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Synthesis and Biological Activities of Some Novel Triazolothiadiazines and Schiff Bases Derived from 1,2,4-Triazole

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Synthesis and Biological Activities of Some Novel Triazolothiadiazines and Schiff Bases Derived from 1,2,4-Triazole

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3-substituted-4-amino-5-mercapto-1,2,4-triazoles are versatile compounds for constructing various biologically active heterocycles. To find more 1,2,4-triazole derivatives that may possess significant biological activities, we synthesized a number of novel 3-(4-ethoxyphenyl)-6-aryl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines and 4-(arylmethylidene)amino-5-(4-ethoxyphenyl)-3-mercapto-4H-1,2,4-triazoles. All the title compounds were characterized by elemental analysis and NMR data, and the compound **5f** *was investigated with X-ray crystallography (CCDC No. 611639). The plant-growth regulating effects of those Schiff bases were examined, and they showed an inhibiting effect on the growth of wheat radicles and radish radicles.*

Keywords 1,2,4-triazoles; biological activities; crystal structure; Schiff base; synthesis; triazolothiadiazines

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INTRODUCTION

Triazoles and their heterocyclic derivatives represent an interesting class of compounds possessing a wide spectrum of biological activities, such as analgesic,[1] anthelmintic,[2] antitubercular,[3] plant-growth regulating,[4] antiviral,[5] antifungal[6] and anticancer[7] activities. In a previous article, Ye et al. reported the synthesis of some compounds containing the triazolothiadiazine ring, which possess a moderate promoting effect on the growth of mung bean sprouts.[8] In view of these facts and as a continuation of our research on the synthesis and biological properties of triazole derivatives, we have synthesized a series of 4-ethoxyphenyl substituted fused-triazole systems and determined the plant-growth regulating effects of some title compounds.

RESULTS AND DISCUSSION

In ^{1}H NMR spectra of triazolothiadiazines, the characteristic downfield signal at δ 13.8 ppm attributed to the –N=C–SH moiety was absent. A sharp signal at δ 5.8 ppm attributable to the N–NH_2 group in the parent triazole was also absent in the cyclized product. In NMR spectra of the title compounds **5a–5j**, the observation of additional resonances assigned to the SCH_2 (δ 4.4–4.5 ppm in ^{1}H NMR spectra and 22.8–25.8 ppm in ^{13}C NMR spectra) confirmed the ring closure. Concerning ^{1}H NMR and ^{13}C NMR spectra of fluoro-substituted compounds **5e** and **5f**, it should be noted that the second-order pattern representative of a substituted phenyl ring was further complicated due to the presence of couplings with ^{19}F.

In an attempt to prepare ring-closed derivatives **7**, we applied a previously reported procedure[9] and treated triazole **4** with the appropriate benzaldehyde, maintaining pH values during the reaction at 5–6 because the acidity of the reaction medium is crucial, as reported previously.[9] However, with seven differently substituted benzaldehydes that we have used to carry out this reaction under the previously mentioned conditions, we could only obtain open-chain hydrazones **6a–g**. Compounds **6a–g** were established unambiguously by ^{1}H NMR and ^{13}C NMR data. In ^{1}H NMR and ^{13}C NMR spectra we observed the peak of the –N=CH– proton at 9.49–10.15 ppm and the corresponding carbon at about 150 ppm, which correspond to the previously mentioned open-chain structure. A downfield signal appearing at 10.7–11.7 ppm is attributed to the –NH–C=S moiety. A triplet at 1.5 ppm in the ^{1}H NMR spectra and the corresponding carbon at about 14 ppm ^{13}C NMR spectra are attributable to the $-CH_3$ group. A quartet at 4.1 ppm in the ^{1}H NMR spectra and the corresponding carbon at about 63 ppm ^{13}C NMR spectra are attributable to the $-OCH_2-$group. The remaining protons resonated as multiplets in the aromatic region δ 7.0–7.9 ppm.

