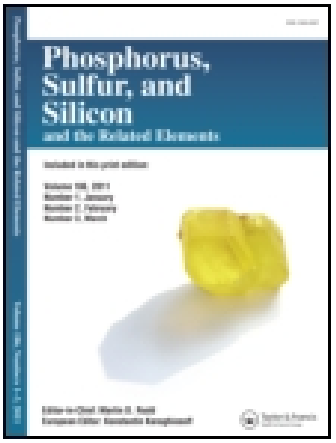

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Synthesis, Structure, and Properties of the 2-[5-(Aryloxyacetyl)-Amino-1,3,4-Thiadiazol-2-Ylthio] Propionate Derivatives

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SYNTHESIS, STRUCTURE, AND PROPERTIES OF THE 2-[5-(ARYLOXYACETYL)-AMINO-1,3,4-THIADIAZOL-2-YLTHIO] PROPIONATE DERIVATIVES

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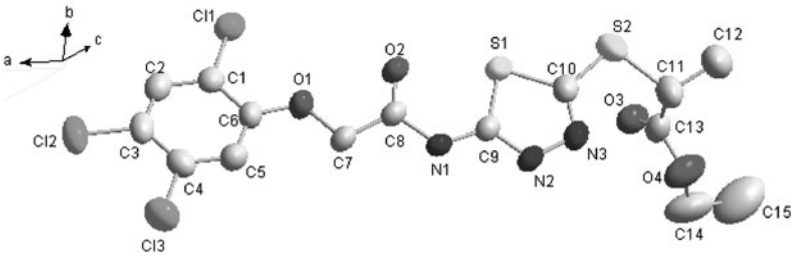
GRAPHICAL ABSTRACT



Abstract *A series of novel 2-[5-(aryloxyacetyl)-amino-1,3,4-thiadiazol-2-ylthio] propionate derivatives were synthesized in high yield, and their structures were characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis, coupled with one selected single-crystal X-ray structure determination. The herbicidal activities of target compounds were assessed. The preliminary bioassay results showed that some compounds exhibited moderate to strong herbicidal symptoms in preemergence and postemergence tests. At 150 g/ha, S. tritici. show tolerance, while E. crus-galli L., E. Dahuricus, A. retroflexus, and C. glaucum L. were killed or severely injured. The activity of some compounds was comparable to the commercial herbicide 2,4-D. A suitable electron-withdrawing substituent at the 2- and/or 4-position of the phenyl ring was essential for high herbicidal activity. Moreover, the antifungal activities of the compounds have also been studied. The compounds were found to possess broad-spectrum antifungal activity.*

Keywords 1,3,4-thiadiazole; phenoxy acid; crystal structure; biological activity

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INTRODUCTION

Heterocyclic compounds, as the main sources of lead molecules, play an important role in agrochemicals. In the 1960s, Merck & Co. Int. discovered and developed thiabendazole as a fungicide.[1] Afterward, many thiazoles including a number of widely used fungicides (e.g., tricyclazole, probenazole, and trifluzamide) and herbicides (e.g., buthiuron, thiazfluron, and tebuthiuron) have been introduced into the pesticide market.[2] 1,3,4-Thiadiazoles, as an important class of sulfur-containing compounds with various interesting properties, are becoming a rapidly growing and independent branch of the chemistry of thiazoles.[3,4] They displayed a wide range of biological and pharmaceutical activities and have attracted considerable attention. Some of them exhibited anti-HIV, insecticidal, fungicidal, antiviral activities, and herbicidal activity.[5–9]

A variety of substituted phenoxy acids exhibit plant growth regulating and herbicidal activity. Substituents that are most effective in enhancing these activities are halogens and methyl groups.[10] The development of phenoxyalkanoic acid herbicides dates from the 1940s. 2,4-D (2,4-dichlorophenoxy acetic acid) is the successful representative, which is a readily systemic herbicide. The toxicity, herbicidal effects and environmental persistence have been studied in detail.[11] The presence of an alkyl ester often leads to increased lipid solubility and the 2-substituted ethyl propionate as a reactive group is widely used in pesticides (e.g., Fenoxaprop-ethyl, Fentiaprop-ethyl, and Quizalofop-ethyl).[12]

In order to continue the research in thiadiazoles and aryloxycarboxylic acid biological interests,[13,14] we decided to introduce the phenoxy acid and propionate as active groups into the thiadiazole molecule to improve their herbicidal activity, in this paper. Thus, a series of 2-[5-(aryloxyacetyl)-amino-1,3,4-thiadiazol-2-ylthio] propionate derivatives were synthesized, characterized and their herbicidal activity was evaluated. Surprisingly, several compounds also exhibit favorable fungicidal activities. The synthetic route of compounds is shown in Scheme 1.

