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2-Hydroxypropyl derivatives of 1,2,3-thiadiazole and 1,2,3-triazole: Synthesis and antifungal activity*

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Abstract: A series of novel 5-(2-hydroxypropyl)amino-1,2,3-thiadiazole and 5-(2-hydroxypropyl)sulfanyl-1,2,3-triazole derivatives were designed and synthesized as candidate fungicides. The new compounds were identified by NMR and IR spectroscopy, mass spectrometry, and elemental analysis. Their antifungal activities were evaluated.

Keywords: alcohol; fungicides; synthesis; thiadiazoles; triazoles.

INTRODUCTION

Many heterocyclic compounds based upon nitrogen and sulfur heteroatoms have been extensively studied on the basis of reported pesticidal activities. Among the five-membered *N*- and *S*-heterocycles, some triazoles, thiazoles, and thiadiazoles have been commercialized as agrochemicals all over the world [1–4]. Those compounds bearing a 1,2,3-thiadiazole group are biologically versatile, and display a range of anti-inflammatory, antitumor, hypotensive, antibacterial, and antiallergic activities [5–9].

Our group has focused on the synthesis and characterization of various 1,2,3-thiadiazole derivatives and their biological activities.

RESULTS AND DISCUSSION

To modify 1,2,3-thiadiazole derivatives, in particular, to introduce a hydroxyl group we used an alkylation reaction of ethyl 5-amino-1,2,3-thiadiazole-4-carboxylate **1** with epichlorohydrin. This alkylation agent was chosen since it offers two centers for nucleophilic attack: the chloro group for substitution and the epoxy group for addition.

It is known [10] that 5-amino-1,2,3-thiadiazoles **1** undergo Dimroth rearrangement in basic media to yield 1,2,3-triazole derivatives. In an attempt to avoid that outcome, we attempted to react thiadiazoles **1** with epichlorohydrin in ethanol solution under reflux. However, no alkylation products were detected under such reaction conditions.

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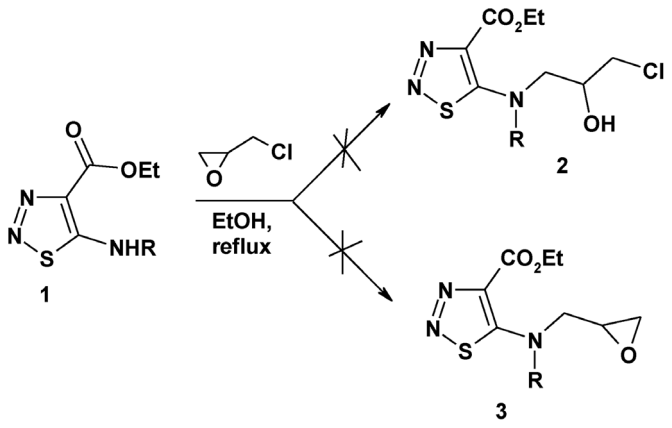
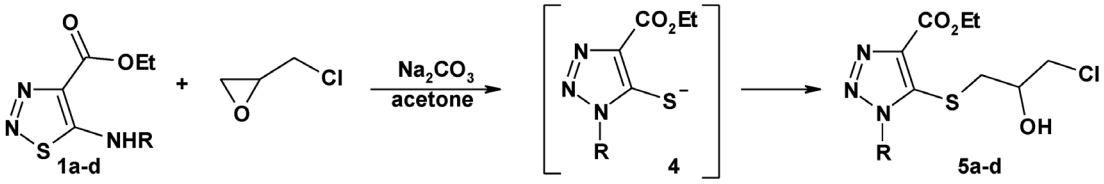


When the reaction was conducted in acetone, in the presence of a base (Na_2CO_3), Dimroth rearrangement took place as expected, and epichlorohydrin underwent nucleophilic attack on the epoxy group by the presumed thiolate intermediate **4**, to furnish 5-(3-chloro-2-hydroxypropyl-1)-sulfanyl-1,2,3-triazoles **5a–d** in 53–85 % yields.