TABLE I Effect of the Title Compounds on Wheat- and Radish-Radicles Growth

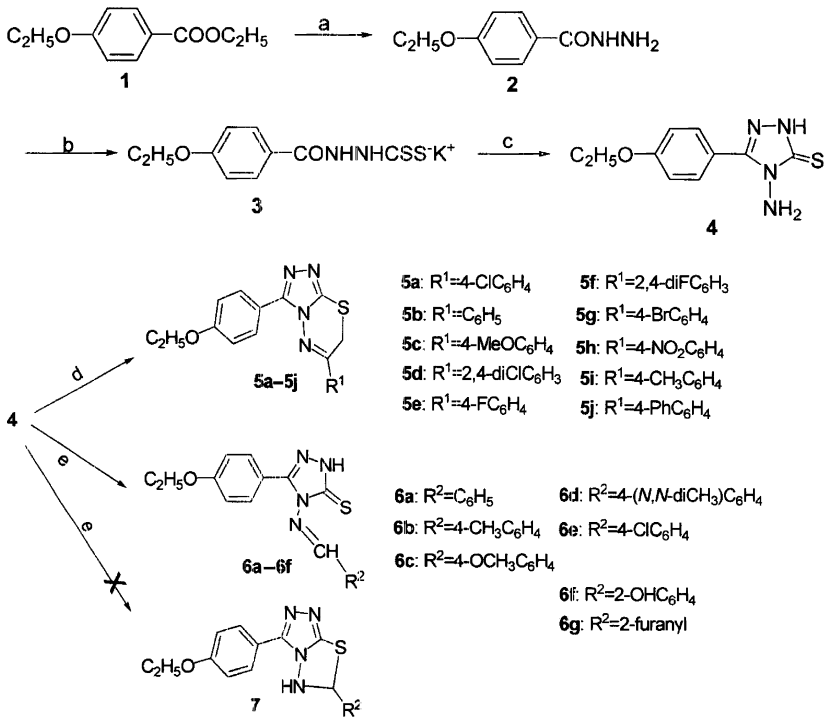
	Growth Promotion on Wheat Radicles (%)		Growth Promotion on Radish Radicles (%)	
Compound	5 ppm	1 ppm	5 ppm	1 ppm
6a	−60.1	−59.2	−43.1	−41.0
6b	−49.8	−60.2	−12.3	−38.5
6c	−100	−80.0	−100	−63.6
6d	−90.5	−84.0	−87.7	−66.7
6e	−87.9	−73.9	−81.5	−50.0
6f	−83.2	−79.0	−74.5	−63.6
6g	−82.6	−77.1	−75.4	−63.6

The effect of the title compounds **6a–g** on sprouting wheat and radish seeds was been investigated. After treating with a culture solution of 5 μg/mL of the title compounds **6a–g** for 36 h, the lengths of wheat radicles ("radicle" refers to the part of a plant embryo that develops into a root) were measured with reference of distilled water, then the growth-promoting percentages were calculated. Using same method, the percentage concentration of 1 μg/mL and corresponding values on radish radicles were also obtained. The results are shown in Table I. The results indicate that newly syhthesized compounds **6a–g** show an inhibiting effect on the growth of wheat and radish radicles at a mass concentration of 5 μg/mL and 1 μg/mL, and therefore the structures need to be optimized.

EXPERIMENTAL

All melting points were determined on an XT-4A apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Advance 300 spectrometer in DMSO-d_6 or $CDCl_3$ solutions using TMS as an internal reference. Elemental analyses were carried out with an EA 1112 elemental analyzer. The crystal structure was measured on a Bruker APEX area-detector diffractometer. All reagents used were analytical reagents.

Ethyl 4-ethoxybenzoate 1 (50 mL) and 85% hydrazine hydrate (25 mL) were converted first to the corresponding hydrazide **2**. Hydrazide **2** (0.1 mol) was heated with carbon disulfide (10 mL) in the presence of absolute ethanol (100 mL) and potassium hydroxide (10 g) to afford intermediate potassium acylhydrazine dithioformate **3** (Scheme 1). This salt (0.05 mol) underwent ring closure with an excess of 85% hydrazine hydrate (0.16 mol) to give 4-amino-3-(4-ethoxyphenyl)-5-mercapto-1,2,4-triazole **4**. Heating at reflux triazole



SCHEME 1 (a) $NH_2NH_2H_2O$ 85%; (b) CS_2, EtOH, KOH, reflux; (c) $NH_2NH_2H_2O$ 85%, reflux; (d) R^1COCH_2X (X=Br, Cl), EtOH, reflux; (e) R^2CHO, EtOH, pH = 5–6, reflux.

4 (1 mmol) with absolute ethanol (1 5 mL) and the appropriate substituted phenacyl bromide (or chloride) (1 mmol) provided the 3,6-disubstituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines **5a–j**.

Purified product **5f** was dissolved in 95% ethanol and kept at r.t. for 5 d, and single crystals of **5f** were formed. The structure of **5f** is shown in Figure 1. Fractional coordinates and mean temperature factors with estimated standard deviations for non–hydrogen atoms are listed in Table II and selected bond angles are given in Table III. Geometric calculations were performed using the program SHELXL-97.

The reaction of triazole **4** and the appropriate benzaldehyde in absolute ethanol maintaining pH values during the reaction at 5–6 afforded Schiff bases **6a–g**.