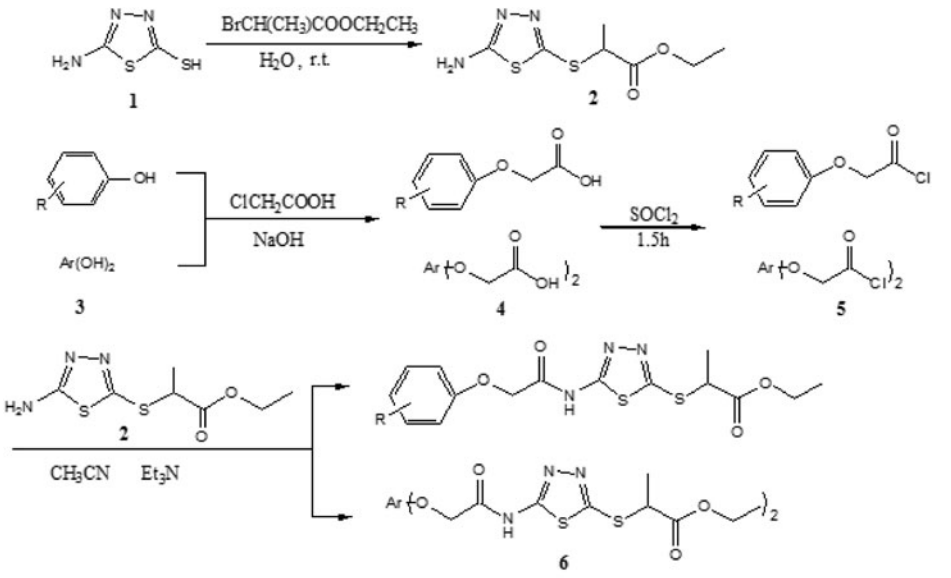
RESULTS AND DISCUSSION

Syntheses and Characterization

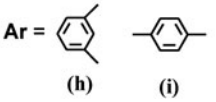
A number of aryloxyacetic acid analogues have been reported as herbicides, which provided a guide to here synthesis. As a first step, **2** were prepared by the reaction of 2-amino-5-mercapto-1,3,4-thiadiazole and ethyl 2-bromopropionate in aqueous media. Then, aryloxyacetic acid was acylated with thionyl chloride to provide acyl chloride **5** in high yield. Finally, **5** upon further reaction with **2** gave 2-[5-(aryloxyacetyl)-amino-1,3,4-thiadiazol-2-ylthio] propionate derivatives **6a** to **6i** in moderate reaction yields. The synthetic route is shown in Scheme 1.

A characteristic feature of IR spectra in the **6** series is the strong absorption by N—H and C=O groups. For example, **6a** shows strong stretching vibration of the C=O group at 1730 cm^{-1} and of the N—H group at 3173 cm^{-1}. In the ^1H NMR spectra, a characteristic feature in the **6** series is the presence of singlet signals in low fields belonging to an NH proton. Taking **6a** as an example, the protons of NH groups appear as one singlet signal at 10.63 ppm (Figure S1 Supplemental Materials).

The structure of **6f** was further identified by a single-crystal X-ray diffraction analysis (Figure 1). The heterocyclic ring is planar within experimental error and the heterocyclic bond distances compare well with those of related molecules.[15,16] The dihedral angle formed by the trichlorobenzene and the thiadiazole ring is 12.24(129)°. In the crystal structure,



R: H-**(a)** 2-Cl-**(b)** 4-Cl-**(c)** 2-Cl-4-Cl-**(d)** 4-OCH_3-**(e)** 2-Cl-4-Cl-5-Cl-**(f)** 2-Cl-4-Cl-6-Cl-**(g)**



Scheme 1

intermolecular N1–H1···N6, N4–H4···N2 hydrogen bonds form centrosymmetric dimers (Figure S3). Selected bond lengths and angles are listed in Table 1. Hydrogen bonding parameters are shown in Table S1.

