.92–7.85 (m, 2H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.48–7.40 (m, 3H), 5.31 (s, 1H), 4.69 (d, *J* = 2.9 Hz, 2H). ¹³C NMR (101 MHz, DMSO) δ 164.0, 158.4, 144.1, 131.0, 129.7, 128.5, 128.3 (q, ²J_{CF} = 31.3 Hz), 125.7 (q, ³J_{CF} = 3.0 Hz), 125.7, 124.7 (q, ¹J_{CF} = 273.1 Hz) 124.7, 46.1. Mp 192–195 °C. LC/MS (ESI): $m/z = 318.0$ [M–1][–]. HRMS (ESI): m/z [M+1]⁺ calcd for C₁₆H₁₂F₃N₃O, 320.1011; found, 320.1012.

N-Ethyl-5-phenyl-1,3,4-oxadiazol-2-amine (4g). Yield, 99% (94 mg, white solid). ¹H NMR (400 MHz, CDCl₃) δ 7.97–7.83 (m, 2H), 7.52–7.39 (m, 3H), 5.20 (s, 1H), 3.57–3.42 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 163.5, 159.0, 130.4, 128.8, 125.8, 124.6, 38.6, 15.1. Mp 122–126 °C. LC/MS (ESI): $m/z = 187.9$ [M–1][–].

N-(2,4-Dimethoxybenzyl)-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (4h). Yield, 80% (143 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 8.41–8.29 (m, 3H), 8.04 (d, *J* = 9.0 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 1H), 6.50 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.38 (d, *J* = 5.9 Hz, 2H), 3.81 (s, 3H), 3.75 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 164.8, 160.6, 158.4, 156.8, 148.5, 130.2, 129.9, 126.5, 125.1, 118.5, 104.8, 98.8, 56.0, 55.7, 41.5. Mp 182–184 °C. LC/MS (ESI): $m/z = 355.0$ [M–1][–]. HRMS (ESI), m/z [M+1]⁺ calcd for C₁₇H₁₆N₄O₅, 357.1199; found, 357.1200.

N,5-Diphenyl-1,3,4-oxadiazol-2-amine (4i). Yield, 94% (112 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 10.68 (s, 1H), 8.01–7.86 (m, 2H), 7.72–7.51 (m, 5H), 7.38 (t, *J* = 7.9 Hz, 2H), 7.02 (t, *J* = 7.3 Hz, 1H). ¹³C NMR (101 MHz, DMSO) δ 160.4, 158.2, 139.1, 131.4, 129.8, 129.6, 126.0, 124.4, 122.4, 117.6. Mp 213–216 °C. LC/MS (ESI): $m/z = 236.0$ [M–1][–].

N-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (4j). Yield, 72% (96 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 7.96–7.83 (m, 2H), 7.65–7.49 (m, 5H), 6.96 (d, *J* = 9.0 Hz, 2H), 3.74 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 160.7, 158.0, 155.0, 132.4, 131.3, 129.8, 125.9, 124.5, 119.1, 114.8, 55.7. Mp 211–215 °C. LC/MS (ESI): $m/z = 266.0$ [M–1][–].

N-(4-Fluorophenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (4k). Yield, 96% (123 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 10.70 (s, 1H), 7.98–7.84 (m, 2H), 7.70–7.53 (m, 5H), 7.30–7.11 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 160.4, 158.2, 157.8 (¹J_{CF} = 238.4 Hz), 135.5 (⁴J_{CF} = 2.0 Hz), 131.4, 129.8, 126.0, 124.3, 119.1 (³J_{CF} = 8.1 Hz), 116.1 (²J_{CF} = 23.2 Hz). Mp 244–247 °C. LC/MS (ESI): $m/z = 254.0$ [M–1][–]. HRMS (ESI): m/z [M+1]⁺ calcd for C₁₄H₁₀FN₃O, 256.0886; found, 256.0897.

