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THE SYNTHESIS OF 2-(5-(ARYLOXYMETHYL)-1,3,4-THIADIAZOL-2-YLTHIO)-*N*-ARYLACETAMIDES AT ROOM TEMPERATURE VIA GRINDING

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Fifteen 2-(5-(aryloxymethyl)-1,3,4-thiadiazol-2-ylthio)-N-arylacetamides were efficiently synthesized from the reaction of 2-chloro-N-arylacetamide with 5-(aryloxymethyl)-1,3,4-thiadiazole-2-thiol under solvent-free conditions at room temperature via grinding. The key advantages of the method are the short reaction time, high yields, simple workup, and environmentally friendly conditions compared to conventional heating.

Keywords Acetamides; grinding; synthesis; 1,3,4-thiadiazoles

INTRODUCTION

The 1,3,4-thiadiazole derivatives have attracted continuing interest over the past several years because of their various biological activities.[1–4] In particular, a few various substituted 1,3,4-thiadiazoles have been found to exhibit anticancer, antitumor, and anticonvulsant activities.[5–9] Additionally, a large number of *N*-arylacetamide derivatives have demonstrated anticancer, antibacterial, antifungal, antimalarial, and anti-HIV activities.[10–13] 1,3,4-Thiadiazole and *N*-arylacetamide moieties are perspective scaffolds for the design of drugs. There have been some reports on the synthesis of heterocyclic acetanilides. Shah et al. have completed the preparation of heterocyclic acetanilides by the reaction of 5-(4-acetylanminophenyl)-1,3,4-oxadiazole-2-thione with 2-chloro-*N*-phenylacetamide in an aqueous solution of potassium hydroxide at 80°C for 12 h.[14] Recently, Sahu et al. completed the synthesis of heterocyclic acetanilides by refluxing 4-aminoquinaldine with 2-chloro-*N*-phenylacetamide in dry DMSO for 8 h.[15] More recently, the reaction of 2,3-dihydroimidazo[1,2-b]isoquinolin-5(1H)-one with 2-chloro-*N*-phenylacetamide in DMF

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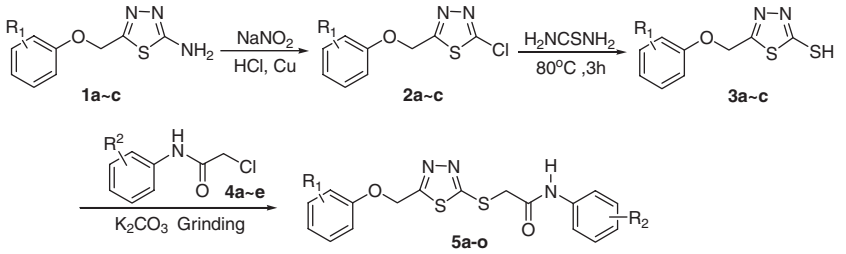
under microwave irradiation to afford heterocyclic acetanilides was also reported.[16] However, in spite of their potential utility in the preparation of these types of compounds, many of these methods involve an organic solvent, long reaction times, and unsatisfactory yields. Furthermore, to the best of our knowledge, there has been no report on the synthesis of heterocyclic acetanilide analogs containing aryoxylmethyl-1,3,4-thiadiazole scaffold under grinding at room temperature. Consequently, a simple and efficient approach for the synthesis of aryoxylmethyl-1,3,4-thiadiazole–functionalized *N*-phenylacetamide was of great interest to our group.

Recently, many solventless organic reactions have been studied.[17] Compared to the reactions in an organic solvent, solventless reactions are often rapid, occur in high yields, and have environmental and economic advantages. Solventless organic reactions based on grinding of two macroscopic particles together mostly involve the formation of a liquid phase prior to reaction, i.e., formation of a eutectic melt of uniform distribution where the reacting components, being in close proximity, are poised to react in a controlled way.

Based on the above background, we have designed and synthesized a series of new compounds containing the 1,3,4-thiadiazole ring and *N*-arylacetamide under grinding at room temperature.