5a: 6-(4-Chlorophenyl)-3-(4-ethoxyphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine

To a solution of compound **4** (236 mg, 1 mmol) in absolute C_2H_5OH (20 mL) was added 2-bromo-4′-chloroacetophenone (233 mg, 1 mmol).

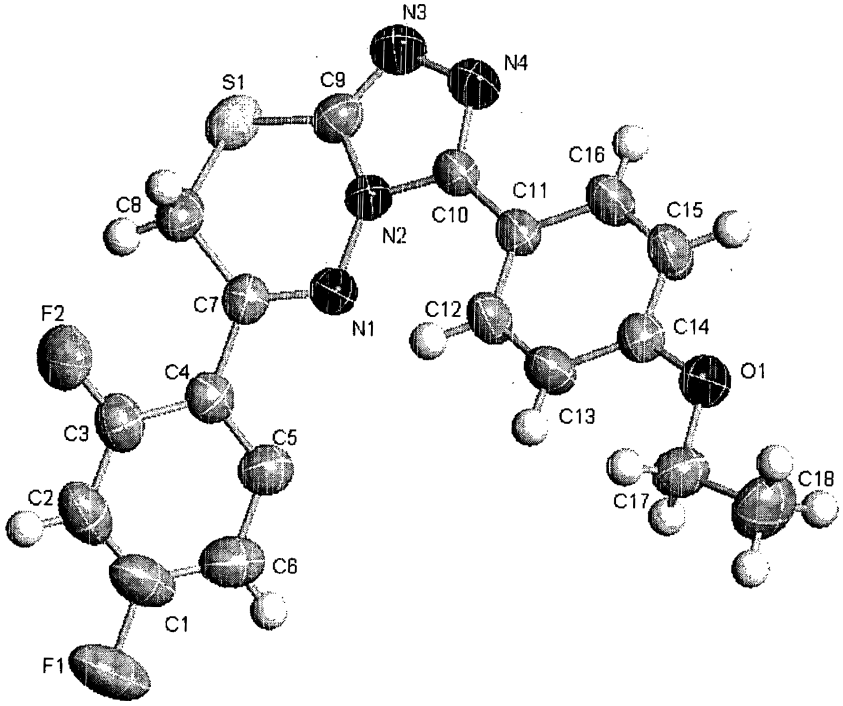


FIGURE 1 An ORTEP drawing of compound **5f** showing the atom numbering scheme.

The mixture was refluxed for 7 h. The solid obtained on cooling was filtered, washed with cold water, dried, and recrystallized from C_2H_5OH to give the title compound (yield: 73.0%). M.p. 215–217°C; ^{1}H NMR (300 MHz, DMSO-d_6, 25°C, TMS) δ (ppm) = 7.97 (dd, J = 8.6Hz, 4H, ArH), 7.38 (dd, J = 8.9Hz, 4H, ArH), 4.41 (s, 2H, SCH_2), 4.11 (q, J = 6.9Hz, 2H, OCH_2), 1.36 (t, J = 6.9Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ (ppm) = 160.26, 155.00, 151.76, 142.06, 136.94, 132.61, 129.71, 129.52, 129.41, 118.31, 114.87, 63.54, 22.85, 14.76; elemental anal. calcd. (%) for $C_{18}H_{15}ClN_4OS$(370.9): C 58.30, H 4.08, N 15.11, S 8.65; found: C 58.50, H 4.16, N 15.00, S 8.59.

The following compounds were prepared by an analogous procedure.

5b: 3-(4-Ethoxyphenyl)-6-phenyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine

Yield: 68.3%; m.p. 189–191°C; ^{1}H NMR (300 MHz, DMSO-d_6, 25°C, TMS) δ (ppm) = 8.00 (d, J = 8.6Hz, 2H, ArH), 7.62–7.55 (m, 5H, ArH), 7.14 (q, J = 2.7Hz, 2H, ArH), 4.44 (s, 2H, SCH_2), 4.13 (q, J = 6.9Hz,

TABLE II Crystal Data and Summary of Data Collection and Structure Refinement

Compound	$C_{18}H_{13}F_2N_4O\,S$
Color	Yellow
Formula weight	317.38
Crystal system	Triclinic
Temperature, °C	25(298K)
Cell constants	
a (Å)	9.243(3)
b (Å)	10.332(3)
c (Å)	10.807(3)
α (Å)	70.109(5)
β (Å)	66.434(4)
γ (Å)	69.239(5)
Volume (Å^3)	860.5(4)
Formula units	2
Calculated density (g/cm^{-3})	1.433
F(000)	382
Absorption coefficient, μm^{-3}	0.223
Limiting indices	$-10 \le h \le 10$; $-12 \le k \le 12$; $-12 \le l \le 12$
Reflections collected/unique	4544/2997 [R(int) = 0.0114]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9425 and 0.9101
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2997/0/239
Goodness of fit on F^2	1.027
Final R indices	$R_1 = 0.0483$, $wR_2 = 0.1247$
Largest diff. peak and hole (e Å^{-3})	0.434 and −0.327