N-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (4l). Yield, 87% (123 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 11.54 (s, 1H), 8.30 (d, *J* = 9.2 Hz, 2H), 7.98–7.90 (m, 2H), 7.83 (d, *J* = 9.2 Hz, 2H), 7.64–7.55 (m, 3H). ¹³C NMR (101 MHz, DMSO) δ 159.7, 159.1, 145.3, 141.7, 131.8, 129.9, 126.3, 126.0, 124.0, 117.4. Mp 263–266 °C. LC/MS (ESI): $m/z = 281.0$ [M–1][–].

N-(4-Methoxyphenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (4m). Yield, 74% (116 mg, orange solid). ¹H NMR (400 MHz, DMSO) δ 10.63 (s, 1H), 8.40 (d, *J* = 8.9 Hz, 2H), 8.11 (d, *J* = 8.9 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 3.75 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 161.4, 156.8, 155.2, 148.8, 132.0, 123.0, 127.0, 125.1, 119.4, 114.9, 55.7. Mp 270–272 °C. LC/MS (ESI): $m/z = 311.0$ [M–1][–].

Representative Procedure for the Preparation of 2-Amino-1,3,4-thiadiazole (5a–5h). *p*-TsCl (114 mg, 0.60 mmol) was added to a stirred solution of thiosemicarbazide **3a** (143 mg, 0.50 mmol) and triethylamine (111 mg, 1.10 mmol) in 4 mL of NMP. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with DCM (15 mL) and distilled water (10 mL), and then the aqueous layer was removed. The aqueous layer was back-extracted with DCM (3 × 10 mL). The combined organic layers were dried over MgSO₄ and evaporated to afford the crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford 123 mg (92% yield, white solid) of the desired 2-amino-1,3,4-thiadiazole **5a**. ¹H NMR (400 MHz, CDCl₃) δ 7.82–7.76 (m, 2H), 7.43–7.31 (m, 8H), 5.72 (s, 1H), 4.60 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 169.5, 158.4, 137.0, 131.0, 123.0, 128.9, 128.9, 128.1, 127.8, 126.9, 50.8. Mp 179–181 °C. LC/MS (ESI): $m/z = 266.0$ [M–1][–].

N-Benzyl-5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-amine (5b). Yield, 81% (120 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 8.34 (t, *J* = 5.8 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.45–7.22 (m, 5H), 7.02 (d, *J* = 8.9 Hz, 2H), 4.53 (d, *J* = 5.8 Hz, 2H), 3.81 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 168.3, 160.9, 156.6, 139.1, 128.9, 128.3, 128.0, 127.6, 123.9, 115.0, 55.8, 48.5. Mp 165–167 °C. LC/MS (ESI): $m/z = 295.9$ [M–1][–].

N-Benzyl-5-(4-fluorophenyl)-1,3,4-thiadiazol-2-amine (5c). Yield, 87% (124 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 8.45 (t, *J* = 5.8 Hz, 1H), 7.87–7.75 (m, 2H), 7.45–7.24 (m, 7H), 4.55 (d, *J* = 5.7 Hz, 2H). ¹³C NMR (101 MHz, DMSO) δ 169.0, 163.2 (¹J_{CF} = 248.5 Hz), 155.6, 139.0, 119.9 (³J_{CF} = 9.1 Hz), 128.9, 128.0, 127.9 (⁴J_{CF} = 3.0 Hz), 127.6, 116.7 (²J_{CF} = 22.2 Hz); 48.5. Mp 172–174 °C. LC/MS (ESI): $m/z = 284.0$ [M–1][–]. HRMS (ESI): m/z [M+1]⁺ calcd for C₁₅H₁₂FN₃S, 286.0814; found, 286.0824.

N-Benzyl-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (5d). Yield, 63% (98 mg, yellow solid). ¹H NMR (400 MHz, DMSO) δ 8.74 (t, *J* = 5.7 Hz, 1H), 8.30 (d, *J* = 8.9 Hz, 2H), 8.02 (d, *J* = 8.9 Hz, 2H), 7.46–7.24 (m, 5H), 4.59 (d, *J* = 5.8 Hz, 2H). ¹³C NMR (101 MHz, DMSO) δ 170.2, 154.5, 148.0, 138.7, 137.1, 128.9, 128.1, 127.8, 127.6, 124.9, 48.6. Mp 198–200 °C. LC/MS (ESI): $m/z = 310.9$ [M–1][–].