Biological Activity

Herbicidal Studies. As an initial evaluation, all of the title compounds were tested at a dosage of 150 g ai/ha for preemergence and postemergence herbicidal activities on E. dahuricus, E. crus-galli L., A. retroflexus, C. glaucum L., Brassica chinensis L., and

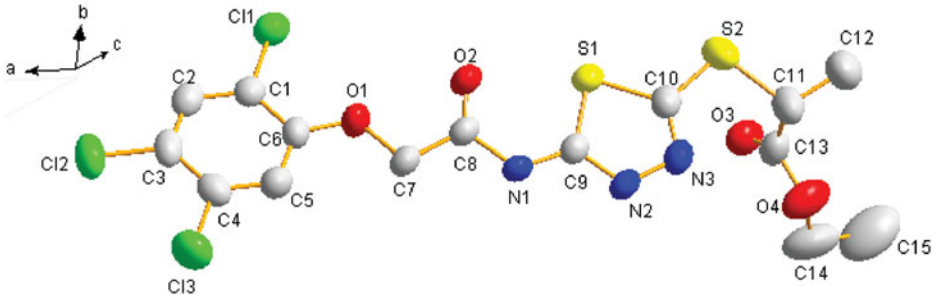


Figure 1 Molecular structure of the title compound **6f**, with 50% probability thermal ellipsoids. Color code: Cl, green; O, red; N, blue; S, yellow; C, gray. H atoms are omitted for clarity.

Table 1 Selected bond distances (Å) and angles (°) for **6f**

C1–Cl1	1.737(5)	C3–Cl2	1.759(5)	C4–Cl3	1.720(5)
		Bond lengths			
C6–O1	1.384(5)	C7–O1	1.447(5)	C7–C8	1.529(6)
C8–O2	1.181(5)	C8–N1	1.409(5)	C9–N2	1.347(5)
C9–N1	1.382(5)	C9–S1	1.711(5)	C10–N3	1.298(6)
C10–S2	1.738(5)	C10–S1	1.790(5)	C11–C13	1.373(7)
C11–C12	1.496(7)	C11–S2	1.866(5)	C13–O3	1.137(6)
C13–O4	1.333(6)	C14–O4	1.346(7)	C14–C15	1.513(11)
N2–N3	1.396(5)				
		Bond angles			
C2–C1–Cl1	118.5(3)	C6–C1–Cl1	118.3(3)	C2–C3–Cl2	119.3(4)
C4–C3–Cl2	123.2(4)	C5–C4–Cl3	119.1(4)	C3–C4–Cl3	118.9(4)
O1–C6–C5	125.3(4)	O1–C6–C1	118.0(4)	O1–C7–C8	106.4(4)
O2–C8–N1	121.1(4)	O2–C8–C7	122.2(4)	N1–C8–C7	116.7(4)
N2–C9–N1	123.1(4)	N2–C9–S1	113.3(3)	N1–C9–S1	123.5(3)
N3–C10–S2	123.3(4)	N3–C10–S1	115.9(4)	S2–C10–S1	120.8(3)
C13–C11–C12	108.7(5)	C13–C11–S2	109.1(4)	C12–C11–S2	111.6(4)
O3–C13–O4	129.7(5)	O3–C13–C11	122.8(5)	O4–C13–C11	107.3(5)
O4–C14–C15	111.2(7)	C9–N1–C8	124.0(4)	C9–N2–N3	114.9(4)
C10–N3–N2	109.5(3)	C6–O1–C7	121.0(4)	C13–O4–C14	116.9(5)
C9–S1–C10	86.4(2)	C10–S2–C11	102.9(2)		

S. tritici. Compounds 2,4-D was selected as control. In general, the compounds were more active on monocotyledonous than dicotyledonous species with the difference being most apparent in postemergence evaluations (Table S1). Especially, the title compounds **6f** displayed notable herbicidal activity higher than commercial herbicide 2,4-D in some cases.