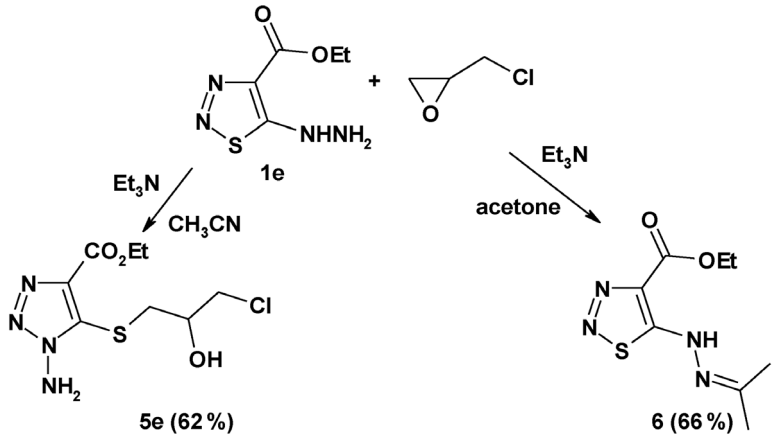


1a R = C_6H_5
1b R = 4-MeC_6H_4
1c R = 4-MeOC_6H_4
1d R = $C_6H_5CH_2$

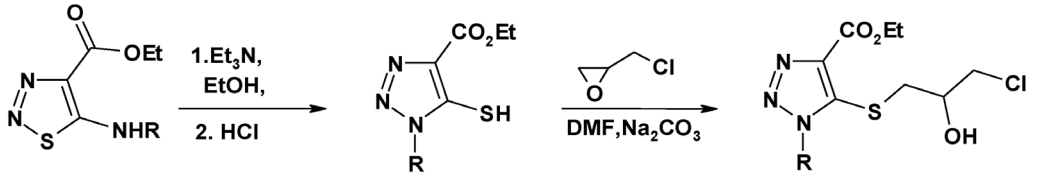
5a R = C_6H_5 (65 %)
5b R = 4-MeC_6H_4 (85 %)
5c R = 4-MeOC_6H_4 (53 %)
5d R = $C_6H_5CH_2$ (62 %)

The structures of the products were determined by spectroscopic methods. Thus, ^{1}H NMR spectra of the 1,2,3-triazoles **5a–d** displayed the following groups of signals. A doublet at range 5.21–5.54 ppm is characteristic for a free OH group. The 3'-chloro-2'-hydroxypropyl group gives rise to a characteristic multiplet at 3.66–3.73 ppm for the 2'-CH-fragment, a doublet at 3.36–3.48 ppm for 3'-CH_2 and two doublets of doublets at 2.94–3.17 ppm for 1'-CH_2. Mass spectrometry of the products also confirmed the empirical formulae arising from nucleophilic addition, since diagnostic molecular ion peaks and isotopic ion peaks characteristic of the chlorine atom were present in all cases.

The reaction of 5-hydrazinyl-1,2,3-thiadiazole **1e** with epichlorohydrin in acetone leads to hydrazone **6**. It noteworthy that Dimroth rearrangement [11] was not observed despite the basicity of the reaction medium. However, the expected product **5e** of rearrangement and alkylation was formed when acetonitrile was used as a solvent.



The triazole structure of heterocycle **5** was confirmed by isolation of intermediate mercapto derivative **7**. Treatment of 5-amino-1,2,3-thiadizoles **1** in ethanol solution under refluxing for 2 h in the presence of triethylamine, followed by treatment with 6 M HCl, gave 5-mercapto-1,2,3-triazoles **7** in yields of 62–66 %, which were then alkylated with epichlorhydrin in dimethylformamide (DMF) in the presence of Na_2CO_3.

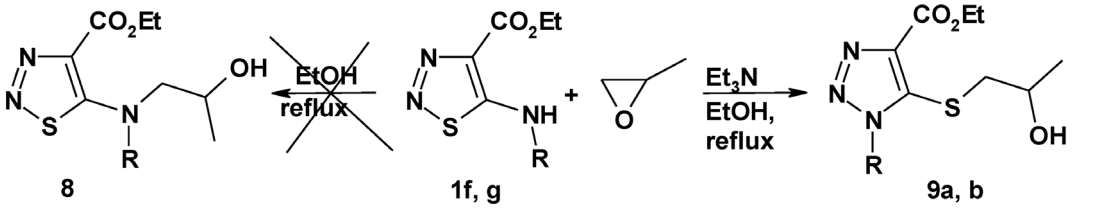


1b,c
1b R = 4-MeC$_6$H$_4$
1c R = 4-MeOC$_6$H$_4$

7a,b
7a R = 4-MeC$_6$H$_4$ (62 %)
7b R = 4-MeOC$_6$H$_4$ (66 %)

5 b,c
5b R = 4-MeC$_6$H$_4$ (85 %)
5c R = 4-MeOC$_6$H$_4$ (46 %)

We also studied the alkylation reaction of ethyl 5-amino-1,2,3-thiadiazole-4-carboxylate **1** with propylene oxide. As described for the previous case, the reaction was first attempted in refluxing ethanol, but these conditions failed to yield product **8**, even when the ratio of propylene oxide was increased fivefold.