N-(4-Methoxybenzyl)-5-phenyl-1,3,4-thiadiazol-2-amine (5e). Yield, 73% (109 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 8.39 (t, *J* = 5.6 Hz, 1H), 7.80–7.70 (m, 2H), 7.51–7.39 (m, 3H), 7.33 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 4.47 (d, *J* = 5.6 Hz, 2H), 3.74 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 173.6, 163.8, 161.3, 136.1, 135.6, 134.9, 134.4, 134.2, 131.5, 119.0, 60.3, 52.9. Mp 128–130 °C. LC/MS (ESI): $m/z = 295.9$ [M–1][–].

5-Phenyl-N-(4-(trifluoromethyl)benzyl)-1,3,4-thiadiazol-2-amine (5f). Yield, 67% (112 mg, white solid). ¹H NMR (400 MHz, DMSO) δ 8.57 (t, *J* = 5.9 Hz, 1H), 7.81–7.70 (m, 4H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.51–7.41 (m, 3H), 4.66 (d, *J* = 5.6 Hz, 2H). ¹³C NMR (101 MHz, DMSO) δ 168.7, 157.1, 144.1, 131.2, 130.2, 129.6, 128.6, 126.9, 128.2 (²J_{CF} = 31.3 Hz), 125.7 (³J_{CF} = 3.8 Hz), 124.8 (¹J_{CF} = 273.7 Hz), 47.9. Mp 153–155 °C. LC/MS (ESI): $m/z = 333.9$ [M–1][–]. HRMS (ESI): m/z [M+1]⁺ calcd for C₁₆H₁₂F₃N₃S, 336.0782; found, 336.0782.

N-Ethyl-5-phenyl-1,3,4-thiadiazol-2-amine (5g). Yield, 94% (96 mg, white solid). ¹H NMR (400 MHz, CDCl₃) δ 7.89–7.76 (m, 2H), 7.49–7.37 (m, 3H), 5.78 (s, 1H), 3.46 (q, *J* = 7.2 Hz, 2H),

1.38 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.0, 157.7, 131.1, 129.8, 128.9, 126.8, 42.1, 14.7; mp 175–178 °C. LC/MS (ESI): $m/z = 204.1$ [$\text{M}-1$] $^-$.

N-(2,4-Dimethoxybenzyl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (5h). Yield, 87% (162 mg, white solid). ^1H NMR (400 MHz, DMSO) δ 8.46 (s, 1H), 8.30 (d, $J = 8.9$ Hz, 2H), 8.02 (d, $J = 8.9$ Hz, 2H), 7.24 (d, $J = 8.3$ Hz, 1H), 6.60 (d, $J = 2.3$ Hz, 1H), 6.51 (dd, $J = 8.3, 2.4$ Hz, 1H), 4.45 (d, $J = 5.5$ Hz, 2H), 3.83 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.1, 160.7, 158.6, 154.1, 147.9, 137.2, 130.2, 127.6, 124.9, 118.2, 104.9, 98.9, 56.0, 55.7, 43.8. Mp 213–217 °C. LC/MS (ESI): $m/z = 371.0$ [$\text{M}-1$] $^-$. HRMS (ESI): m/z [$\text{M}+1$] $^+$ calcd for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_5$, 373.0971; found, 373.0959.

