One pot synthesis and reactions of novel 5-amino[1,3]thiazolo[3,2-*b*][1,2,4]triazoles

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Abstract

5-Mercapto-3-phenyl-1,2,4-triazole **8** was reacted with a variety of cyano compounds containing active methylene group such as ethyl cyanoacetate, cyanoacetamide and malonitrile in boiling acetic acid in the presence of concentrated sulfuric acid, to give the corresponding 5-amino-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxylate **10a**. While on using cyanoacetamide or malonitrile the 5-amino-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxamide **10b** was obtained in one step reaction. Reaction of **10b** with triethyl orthoformate, acetic anhydride, benzaldehyde, benzoyl chloride and/or carbon disulfide gave the corresponding 2-phenyl[1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-*d*]pyrimidinones **15-18** in good yield. Upon treatment of 5-mercapto-3-phenyl-1,2,4-triazole **8** with chloroacetonitrile and benzaldehyde in boiling acidified acetic acid afforded 6-benzylidene-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-one **19** rather than the isomeric product 6-benzylidene-3-phenyl[1,3]thiazolo[2,3-*c*][1,2,4]triazol-5(6*H*)-one **20** in one pot reaction. The mechanism of the reactions is under investigation and the structures of all new compounds were elucidated using IR, ^{1}H-NMR, ^{13}C-NMR, mass spectral data and elemental analysis. The biological activity of selected compounds was investigated and summarized.

Keywords: Acidified acetic acid condition (AcOH/H^{+}), α-hydrogen, nitriles, one pot reaction, thiazolotriazoles, triazolothiazolopyrimidinones

Introduction

The thiazole nucleus is present in various molecules having biological activity.[1-13] The 1,2,4-triazole moiety is present in antiarthritic and antipyretic compounds.[14-19] Many thiazolo[3,2-*b*][1,2,4]triazoles have been investigated as antibacterials,[20,21] anticancer,[22] anti-inflammatory,[23-

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[25] antimicrobial [24] and analgesic[25] compounds. To the best of our knowledge the title compounds have been synthesized by three main routes according to a literature survey. In the first route the triazole ring is built onto a thiazole ring via reaction of 2-imino-3-amino thiazoles with acids,[26] anhydrides[27] or phosgene immonium chloride,[28] or cyclization of 2-acylamino-3-amino thiazolines.[29] In the second route the thiazole ring is built onto a triazole ring via reaction of 3-mercapto-1,2,4-triazoles with α-haloketones[27,30] followed by cyclization of the thiomethylketone intermediate using PPA,[31] via reaction of 3-mercapto-1,2,4-triazoles with allyl bromide in the presence of aqueous sodium hydroxide solution,[32] or in a one step reaction using the mercaptotriazole, chloroacetic acid and aromatic aldehydes.[33-39] The third route involves chalcones reacting with bis(1*H*-1,2,4-triazolyl)sulfoxide to form thiazolo[3,2-*b*][1,2,4]triazoles.[40] The present study is part of our program aimed at developing easy routes for the synthesis of fused heterocyclic compounds starting with cyano compounds containing active methylene groups. Thus we applied our method for the synthesis of thiazolo[3,2-*a*]benzimidazoles **1**,[41] imidazo[2,1-*b*]thiazoles **2**,[42,43] 2-benzylthiazolo[3,2-*b*][1,2,4]triazoles **3**,[44] 1,2,4-triazolo[2,1-*b*][1,3,4]thiadiazoles **4**[45] and 3-phenyl-s-triazolo[3,4-*b*][1,3,4]thiadiazines **5-7**,[45] using ketones containing active methyl or methylene group, in short reaction times and good reaction yields (Figure 1).

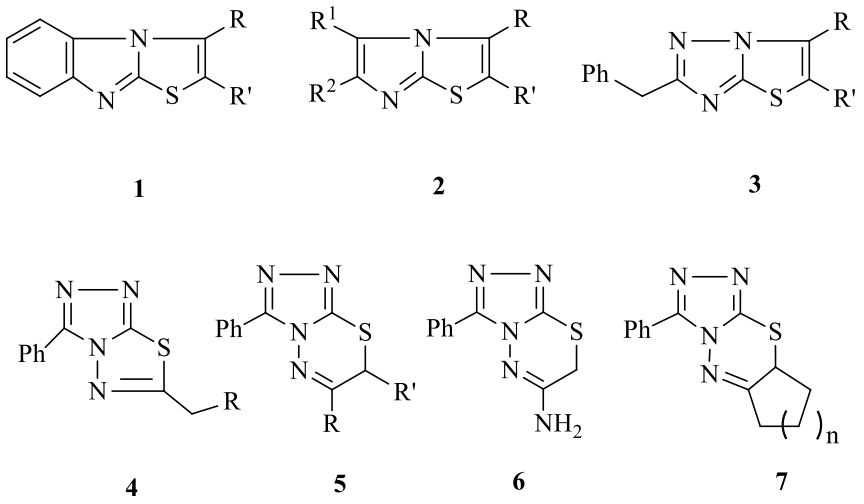

Figure 1. Thiazolotriazole and thiadiazine derivatives.