It's particularly worth noting that most compounds showed a high degree of selectivity with wheat in both preemergence and postemergence assays. For example, compound **6e**

Table 2 Crystallographic and data collection parameters for **6f**

Compound	**6f**
Empirical formula	$C_{15}H_{14}Cl_3N_3O_4S_2$
Formula weight	470.76
Crystal system	triclinic
Space group	P-1
a, b, c (Å)	11.233(9), 13.327(8), 14.317(2)
α $\beta\gamma$ (°)	100.88(4)°, β=98.50(5)°, 113.95(7)°
V (Å^3), Z	1862.4(19), 4
Calculated density(g cm^{-3})	1.679
F(000)	960
Absorption coefficient (mm^{-1})	0.745
Reflections collected/unique	12342,6524
θ range for data collection (^{O})	3.11–25.00
Data/restraints/parameters	6524 / 12 / 491
Goodness-of-fit on F^2	1.034
R indices [$I > 2\sigma(I)$] R_1, wR_2	0.06551, 0.1419
R indices (all data) R_1, wR_2	0.0996, 0.1593

displayed remarkable promoting activity (41% in postemergence tests) on the wheat's growth, thus indicating that compound **6e** might selectively control weeds in wheat fields.

The structure-activity relationship is as follows:

Compound **6a** with the no *para* substituent on the phenyl ring had little inhibitory effect on weed development as compared with compound **6b–g** with chlorine or methoxy (most at the 2- and/or 4-position), indicating that the herbicidal activity was critically dependent on the combined effect of the suitable group(s) (chlorine or methoxy) substituents. The replacement of chlorine by an alkoxy group did not affect the herbicidal activity obviously. Meanwhile, the structures of ester moiety also played a role in activity of compounds **6**. In our previous work, the 2-substituted ethyl propionate group modified by the replacement of ethyl acetate, those good activities prompted the authors to synthesize a series of propanoate analogues as shown in Scheme 1. We found that the introduction of propanoate to 1,3,4-thiadiazole increased the herbicidal activity, which is consistent with previous reports.[17] Additionally, di-substituted compounds **6h** and **6i** were significantly more active than most of mono-substituted derivatives **6a**–**e**, these changes may be attributable to the di-substituted compounds are more lipophilic than the mono-substituted ones. The observed results conform to the superposition principle of reinforcement of biological activities.[18]

Experimental details and the activities (Table S1) are presented in the Supplemental Materials.

Antifungal Studies. The antifungal activities of the compounds **6a–i** were performed by the poisoned food technique against the fungi viz., Alternaria alternata, Fusarium oxysporum, Alternaria soluni, Botrytis Cinerea, and Fusarium sulphureum cultured on potato dextrose agar as medium.[19] The fungal activity of each compound was compared with 2,4-D and the commercial fungicide griseofulvinas as standard drug.

Investigation of antifungal activity of the compounds **6a-i** showed that all compounds displayed a degree of fungicidal activity against the test fungi, and relatively more active at the given dilutions against the fungi chosen in comparison to the 2,4-D, but less than that of the commercial fungicide griseofulvinas. Among them, compounds **6c**, **6d**, and **6f** displayed high fungicidal activity against Alternaria alternata and Fusarium sulphureum (Table S2).

Experimental details and the activities (Table S2) are presented in the Supplemental Materials.

CONCLUSION

In conclusion, as part of continuous efforts to search for new herbicides with high efficacy, broad-spectrum activity, and safety to crops, 1,3,4-thiadiazoles and phenoxy acid were used as lead compounds for further optimization. A new series of 2-[5-(aryloxyacetyl)-amino-1,3,4-thiadiazol-2-ylthio] propionate analogues were synthesized by a simple, rapid, and cost-effective method, and their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, elementary analysis, and X-ray diffraction analysis. Preliminary bioassay data showed that some of them possess commercial levels of herbicidal activity comparable to the commercial herbicide 2,4-D, while S. tritici. show tolerance. These compounds could be lead compounds for further discovery of herbicides. At the same time, some compounds had interesting fungicidal activity even at 50 ppm. The title compounds have a broad prospect of application in agriculture as novel pesticides.

EXPERIMENTAL

All of the chemicals are commercially available and used without further purification. Melting points were measured on an X-4 digital melting-point apparatus (uncorrected). Elemental analyses were performed with a Perkin-Elmer 2400 elemental analyzer. The IR (KBr pellet) spectra were recorded on a Perkin-Elmer FT-IR spectrometer in the 4000–400 cm^{-1} range. NMR spectra were recorded on a Varian Mercury Plus-400 MHz spectrometer. Compounds **1**and **4** were prepared according to the literature methods.[20,21]