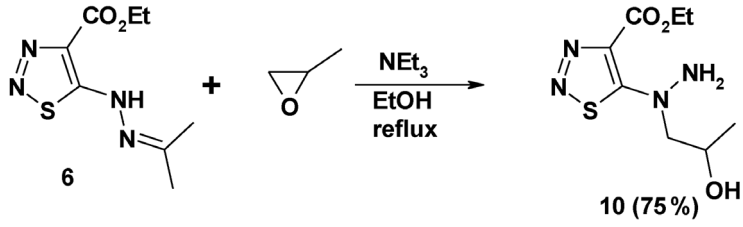
8

1f, g
1f R = 4-EtOC$_6$H$_4$
1g R = 3-MeC$_6$H$_4$

9a, b
9a R = 4-EtOC$_6$H$_4$ (80 %)
9b R = 3-MeC$_6$H$_4$ (82 %)

However, if the base (triethylamine) was included in the reaction mixture, Dimroth rearrangement [11] took place as in the case of alkylation with epichlorhydrin. The 5-amino-1,2,3-thiadiazole **1** was thus transformed into intermediate 5-mercapto-1,2,3-triazole **7** which then reacted with propylene oxide to give ethyl 1-aryl-5-(hydroxypropyl-2)sulfanyl-1,2,3-triazole-4-carboxylates **9** in 80 % yield.

In contrast to amines **1a–d,f,g** and hydrazine **1e**, the hydrazone **6** in reaction with propylene oxide conducted itself in other way. We established that hydrazone **6** alkylation with double excess of propylene oxide in ethanol with triethylamine presence after refluxing for 2 h took place and the individual product was obtained. In ^{1}H NMR spectrum of the product signals for ethyl ester group, hydroxypropyl-2 fragment as a multiplet at 3.72–3.84 ppm for the 2'-CH-fragment, AB system at 2.85 and 3.21 ppm for 1'-CH_2, and a doublet at 1.26 ppm for 3'-CH_3. Also, a broad singlet integrated for 2 protons was registrated at 6.04 ppm, which we assumed to be an amino proton signal. The presence of the amino group in the compound was confirmed by IR data. There were no signals for *iso*-propylidene fragment at NMR spectrum. According to all these data we suppose the structure **10**.



Fungicide activities against the representative typical fungi often occurring in the Chinese agroecosystem such as: AS: *Alternaria solani*; AK: *Alternaria kikuchiana*; BC: *Botrytis cinerea*; CB, *Cercospora beticola*; CC: *Cercosporara chidicola*; CL: *Colletotrichum lagenarium*; FO: *Fusarium oxysporum cucumerinum*; GZ: *Gibberella zeae*; PP: *Physalospora piricola*; PS: *Pellicularia sasakii*; SS: *Sclerotinia sclerotiorum*; and VD: *Verticilium dahliae* were detected at 50 μg/mL. The results indicated that some compounds had good fungicide activity (Table 1). Compounds **5b,d** inhibited >65 % of the growth to CC and CB, respectively. Thiadiazole **1d** is active to inhibit the growth of fungi PP, BC, CL, VD, and CC, too.

Table 1 Fungicide activity of the title compounds (percent).[a]

Compd.	SS	PS	PP	GZ	FO	AS	BC	CL	PI	CB	VD	CC
1d	nt	29.6	66.7	29.4	25.0	25.0	66.7	76.5	25.0	33.3	66.6	66.6
1f	6.8	2.6	nt	21.1	16.7	nt	30.4	48.5	16.2	20	30	nt
1g	nt	40.1	8.9	14.7	16.1	18.2	46.4	9.1	28.1	28.6	28.6	nt
5	13.6	12.8	nt	10.5	13.9	60.0	60.9	60.6	5.4	20.0	20.0	nt
5b	nt	nt	27.8	11.8	25.0	nt	61.9	29.4	nt	nt	33.3	66.6
5c	nt	21.6	13.2	16.7	30	12.5	nt	36.0	25.0	11.1	14.3	10.0
5d	nt	37.0	38.9	5.9	16.7	50.0	71.4	52.9	18.8	66.6	33.3	50.0
5e	nt	18.2	42.2	17.6	9.7	nt	21.4	27.3	nt	nt	nt	nt