In our laboratory, we discovered that acidified acetic acid condition (AcOH/H^+), which we apply here, for synthesis of a variety of multifunctional compounds possess distinct advantages such as short reaction time, one-pot reaction, using cyano compounds containing active methylene group directly which are safe and cheap materials, without formation of highly toxic, irritant and dangerous halocyano derivatives. Further the syntheses afforded products with an amino group adjacent to the ester or amide group at the 5- and 6-positions of the thiazolo[3,2-*b*][1,2,4]triazole, which could not be obtained using the classical methods. Also, the acidified

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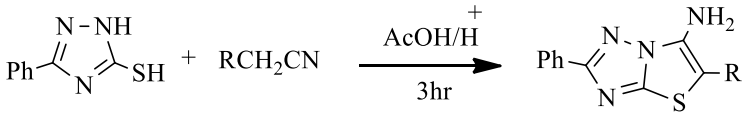
acetic acid conditions could be used for synthesis of thiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-one directly. Here we descibe our attempts to generalize this reaction so that it can be applied for the synthesis of multifunctional fused heterocycles.

Results and Discussion

On heating of 5-mercapto-3-phenyl-s-triazole **8** under reflux with cyano compounds containing active methylene group such as ethyl cyanoacetate, cyanoacetamide and malononitrile **9a-c** using the acidified acetic acid method (AcOH/H^+), 5-amino-2-phenyl-6-substituted[1,3]thiazolo[3,2-*b*][1,2,4]triazoles **10a,b** were obtained in 30 - 50 % yields (Scheme 1).

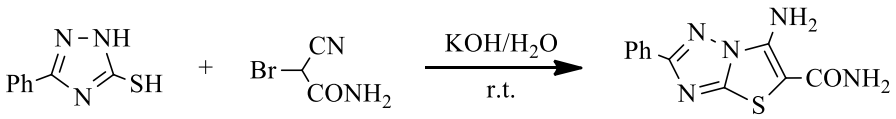


8 **9a-c** **10a,b**

R = **a**; COOEt, **b**; $CONH_2$, **c**; CN

Scheme 1. Reaction of 5-mercapto-3-phenyl-s-triazole **8** with compounds containing an active methylene.

The structures of compounds **10a,b** were confirmed on the basis of their elemental analysis, IR, ^{1}H-NMR and mass spectral analysis. The IR spectra of compounds **10a** showed bands at 3400-3300 cm^{-1} (NH_2**)** and 1680 cm^{-1} (C=O ester), while **10b** showed bands at 3400-3190 cm^{-1} (NH_2) and 1660 cm^{-1} (C=O amide) besides the expected bands. The ^{1}H-NMR spectra of compounds **10a,b** were characterized by the appearance of multiple signals at δ 7.4-8.1 attributed to the aromatic protons, in addition the compound **10a** showed a triplet signal at δ 1.1 and a quartet signal at δ 4.2 attributed to ethyl group. The mass spectra of **10a,b** showed the molecular ion peaks at *m/z* 288.7 (100%) and 259.1 (100%) respectively. Further, the structure of compound **10b** was confirmed by unequivocal synthesis via the reaction of **8** with bromocyanoacetamide in an aqueous solution of potassium hydroxide (Scheme 2).



8 **10b**

Scheme 2. Reaction of 5-mercapto-3-phenyl-s-triazole **8** with bromocyanoacetamide.

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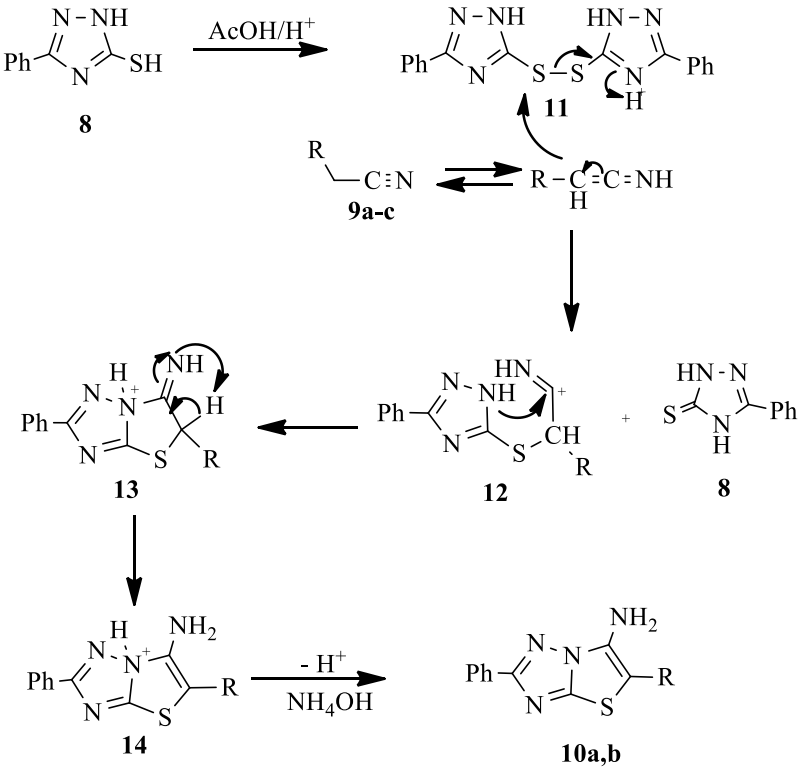
The proposed reaction mechanism is summarized in Scheme 1. It may proceed *via* the formation of dimeric disulfide **11** followed by nucleophilic attack by the imine form on the dimeric disulfide to give the carbonium ion **12**, which undergoes intramolecular cyclization to produce the cyclized imino structures **13**. Protonation of **13** in the presence of acid medium gives the cyclized carbonium ion **14** followed by deportation to yield the cyclized compounds **10a,b** as shown in the following (Scheme 3).