General Synthetic Procedure for Target Compounds 6a–i

The 2-amino-5-mercapto-1,3,4-thiadiazole **1** (5 mmol) was dissolved in NaOH (5 mmol, 15 mL) at room temperature. Ethyl 2-bromopropionate (5 mmol) was added to the solution obtained and the mixture was stirred for 20 min. After that, the solid precipitate was filtered off, washed with cold water, air dried, and then recrystallized from ethanol to give 2-(5-amino-1,3,4-thiadiazol-2-ylthio) propanoate **2** in 78% yield as pale yellow solid. Mp 79–80°C; ^{1}H NMR($CDCl_3$, 400 MHz) δ_H: 1.25–1.28 (t, 3H, CH_3, J = 6.0 Hz), 1.57–1.59 (d, 3H, CH_3, J = 8.0 Hz), 4.03–4.08 (q, 1H, SCH, J = 12.0 Hz), 4.16–4.22 (q, 2H, OCH_2, J = 16.0 Hz).4.35 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 14.0, 17.5, 46.0, 61.8, 150.0, 170.9, 171.4; IR (KBr) ν: 3266 (NH_2), 1736 (OC=O), 1501, 1449, 1321, 1094 (C=N−N=C−S) cm^{-1}; Anal. calcd for $C_7H_{11}N_3O_2S_2$: C36.04, H 4.75, N 18.01; found C 36.10, H 4.77, N 17.93.

To a 50 mL round-bottom flask was added phenoxyalkanoic acid **4** (5 mmol) and $SOCl_2$ (5 mL). The mixture was refluxed for 4 h, and the excess $SOCl_2$ was removed under vacuum. The crude diacyl chloride was dissolved in CH_3CN (5 mL) and added dropwise through a dropping funnel to the mixture of 2-(5-amino-1,3,4-thiadiazol-2-ylthio) propanoate **2** (4.5 mmol) and Et_3N (4.2 mL, 30 mmol) in CH_3CN (15 mL) on an ice bath. This mixture was vigorously stirred at room temperature for an additional 12 h after completion of the addition. The product was evaporated under reduced pressure washed with water and brine, dried and recrystallized from ethanol to give the title compounds **6.**

Ethyl 2-[5-(2-phenoxyacetamido)-1,3,4-thiadiazol-2-ylthio]propanoate (6a). Colorless crystals, yield 81%, mp 115–117°C; ^{1}H NMR($CDCl_3$, 400 MHz) δ_H: 1.25–1.28 (t, 3H, CH_3, J = 6.2 Hz), 1.63–1.65 (d, 3H, CH_3, J = 7.2 Hz), 4.20–4.23 (q, 2H, OCH_2, J = 7.2 Hz), 4.30–4.36 (q, 1H, SCH, J = 14.4 Hz), 4.79–4.80 (s, 2H, $COCH_2$), 6.96–7.37 (m, 5H, ArH), 10.63 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 14.0, 17.8, 45.7, 61.8, 66.7, 114.7, 122.5, 129.8, 156.8, 158.1, 159.5, 166.7, 171.2; IR (KBr) ν: 3173 (NH), 1730 (OC=O), 1583, 1497, 1306, 1072 (C=N−N=C−S) cm^{-1}; Anal. calcd for $C_{15}H_{17}N_3O_4S_2$: C 49.03, H 4.66, N 11.44; found C 49.08, H 4.72, N 11.54.

Ethyl 2-{5-[2-(2-chlorophenoxy)acetamido]-1,3,4-thiadiazol-2-ylthio}propanoate (6b). White crystals, yield 86%, mp 138–139°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.22–1.24 (t, 3H, CH_3, J = 4.0 Hz), 1.61–1.63 (d, 3H, CH_3, J = 7.2 Hz), 4.15–4.20 (q, 2H, OCH_2, J = 10.0 Hz), 4.26–4.32 (q, 1H, SCH, J = 14.4 Hz), 4.79–4.88 (s, 2H, $COCH_2$), 6.59–7.28 (m, 4H, ArH), 11.63 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 14.0, 17.8, 45.6, 61.9, 67.0, 116.1, 127.6, 129.7, 155.5, 158.3, 159.5, 166.3, 171.0; IR (KBr) ν: 3186 (NH), 1725 (OC=O), 1587, 1495, 1306, 1077 (C=N–N = C–S) cm^{-1}; Anal. calcd for $C_{15}H_{16}N_3O_4S_2Cl$: C 44.83, H 4.01, N 10.46; found C 44.88, H 3.89, N 10.51.