1a: R_1 = H, **1b**: R_1 = 4-CH_3, **1c**: R_1 = 2-Cl;

4a: R_2 = H, **4b**: R_2 = 4-CH_3, **4c**: R_2 = 4-Cl, **4d**: R_2 = 4-NO_2, **4e**: R_2 = 2-NO_2.

Scheme 1

RESULTS AND DISCUSSION

As described in Scheme 1, the starting material 2-amino-5-(aryloxymethyl)-1,3,4-thiadiazoles (**1a–c**) were synthesized according to previously work.[18] In a typical experimental procedure, 2-chloro-5-(aryloxymethyl)-1,3,4-thiadiazoles (**2a**–**c**) were obtained from the reaction of compounds **1a–c** with sodium nitrite in water, in the presence of concentrated hydrochloric acid and metallic copper powder. A mixture of compounds **2a–c** and excess thiourea in ethanol was refluxed to afford compounds **3a–c**. Treatment of compound **3a**, compound **4a**, and K_2CO_3 at room temperature under solventless conditions via grinding afforded compound **5a** in excellent yield (Table II, entry 1) .

To optimize the reaction conditions for the preparation of compound **5**, the reaction of **3a** with **4a** was selected as a model reaction. The reaction time, the nature of the base, and the influence of **3a**:**4a** molar ratios on the yield of the reaction are summarized in Table I. According to these data, the best reaction time is 10 min. We also screened

Table I Influence of reaction time, catalyst, and **3a**:**4a** molar ratio

Entry	Base[a]	Time (min)	**3a**:**4a**	Yield[b] (%)
1	K_2CO_3	10	1:1.1	90
2	K_2CO_3	10	1:1.2	93
3	K_2CO_3	10	1:1.3	93
4	K_2CO_3	5	1:1.2	80
5	K_2CO_3	15	1:1.2	94
6	Na_2CO_3	10	1:1.2	90
7	Cs_2CO_3	10	1:1.2	95
8	KOH	10	1:1.2	85
9	NaOH	10	1:1.2	82

[a]Reaction conditions: base (1 equiv), at room temperature with grinding.
[b]Isolated yields of purified compounds.

different inorganic bases for their ability to catalyze the reaction. Inorganic bases such as K_2CO_3, Na_2CO_3, Cs_2CO_3, KOH, and NaOH all furnished the desired products (Table I). However, salts of carbonate (K_2CO_3, Na_2CO_3, and Cs_2CO_3) were found to be the effective catalysts for this transformation. Taking the above experiment data and the cost of the base into account, we selected K_2CO_3 as a base to promote the reaction using a molar ratio of compounds **3a**:**4a** as 1:1.2 with grinding for 10 min at room temperature.

Under the optimized conditions, 15 compounds (**5a–o**) were efficiently synthesized from the reaction of **3a–c** with **4a–e** under solvent-free conditions at room temperature via grinding (Table II). To compare this procedure with the conventional method, we also carried out these reactions under reflux conditions in ethanol for 2 h and observed that

Table II The synthesis of arylacetamides **5a–o** at room temperature via grinding

				Yield (%)[a]	
Entry	Product	R^1	R^2	Reflux[b]	Grinding[c]
1	**5a**	H	H	85	93
2	**5b**	H	4-CH_3	83	94
3	**5c**	H	4-Cl	86	94
4	**5d**	H	4-NO_2	65	79
5	**5e**	H	2-NO_2	71	74
6	**5f**	4-CH_3	H	83	83
7	**5g**	4-CH_3	4-CH_3	82	87
8	**5h**	4-CH_3	4-Cl	85	93
9	**5i**	4-CH_3	4-NO_2	67	73
10	**5j**	4-CH_3	2-NO_2	62	77
11	**5k**	2-Cl	H	80	89
12	**5l**	2-Cl	4-CH_3	83	92
13	**5m**	2-Cl	4-Cl	85	90
14	**5n**	2-Cl	4-NO_2	60	72
15	**5o**	2-Cl	2-NO_2	65	81