Scheme 3. Reaction mechanism of formation of compounds **10a,b**.

The suggested mechanism[45] is supported by formation of disulfide **11** in 81% yield on refluxing the 5-mercapto-3-phenyl-s-triazole **8** in acetic acid in the presence of concentrated sulfuric acid in the absence of an active methylene compound.[44] The formation of compound **10b** showed that the cyano group of **10c** undergoes hydrolysis to the corresponding amide.

Interaction of 5-amino-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxamide **10b** with triethyl orthoformate, acetic anhydride, benzaldehyde in the presence of piperidine (or benzoyl chloride) and carbon disulfide in alcoholic potassium hydroxide afforded 2-phenyl[1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-*d*]pyrimidin-8(7*H*)-one **15** in 53% yield, 6-methyl-2-phenyl[1,2,4]triazolo[2',3':3,2] [1,3]thiazolo[4,5-*d*]pyrimidin-8(7*H*)-one **16** in 60% yield, 2,6-diphenyl[1,2,4]triazolo[2',3':3,2] [1,3]thiazolo[4,5-*d*]pyrimidin-8(7*H*)-one **17** in 45% yield and 2-phenyl-6-thioxo[1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-*d*]pyrimidin-8(7*H*)-one **18** in 52% yield, respectively as shown in Scheme 4.

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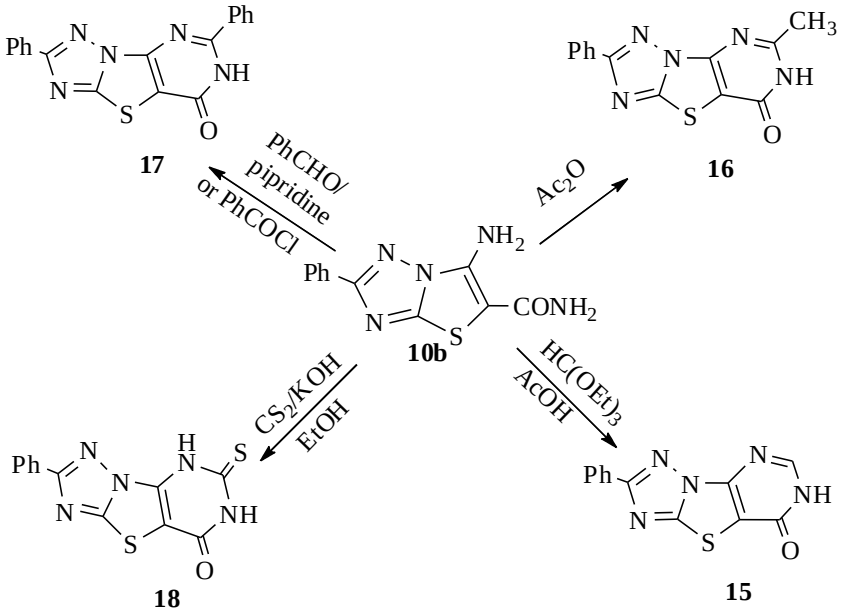

Scheme 4. Formation of [1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-d]pyrimidin-8(7*H*)-ones.

The structures of compounds **15-18** were confirmed on the basis of their elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and the mass spectral data. The IR spectra lacked the amino (NH_2) and amide ($CONH_2$) absorption peaks and showed bands at 3150-3050 cm^{-1} (NH aromatic), 2998-2980 cm^{-1} (CH aliphatic), 1680-1659 cm^{-1} (C=O), 1537-1516 cm^{-1} (C=N) and the aromatic skeleton bands at 1481-1450 cm^{-1}. The ^{1}H-NMR spectra of compounds **15-18** were characterized by the appearance of multiple signals at δ 7.5-8.2 ppm attributed to the aromatic protons and single broad signal at δ 13.4-13.6 ppm attributed to NH, in addition compounds **15** and **16** showed two singlet signals at δ 8.6 and 2.0 ppm attributed to CH and methyl group respectively. The ^{13}C-NMR spectra of compounds **15-18** in DMSO-d_6 showed signals at δ 166.81-167.75 ppm attributed to the carbonyl groups, in addition to the other carbons at the expected chemical shifts. The mass spectra of **15-18** showed the molecular ion peaks $M^{\cdot+}$ at 269.9 (100%), 283.9 (100%), 345.6 (0.55%) and 301.8 (1.7%) respectively.