Ethyl 2-{5-[2-(4-chlorophenoxy)acetamido]-1,3,4-thiadiazol-2-ylthio}propanoate (6c). White crystals, yield 87%, mp 126–127°C; ^{1}H NMR ($CDCl_3$, 400 MHz)

δ_H: 1.25–1.28 (t, 3H, CH_3, $J = 6.0$ Hz), 1.65–1.67 (d, 3H, CH_3, $J = 7.2$ Hz), 4.19–4.24 (q, 2H, OCH_2, $J = 14.0$ Hz), 4.35–4.40 (q, 1H, SCH, $J = 14.4$ Hz), 4.82 (s, 2H, $COCH_2$), 6.96–7.47 (m, 4H, ArH), 10.22 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 14.0, 17.8, 45.6, 61.9, 68.0, 114.7, 123.6, 128.1, 130.7, 152.5, 158.6, 165.9, 171.1; IR (KBr) ν: 3141 (NH), 1714 (OC=O), 1551, 1484, 1306, 1079 (C=N−N=C−S) cm^{-1}; Anal. calcd for $C_{15}H_{16}N_3O_4S_2Cl$: C 44.83, H 4.01, N 10.46; found C 45.01, H 4.02, N 10.52.

Ethyl 2-{5-[2-(2,4-dichlorophenoxy)acetamido]-1,3,4-thiadiazol-2-ylthio} propanoate (6d). White crystals, yield 82%, mp 145–146°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.26–1.29 (t, 3H, CH_3, $J = 7.2$ Hz), 1.64–1.66 (d, 3H, CH_3, $J = 6.8$ Hz), 4.19–4.24 (q, 2H, OCH_2, $J = 14.4$ Hz), 4.33–4.39 (q, 1H, SCH, $J = 14.8$ Hz), 4.81 (s, 2H, $COCH_2$), 6.90–7.46 (m, 3H, ArH), 10.32 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 14.1, 17.8, 45.7, 61.9, 68.2, 115.5, 124.5, 128.1, 130.5, 151.3, 158.5, 165.4, 171.1; IR (KBr) ν: 3149 (NH), 1714 (OC=O), 1558, 1481, 1307, 1080 (C=N−N=C−S) cm^{-1}; Anal. calcd for $C_{15}H_{15}N_3O_4S_2Cl_2$: C 41.29, H 3.47, N 9.63; found C 41.38, H 3.42, N 9.57.

Ethyl 2-{5-[2-(4-methoxyphenoxy)acetamido]-1,3,4-thiadiazol-2-ylthio} propanoate (6e). White crystals, yield 83%, mp 105–106°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.25–1.29 (t, 3H, CH_3, $J = 7.2$ Hz), 1.64–1.65 (d, 3H, CH_3, $J = 7.2$ Hz), 3.76–3.78 (s, 3H, OCH_3), 4.20–4.25 (q, 2H, OCH_2, $J = 11.2$ Hz), 4.32–4.37 (q, 1H, SCH, $J = 14.4$ Hz), 4.73 (s, 2H, $COCH_2$), 6.86–7.27 (m, 4H, ArH), 10.45 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 14.0, 17.8, 45.6, 55.6, 61.9, 67.6, 114.9, 115.8, 150.8, 155.0, 158.1, 159.1, 166.8, 171.1; IR (KBr) ν: 3192 (NH), 1733 (OC=O), 1578 1508, 1304, 1075 (C=N−N=C−S) cm^{-1}; Anal. calcd for $C_{16}H_{19}N_3O_5S_2$: C 48.35, H 4.82, N 10.57; found C 48.44, H 4.75, N 10.48.

Ethyl 2-{5-[2-(2,4,5-trichlorophenoxy)acetamido]-1,3,4-thiadiazol-2-ylthio}propanoate (6f). White crystals, yield 81%, mp 148–149°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.25–1.27 (t, 3H, CH_3, $J = 4.8$ Hz), 1.63–1.65 (d, 3H, CH_3, $J = 7.2$ Hz), 4.18–4.23 (q, 2H, OCH_2, $J = 14.4$ Hz), 4.29–4.35 (q, 1H, SCH, $J = 14.8$ Hz), 4.85 (s, 2H, $COCH_2$), 7.10–7.55 (m, 2H, ArH), 10.85 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 14.0, 17.7, 45.6, 61.9, 68.2, 116.3, 122.8, 126.6, 131.3, 131.6, 151.7, 158.6, 159.3, 165.1, 171.0; IR (KBr) ν: 3170 (NH), 1742 (OC = O), 1569, 1477, 1306, 1084 (C = N–N = C–S) cm^{-1}; Anal. calcd for $C_{15}H_{14}N_3O_4S_2Cl_3$: C 38.27, H 3.00, N 8.93; found C 38.41, H 3.12, N 8.82.