[a]AS: *Alternaria solani*; AK: *Alternaria kikuchiana*; BC: *Botrytis cinerea*; CB: *Cercospora beticola*; CC: *Cercosporara chidicola*; CL: *Colletotrichum lagenarium*; FO: *Fusarium oxysporum cucumerinum*; GZ: *Gibberella zeae*; PP: *Physalospora piricola*; PS: *Pellicularia sasakii*; SS: *Sclerotinia sclerotiorum*; VD: *Verticilium dahliae*; nt: not tested.

CONCLUSION

Synthetic routes are established for Dimroth rearrangement. In basic media, alkylation of 5-aminosubstituted-1,2,3-thiadiazole **1** with both epichlorohydrin and propylene oxide leads only to rearrangement products. Whereas in the same media, alkylation of hydrazone **6** keeps the 1,2,3-thiadiazole cycle and Dimroth rearrangement does not take place.

In summary, 5-(2-hydroxypropyl)amino-1,2,3-thiadiazole and 5-(2-hydroxypropyl)sulfanyl-1,2,3-triazole derivatives are new classes of lead compounds to control plant fungal diseases. Further evaluations are necessary to determine the antifungal spectrum of these compounds and their effects on plant protection in the field.

EXPERIMENTAL

Apparatus: Proton and carbon NMR spectra (^{1}H and ^{13}C NMR) were recorded on a Bruker DRX-400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz) spectrometer. Melting points were determined using Stuart SM.P.3. Infrared (IR) spectra were recorded on Fourier transform ALPHA-E spectrometer and are reported in cm^{-1}. Mass spectra were obtained with MAT11 spectrometer. Analytical thin layer chromatography (TLC) was performed on DC-Plastikfolen Kieselgel 60 F254.

General procedure for synthesis of ethyl 5-amino-1,2,3-thiadiazole-4-carboxylates 1a–g

To a solution of ethyl 5-chloro-1,2,3-thiadiazole-4-carboxylate (1.93 g; 10 mmol) in ethanol (10 mL), the corresponding amine (20 mmol) was added. The reaction mixture was cooled to –15 °C for 2 h, then the precipitate was filtrated, washed with water (10 mL), and dried.

Ethyl 5-phenylamino-1,2,3-thiadiazole-4-carboxylate (1a): Yield 1.93 g (76 %); m.p. 94 °C. ^{1}H NMR (DMSO-d_6): 10.15 (1H, s, NH), 7.17–7.48 (5H, m, ArH), 4.47 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 1.45 (3H, t, J = 7.0 Hz, OCH$_2$$CH_3$). Calcd. for $C_{11}H_{11}N_3O_2S$, %: N 16.86; S 12.86; found, %: N 16.93; S 12.77.

Ethyl 5-p-tolylamino-1,2,3-thiadiazole-4-carboxylate (1b): Yield 1.77 g (67 %); m.p. 74 °C. ^{1}H NMR (DMSO-d_6): 10.03 (1H, s, NH), 7.21–7.24 (4H, m, ArH), 4.47 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 2.35 (3H, s, CH$_3$), 1.45 (3H, t, J = 7.0 Hz, OCH$_2$$CH_3$). Calcd. for $C_{12}H_{13}N_3O_2S$, %: N 15.96; S 12.18; found, %: N 16.12; S 12.29.

Ethyl 5-(4-methoxyphenyl)amine-1,2,3-thiadiazole-4-carboxylate (1c): Yield 2.36 g (95 %); m.p. 125 °C. ^{1}H NMR (DMSO-d_6): 9.88 (1H, s, NH), 7.28 (2H, dd, J_1 = 6.7 Hz, J_2 = 2.1 Hz, ArH), 6.96 (2H, dd, J_1 = 6.7 Hz, J_2 = 2.4 Hz, ArH), 4.44 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 1.43 (3H, t, J = 7.0 Hz, OCH$_2$$CH_3$). IR (neat), ν/cm^{-1}: 3227 (N–H), 1661 (C=O). Calcd. for $C_{12}H_{13}N_3O_3S$, %: N 15.04; S 11.48; found, %: N 14.87; S 11.42.