Reaction of 5-mercapto-3-phenyl-1,2,4-triazole **8** with chloroacetonitrile and benzaldehyde in boiling acidified acetic acid afforded directly one pure product, which was identified as **19** rather than **20** (Scheme 5).

The formation of **19** can be explained by S-alkylation of **8** followed by intramolecular cyclization *via* nucleophilic attack of NH to the cyano group to form the cyclized imine derivative **22**, which undergoes hydrolysis to the ketone **23** followed by condensation with benzaldehyde to give the product. The intermiediacy of ketone **23** was verified by refluxing **8** with chloroacetic acid and benzaldehyde or by refluxing 2-[(5-phenyl[1,2,4]triazolo-3-yl)thio]acetonitrile/acetic acid **21a,b**, which were prepared by the reaction of 3-phenyl-5-mercapto-1,2,4-triazole **8** with chloroacetic acid or chloroacetonitrile in alcoholic potassium

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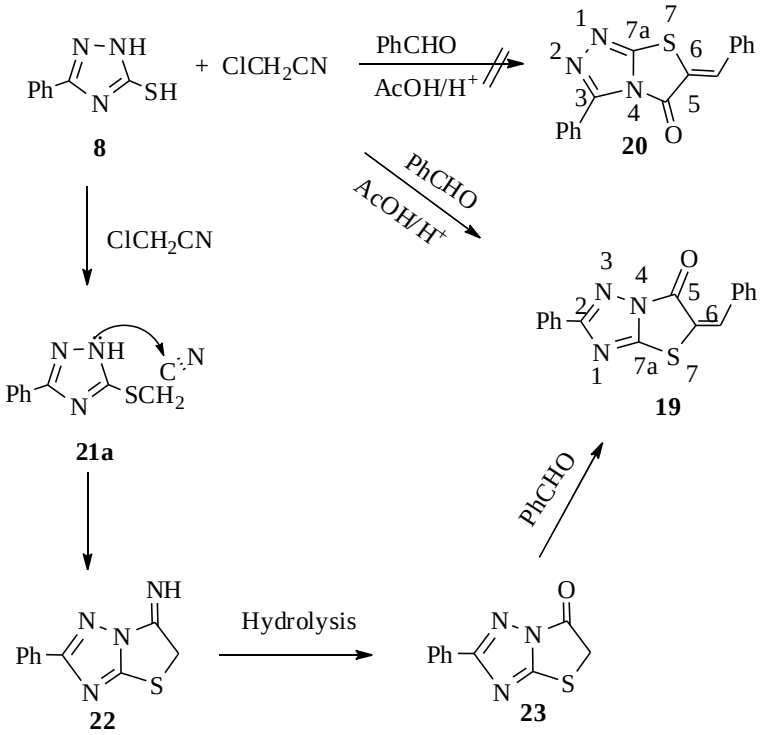
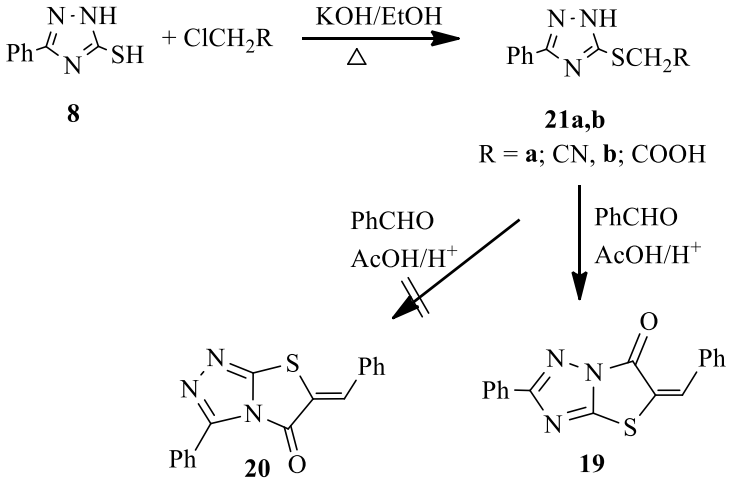
hydroxide solution, and benzaldehyde under the same reaction conditions, both of which also gave product **19** (Scheme 6).



Scheme 5. Reaction of mercaptotriazole **8** with chloroacetonitrile.



Scheme 6. Reaction of triazolethioacetonitrile and triazole thioacetic acid with PhCHO using acidified acetic acid condition.