[a]Isolated yield of purified product.
[b]Reaction conditions: **3a** (2 mmol), K_2CO_3 (2 mmol), **4a** (2.4 mmol), in 3 mL ethanol was refluxed for 2 h.
[c]Reaction conditions: **3a** (2 mmol), K_2CO_3 (2 mmol), **4a** (2.4 mmol), at room temperature, grinding for 10 min.

these reactions can also be completed smoothly to afford the desired products (Table II). According to Table II, it is evident that R^1 groups, such as methyl or chlorine, reacted smoothly with 2-chloro-*N*-phenylacetamide to produce high yields of products. However, when R^2 is NO_2, lower yields of the products were witnessed (Table II, entries 4, 5, 9, 10, 14, and 15). The structures of the synthesized compounds **5a–o** were confirmed by elemental analyses and spectroscopic data (^{1}H NMR, ^{13}C NMR, MS, and IR). The yields, physicochemical properties, and the spectroscopic data of the prepared compounds are given in the Experimental section.

The IR spectrum of **5** displayed bands at 3360–3310 cm^{-1} and 1690–1660 cm^{-1} due to −NH− and −C=O stretching frequencies, respectively. The ^{1}H NMR spectrum of **5** exhibited two singlets at δ 4.07 and 5.40, which accounts for four methylene protons attributed to the $-SCH_2-$ and $-OCH_2-$ protons, respectively. Aromatic protons resonated as a multiplet at δ 6.99–7.55 and a singlet at δ 9.46, which accounts for the −NH− proton. The ^{13}C NMR of **5** displayed peaks that account for all the carbon atoms in the molecules.

In conclusion, we have developed a simple and efficient method for the synthesis of 2-(5-(aryloxymethyl)-1,3,4-thiadiazol-2-ylthio)-*N*-arylacetamides derivatives via grinding at room temperature in solvent-free conditions. The mildness of the reaction conditions, experimental simplicity, compatibility with various functional groups, efficient yields, short reaction times, and easy workup make this procedure attractive for the synthesis of a variety of these derivatives.

EXPERIMENTAL

All reagents were obtained commercially and used without further purification. 2-Chloro-*N*-arylacetamide derivatives (**4a–e**) were synthesized according to the methods in the literature.[19] Melting points were determined on an XT-4 electrothermal micromelting-point apparatus and are uncorrected. IR spectra were recorded using KBr pellets on a Digilab Merlin FT-IR spectrophotometer. NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz, respectively, on a Varian Mercury plus-400 instrument using DMSO or $CDCl_3$ as solvent and TMS as internal standard. Mass spectroscopy (MS) spectra were recorded on a Trace DSQ mass spectrometer. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instrument.

General Synthetic Procedure for Compounds (2a–c)

Compound **1a** (2.07 g, 10.0 mmol) was ground with an excess of $NaNO_2$ (2.07 g, 30.0 mmol) and the mixture was introduced in small portions and with stirring into an ice-cooled solution of conc. HCl (30 mL) and water (13 mL) containing Cu powder (0.50 g). The reaction mixture was allowed to reach room temperature and stirred for an additional 4 h then heated to 55°C until the evolution of gas ceased. The reaction mixture was cooled and extracted with $CHCl_3$ (3 × 40 mL). The combined extracts were washed with aqueous dilute H_2SO_4 and aqueous saturated $NaHCO_3$ solution, and then dried over anhydrous $MgSO_4$. The solvent was evaporated to give crude **2a**. The product was recrystallized from ethanol to give 1.4 g of **2a** in 62% yield; mp 54–56°C.

2-Chloro-5-(phenoxymethyl)-1,3,4-thiadiazole (2a). Yield: 62%. Yellow crystal; Mp: 54–56°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.41 (s, 2H, OCH_2), 6.98–7.07 (m, 3H, ArH), 7.19–7.27 (m, 2H, ArH). IR (KBr) ν: 3067, 2924, 2860, 1690, 1594 cm^{-1}. Anal.calcd for $C_9H_7ClN_2OS$: C, 47.69; H, 3.11; N, 12.36. Found: C, 47.83; H, 3.21; N, 12.20.