Ethyl 5-benzylamino-1,2,3-thiadiazole-4-carboxylate (1d): Yield 0.79 g (30 %); m.p. 68 °C. ^{1}H NMR (DMSO-d_6): 8.83–8.86 (1H, m, NH), 7.25–7.34 (5H, m, ArH), 4.62 (2H, d, J = 5.8 Hz, CH$_2$), 4.40 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 1.41 (3H, t, J = 7.0 Hz, OCH$_2$$CH_3$). Calcd. for $C_{12}H_{13}N_3O_2S$, %: N 15.96; S 12.18; found, %: N 16.23; S 11.98.

Ethyl 5-hydrazine-1,2,3-thiadiazole-4-carboxylate (1e): Yield 1.37 g (73 %); m.p. 83 °C. ^{1}H NMR (DMSO-d_6): 9.06 (1H, br.s., NH), 5.58 (2H, br.s., NH), 4.35 (2H, q, J = 7.2 Hz, OCH_2CH$_3$), 1.38 (3H, t, J = 7.2 Hz, OCH$_2$$CH_3$). IR (neat), ν/cm^{-1}: 3293 (N–H), 3231 and 3152 (NH$_2$). Calcd. for $C_5H_8N_4O_2S$, %: N 29.79; S 17.04; found, %: N 29.93; S 16.87.

Ethyl 5-(4-ethoxyphenyl)amine-1,2,3-thiadiazole-4-carboxylate (1f): Yield 0.35 g (40 %); m.p. 92 °C. ^{1}H NMR (DMSO-d_6): 9.89 (1H, br.s., NH), 7.35 and 7.00 (4H, d, J = 8.9 Hz, ArH), 4.43 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 4.05 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 1.37 (3H, t, J = 7.0 Hz,

OCH_2CH_3), 1.33 (3H, t, J = 7.0 Hz, OCH_2CH_3). IR (neat), ν/cm^{-1}: 3389 (N–H), 1659 (C=O). Calcd. for $C_{13}H_{15}N_3O_3S$, %: N 14.32; S 10.93; found, %: N 14.29; S 10.86.

Ethyl 5-(2-methylphenyl)amine-1,2,3-thiadiazole-4-carboxylate (1g): Yield 1.97 g (75 %); m.p. 126 °C. ^{1}H NMR (DMSO-$d_{6+}CCl_4$): 10.02 (1H, br.s., NH), 7.25–7.34 (3H, m, ArH), 7.13–7.20 (1H, mArH), 4.47 (2H, q, J = 7.0 Hz, OCH_2CH_3), 2.34 (3H, s, CH_3), 1.46 (3H, t, J = 7.0 Hz, OCH_2CH_3). Calcd. for $C_{12}H_{13}N_3O_2S$, %: N 15.96; S 12.18; found, %: N 15.72; S 11.97.

General procedure for synthesis of ethyl 5-(3-chloro-2-hydroxy-propyl)sulphanyl-1,2,3-triazole-4-carboxylate 5a–e

Method A: To a suspension of 5-aminosubstitutient 1,2,3-thiadiazole **1** (3.5 mmol) in acetone (5 mL) sodium carbonate (3,5 mmol), epichlorhydrin (14 mmol) were added. The mixture was refluxed for 3 h, then sodium carbonate was filtrated, the solvent was evaporated. The product was crystallized from diethyl ether.

Method B: To a solution of 5-mercapto-1,2,3-triazole **7** (3.5 mmol) in DMF (ratio 1 mL of solvent to 1 mg of **7**) Na_2CO_3 (3.5 mmol) and epichlorohydrin (14 mmol) were added. The reaction mixture was heated till everything has been dissolved then it was kept for 4 h at room temperature. Water (10 mL) was added. The precipitate was filtrated and dried. If it is necessary, precipitate could be recrystallized from ethanol.

Ethyl 5-(3-chloro-2-hydroxy-propyl)sulphanyl-1-phenyl-1,2,3-triazole-4-carboxylate (5a): yield 0.78 g (65 %); m.p. 95–94 °C. ^{1}H NMR (DMSO-d_6): 7.61 (5H, s, ArH), 5.54 (1H, d, J = 5.2 Hz, OH), 4.42 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.66 (1H, m, CH), 3.36 (2H, d, J = 5.5 Hz, CH_2Cl), 3.12 (1H, dd, J_1 = 13.4 Hz, J_2 = 4.5 Hz, CH_2S), 2.99 (1H, dd, J_1 = 13.4 Hz, J_2 = 6.7 Hz, CH_2S), 1.43 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR (DMSO-d_6): 14.05, 20.73, 38.92, 47.84, 60.78, 69.53, 126.12, 129.67, 132.79, 136.48, 139.59, 140.16, 160.01. IR (neat), ν/cm^{-1}: br. 3352 (O–H), 1724 (C=O), 842 (C–Cl). Calcd. for $C_{14}H_{16}ClN_3O_3S$, %: N 12.29; S 9.38; found %: N 12.47; S 9.12.