Representative Procedure for the Preparation of 2-amino-1,3,4-thiadiazole (5i–5m). *p*-TsCl (114 mg, 0.60 mmol) was added to a stirred solution of thiosemicarbazide **3i** (136 mg, 0.50 mmol) and triethylamine (111 mg, 1.10 mmol) in 4 mL of NMP. The reaction mixture was stirred at room temperature for 2 h and extracted with DCM (15 mL) and distilled water (10 mL), after which the aqueous layer was removed. The aqueous layer was back-extracted with DCM (3 \times 10 mL). The combined organic layers were dried over MgSO_4 and evaporated to afford the crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford 107 mg of a mixture of 2-amino-1,3,4-oxadiazole and 2-amino-1,3,4-thiadiazole. The mixture was separated by preparative TLC to confirm the authenticity of the desired 2-amino-1,3,4-thiadiazole **5i**. Yield, 40% (yield is determined by NMR integration of mixture, white solid). ^1H NMR (400 MHz, CDCl_3) δ 9.30 (s, 1H), 7.96–7.82 (m, 2H), 7.51–7.37 (m, 7H), 7.18–7.09 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 169.1, 151.0, 135.0, 130.8, 129.8, 129.8, 129.2, 129.0, 128.7, 126.3. Mp 279–283 °C. LC/MS (ESI): $m/z = 252.0$ [$\text{M}-1$] $^-$.

N-(4-Methoxyphenyl)-5-phenyl-1,3,4-thiadiazol-2-amine (5j). Yield, 53% (yield is determined by NMR integration of mixture, white solid). ^1H NMR (400 MHz, CDCl_3) δ 7.83 (dd, $J = 6.9, 1.9$ Hz, 2H), 7.47–7.40 (m, 3H), 7.39–7.32 (m, 2H), 6.95 (d, $J = 8.7$ Hz, 2H), 3.83 (t, $J = 2.1$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.3, 159.9, 151.1, 130.7, 130.3, 129.0, 128.6, 127.6, 126.4, 114.9, 55.8. Mp 227–229 °C. LC/MS (ESI): $m/z = 282.0$ [$\text{M}-1$] $^-$.

N-(4-Fluorophenyl)-5-phenyl-1,3,4-thiadiazol-2-amine (5k). Yield, 44% (yield is determined by NMR integration of mixture, white solid). ^1H NMR (400 MHz, CDCl_3) δ 9.34 (s, 1H), 7.88–7.82 (m, 2H), 7.48–7.41 (m, 5H), 7.15–7.08 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 169.1, 162.5 (d, $^1J_{\text{CF}} = 248.0$ Hz), 151.1, 131.6 (d, $^3J_{\text{CF}} = 9.4$ Hz), 131.3 (d, $^4J_{\text{CF}} = 3.1$ Hz), 130.8, 129.0, 128.8, 126.2, 116.7 (d, $^2J_{\text{CF}} = 22.6$ Hz). Mp 247–250 °C. LC/MS (ESI): $m/z = 269.9$ [$\text{M}-1$] $^-$.

N-(4-Methoxyphenyl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (5m). Yield, 84% (yield is determined by NMR integration of mixture, white solid). ^1H NMR (400 MHz, DMSO) δ 10.59 (s, 1H), 8.31 (d, $J = 8.9$ Hz, 2H), 8.08 (d, $J = 8.9$ Hz, 2H), 7.57 (d, $J = 9.0$ Hz, 2H), 6.97 (d, $J = 9.0$ Hz, 2H), 3.75 (s, $J = 4.0$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.6, 155.5, 155.0, 148.1, 136.7, 1334.1, 127.9, 124.9, 120.2, 114.8, 55.7. Mp 238–242 °C. LC/MS (ESI): $m/z = 326.9$ [$\text{M}-1$] $^-$. HRMS (ESI): m/z [$\text{M}+1$] $^+$ calcd for $\text{C}_{15}\text{H}_{12}\text{N}_4\text{O}_5$, 329.0708; found, 329.0710.