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Based on the previously reported studies using similar compounds,[46,47] the higher nucleophilicity of N-2 than N-4 due to the alpha N effect. Molecular modeling calculations (MM2) indicated that isomer 19 is more stable than 20, while the E-isomer (HF = 137.64 kcal/mol) of 19 is more favorable than the Z-isomer (137.65 Kcal/mol), Figure 2.[47]

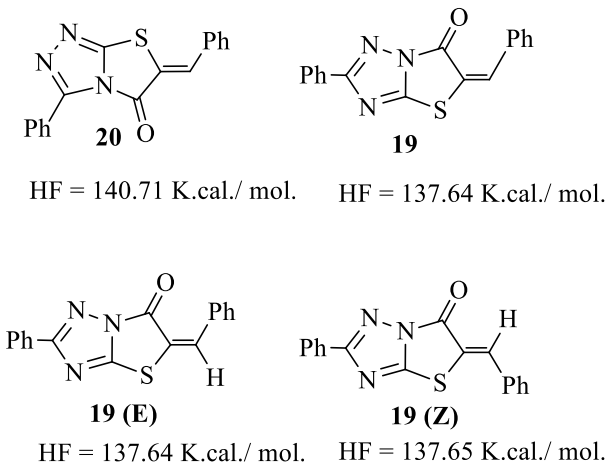
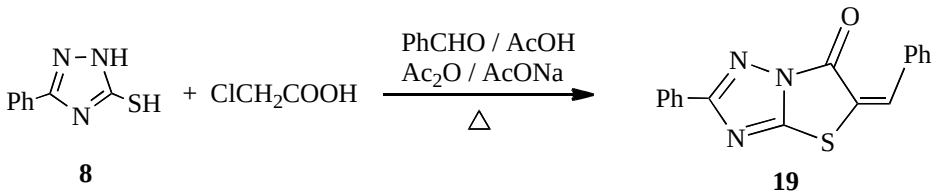


Figure 2. Isomers of compounds **19** and **20**.

The structures of compounds **19** and **21a,b** were confirmed on the basis of their elemental analysis and spectral data. The IR of compounds **21a,b** showed bands at 3270-3175 (NH), 3100-3090 (CH aromatic), 2920 (CH aliphatic), 1550 (C=N) and the aromatic skeleton bands at 1460-1410 cm^{-1}, in addition at 2210 cm^{-1} (C≡N) in compound **21a** and 1710 cm^{-1} (C=O) in compound **21b** respectively. The IR spectrum of compound **19** lacked the NH absorption peak and showed the C=O and C=C peaks at 1725 and 1560 cm^{-1} respectively. The ^{1}H-NMR spectra of compounds **19**, **21a** and **21b** showed singlet signals at δ 8.1, 4.15 and 4.05 ppm attributed to (C=C<u>H</u>) , (C<u>H</u>$_2$CN) and (C<u>H</u>$_2$COOH) groups respectively. The mass spectrum of compound **19** showed the molecular ion peak at *m/z* 305.1 (100%). Further, the structure of compound **19** was chemically confirmed by an alternative synthesis[46] (Scheme 7).



Scheme 7. Synthesis of **19** using benzaldehyde and AcOH, Ac_2O and AcONa.

Biological activity

One of the purposes of the present work was to synthesize new heterocyclic compounds which might be of certain biological interest. Some of the newly synthesized compounds were screened

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for their antibacterial and antifungal activity. For antibacterial studies microorganisms employed were *Serratia marcescens*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus cereus* and *Escherichia coli*. For antifungals, *Candida albicans*, *Geotrichum candidum*, *Aspergillus flavus*, *Trichophyton rubrum*, *Scopulariopsis bervicaulis* and *Fusarium oxysporum* were used. Both microbial studies were assessed by minimum inhibitory concentration (MIC) by serial dilution method.[48] For this the compound whose MIC has to be deretmined was dissolved in serially diluted DMSO, then a standard drop of the culture prepared for the assay was added to each of the dilutions and incubated for 16-18 h at 37 °C (Tables 1 and 2).

Table 1. The antibacterial activity (inhibition zone in (mm) and MICs given in brackets) of some selected compounds

Sample	*Serratia marcescens*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Bacillus cereus*	*Escherichia coli*
10a	10(20)	-	-	-	12(20)
10b	10(20)	-	-	12(10)	15(20)
15	10(20)	-	-	-	-
16	10(20)	-	-	-	12(20)
17	10(20)	-	-	-	12(20)
18	10(20)	-	13(20)	12(2.5)	12(20)
DMSO	10(20)	-	-	-	-
CHL*	12(1.25)	14(5.0)	10(1.25)	34(0.3)	12(0.3)

*CHL = Chloramphenicol as standard.