2-((4-Methylphenoxy)methyl)-5-chloro-1,3,4-thiadiazole (2b). Yield: 81%. Yellow crystal; Mp: 66–68°C. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 2.30$ (s, 3H, CH_3), 5.40 (s, 2H, OCH_2), 6.87 (d, $J = 8.4$ Hz, 2H, ArH), 7.11 (d, $J = 8.0$ Hz, 2H, ArH). IR (KBr) ν: 3067, 2919, 2856, 1614, 1511 cm^{-1}. Anal. calcd for $C_{10}H_9ClN_2OS$: C, 49.90; H, 3.77; N, 11.64. Found: C, 50.07; H, 3.59; N, 11.50.

2-((2-Chlorophenoxy)methyl)-5-chloro-1,3,4-thiadiazole (2c). Yield: 75%. Yellow crystal; Mp: 117–119°C. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 5.42$ (s, 2H, OCH_2), 6.99–7.05 (m, 2H, ArH), 7.08–7.12 (m, 1H, ArH), 7.23–7.28 (m, 1H, ArH). IR (KBr) ν: 3065, 2919, 2857, 1610, 1515 cm^{-1}. Anal. calcd for $C_9H_6Cl_2N_2OS$: C, 41.40; H, 2.32; N, 10.73. Found: C, 41.21; H, 2.43; N, 10.55.

General Synthetic Procedure for Compounds (3a–c)

A mixture of **2a** (2.27 g, 10 mmol) and excess thiourea (2.34 g, 30 mmol) in 20 mL ethanol was refluxed for 3 h. After cooling, conc. HCl (3 mL) and water (20 mL) were added, and the solids isolated by filtration were washed with water and recrystallized from EtOH-H_2O giving 1.9 g **3a** in 85% yield; mp 123–124°C.

5-(Phenoxymethyl)-1,3,4-thiadiazole-2-thiol (3a). Yield: 85%. Yellow crystal; Mp: 123–124°C. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 5.42$ (s, 2H, OCH_2), 6.99–7.09 (m, 3H, ArH), 7.19–7.25 (m, 2H, ArH), 14.75 (s, 1H, SH). IR (KBr) ν: 3107, 1710, 1591 cm^{-1}. Anal. calcd for $C_9H_8N_2OS_2$: C, 48.19; H, 3.95; N, 12.49. Found: C, 48.08; H, 4.08; N, 12.35.

5-((4-Methylphenoxy)methyl)-1,3,4-thiadiazole-2-thiol (3b). Yield: 89%. Brown crystal; Mp: 155–157°C ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 2.23$(s, 3H, CH_3), 5.41 (s, 2H, OCH_2), 6.86 (d, $J = 8.4$ Hz, 2H, ArH), 7.11 (d, $J = 8.0$ Hz, 2H, ArH), 14.76 (s, 1H, SH). IR (KBr) ν: 3108, 1708, 1590 cm^{-1}. Anal. calcd for $C_{10}H_{10}N_2OS_2$: C, 50.40; H, 4.23; N, 11.72. Found: C, 50.58; H, 4.36; N, 11.60.

5-((2-Chlorophenoxy)methyl)-1,3,4-thiadiazole-2-thiol (3c). Yield: 85%. Brown crystal; Mp: 184–186°C. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 5.42$ (s, 2H, OCH_2), 6.98–7.05 (m, 2H, ArH), 7.07–7.12 (m, 1H, ArH), 7.22–7.26 (m, 1H, ArH), 14.75 (s, 1H, SH). IR (KBr) ν: 3107, 1705, 1583 cm^{-1}. Anal. calcd for $C_9H_7ClN_2OS_2$: C, 41.78; H, 2.73; N, 10.83. Found: C, 41.60; H, 2. 85; N, 10.96.

General Synthetic Procedure for Compounds (5a–o)

A mixture of **3a** (0.45 g, 2 mmol), **4a** (0.41g, 2.4 mmol), and K_2CO_3 (0.28 g, 2 mmol) was thoroughly mixed in a mortar followed by grinding until the completion of the reaction as indicated by TLC (10–20 min). The resulting material was washed with water to afford the crude product. The pure product was obtained by recrystallization from DMF-EtOH.