Representative Procedure for the Preparation of N-Benzyl-N-(2,4-dimethoxybenzyl)-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (6a). Benzyl chloride (46 mg, 0.36 mmol) was added to a stirred solution of 2-amino-1,3,4-oxadiazole **4h** (107 mg, 0.3 mmol) and NaH (14.4 mg, 0.36 mmol, 60% dispersion in mineral oil) in 1 mL of NMP. The reaction mixture was stirred at room temperature for 8 h. The reaction mixture was extracted with ethyl acetate (10 mL) and distilled water (5 mL), and then the aqueous layer was removed. The aqueous layer was back-extracted with ethyl acetate (3 \times 5 mL). The combined organic layers were washed with brine (5 mL) and then dried over MgSO_4 . The organic layers were evaporated to afford the crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford 116 mg (87% yield, yellow oil) of the desired *N*-benzyl-*N*-(2,4-dimethoxybenzyl)-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine **6a**. ^1H NMR (400 MHz, DMSO) δ 8.35 (d, $J = 8.8$ Hz, 2H), 8.09 (d, $J = 8.8$ Hz, 2H), 7.38–7.26 (m, 5H), 7.22 (d,

$J = 8.3$ Hz, 1H), 6.56 (d, $J = 2.1$ Hz, 1H), 6.50 (dd, $J = 8.3, 2.1$ Hz, 1H), 4.65 (s, 2H), 4.57 (s, 2H), 3.74 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 165.3, 161.0, 158.9, 157.2, 148.5, 137.2, 131.0, 130.1, 129.0, 128.0, 127.9, 126.6, 125.0, 116.3, 105.1, 98.2, 55.9, 55.7, 51.8, 47.2. LC/MS (ESI): $m/z = 447.0$ [$\text{M}+1$] $^+$. HRMS (ESI): m/z [$\text{M}+1$] $^+$ calcd for $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_5$, 447.1668; found, 447.1667.

Representative Procedure for the Preparation of N-Benzyl-N-(2,4-dimethoxybenzyl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (7a). Benzyl chloride (46 mg, 0.36 mmol) was added to a stirred solution of 2-amino-1,3,4-thiadiazole **5h** (112 mg, 0.3 mmol) and NaH (14.4 mg, 0.36 mmol, 60% dispersion in mineral oil) in 1 mL of NMP. The reaction mixture was stirred at room temperature for 8 h. The reaction mixture was extracted with ethyl acetate (10 mL) and distilled water (5 mL), and then the aqueous layer was removed. The aqueous layer was back-extracted with ethyl acetate (3 \times 5 mL). The combined organic layers were washed with brine (5 mL) and then dried over MgSO_4 . The organic layers were evaporated to afford the crude yellow solid. The crude yellow solid was triturated with diethyl ether/ethyl acetate (95:5) to afford 111 mg (80% yield, yellow solid) of desired *N*-benzyl-*N*-(2,4-dimethoxybenzyl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine **7a**. ^1H NMR (400 MHz, DMSO) δ 8.29 (d, $J = 8.8$ Hz, 4H), 8.00 (d, $J = 8.8$ Hz, 4H), 7.37–7.25 (m, 11H), 7.16 (d, $J = 8.3$ Hz, 2H), 6.59 (d, $J = 2.2$ Hz, 2H), 6.50 (dd, $J = 8.3, 2.3$ Hz, 2H), 4.80 (s, 4H), 4.65 (s, 4H), 3.77 (s, 6H), 3.75 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 192.3, 172.3, 161.0, 158.9, 154.8, 147.9, 136.9, 130.5, 129.0, 127.9, 127.8, 127.5, 124.9, 115.6, 105.0, 99.0, 55.9, 55.7, 55.2, 52.1. Mp 176–178 °C. LC/MS (ESI): $m/z = 463.0$ [$\text{M}+1$] $^+$. HRMS (ESI): m/z [$\text{M}+1$] $^+$ calcd for $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_5$, 463.1440; found, 463.1441.