2H, OCH_2), 1.34 (t, $J = 6.9$Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ (ppm) = 160.03, 155.94, 134.02, 132.01, 129.59, 129.26, 127.66, 127.54, 118.01, 114.90, 114.81, 63.46, 22.89, 14.72; elemental anal. calcd. (%) for $C_{18}H_{16}N_4OS$(336.4): C 64.26, H 4.79, N 16.65, S 9.53; found: C 64.06, H 4.58, N 16.41, S 9.42.

5c: 3-(4-Ethoxyphenyl)-6-(4-methoxyphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine

Yield: 69.1%; m.p. 201–202°C; ^{1}H NMR (300 MHz, DMSO-d_6, 25°C, TMS) δ (ppm) = 8.00–7.95 (m, 4H, ArH), 7.13–7.10 (m, 4H, ArH), 4.39 (s, 2H, SCH_2), 4.11 (q, $J = 6.9$Hz, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 1.35 (t, $J = 6.9$Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) = 162.24, 159.94, 155.27, 151.28, 141.91, 129.37, 125.58, 118.36, 114.59, 114.55, 114.13, 63.29, 55.55, 22.48, 14.58; elemental anal. calcd. (%) for $C_{19}H_{18}N_4O_2S$ (366.4):

TABLE III Fractional Coordinates and Mean Temperature Factors with Estimated Standard Deviations for Non–hydrogen Atoms

	x	y	z	U(eq)
S(1)	10990(1)	8856(1)	1574(1)	64(1)
F(1)	1443(2)	9958(2)	5028(2)	116(1)
F(2)	6666(3)	7444(2)	5033(2)	85(1)
F(2′)	5597(7)	10078(7)	933(6)	85(1)
O(1)	7739(2)	4970(2)	−3153(2)	64(1)
N(1)	8394(2)	8096(2)	961(2)	48(1)
N(2)	10042(2)	7697(2)	227(2)	47(1)
N(3)	12612(2)	7760(2)	−734(2)	64(1)
N(4)	12202(2)	7212(2)	−1528(2)	61(1)
C(1)	3054(3)	9566(3)	4330(3)	76(1)
C(2)	4061(3)	8684(3)	5056(3)	74(1)
C(3)	5683(3)	8316(2)	4331(2)	60(1)
C(4)	6308(2)	8793(2)	2903(2)	50(1)
C(5)	5206(3)	9692(2)	2207(2)	61(1)
C(6)	3568(3)	10101(3)	2920(3)	75(1)
C(7)	8060(2)	8316(2)	2156(2)	47(1)
C(8)	9321(3)	8099(2)	2798(2)	59(1)
C(9)	11304(3)	8048(2)	292(2)	54(1)
C(10)	10664(2)	7195(2)	−960(2)	48(1)
C(11)	9803(2)	6665(2)	−1481(2)	47(1)
C(12)	8306(3)	6362(2)	−724(2)	57(1)
C(13)	7565(3)	5830(2)	−1252(2)	58(1)
C(14)	8330(2)	5554(2)	−2559(2)	52(1)
C(15)	9832(3)	5849(3)	−3333(2)	62(1)
C(16)	10555(3)	6388(3)	−2804(2)	60(1)
C(17)	6131(3)	4754(3)	−2442(3)	64(1)
C(18)	5747(4)	4179(3)	−3337(3)	90(1)

C 62.28, H 4.95, N 15.29, S 8.75; found: C 62.09, H 4.77, N 15.01, S 8.69.

5d: 6-(2,4-Dichlorophenyl)-3-(4-ethoxyphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine

Yield: 69.0%; m.p. 187–189°C; ^{1}H NMR (300 MHz, DMSO-d_6, 25°C, TMS) δ (ppm) = 7.98–7.74 (m, 5H, ArH), 7.13 (d, 2H, ArH), 4.30 (s, 2H, SCH_2), 4.11 (q, J = 6.9Hz, 2H, OCH_2), 1.35 (t, J = 6.9Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) = 160.73, 159.90, 132.47, 131.66, 130.21, 129.95, 129.62, 129.52, 128.20, 127.73, 114.78, 114.62, 114.51, 63.44, 25.79, 14.68; elemental anal. calcd. (%) for $C_{18}H_{14}Cl_2N_4OS$(405.3):

TABLE IV Selected Bond Lengths (Å)