2-(5-(Phenoxymethyl)-1,3,4-thiadiazol-2-ylthio)-N-phenylacetamide (5a). Yield: 93%. Grey crystal; Mp: 127–129°C. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 4.07$ (s, 2H, SCH_2), 5.44 (s, 2H, OCH_2), 6.97–7.11 (m, 4H, ArH), 7.25–7.37 (m, 4H, ArH), 7.52–7.55 (m, 2H, ArH), 9.50 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 37.5$, 64.6, 114.8, 119.8, 122.3, 124.4, 128.9, 129.8, 137.8, 157.2, 165.9, 167.7, 168.2. MS: *m/z* 357 (M^+). IR (KBr) ν: 3300, 1671, 1597 cm^{-1}. Anal. calcd for $C_{17}H_{15}N_3O_2S_2$: C, 57.12; H, 4.23; N, 11.76. Found: C, 57.29; H, 4.41; N, 11.61.

2-(5-(Phenoxymethyl)-1,3,4-thiadiazol-2-ylthio)-N-(4-methylphenoxy)acetamide (5b). Yield: 94%. Yellow crystal; Mp: 156–158°C. ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 2.21$ (s, 3H, CH_3), 4.03 (s, 2H, SCH_2), 5.36 (s, 2H, OCH_2), 6.92–7.11 (m,

3H, ArH), 7.14–7.17 (m, 2H, ArH), 7.25–7.38 (m, 2H, ArH), 7.51–7.54 (m, 2H, ArH), 9.60 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 20.2, 37.5, 64.7, 114.3, 118.6, 121.3, 122.5, 129.4, 129.8, 137.2, 156.6, 165.8, 167.4, 167.6. MS: *m/z* 371 (M^+). IR (KBr) ν: 3300, 1671, 1597 cm^{-1}. Anal. calcd for $C_{18}H_{17}N_3O_2S_2$: C, 58.20; H, 4.21; N, 11.31. Found: C, 58.37; H, 4.36; N, 11.47.

2-(5-(Phenoxymethyl)-1,3,4-thiadiazol-2-ylthio)-N-(4-chlorophenyl)acetamide (5c). Yield: 94%. White crystal; Mp: 165–167°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.08 (s, 2H, SCH_2), 5.49 (s, 2H, OCH_2), 6.95–7.13 (m, 3H, ArH), 7.17–7.21 (m, 2H, ArH), 7.26–7.37 (m, 2H, ArH), 7.51–7.55 (m, 2H, ArH), 9.67 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 37.5, 65.6, 114.6, 120.7, 123.2, 127.6, 129.7, 130.8, 136.7, 156.9, 165.8, 168.2, 169.1. MS: *m/z* 393 ($M+2^+$). IR (KBr) ν: 3310, 1670, 1597 cm^{-1}. Anal. calcd for $C_{17}H_{14}ClN_3O_2S_2$: C, 52.10; H, 3.60; N, 10.72. Found: C, 52.25; H, 3.77; N, 10.61.

2-(5-(Phenoxymethyl)-1,3,4-thiadiazol-2-ylthio)-N-(4-nitrophenyl)acetamide (5d). Yield: 79%. Yellow crystal; Mp: 165–167°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.43 (s, 2H, SCH_2), 5.39 (s, 2H, OCH_2), 6.97–7.15 (m, 3H, ArH), 7.25–7.31 (m, 2H, ArH), 7.64–7.78 (m, 2H, ArH), 7.99–8.04 (m, 2H, ArH), 10.97 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 38.0, 65.5, 114.7, 120.4, 123.2, 125.6, 129.6, 143.7, 145.4, 157.0, 164.4, 168.3, 168.9. MS: *m/z* 402 (M^+). IR (KBr) ν: 3302, 1675, 1597 cm^{-1}. Anal. calcd for $C_{17}H_{14}N_4O_4S_2$: C, 50.74; H, 3.51; N, 13.92. Found: C, 50.57; H, 3.65; N, 13.75.