Representative Procedure for the Preparation of N-(2,4-Dimethoxybenzyl)-N-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-benzamide (6b). Benzoyl chloride (51 mg, 0.36 mmol) was added to a stirred solution of 2-amino-1,3,4-oxadiazole **4h** (107 mg, 0.3 mmol) and NaH (14.4 mg, 0.36 mmol, 60% dispersion in mineral oil) in 6 mL of THF. The reaction mixture was stirred at room temperature for 1 h and extracted with ethyl acetate (10 mL) and distilled water (5 mL), after which the aqueous layer was removed. The aqueous layer was back-extracted with ethyl acetate (3 \times 5 mL). The combined organic layers were washed with brine (5 mL) and then dried MgSO_4 . The organic layers were evaporated to afford the crude pale yellow solid. The crude pale yellow solid was triturated with diethyl ether/ethyl acetate (95:5) to afford 57 mg (41% yield, pale yellow solid) of desired *N*-(2,4-dimethoxybenzyl)-*N*-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-benzamide **6b**. ^1H NMR (400 MHz, DMSO) δ 8.39 (d, $J = 8.9$ Hz, 2H), 8.00 (d, $J = 8.8$ Hz, 2H), 7.55–7.47 (m, 3H), 7.45–7.33 (m, 3H), 6.58–6.50 (m, 2H), 5.09 (s, 2H), 3.75 (s, 3H), 3.58 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.2, 161.8, 161.3, 161.0, 158.7, 149.7, 134.6, 132.1, 131.4, 129.1, 128.8, 128.1, 127.8, 125.2, 116.0, 105.2, 98.7, 55.9, 55.7, 47.5. Mp 166–168 °C. LC/MS (ESI): $m/z = 461.0$ [$\text{M}+1$] $^+$. HRMS (ESI): m/z [$\text{M}+1$] $^+$ calcd for $\text{C}_{24}\text{H}_{21}\text{N}_4\text{O}_6$, 461.1461; found, 461.1477.

N-(2,4-Dimethoxybenzyl)-N-(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)benzamide (7b). Yield, 82% (117 mg, pale yellow solid). ^1H NMR (400 MHz, DMSO) δ 8.36 (d, $J = 8.6$ Hz, 2H), 8.24 (d, $J = 8.8$ Hz, 2H), 7.67–7.49 (m, 5H), 7.07 (d, $J = 8.4$ Hz, 1H), 6.48 (d, $J = 2.2$ Hz, 1H), 6.43 (dd, $J = 8.4, 2.2$ Hz, 1H), 5.30 (s, 2H), 3.70 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 171.1, 161.8, 161.0, 160.5, 158.1, 148.8, 136.3, 133.8, 131.8, 129.7, 129.0, 128.6, 127.9, 125.0, 116.0, 104.9, 98.8, 55.7, 55.6, 49.8. Mp 178–180 °C. LC/MS (ESI): $m/z = 477.0$ [$\text{M}+1$] $^+$. HRMS (ESI): m/z [$\text{M}+1$] $^+$ calcd for $\text{C}_{24}\text{H}_{21}\text{N}_4\text{O}_5$, 477.1233; found, 477.1240.

Representative Procedure for the Preparation of N-(2,4-Dimethoxybenzyl)-4-methyl-N-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (6c). *p*-TsCl (69 mg, 0.36 mmol) was added to a stirred solution of 2-amino-1,3,4-oxadiazole **4h** (107 mg, 0.3 mmol) and NaH (14.4 mg, 0.36 mmol, 60% dispersion in mineral oil) in 6 mL of THF. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with ethyl acetate (10 mL) and distilled water (5 mL), and then the aqueous layer was removed. The aqueous layer was back-extracted with ethyl

acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and then dried over MgSO₄. The organic layers were evaporated to afford the crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford 92 mg (60% yield, pale yellow solid) of the desired *N*-(2,4-dimethoxybenzyl)-4-methyl-*N*-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)benzenesulfonamide **6c**. ¹H NMR (400 MHz, DMSO) δ 8.43 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 1H), 6.47 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.43 (d, *J* = 2.4 Hz, 1H), 4.97 (s, 2H), 3.73 (s, 3H), 3.48 (s, 3H), 2.42 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 161.4, 159.7, 158.7, 149.7, 145.6, 135.0, 131.4, 130.3, 128.8, 128.4, 127.9, 125.3, 125.2, 114.8, 105.0, 98.7, 55.8, 55.7, 50.0, 21.5. Mp 108–112 °C. LC/MS (ESI): *m/z* = 511.0 [M+1]⁺. HRMS (ESI): *m/z* [M+1]⁺ calcd for C₂₄H₂₃N₄O₇S, 511.1287; found, 511.1294.