Ethyl 2-{5-[2-(2,4,6-trichlorophenoxy)acetamido]-1,3,4-thiadiazol-2-ylthio}propanoate (6g). Pale yellow crystals, yield 78%, mp 138–140°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.24–1.28 (t, 3H, CH_3, $J = 7.6$ Hz), 1.64–1.66 (d, 3H, CH_3, $J = 7.6$ Hz), 4.19–4.23 (q, 2H, OCH_2, $J = 8.8$ Hz), 4.32–4.37 (q, 1H, SCH, $J = 14.4$ Hz), 4.78 (s, 2H, $COCH_2$), 7.39 (s, 2H, ArH), 10.50 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 14.0, 17.9, 45.6, 61.9, 70.6, 129.0, 129.5, 131.2, 148.5, 158.2, 158.7, 165.5, 171.1; IR (KBr) ν: 3068 (NH), 1728 (OC=O), 1557, 1456, 1309, 1051 (C=N−N=C−S) cm^{-1}; Anal. calcd for $C_{15}H_{14}N_3O_4S_2Cl_3$: C 38.27, H 3.00, N 8.93; found C 38.38, H 3.04, N 8.88.

Diethyl 2,2′-{[5,5′-((2,2′-(1,3-phenylenebis(oxy))bis(acetyl))bis(azanediyl)) bis(1,3,4-thiadiazole-5,2-diyl)]bis(sulfanediyl)}dipropanoate (6h). Yellow crystals, yield 80%, mp 126–128°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.27–1.29 (t, 6H, CH_3, $J = 4.8$ Hz), 1.63–1.65 (d, 6H, CH_3, $J = 7.6$ Hz), 4.20–4.24 (q, 4H, OCH_2, $J = 10.4$ Hz), 4.30–4.35 (q, 2H, SCH, $J = 14.4$ Hz), 4.79–4.82 (s, 4H, $COCH_2$), 6.90–7.33 (m, 4H, ArH), 10.77 (s, 2H, NH); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 14.0, 17.8, 45.6, 61.9, 66.8,

102.6, 108.4, 130.6, 158.2, 159.6, 166.5, 171.1; IR (KBr) ν: 3181 (NH), 1732 (OC=O), 1571, 1491, 1300, 1069 (C=N−N=C−S) cm^{-1}; Anal. calcd for $C_{24}H_{28}N_6O_8S_4$: C 43.89, H 4.30, N 12.80; found C 43.82, H 4.25, N 12.77.

Diethyl 2,2′-{[5,5′-((2,2′-(1,4-phenylenebis(oxy))bis(acetyl))bis(azanediyl)) bis(1,3,4-thiadiazole-5,2-diyl)]bis(sulfanediyl)}dipropanoate (6i). Yellow crystals, yield 82%, mp 168–170°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.25–1.28 (t, 6H, CH_3, $J = 4.8$ Hz), 1.63–1.65 (d, 6H, CH_3, $J = 7.6$ Hz), 4.17–4.23 (q, 4H, OCH_2, $J = 10.0$ Hz), 4.30–4.35 (q, 2H, SCH, $J = 14.4$ Hz), 4.74–4.78 (s, 4H, $COCH_2$), 6.82–7.27 (m, 4H, ArH), 10.82 (s, 2H, NH); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 14.1, 17.9, 45.7, 61.9, 67.4, 116.2, 152.2, 158.4, 158.9, 166.3, 171.1; IR (KBr) ν: 3182 (NH), 1730 (OC=O), 1574,1506, 1305, 1071 (C=N−N=C−S) cm^{-1}; Anal. calcd for $C_{24}H_{28}N_6O_8S_4$: C 43.89, H 4.30, N 12.80; found C 43.72, H 4.36, N 12.69.