Table 2. The antifungal activity (inhibition zone in (mm) and MICs given in brackets) of some selected compounds

Sample	*Candida albicans*	*Geotrichum candidum*	*Aspergillus flavus*	*Trichophyton rubrum*	*Scopulariopsis bervicaulis*	*Fusarium oxysporum*
10a	-	11(20)	-	10(20)	-	-
10b	-	11(20)	-	-	-	-
15	-	-	-	-	-	-
16	-	12(20)	-	-	-	-
17	-	11(20)	-	-	-	-
18	-	12(20)	-	-	-	-
DMSO	-	-	-	-	-	-
CLO*	25(0.3)	24(0.3)	24(2.5)	36(1.25)	26(2.5)	20(10)

*CLO = Clotrimazole as standard.

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Experimental Section

General. Melting points were determined using Gallen Camp melting point apparatus and are uncorrected. IR spectra were measured on a Shimatzu-470 spectrometer using KBr techniques. ^{1}H-NMR spectra were measured on a Varian EM-390, 90MHz spectrometer (Spectral Unit, Assiut University, Egypt) or a Bruker DX 400-MHz spectrometer (Department of Physical Chemistry, Geneva) using $CDCl_3$ or DMSO-d_6 as a solvent and TMS as internal standard. ^{13}C NMR spectra were measured on a Bruker DX 400-MHz spectrometer. Mass spectra were recorded on Jeol-Jms-600H spectrometer using the direct inlet system. The elemental analyses were performed using Perkin-Elmer elemental analyzer 240-C.

5-Amino-2-phenyl-6-substituted[1,3]thiazolo[3,2-*b*][1,2,4]triazoles (10a,b). General procedure

A mixture of 5-mercapto-3-phenyl-1,2,4-triazole[46] **8** (0.88 g, 0.005 mol) and cyano compound **9a-c** (0.005 mol) in glacial AcOH (25 mL) and a catalytic amount of concentrated acid (H_2SO_4) (6-8 drops) was refluxed for 3 h. The reaction mixture was then cooled diluted with H_2O (10 mL) and neutralized with NH_3 solution. The crude product thus obtained was collected by filtration, washed with H_2O (3x) and crystallized from EtOH to give **10a,b** as colorless crystals in 30 and 50% yields respectively.

Ethyl 5-amino-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxylate (10a).Yield; 0.43 g (30%), colorless crystals (EtOH), mp 186-188 °C. IR (KBr): ν = 3400-3300 (NH_2), 3050 (C–H arom.), 2990 (C–H aliph.), 1680 (C=O), 1628 (C=N), 1489 cm^{-1} (C=C). ^{1}H NMR (90 MHz, DMSO-d_6): δ = 1.1 (t, *J* = 2.7 Hz, 3H, CH_2CH_3), 2.1 (s, 2H, NH_2), 4.2 (q, *J* = 2.7, 2H, CH_2CH_3) 7.4–8.1 (m, 5 H, H-arom.). MS (EI, 70 eV): *m*/*z* (%) = 288.7 [M^+] (100), 259.8 (2), 241.9 (12), 214.9 (31), 189.1 (13), 176.9 (10), 143.9 (12), 102.9 (13), 77.1 (8), 67.9 (4), 56.8 (1). Anal. Calcd for $C_{13}H_{12}N_4O_2S$ (288.32): C, 54.15; H, 4.20; N, 19.43; S, 11.12%. Found: C, 53.98; H, 4.11; N, 19.60; S, 11.22%.

5-Amino-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxamide (10b). Method A. This compound was obtained according to the General Procedures as colorless crystals after crystallization from EtOH, Yield 0.65 g (50%), mp. 290-291 °C. IR (KBr): ν = 3400-3190 (NH_2), 3010 (C–H arom.), 2995 (C–H aliph.), 1660 (C=O), 1620 (C=N), 1480 cm^{-1} (C=C). ^{1}H NMR (90 MHz, DMSO-d_6): δ = 7.2 (s, 2H, NH_2), 7.4 (s, 2H, $CONH_2$) 7.5–8.0 (m, 5 H, H-arom.). MS (EI, 70 eV): *m*/*z* (%) = 259.1 [M^+] (100), 242.1 (41), 216.1 (19), 189.1 (12), 144.1 (18), 103.2 (41), 77.1 (20), 65.1 (3), 56.7 (6). Anal. Calcd for $C_{11}H_9N_5OS$ (259.29): C, 50.96; H, 3.50; N, 27.01; S, 12.37%. Found: C, 50.99; H, 3.36; N, 26.97; S, 11.97%.

Method B. This compound was obtained from the reaction of bromo cyanoacetamide and compound **8** as follows: A sample of 5-mercapto-3-phenyl-s-triazole **8** (0.88 g, 0.005 mol) was dissolved in an aqueous solution of KOH (0.28 g, 0.005 mol) with continuous stirring at room temperature, then a solution of bromo cyanoacetamide (0.81 g, 0.005 mole) in EtOH was added dropwise over a period of 30 min. The reaction mixture was stirred for further 2 h at room

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temperature. The crude product thus obtained was collected by filtration, washed with H_2O and crystallized from EtOH to give **10b** as colorless needles, yield 1.12 g, (86%), mp 290-291 ºC. The analysis of this compound was in agreement with that obtained using the acidified acetic acid method, Method A.