***N*-(2,4-Dimethoxybenzyl)-4-methyl-*N*-(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)benzenesulfonamide (7c)**. Yield, 97% (153 mg, pale yellow solid). ¹H NMR (400 MHz, DMSO) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.19 (d, *J* = 9.2 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.46 (dd, *J* = 12.0, 2.4 Hz, 1H), 5.10 (s, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 2.51 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 163.5, 163.0, 161.0, 158.4, 149.1, 146.1, 135.5, 134.2, 130.8, 129.3, 128.8, 127.7, 124.9, 115.4, 105.1, 98.8, 55.9, 55.6, 48.8, 21.5. Mp 143–146 °C. LC/MS (ESI): *m/z* = 526.9 [M+1]⁺. HRMS (ESI): *m/z* [M+1]⁺ calcd for C₂₄H₂₃N₄O₆S₂, 527.1059; found, 527.1061.

■ ASSOCIATED CONTENT

● Supporting Information

Full analytical data of compounds, along with copies of ¹H NMR, ¹³C NMR, LC/MS, and HRMS spectra of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ydgong@dongguk.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by grants from the National Research Foundation of Korea (2010-0004128) funded by the Ministry of Education, Science and Technology, and (2010) by the Ministry of Knowledge Economy, Korea.

■ REFERENCES

- (1) (a) Matin, A.; Gavande, N.; Kim, M. S.; Yang, N. X.; Salam, N. K.; Hanrahan, J. R.; Roubin, R. H.; Hibbs, D. E. *J. Med. Chem.* **2009**, *52*, 6835. (b) Priego, E. M.; Kuenzel, J. V. F. D.; IJzerman, A. P.; Camarasa, M. J.; Perez-Perez, M. J. *J. Med. Chem.* **2002**, *45*, 3337. (c) Galal, S. A.; El-All, A. S. A.; Abdallah, M. M.; El-Diwani, H. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2420. (d) Lahm, G. P.; Stevenson, T. M.; Selby, T. P.; Freudenberg, D. C.; Flexner, L.; Bellin, C. A.; Dubas, C. M.; Smith, B. K.; Hughes, K. A.; Hollingshaus, J. G.; Clark, C. E.; Benner, E. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6274.
- (2) (a) Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1993**, *36*, 1090. (b) Song, Y.; Connor, D. T.; Sercel, A. D.; Sorenson, R. J.; Doubleday, R.; Unangst, P. C.; Roth, B. D.; Beylin, V. G.; Gilbertsen, R. B.; Chan, K.; Schrier, D. J.; Guglietta, A.; Bornemeier, D. A.; Dyer, R. D. *J. Med. Chem.* **1999**, *42*, 1161. (c) Boschelli, D. H.; Connor, D. T.; Bornemeier, D. A.; Dyer, R. D.; Kennedy, J. A.; Kuipers, P. J.; Okonkwo, G. C.; Schrier, D. J.; Wright, C. D. *J. Med. Chem.* **1993**, *36*, 1802.
- (3) (a) El-Emam, A. A.; Al-Deeb, O. A.; Al-Omar, M.; Lehmann, J. *Bioorg. Med. Chem.* **2004**, *12*, 5107. (b) Dogan, H. N.; Duran, A.;

Rollas, S.; Sener, G.; Uysal, M. K.; Gülen, D. *Bioorg. Med. Chem.* **2002**, *10*, 2893.