S(1)	C(9)	1.730(2)
S(1)	C(8)	1.807(2)
F(1)	C(1)	1.354(3)
F(2)	C(3)	1.311(3)
F(2′)	C(5)	1.232(6)
O(1)	C(14)	1.360(2)
O(1)	C(17)	1.434(3)
N(1)	C(7)	1.282(2)
N(1)	N(2)	1.389(2)
N(2)	C(9)	1.371(3)
N(2)	C(10)	1.378(3)
N(3)	C(9)	1.295(3)
N(3)	N(4)	1.394(3)
N(4)	C(10)	1.308(3)
C(1)	C(2)	1.345(4)
C(1)	C(6)	1.373(4)
C(2)	C(3)	1.366(3)
C(3)	C(4)	1.390(3)
C(4)	C(5)	1.390(3)
C(4)	C(7)	1.475(3)
C(5)	C(6)	1.378(3)
C(7)	C(8)	1.499(3)
C(8)	H(8B)	0.9700
C(10)	C(11)	1.459(3)
C(11)	C(12)	1.382(3)
C(11)	C(16)	1.397(3)
C(12)	C(13)	1.374(3)
C(13)	C(14)	1.382(3)
C(14)	C(15)	1.385(3)
C(15)	C(16)	1.367(3)
C(17)	C(18)	1.493(3)

C 53.34, H 3.48, N 13.82, S 7.91; found: C 53.21, H 3.29, N 13.94, S 7.85.

5e: 3-(4-Ethoxyphenyl)-6-(4-fluorophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine

Yield: 72.0%; m.p. 215–217°C; ^{1}H NMR (300 MHz, DMSO-d_6, 25°C, TMS) δ (ppm) = 7.98–7.93 (m, 4H, ArH), 7.13–7.04 (m, 4H, ArH), 4.42 (s, 2H, SCH_2), 4.10 (q, J = 6.9Hz, 2H, OCH_2), 1.36 (t, J = 6.9Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) = 166.73, 159.89, 149.21, 130.37, 130.26, 129.69,

TABLE V Selected Bond Angles (°)

C(9)	S(1)	C(8)	94.59(10)
C(14)	O(1)	C(17)	118.13(16)
C(7)	N(1)	N(2)	115.91(16)
C(9)	N(2)	C(10)	105.37(16)
C(9)	N(2)	N(1)	127.62(17)
C(10)	N(2)	N(1)	125.05(16)
C(9)	N(3)	N(4)	106.54(17)
C(10)	N(4)	N(3)	108.90(17)
C(2)	C(1)	F(1)	118.2(3)
C(2)	C(1)	C(6)	123.8(2)
F(1)	C(1)	C(6)	118.1(3)
C(1)	C(2)	C(3)	117.1(2)
F(2)	C(3)	C(2)	117.3(2)
F(2)	C(3)	C(4)	119.6(2)
C(2)	C(3)	C(4)	123.0(2)
C(5)	C(4)	C(3)	117.2(2)
C(5)	C(4)	C(7)	121.67(18)
C(3)	C(4)	C(7)	121.08(19)
F(2′)	C(5)	C(6)	116.1(4)
F(2′)	C(5)	C(4)	122.8(3)
C(6)	C(5)	C(4)	120.8(2)
C(1)	C(6)	C(5)	118.1(2)
N(1)	C(7)	C(4)	115.47(17)
N(1)	C(7)	C(8)	124.01(18)
C(4)	C(7)	C(8)	120.52(17)
C(7)	C(8)	S(1)	111.71(15)
N(3)	C(9)	N(2)	110.76(19)
N(3)	C(9)	S(1)	128.83(16)
N(2)	C(9)	S(1)	120.31(16)
N(4)	C(10)	N(2)	108.40(17)
N(4)	C(10)	C(11)	124.82(18)
N(2)	C(10)	C(11)	126.72(17)
C(12)	C(11)	C(16)	117.37(19)
C(12)	C(11)	C(10)	124.04(17)
C(16)	C(11)	C(10)	118.54(18)
C(13)	C(12)	C(11)	121.72(19)
C(12)	C(13)	C(14)	120.19(19)
O(1)	C(14)	C(13)	124.91(19)
O(1)	C(14)	C(15)	116.16(17)
C(13)	C(14)	C(15)	118.91(19)
C(16)	C(15)	C(14)	120.52(19)
C(15)	C(16)	C(11)	121.27(19)
O(1)	C(17)	C(18)	107.5(2)

129.60, 129.51, 117.83, 116.51, 116.22, 114.80, 114.50, 114.47, 109.46, 63.46, 22.82, 14.65; elemental anal. calcd. (%) for $C_{18}H_{15}FN_4OS$(354.4): C 61.00, H 4.27, N 15.81, S 9.05; found: C 61.21, H 4.21, N 15.94, S 8.95.