2-(5-(Phenoxymethyl)-1,3,4-thiadiazol-2-ylthio)-N-(2-nitrophenyl)acetamide (5e). Yield: 74%. Yellow crystal; Mp: 140–142°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.49 (s, 2H, SCH_2), 5.37 (s, 2H, OCH_2), 6.95–7.15 (m, 3H, ArH), 7.23–7.30 (m, 2H, ArH) 7.64–7.72 (m, 1H, ArH), 7.84–7.92 (m, 2H, ArH), 8.09–8.15 (m, 1H, ArH), 10.69 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 38.1, 65.4, 114.9, 120.1, 121.5, 122.5, 125.4, 129.8, 134.6, 135.4, 141.6, 155.7, 165.6, 166.8, 168.2. MS: *m/z* 402 (M^+). IR (KBr) ν: 3300, 1670, 1597 cm^{-1}. Anal. calcd for $C_{17}H_{14}N_4O_4S_2$: C, 50.74; H, 3.51; N, 13.92. Found: C, 50.55; H, 3.63; N, 13.80.

2-(5-((4-Methylphenoxy)methyl)-1,3,4-thiadiazol-2-ylthio)-N-phenylacetamide (5f). Yield: 83%. White crystal; Mp: 141–143°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.23 (s, 3H, CH_3), 4.05 (s, 2H, SCH_2), 5.43 (s, 2H, OCH_2), 6.89 (dd, J = 6.0 Hz, J = 2.0 Hz, 2H, ArH), 6.97–7.11 (m, 3H, ArH), 7.25–7.33 (m, 2H, ArH), 7.51–7.55 (m, 2H, ArH), 9.51 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 21.2, 37.5, 64.6, 114.8, 119.7, 124.5, 128.5, 130.0, 130.4, 137.8, 157.0, 165.8, 167.7, 168.1. MS: *m/z* 371 (M^+). IR (KBr) ν: 3315, 1675, 1597 cm^{-1}. Anal. calcd for $C_{18}H_{17}N_3O_2S_2$: C, 58.20; H, 4.61; N, 11.31. Found: C, 58.03; H, 4.72; N, 11.47.

2-(5-((4-Methylphenoxy)methyl)-1,3,4-thiadiazol-2-ylthio)-N-(4-methylphenoxy)acetamide (5g). Yield: 87%. White crystal; Mp: 168–170°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.21 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 4.06 (s, 2H, SCH_2), 5.44 (s, 2H, OCH_2), 6.87 (dd, J = 6.0 Hz, J = 2.0 Hz, 2H, ArH), 7.04 (d, J = 8.4 Hz, 2H, ArH), 7.23–7.37 (m, 2H, ArH), 7.45–7.51 (m, 2H, ArH), 9.47 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 20.2, 21.3, 37.5, 64.6, 114.8, 120.6, 128.5, 130.0, 130.3, 134.2, 137.8, 156.8, 165.8, 166.2, 168.0. MS: *m/z* 385 (M^+). IR (KBr) ν: 3309, 1678, 1597 cm^{-1}. Anal. calcd for $C_{19}H_{19}N_3O_2S_2$: C, 59.20; H, 4.97; N, 10.90. Found: C, 59.01; H, 4.82; N, 11.05.

2-(5-((4-Methylphenoxy)methyl)-1,3,4-thiadiazol-2-ylthio)-N-(4-chlorophenyl)acetamide (5h). Yield: 93%. Grey crystal; Mp: 174–176°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.21 (s, 3H, CH_3), 4.09(s, 2H, SCH_2), 5.44 (s, 2H, OCH_2), 6.90 (dd, J = 6.4 Hz, J = 2.0 Hz, 2H, ArH), 7.07 (d, J = 8.0 Hz, 2H, ArH), 7.25–7.37 (m, 2H, ArH),

7.51–7.56 (m, 2H, ArH), 9.55 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 21.2, 37.5, 64.6, 114.9, 119.7, 122.1, 124.4, 129.0, 130.6, 137.7, 156.9, 165.8, 165.9, 167.4. MS: *m/z* 407 ($M+2^+$). IR (KBr) ν: 3310, 1674, 1597 cm^{-1}. Anal. calcd for $C_{18}H_{16}ClN_3O_2S_2$: C, 53.26; H, 3.97; N, 10.35. Found: C, 53.39; H, 3.81; N, 10.18.