X-Ray Diffraction

A single light yellow crystal of compound **6f** having approximate dimensions of 0.24 mm × 0.22 mm × 0.20 mm was mounted on the top of a glass fiber in a random orientation. All X-ray crystallographic data were collected on a Bruker SMART APEX II CCD diffractometer equipped with a graphite-monochromatized Mo Ka radiation (λ = 0.71073 Å) radiation using φ/ω scan technique at 293 K. The structures were solved by a direct method and refined by a full-matrix least-squares procedure based on F^2 using the SHELXTL program package. The molecular structure of compound **6f** is shown in Figure 1, and a summary of the crystallographic data and refinement parameters are given in Table 2. CCDC 946566 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge B2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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SUPPLEMENTAL MATERIAL

Supplementary data for this article can be accessed on the publisher's website, www.tandfonline.com/gpss

REFERENCES

1. Wang, H.; Yang, Z. K.; Fan, Z. J.; Wu, Q. J.; Zhang, Y. J.; Mi, N.; Wang, S. X.; Zhang, Z. C.; Song, H. B.; Liu, F. *J. Agric. Food Chem.* **2011**, 59, 628-634.
2. Zuo, X.; Mi, N.; Fan, Z. J.; Zheng, Q. X.; Zhang, H. K.; Wang, H.; Yang, Z. K. *J. Agric. Food Chem.* **2010**, 58, 2755-2762.
3. Wetzel, C.; Kunz, P. C.; Kassack, M. U.; Hamacher, A.; Böhler, P.; Watjen, W.; Ott, I.; Rubbiani, R.; Spingler, B. *Dalton Trans*. **2011**, 40, 9212-9220.

4. Song, X. J.; Tan, X. H. *Phosphorus, Sulfur, and Silicon.* **2008**, 183, 1755-1765.
5. Wei, M. X.; Feng, L.; Li X. Q.; Zhou, X. Z.; Shao, Z. H. *Eur. J. Med. Chem.* **2009**, 44, 3340-3344.
6. Chen, H.; Li, Z.; Han, Y. *J. Agric. Food Chem.* **2000**, 48, 5312-5315.
7. Rostom, S. A. F.; El-Ashmawy, I. M.; Razik, H. A. A. E.; Badr, M. H.; Ashour, H. M. A. *Bioorgan. Med. Chem.* **2009**, 17, 882-895.
8. Deng, X. Y.; Liao, G. H.; Long, Q. W.; Gao, Y. J.; Peng, H.; He, H. W. *Phosphorus, Sulfur, and Silicon*. **2013**, 188, 663-671.
9. Bhati, S. K.; Kumar, A. *Eur. J. Med. Chem.* **2008**, 43, 2323-2330.
10. Thomas, G. J. *J. Agric. Food Chem.* **1984**, 32, 747-749.
11. Thompson, D. G.; Stephenson, G. R.; Solomon, K. R.; Skepasts, A. V. *J. Agric. Food Chem.* **1984**, 32, 578-581.
12. Lefsrud, C.; Hall, J. C. *Pestic. Biochem. Physiol.* **1989**, 34, 218-227.
13. Hu, B.; Yao, X. Q.; Lu Y. Y.; Wei, T. B.; Zhang, Y. M. *Chin. J. Inorg. Chem.* **2012**, 28, 2581-2586.
14. Wei, T. B.; Hua, M. T.; Shi, H. X.; Liu, Y.; Zhang, Y. M. *J. Chem. Res.* **2010**, 34, 452-454.
15. Pedregosa, J. C.; Casanova, J.; Alzuet, G.; Borrás, J.; García-Granda, S.; Diaz, M. R.; Gutierrez-Rodriguez, A. *Inorg. Chim. Acta.* **1995**, 232, 117-124.
16. Camí, G.; Server-Carrió, J.; Fustero, S.; Pedregosa, J. *Acta Crystallogr. Sect. C.* **2000**, 56, 209-210.
17. Makino, K.; Yoshioka, H. *J. Fluorine Chem.* **1987**, 37, 119-124.
18. Wei, T. B.; Leng, Y. L.; Wang, Y. C.; Zhang, J. H.; Zhang, Y. M. *Chin. J. Org. Chem.* **2009**, 29, 216-221.
19. Bansal, R. K.; Kabra, V.; Munjal, R.; Gupta, N. *Phosphorus, Sulfur, and Silicon*. **1994**, 97, 141-147.
20. Misra, U.; Shukla, S.; Gurtu, S.; Saxena, A. K.; Shanker, K. *Boll Chim Farm.* **1995**, 134, 492-496.
21. Wei, T. B.; Liu, H.; Li, M. L. *Synth. Commun.* **2005**, 35, 1759-1764.