5f: 3-(4-Ethoxyphenyl)-6-(2,4-difluorophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine

Yield: 68.7%; m.p. 190–191°C; ^{1}H NMR (300MHz, DMSO-d_6, 25°C, TMS) δ (ppm) = 7.94–7.86 (m, 3H, ArH), 7.58–7.53 (m, 1H, ArH), 7.30–7.28 (m, 1H, ArH), 7.09–7.06 (m, 2H, ArH), 4.33 (d, 2H, SCH_2), 4.08 (q, J = 6.9Hz, 2H, OCH_2), 1.34 (t, J = 6.9Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) = 165.91, 165.74, 162.57, 162.40, 160.07, 159.19, 159.02, 152.79, 152.76, 151.51, 141.84, 132.16, 132.12, 132.03, 131.98, 129.42, 119.64, 119.59, 119.49, 119.44, 118.00, 114.58, 112.79, 112.75, 112.50, 112.46, 105.68, 105.34, 104.99, 63.29, 24.86, 24.78, 14.55; elemental anal. calcd. (%) for $C_{18}H_{14}F_2N_4OS$(372.4): C 58.06, H 3.79, N 15.05, S 8.61; found: C 58.13, H 3.86, N 15.12, S 8.51.

5g: 6-(4-Bromophenyl)-3-(4-ethoxyphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine

Yield: 72.6%; m.p. 230–232°C; ^{1}H NMR (300MHz, DMSO-d_6, 25°C, TMS) δ (ppm) = 8.03–7.91 (m, 4H, ArH), 7.79 (d, J = 8.6Hz, 2H, ArH), 7.11 (d, J = 8.8Hz, 2H, ArH), 4.41 (s, 2H, SCH_2), 4.12 (q, J = 6.9Hz, 2H, OCH_2), 1.35 (t, J = 6.9Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) = 160.19, 155.04, 151.67, 141.97, 132.93, 132.28, 129.61, 129.53, 125.81, 118.28, 114.81, 63.46, 22.74, 14.71; elemental anal, calcd. (%) for $C_{18}H_{15}BrN_4OS$(415.3): C 52.06, H 3.64, N 13.49, S 7.72; found: C 52.19, H 3.52, N 13.56, S 7.65.

5h: 3-(4-Ethoxyphenyl)-6-(4-nitrophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine

Yield: 67.6%; m.p. 239–241°C; ^{1}H NMR (300MHz, DMSO-d_6, 25°C, TMS) δ (ppm) = 8.33 (dd, J = 7.4Hz, 4H, ArH), 7.94 (d, J = 7.0Hz, 2H, ArH), 7.14–7.11 (m, 2H, ArH), 4.50 (s, 2H, SCH_2), 4.11 (q, J = 6.9Hz, 2H, OCH_2), 1.25 (t, J = 6.9Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) = 160.29, 154.27, 151.87, 149.28, 141.92, 139.64, 129.72, 129.07, 124.25, 118.10, 114.87, 63.49, 23.00, 14.71; elemental anal. calcd. (%) for $C_{18}H_{15}N_5O_3S$(381.4): C 56.68, H 3.96, N 18.36, S 8.41; found: C 56.59, H 3.88, N 18.31, S 8.22.

5i: 3-(4-Ethoxyphenyl)-6-(4-methylphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine

Yield: 66.9%; m.p. 225–226°C; ^{1}H NMR (300 MHz, DMSO-d_6, 25°C, TMS) δ (ppm) = 7.93 (dd, J = 8.8Hz, 4H, ArH), 7.38 (d, J = 8.1Hz,

2H, ArH), 7.11 (d, $J = 8.8$Hz, 2H, ArH), 4.40 (s, 1H, SCH_2), 4.12 (q, $J = 6.9$Hz, 2H, OCH_2), 2.40 (s, 3H, $ArCH_3$), 1.36 (t, $J = 6.9$Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 160.14, 155.81, 151.55, 142.28, 142.07, 130.88, 129.83, 129.55, 127.61, 118.44, 114.78, 63.46, 22.77, 21.17, 14.71; elemental anal. calcd. (%) for $C_{19}H_{18}N_4OS$(350.4): C 65.12, H 5.18, N 15.99, S 9.15; found: C 65.01, H 5.09, N 15.94, S 8.99.