Ethyl 5-(3-chloro-2-hydroxy-propyl)sulphanyl-1-*p*-tolyl-1,2,3-triazole-4-carboxylate (5b): Yield 1.06 g (85 %); m.p. 92 °C. ^{1}H NMR (DMSO-d_6): 7.43 and 7.46 (2 × 2H, d, J = 8.6 Hz, ArH), 5.21 (1H, d, J = 6.0 Hz, OH), 4.41 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.67 (1H, m, CH), 3.37 (2H, d, J = 5.5 Hz, CH_2Cl), 2.93 and 3.14 (2H, m, CH_2S), 2.48–2.52 (3H, m, CH_3), 1.42 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR (DMSO-d_6): 14.05, 20.73, 38.87, 47.44, 60.78, 69.53, 126.12, 129.67, 132.79, 136.48, 139.59, 140.16, 160.01. IR (neat), ν/cm^{-1}: 3389 (N–H), 1712 (C=O), 822 (C–Cl). MS, *m/z* (%): 355 $[M]^{+\cdot}$(5). Calcd. for $C_{15}H_{18}ClN_3O_3S$, %: N 11.81; S 9.01; found, %: N 12.01; S 8.98.

Ethyl 5-(3-chloro-2-hydroxy-propyl)sulphanyl-1-(4-methoxyphenyl)-1,2,3-triazole-4-carboxylate (5c): Yield 0.69 g (53 %); m.p. 80 °C. ^{1}H NMR (DMSO-d_6): 7.42–7.53 (2H, m, ArH), 7.07–7.13 (2H, m, ArH), 5.22 (1H, d, J = 5.2 Hz, OH), 4.41 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.89 (3H, s, OCH_3), 3.67 (1H, m, CH), 3.38 (2H, d, J = 5.5 Hz, CH_2Cl), 3.11 (1H, dd, J_1 = 13.4 Hz, J_2 = 4.6 Hz, CH_2S), 2.97 (1H, dd, J_1 = 13.4 Hz, J_2 = 6.4 Hz, CH_2S), 1.43 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR (DMSO-d_6): 14.07, 38.81, 47.48, 55.56, 60.79. 69.55, 114.34, 127.78, 128.03, 136.62, 139.48, 160.06, 160.33. IR (neat), ν/cm^{-1}: 3406 (O–H), 1719 (C=O), 833 (C–Cl). Calcd. for $C_{15}H_{18}ClN_3O_4S$, %: N 11.30; S 8.62; found, %: N 11.52; S 8.79.

Ethyl 1-benzyl-5-(3-chloro-2-hydroxy-propyl)sulphanyl-1,2,3-triazole-4-carboxylate (5d): Yield 0.77 g (62 %); m.p. 55 °C. ^{1}H NMR (DMSO-d_6): 7.19–7.38 (5H, m, ArH), 5.71 (2H, s, CH_2), 5.36 (1H, d, J = 5.2 Hz, OH), 4.37 (2H, d, J = 7.0 Hz, OCH_2CH_3), 3.67–3.73 (1H, m, CH), 3.48 (2H, d, J = 5.5 Hz, CH_2Cl), 3.17 (1H, dd, J_1 = 13.4 Hz, J_2 = 4.3 Hz, CH_2S), 3.01 (1H, dd, J_1 = 13.4 Hz, J_2 = 7.3 Hz, CH_2S), 1.40 (3H, t, J = 7.0 Hz, OCH_2CH_3). IR (neat), ν/cm^{-1}: 3333 (O–H), 1721 (C=O), 841 (C–Cl). Calcd for $C_{15}H_{18}ClN_3O_3S$, %: N 11.81; S 9.01; found, %: N 11.73; S 9.14.