2-Phenyl[1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-*d*]pyrimidin-8(7*H*)-one (15). A mixture of 5-amino-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxamide **10b** (1.3 g, 0.005 mol) and triethyl orthoformate (5 mL) in AcOH (10 mL) was refluxed for 2 h. The solid product thus formed was collected by filtration and crystallized from DMF to give **15** as white crystals; Yield 0.71 g (53%), colorless needles (DMF), mp > 360 °C. IR (KBr): ν = 3100 (NH), 3060 (C–H arom.), 2998 (C–H aliph.), 1678 (C=O), 1516 (C=N), 1478 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.5 (t, 3H, H-arom.), 8.2 (d, 2H, H-arom.), 8.6 (s, 1H, CH), 13.4 ppm (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 167.74 (C=O), 157.87 (C-2=N), 157.77 (C-9a=N), 151.0 (CH), 147.01 (C-4a=C), 131.0 (C-arom.), 130.94 (CH–arom.), 130.47 (C-9a=C), 129.49 (2 CH-arom.), 126.95 (2 CH-arom.). MS (EI, 70 eV): *m*/*z* (%) = 269.9 [M^+] (100), 230.3 (43), 202.3 (140), 147.2 (5), 103.2 (32), 71.3 (17), 57.3 (17). Anal. Calcd for $C_{12}H_7N_5OS$ (269.28): C, 53.52; H, 2.62; N, 26.01; S, 11.91%. Found: C, 53.22; H, 2.45; N, 25.86; S, 11.67%.

6-Methyl-2-phenyl[1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-*d*]pyrimidin-8(7*H*)-one (16). A mixture of 5-amino-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxamide **10b** (1.3 g, 0.005 mol) and Ac_2O (20 mL) was heated under refluxed for 6 h then, after cooling, the excess Ac_2O was removed under reduced pressure to give viscous material which was washed several times with EtOH. The solid product thus formed was collected by filtration and crystallized from (AcOH) to give **16**. Yield: 0.85 g (60%), brown needles (AcOH), mp > 360 °C. IR (KBr): ν = 3050 (NH), 3000 (C–H arom.), 2985 (C–H aliph.), 1671 (C=O), 1518 (C=N), 1481 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.0 (s, 3H, CH_3), 7.5 (t, 3H, H-arom.), 8.1 (d, 2H, H-arom.), 13.5 ppm (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 167.00 (C=O), 155.31 (C-2=N), 157.12 (C-9a=N), 147.01 (C-4a=C), 130.90 (C-arom.), 130.01 (CH–arom.), 130.46 (C_{8a}=C), 129.59 (2 CH-arom.), 126.96 (2 CH-arom.), 25.45 (CH_3). MS (EI, 70 eV): *m*/*z* (%) = 283.9 [M^+] (100), 257.9 (19), 241.9 (18), 216.9 (17), 188.8 (25), 176.9 (51) 144.1 (89), 90.9 (18), 76.9 (57), 56.7 (9). Anal. Calcd for $C_{13}H_9N_5OS$ (283.31): C, 55.11; H, 3.20; N, 24.72; S, 11.32%. Found: C, 54.89; H, 3.05; N, 24.96; S, 11.64%.

2,6-Diphenyl[1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-d]pyrimidin-8(7*H*)-one (17). Method A. A mixture of 5-amino-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole-6-carboxamide **10b** (1.3 g, 0.005 mol) and benzaldehyde (0.58 g, 0.0055 mol) and a few drops of piperidine was fused together for 20 min. The solid mass thus formed was treated by addition of EtOH (10 mL) and refluxed for 3 h. The solid product formed was collected by filtration to give **17**. Yield: 0.71g (40%), colorless needles (AcOH), mp > 360 °C. IR (KBr): ν = 3062 (NH), 3010 (C–H arom.), 1659 (C=O), 1537 (C=N), 1450 cm^{-1} (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.6 (m, 6H, H-arom.), 8.2 (m, 4H, H-arom.), 13.6 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.75 (C=O), 159.05 (C-2=N), 158.41 (C-9a=N), 158.06 (C-6), 147.12 (C-4a=C), 132.97 (CH-arom.), 131.67 (C–arom.), 131.91(CH-arom.), 130.49 (C-8a=C), 129.47 (4CH-arom.), 129.33 (C–

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arom.), 128.80 (2 CH-arom.), 126.99 ppm (2 CH-arom.). MS (EI, 70 eV): *m*/*z* (%) = 345.6 [M^+] (1), 300.7 (100), 254.7 (37), 200.8 (33), 148.6 (2), 103.8 (3), 92.9 (3), 77.8 (2), 68.9 (10), 56.9 (8). Anal. Calcd for $C_{18}H_{11}N_5OS$ (345.38): C, 62.60; H, 3.21; N, 20.28; S, 9.28%. Found: C, 62.45; H, 3.54; N, 20.11; S, 9.36%.