5j: 3-(4-Ethoxyphenyl)-6-(4-biphenylyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine

Yield: 73.9%; m.p. 196–197°C; ^{1}H NMR (300MHz, DMSO-d_6, 25°C, TMS) δ (ppm) = 8.09 (d, $J = 8.3$Hz, 2H, ArH), 7.97 (d, $J = 8.8$Hz, 2H, ArH), 7.88 (d, $J = 8.3$Hz, 4H, ArH), 7.77 (d, $J = 8.8$Hz, 2H, ArH), 7.51 (t, $J = 7.2$Hz, 2H, ArH), 7.43 (t, $J = 7.2$Hz, 1H, ArH), 7.11 (d, $J = 8.8$Hz, 2H, ArH), 4.46 (s, 1H, SCH_2), 4.12 (q, $J = 6.9$Hz, 2H, OCH_2), 1.36 (t, $J = 6.9$Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 160.01, 155.38, 151.48, 143.28, 141.99, 138.77, 132.39, 129.47, 129.10, 128.33, 128.17, 127.23, 126.86, 118.22, 114.63, 63.30, 22.63, 14.59; elemental anal. calcd. (%) for $C_{24}H_{20}N_4OS$(412.5): C 69.88, H 4.89, N 13.58, S 7.77; found: C 69.76, H 4.78, N 13.49, S 7.65.

6a: 4-(Benzylidene)amino-5-(4-ethoxyphenyl)-3-mercapto-4*H*-1,2,4-triazole

Benzaldehyde (117 mg, 1.1 mmol) was added to a solution of 4-amino-5-(4-ethoxyphenyl)-3-mercapto-1,2,4-triazole (**4**, 236 mg, 1 mmol) in ethanol (10 mL). The pH value then was adjusted to 5–6 with diluted HCl, and the mixture was heated at 90°C for 6 h and allowed to stand overnight. The precipitate was filtered, washed with 5% $NaHCO_3$ solution and water, and air-dried. The crude product then was recrystallized from acetone and distilled water (9:1, volume) to yield pure **6a** as a light yellow product (yield: 67.6%). M.p. 184–186°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ (ppm = 1.46 (t, $J = 7.0$Hz, 3H, CH_3), 4.11 (q, $J = 7.0$Hz, 2H, OCH_2), 7.01–7.00 (m, 2H, ArH), 7.58–7.49 (m, 3H, ArH), 7.93–7.90 (m, 4H, ArH), 10.09 (s, 1H, CH=N), 11.10 (s, 1H, NH–C=S); ^{13}C NMR ($CDCl_3$) δ: 14.40, 63.37, 114.25, 117.16, 128.69, 128.72, 130.01, 132.08, 132.31, 149.81, 160.72, 162.55, 163.66; elemental anal. calcd. (%) for $C_{17}H_{16}N_4OS$(324.4): C 62.94, H 4.97, N 17.27, S 9.88; found: C 62.86, H 4.81, N 17.13, S 9.78. The following compounds were prepared by an analogous procedure.

6b: 5-(4-Ethoxyphenyl)-4-(4-methylbenzylidene)amino-3-mercapto-4*H*-1,2,4-triazole

Yield: 62.1% m.p. 196–198°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ (ppm) = 1.46 (t, J = 7.0Hz, 3H, CH_3), 2.45 (s, 3H, $ArCH_3$), 4.11 (q, J = 7.0Hz, 2H, OCH_2), 6.98 (d, J = 8.9Hz, 2H, ArH), 7.30 (d, J = 7.9Hz, 2H, ArH), 7.80 (d, J = 7.9Hz, 2H, ArH), 7.91 (d, J = 8.9Hz, 2H, ArH), 9.93 (s, 1H, CH=N), 11.74 (s, 1H, NH–C=S); ^{13}C NMR ($CDCl_3$) δ: 14.41, 21.47, 63.35, 114.22, 117.26, 128.74, 129.32, 129.46, 129.97, 143.12, 149.63, 160.64, 162.27, 164.25; elemental anal. calcd (%) for $C_{18}H_{18}N_4OS$(338.4): C 63.88, H 5.36, N 16.56, S 9.47; found: C 63.79, H 5.25, N 16.46, S 9.39.

6c: 5-(4-Ethoxyphenyl)-4-(4-methoxybenzylidene)amino-3-mercapto-4*H*-1,2,4-triazole

Yield: 69.0%; m.p. 174–176°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ (ppm = 1.48 (t, J = 7.0Hz, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.11 (q, J = 7.0Hz, 2H, OCH_2), 6.96–7.04 (m, 4H, ArH), 7.85–8.09 (m, 4H, ArH), 9.81 (s, 1H, CH=N), 11.48 (s, 1H, NH–C=S); ^{13}C NMR ($CDCl_3$) δ: 14.39, 55.21, 63.35, 114.02, 114.23, 124.58, 129.45, 129.93, 130.64, 131.69, 149.62, 160.67, 163.09, 164.03; elemental anal. calcd. (%) for $C_{18}H_{18}N_4O_2S$(354.4): C 61.00, H 5.12, N 15.81, S 9.05; found: C 60.95, H 5.01, N 15.84, S 8.91.