2-(5-((4-Methylphenoxy)methyl)-1,3,4-thiadiazol-2-ylthio)-N-(4-nitrophenyl)acetamide (5i). Yield: 73%. Brown crystal; Mp: 159–161°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.23 (s, 3H, CH_3), 4.32 (s, 2H, SCH_2), 5.46 (s, 2H, OCH_2), 6.94 (dd, J = 6.4 Hz, J = 2.0 Hz, 2H, ArH), 7.11 (d, J = 8.0 Hz, 2H, ArH), 7.61–7.76 (m, 2H, ArH), 7.97–8.03 (m, 2H, ArH), 10.57 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 21.2, 37.6, 64.1, 115.0, 122.4, 124.3, 129.0, 130.4, 141.6, 141.9, 155.2, 165.8, 165.9, 167.5. MS: *m/z* 416 (M^+). IR (KBr) ν: 3306, 1669, 1597 cm^{-1}. Anal. calcd for $C_{18}H_{16}N_4O_4S_2$: C, 51.91; H, 3.87; N, 13.45. Found: C, 57.84; H, 3.80; N, 13.59.

2-(5-((4-Methylphenoxy)methyl)-1,3,4-thiadiazol-2-ylthio)-N-(2-nitrophenyl)acetamide (5j). Yield: 77%. Brown crystal: Mp: 130–132°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.22 (s, 3H, CH_3), 4.35 (s, 2H, SCH_2), 5.49 (s, 2H, OCH_2), 6.93 (dd, J = 6.4 Hz, J = 2.0 Hz, 2H, ArH), 7.10–7.14 (m, 2H, ArH), 7.38–7.43 (m, 1H, ArH), 7.72–7.77 (m, 2H, ArH), 8.00 (d, J = 3.6 Hz, 1H, ArH), 10.61 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 21.2, 37.6, 64.1, 115.0, 125.1, 125.3, 125.8, 130.1, 130.7, 130.9, 134.4, 141.9, 155.2, 165.9, 165.9, 167.5. MS: *m/z* 416 (M^+). IR (KBr) ν: 3305, 1677, 1597 cm^{-1}. Anal. calcd for $C_{18}H_{16}N_4O_4S_2$: C, 51.91; H, 3.87; N, 13.45. Found: C, 52.05; H, 3.75; N, 13.57.

2-(5-((2-Chlorophenoxy)methyl)-1,3,4-thiadiazol-2-ylthio)-N-phenylacetamide (5k). Yield: 89%. White crystal; Mp: 155–157°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.09 (s, 2H, SCH_2), 5.46 (s, 2H, OCH_2), 6.99–7.04 (m, 2H, ArH), 7.23–7.26 (m, 2H, ArH), 7.37–7.42 (m, 3H, ArH), 7.48–7.51 (m, 2H, ArH), 9.51 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 37.4, 65.8, 114.3, 120.9, 123.4, 123.6, 127.9, 129.0, 129.8, 130.8, 136.8, 152.8, 165.9, 167.8, 168.2. MS: *m/z* 393 ($M+2^+$). IR (KBr) ν: 3300, 1670, 1597 cm^{-1}. Anal. calcd for $C_{17}H_{14}ClN_3O_2S_2$: C, 52.10; H, 3.60; N, 10.72. Found: C, 52.28; H, 3.75; N, 10.58.