(4) (a) Chapleo, C. B.; Myers, M.; Myers, P. L.; Saville, J. F.; Smith, A. C. B.; Stillings, M. R.; Tulloch, I. F.; Walter, D. S.; Welbourn, A. P. *J. Med. Chem.* **1986**, *29*, 2273. (b) Chapleo, C. B.; Myers, P. L.; Smith, A. C.; Stillings, M. R.; Tulloch, I. F.; Walter, D. S. *J. Med. Chem.* **1988**, *31*, 7.

(5) (a) Turner, S.; Myers, M.; Gadie, B.; Nelson, A. J.; Pape, R.; Saville, J. F.; Doxey, J. C.; Berridge, T. L. *J. Med. Chem.* **1988**, *31*, 902. (b) Turner, S.; Myers, M.; Gadie, B.; Hale, S. A.; Horsley, A.; Nelson, A. J.; Pape, R.; Saville, J. F.; Doxey, J. C.; Berridge, T. L. *J. Med. Chem.* **1988**, *31*, 907. (c) Tyagi, M.; Kumar, A. *Orient. J. Chem.* **2002**, *18*, 125.

(6) (a) Brain, C. T.; Paul, J. M.; Loong, Y.; Oakley, P. J. *Tetrahedron Lett.* **1999**, *40*, 3275. (b) Rostamizadeh, S.; Housaini, S. A. G. *Tetrahedron Lett.* **2004**, *45*, 8753.

(7) (a) Dolman, S. J.; Gosselin, F.; O'Shea, P. D.; Davies, I. E. *J. Org. Chem.* **2006**, *71*, 9548. (b) Kilburn, J. P.; Lau, J.; Jones, R. C. F. *Tetrahedron Lett.* **2001**, *42*, 2583. (c) Fulop, F.; Semega, E.; Dombi, G.; Bernath, G. *J. Heterocycl. Chem.* **1990**, *27*, 951–955. (d) Kucukguzel, G.; Kocatepe, A.; Clercq, E. D.; Sahin, F.; Gulluce, M. *Eur. J. Med. Chem.* **2006**, *41*, 353. (e) Omar, A. M. E.; Aboulwafa, O. *J. Heterocycl. Chem.* **1984**, *21*, 1415.

(8) (a) Al-Omar, M.; Al-Deeb, O. A.; Al-Khamees, H. A.; El-Emam, A. A. *Phosphorus Sulfur Silicon* **2004**, *179*, 2509. (b) Salgm-Gokesen, U.; Gokhan-Kelekci, N.; Goktas, O.; Koysal, Y.; Kilic, E.; Isik, S.; Aktay, G.; Ozalp, M. *Bioorg. Med. Chem.* **2007**, *15*, 5738. (c) D'sidocky, N. R.; Harris, R. L.; Hegde, S. G.; Hilgraf, R.; McCarrick, M. A.; McKie, J. A.; Mortensen, D. S.; Nadolny, L.; Perin-ninkovic, S. M.; Sapienza, J. J.; Wright, J. L. Amino-substituted Heterocycles, compositions thereof, and methods of treatment there with. U.S. Patent 242694, October 02, 2008.

(9) Aryanassab, F.; Halimehjani, A. Z.; Saidi, M. R. *Tetrahedron Lett.* **2010**, *51*, 790.

(10) (a) Severinsen, R.; Kilburn, J. P.; Lau, J. F. *Tetrahedron* **2005**, *61*, 5565. (b) Baxendale, I. R.; Ley, S. V.; Martinelli, M. *Tetrahedron* **2005**, *61*, 5323.

(11) Zoumpoulakis, P.; Camoutsis, C.; Pairas, G.; Sokovic, M.; Glamoclija, J.; Potamitis, C.; Pitsas, A. *Bio. Med. Chem.* **2012**, *20*, 1569.

(12) (a) Hwang, J. Y.; Choi, H.-S.; Lee, D.-H.; Yoo, S.-e.; Gong, Y.-D. *J. Comb. Chem.* **2005**, *7*, 816. (b) Gong, Y.-D.; Lee, T. H. *J. Comb. Chem.* **2010**, *12*, 393.