6d: 5-(4-Ethoxyphenyl)-4-(4-*N,N*-dimethyl)benzylidene)amino-3-mercapto-4*H*-1,2,4-triazole

Yield: 70.4%; m.p. 174–176°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ (ppm) = 1.45 (t, J = 6.9Hz, 3H, CH_3), 3.09 (d, J = 8.4Hz, 6H, NCH_3), 4.11 (q, J = 6.9Hz, 2H, OCH_2), 6.83 (d, J = 8.7Hz, 2H, ArH), 6.96 (d, J = 8.8Hz, 2H, ArH), 7.80 (d, J = 8.8Hz, 2H, ArH), 7.93 (d, J = 8.7Hz, 2H, ArH), 9.49 (s, 1H, CH=N), 11.47 (s, 1H, NH–C=S); ^{13}C NMR ($CDCl_3$) δ: 14.40, 40.31, 63.31, 112.08, 112.11, 114.18, 117.46, 120.27, 129.86, 130.64, 149.46, 152.48, 160.55, 165.33; elemental anal. calcd. (%) for $C_{19}H_{21}N_5OS$(367.5): C 62.10, H 5.76, N 19.06, S 8.73; found: C 61.91, H 5.69, N 18.95, S 8.62.

6e: 4-(4-Chlorobenzylidene)amino-5-(4-ethoxyphenyl)-3-mercapto-4*H*-1,2,4-triazole

Yield: 68.8%; m.p. 174–176°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ (ppm) = 1.46 (t, J = 7.0Hz, 3H, CH_3), 4.11 (q, J = 7.0Hz, 2H, OCH_2), 6.94

(d, $J = 8.7$Hz, 2H, ArH), 7.48 (d, $J = 8.8$Hz, 2H, ArH), 7.79 (d, $J = 8.8$Hz, 2H, ArH), 7.86 (d, $J = 8.7$Hz, 2H, ArH), 10.13(s, 1H, CH=N), 11.73 (s, 1H, NH–C=S); ^{13}C NMR ($CDCl_3$) δ: 14.21, 63.20, 114.07, 116.86, 128.92, 129.48, 129.59, 129.83, 130.40, 138.33 149.65, 160.56, 161.73; elemental anal. calcd. (%) for $C_{17}H_{15}ClN_4OS$(358.9): C 56.90, H 4.21, N 15.61, S 8.94; found: C 56.96, H 4.11, N 15.54, S 8.81.

6f: 5-(4-Ethoxyphenyl)-4-(2-hydroxybenzylidene)amino-3-mercapto-4*H*-1,2,4-triazole

Yield: 64.6%; m.p. 174–176°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ (ppm) = 1.46 (t, $J = 7.0$Hz, 3H, CH_3), 4.11 (q, $J = 7.0$Hz, 2H, OCH_2), 7.00–7.06 (m, 4H, ArH), 7.45–7.49 (m, 2H, ArH), 7.49–7.74 (m, 2H, ArH), 10.13 (s, 1H, OH), 10.15 (s, 1H, CH=N), 10.74 (s, 1H, NH–C=S); ^{13}C NMR ($CDCl_3$) δ: 14.17, 63.24, 114.46, 115.57, 116.14, 117.14, 119.61, 129.53, 133.10, 134.22, 149.61, 159.37, 160.89, 163.10, 166.63; elemental anal. calcd. (%) for $C_{17}H_{16}N_4O_2S$ (340.4): C 59.98, H 4.74, N 16.46, S 9.42; found: C 60.06, H 4.56, N 16.38, S 9.32.

6g: 5-(4-Ethoxyphenyl)-4-(2-furanylidene)amino-3-mercapto-4*H*-1,2,4-triazole

Yield: 67.3%; m.p. 194–196°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ (ppm) = 1.46 (t, $J = 7.0$Hz, 3H, CH_3), 4.11 (q, $J = 7.0$Hz, 2H, OCH_2), 6.64–6.66 (m, 1H, furanyl-H), 6.97–7.00 (m, 2H, ArH), 7.12 (d, 1H, furanyl-H), 7.71 (s, 1H, furanyl-H), 7.92–7.95 (m, 2H, ArH), 10.01 (s, 1H, CH=N), 11.29 (s, 1H, NH–C=S); ^{13}C NMR ($CDCl_3$) δ: 14.20, 63.16, 112.14, 114.09, 116.90, 118.46, 129.82, 146.55, 147.41, 149.53, 151.03, 160.55, 162.19; elemental anal. calcd. (%) for $C_{15}H_{14}N_4O_2S$(314.4): C 57.31, H 4.49, N 17.82, S 10.20; found: C 57.42, H 4.56, N 17.69, S 10.11.

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