Ethyl 1-amino-5-(3-chloro-2-hydroxypropyl)sulphanyl-[1,2,3]-triazole-4-carboxylate (5e): As a solvent acetonitrile was used. Yield 0.77 g (62 %); m.p. 55 °C. ^{1}H NMR (DMSO-d_6): 5.38 (3H,

br. s, OH + NH_2), 4.45 (2H, q, J = 7.0 Hz, O$CH_2$$CH_3$), 4.11–4.23 (1H, m, CH), 3.63 (2H, d, J = 5.5 Hz, CH_2Cl), 3.26 (1H, dd, J_1 = 13.4 Hz, J_2 = 4.3 Hz, CH_2S), 3.09 (1H, dd, J_1 = 13.4 Hz, J_2 = 7.3 Hz, CH_2S), 1.45 (3H, t, J = 7.0 Hz, OCH$_2$CH_3). IR (neat), ν/cm^{-1}: 3412 (O–H), 3271 and 3217 (N–H), 1673 (C=O), 841 (C–Cl). Calcd. for $C_8H_{13}ClN_4O_3S$, %: N 19.96; S 11.42; found, %: N 20.16; S 11.36.

Procedure for synthesis of ethyl 5-(2-(propan-2-ylidene)hydrazinyl)-1,2,3-thiadiazole-4-carboxylate (6) [12]. A solution of ethyl 5-hydrazine-1,2,3-thiadiazole-4-carboxylate **1e** (5 mmol) in acetone (10 mL) was refluxed for 3 h then cooled to room temperature. The precipitate was filtrated. Yield 1.00 g (66 %); m.p. 152 °C. ^{1}H NMR ($DCCl_3$): 10.12 (1H, br.s., NH), 4.49 (2H, q, J = 7.2, O$CH_2$$CH_3$), 2.09 (3H, s, CH_3), 2.01 (3H, s, CH_3), 1.47 (3H, t, J = 7.2 Hz, OCH$_2$$CH_3$). MS, *m/z* (%): 228 ($M^+$, 81 %). Calcd. for $C_8H_{12}N_4O_2S$, %: N 24.54; found, %: N 24.32.

General procedure for synthesis of ethyl 5-sulfanyl-1,2,3-triazole-4-carboxylate (7)

To a solution of 5-amino-1,2,3-thiadiazole **1** (5 mmol) in ethanol (15 mL) triethylamine (15 mmol) was added. The reaction mixture was refluxed overnight then water (10 mL) and 6 N HCl (15 mL) were added. The precipitate was filtrated and washed with water until neutral pH and dried.

Ethyl 5-sulfanyl-1-p-tolyl-1H-1,2,3-triazole-4-carboxylate (7a): Yield 0.82 g (62 %); m.p. 67 °C. ^{1}H NMR (DMSO-d_6): 7.31 and 7.45 (4H, d, J = 8.5 Hz, ArH), 4.26 (2H, q, J = 7.0 Hz, O$CH_2$$CH_3$), 2.46–2.51 (3H, m, CH_3), 1.33 (3H, t, J = 7.0 Hz, OCH$_2$$CH_3$). Calcd. for $C_{12}H_{13}N_3O_2S$, %: N 15.96; S 12.18; found, %: N 15.87; S 12.02.

Ethyl 5-sulfanyl-1-(4-methoxephenyl)-1,2,3-triazole-4-carboxylate (7b): Yield 0.92 g (66 %); m.p. 56 °C. ^{1}H NMR (DMSO-d_6): 7.35 and 7.07 (4H, dd, J_1 = 7.0 Hz, J_2 = 2.1 Hz, ArH), 4.24 (2H, q, J = 7.0 Hz, O$CH_2$$CH_3$), 3.07 (3H, s, CH_3), 1.34 (3H, t, J = 7.0 Hz, OCH$_2$$CH_3$). IR (neat), ν/cm^{-1}: 2470 (S–H), 1676 (C=O). Calcd. for $C_{12}H_{13}N_3O_3S$, %: N 15.04; S 11.48; found, %: N 14.87; S 11.32.

General procedure for synthesis of ethyl 5-(2-hydroxy-propyl)sulphanyl-1,2,3-triazole-4-caroxylate (9)

To a solution of 5-amino-1,2,3-thiadiazole **1** (1 mmol) in ethanol (15 mL) triethylamine (3 mmol) and propylene oxide (2 mmol) were added. The reaction mixture was refluxed for 3 h, then ethanol was evaporated. To the residue chloroform (15 mL) was added and washed with 6 N HCl (15 mL) and water (3 × 15 mL). The organic layer was dried with Na_2SO_4, solvent was evaporated.