2-(5-((2-Chlorophenoxy)methyl)-1,3,4-thiadiazol-2-ylthio)-N-4-(methylphenoxy)acetamide (5l). Yield: 92%. White crystal; Mp: 162–164°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.21 (s, 3H, CH_3), 4.05 (s, 2H, SCH_2), 5.43 (s, 2H, OCH_2), 6.92–7.01 (m, 2H, ArH), 7.13–7.19 (m, 3H, ArH), 7.31–7.35 (m, 1H, ArH), 7.48–7.52 (m, 2H, ArH), 9.50 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 20.2, 37.4, 64.6, 114.9, 120.1, 121.3, 122.4, 124.4, 129.5, 131.0, 135.2, 136.5, 152.9, 165.8, 167.7, 168.2. MS: *m/z* 407 ($M+2^+$). IR (KBr) ν: 3303, 1679, 1597 cm^{-1}. Anal. calcd for $C_{18}H_{16}ClN_3O_2S_2$: C, 53.26; H, 3.97; N, 10.35. Found: C, 53.09; H, 3.83; N, 10.50.

2-(5-((2-Chlorophenoxy)methyl)-1,3,4-thiadiazol-2-ylthio)-N-(4-chlorophenyl)acetamide (5m). Yield: 90%. White crystal; Mp: 168–170°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.05 (s, 2H, SCH_2), 5.55 (s, 2H, OCH_2), 6.99–7.05 (m, 2H, ArH), 7.23–7.28 (m, 3H, ArH), 7.41–7.45 (m, 1H, ArH), 7.48–7.51 (m, 2H, ArH), 9.66 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 37.4, 65.7, 114.3, 120.9, 123.4, 123.5, 127.9, 128.9, 129.3, 130.8, 136.4, 152.8, 165.9, 167.8, 168.2. MS: *m/z* 426 ($M+2^+$). IR (KBr) ν: 3301, 1671, 1597 cm^{-1}. Anal. calcd for $C_{17}H_{13}Cl_2N_3O_2S_2$: C, 47.89; H, 3.07; N, 9.86. Found: C, 48.01; H, 3.19; N, 9.70.

2-(5-((2-Chlorophenoxy)methyl)-1,3,4-thiadiazol-2-ylthio)-N-(4-nitrophenyl)acetamide (5n). Yield: 72%. Yellow crystal; Mp: 179–181°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.37 (s, 2H, SCH_2), 5.50 (s, 2H, OCH_2), 6.98–7.15 (m, 2H, ArH),

7.26–7.33 (m, 2H, ArH), 7.73–7.76 (m, 2H, ArH), 7.96–8.02 (m, 2H, ArH), 10.51 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 37.2, 65.9, 114.9, 116.4, 121.7, 122.7, 127.5, 128.9, 129.6, 141.4, 141.9, 152.8, 165.9, 167.8, 168.2. MS: *m/z* 438 (M+2$^+$). IR (KBr) ν: 3306, 1678, 1598 cm^{-1}. Anal. calcd for $C_{17}H_{13}ClN_4O_4S_2$: C, 46.74; H, 3.00; N, 12.82. Found: C, 46.60; H, 3.14; N, 12.68.

2-(5-((2-Chlorophenoxy)methyl)-1,3,4-thiadiazol-2-ylthio)-N-(2-nitrophenyl)acetamide (5o). Yield: 81%. Yellow crystal; Mp: 134–136°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.36 (s, 2H, SCH_2), 5.52 (s, 2H, OCH_2), 6.99–7.05 (m, 2H, ArH), 7.23–7.27 (m, 2H, ArH), 7.38–7.43 (m, 1H, ArH), 7.73–7.76 (m, 1H, ArH), 7.99–8.03 (m 2H, ArH), 10.62 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 38.5, 64.2, 115.8, 121.6, 122.2, 122.7, 123.1, 125.4, 127.9, 129.7, 135.1, 139.9, 140.4, 154.8, 165.9, 167.8, 168.2. MS: *m/z* 438 (M+2$^+$). IR (KBr) ν: 3306, 1675, 1598 cm^{-1}. Anal. calcd for $C_{17}H_{13}ClN_4O_4S_2$: C, 46.74; H, 3.00; N, 12.82. Found: Found: C, 46.88; H, 3.15; N, 12.67.

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