Ethyl 1-(4-ethoxyphenyl)-5-(2-hydroxypropyl)sulphanyl-1,2,3-triazole-4-carboxylate (9a): Yield 0.24 g (80 %); oil. ^{1}H NMR ($CHCl_3$): 7.45 (2H, d, J = 8.8 Hz, ArH), 7.04 (2H, d, J = 8.8 Hz, ArH), 4.51 (2H, q, J = 7.2 Hz, O$CH_2$$CH_3$), 4.11 (2H, q, J = 7.2 Hz, O$CH_2$$CH_3$), 3.55–3.65 (1H, m, CH), 2.95 (1H, br.s., OH), 2.89 (1H, dd, J_1 = 13.6 Hz, J_2 = 2.8 Hz, CH), 2.59 (1H, dd, J_1 = 13.6 Hz, J_2 = 9.2 Hz, CH), 1.47 (6H, t, J = 7.2 Hz, OCH$_2$$CH_3$), 1.12 (3H, d, J = 7.2 Hz, CH_3). MS, *m/z* (%): 351 $[M]^+$ (23). Calcd. for $C_{16}H_{21}N_3O_4S$, %: N 11.96; S 9.12; found, %: N 11.91; S 9.15.

Ethyl 1-(2-methylphenyl)-5-(2-hydroxypropyl)sulphanyl-1,2,3-triazole-4-carboxylate (9b): Yield 0.26 g (82 %); oil. ^{1}H NMR ($CHCl_3$): 7.53–7.49 (1H, m, HAr), 7.41–7.38 (2H, m, HAr), 7.25–7.24 (1H, m, HAr), 4.52 (2H, q, J = 7.2 Hz, OCH$_2$$CH_3$), 3.59–3.68 (1H, m, CH), 2.89 (1H, dd, J_1 = 13.6 Hz, J_2 = 2.8 Hz, CH), 2.56 (1H, dd, J_1 = 13.6 Hz, J_2 = 9.2 Hz, CH), 2.07 (3H, s, CH_3), 1.48 (3H, t, J = 7.2 Hz, OCH$_2$$CH_3$), 1.11 (3H, d, J = 7.2 Hz, CH_3). MS, *m/z* (%): 321 $[M]^+$ (5). Calcd. for $C_{15}H_{19}N_3O_3S$, %: N 13.07; S 9.98; found, %: N 13.01, S 10.15.

Ethyl 5-(2-(2-hydroxypropyl)hydrazine)-1,2,3-thiadiazole-4-carboxylate (10): To a solution of 5-hydrazino-1,2,3-thiadiazole **1e** (1 mmol) in ethanol (15 mL) triethylamine (3 mmol) and propylene oxide (2 mmol) were added. The reaction mixture was refluxed 3 h, then ethanol was evaporated. To the residue chloroform (15 mL) was added and washed with 6 N HCl (15 mL) and water (3 × 15 mL). The organic layer was dried with Na_2SO_4, solvent was evaporated. Yield 0.25 g (75 %); oil. ^{1}H NMR

($CHCl_3$): 6.04 (2H, br.s., NH_2), 4.46 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.72–3.84 (1H, m, CH), 3.21 (1H, dd, J_1 = 14.2 Hz, J_2 = 2.8 Hz, CH), 2.85 (1H, dd, J_1 = 14.2 Hz, J_2 = 8.8 Hz, CH), 1.44 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.26 (3H, d, J = 7.2 Hz, CH_3). IR (neat), ν/cm^{-1}: br. 3483 (O–H), 3384 and 3313 (N–H), 1725 (C=O). MS, *m/z* (%): 246 $[M]^{+\cdot}$(4). Calcd. for $C_8H_{14}N_4O_3S$, %: C 39.01; H 5.73; N 22.75; S 13.02; found, %: C 38.93; H 5.87; N 22.68; S 13.11.

Biological screening: Fungicidal activity of the target compounds was evaluated according to the standard operation practice (SOP) by the fungi growth inhibition method described [13]. Fungi used in these studies included AS: *Alternaria solani*; AK: *Alternaria kikuchiana*; BC: *Botrytis cinerea*; CB: *Cercospora beticola*; CC: *Cercosporara chidicola*; CL: *Colletotrichum lagenarium*; FO: *Fusarium oxysporum cucumerinum*; GZ: *Gibberella zeae*; PP: *Physalospora piricola*; PS: *Pellicularia sasakii*; SS: *Sclerotinia sclerotiorum* and VD: *Verticilium dahliae.* The test concentration detected was 50 μg/mL.

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