Method B. A mixture of 5-amino-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxamide (**10b**; 1.3 g, 0.005 mol) and benzoyl chloride (5 mL) was refluxed for 1 h then, after cooling, the reaction mixture was treated with petroleum ether and the product thus formed was collected by filtration and crystallized from AcOH to give **17** as colorless needles, yield 0.81 g, 46%, mp > 360 ºC. The analysis of this compound was in satisfactorily agreement with that obtained in Method A.

2-Phenyl-6-thioxo[1,2,4]triazolo[2',3':3,2][1,3]thiazolo[4,5-*d*]pyrimidin-8(7*H*)-one (18). A mixture of 5-amino-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole-6-carboxamide **10b** (1.3 g, 0.005 mol), CS_2 (5 mL) and KOH (0.31 g, 0.0055 mol) in EtOH (20 mL) was refluxed for 4 h. The reaction mixture was then cooled, diluted with cold H_2O and acidified with AcOH. The precipitate thus formed was collected by filtration, washed with H_2O several times to give **18**. Yield: 0.78 g (52%), brown needles (AcOH), mp 320 °C. IR (KBr): ν = 3150-3070 (2 NH), 3010 (C–H arom.), 1680 (C=O), 1650 (C=S), 1520 (C=N), 1470 cm^{-1} (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.1 (s, 1H, NH), 7.0 (t, 3H, H-arom.), 8.1 (d, 2H, H-arom.), 12.3 ppm (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 172.9 (C=S), 166.81 (C=O), 155.30 (C-2=N), 157.51 (C-9a=N), 147.10 (C-4a=C), 130.91 (C-arom.), 130.50 (CH–arom.), 129.49 (C_{8a}=C), 129.14 (2 CH-arom.), 127.01 (2 CH-arom.). MS (EI, 70 eV): *m*/*z* (%) = 301.8 [M^+] (2), 290.1 (5), 255.7 (36), 234.9 (2), 225.8 (3), 223.7 (9), 191.9 (18), 177.2 (40), 160.1 (23), 127.9 (22), 118.7 (11), 104.1 (12), 95.8 (15), 75.9 (100), 63.8 (52), 56.8 (4). Anal. Calcd for $C_{12}H_7N_5OS_2$ (301.35): C, 47.83; H, 2.34; N, 23.24; S, 21.28%. Found: C, 47.49; H, 2.13; N, 23.55; S, 21.63%.

(*E*)-6-Benzylidene-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-one (19). Method A. A mixture of 5-mercapto-3-phenyl-1,2,4-triazole **8** (0.88 g, 0.005 mol) and benzaldehyde (0.53 g, 0.005 mol) and chloroacetonitrile (0.38 g, 0.005 mol) in glacial AcOH (25 mL) and a catalytic amount of conc. H_2SO_4 was refluxed 5 h. The mixture was concentrated, followed by addition of cold H_2O (10 mL) and neutralized with NH_3 soln. The crude product thus obtained was collected by filtration, washed with H_2O to give **19**. Yield: 1.10 g (70%), brown needles (AcOH), mp 230-231 °C (reported mp 230-231 °C[46]). IR (KBr): ν = 3050 (C–H arom.), 2995 (C–H aliph.), 1725 (C=O), 1560 (C=N), 1490 cm^{-1} (C=C). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.4–8.1 (m, 10H, H-arom.), 8.1 ppm (s, 1H, CH). MS (EI, 70 eV): *m*/*z* (%) = 305.1 [M^+] (100), 276.7 (2), 11.1 (2), 173.8 (7), 146.8 (4), 133.9 (12), 102.9 (25), 76.1 (3), 56.8 (1). Anal. Calcd for $C_{17}H_{11}N_3OS$ (305.35): C, 66.87; H, 3.63; N, 13.76; S, 10.50%. Found: C, 66.16; H, 3.76; N, 13.80; S, 10.18%.

Method B. A mixture of [(5-phenyl-1,2,4-triazolo-3-yl)thio]acetonitrile/acetic acid **21a,b** (0.005 mol) and benzaldehyde (0.005 mol) in glacial AcOH (25 mL) and a catalytic amount of conc. H_2SO_4 (6-8 drops) was refluxed for 5 h. The solvent was concentrated, followed by addition of cold H_2O (10 mL) and neutralized with NH_3 solution. The crude product thus obtained was collected by filtration, washed with H_2O and crystallized from AcOH to give **19** as brown

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needles in, yield 1.29 g, 85% (from **21a**) and 1.22 g, 80% yield (from **21b**) respectively, mp 230-231 ºC. The analysis of this compound was in agreement with that obtained using the acidified acetic acid method.

[(5-Phenyl-1,2,4-triazolo-3-yl)thio]acetonitrile/acetic acid (21a,b). General procedure
To a solution of 5-mercapto-3-phenyl-1,2,4-triazole **8** (0.88 g, 0.005 mol) in absolute EtOH (15 mL) and KOH (0.56 g, 0.01 mol), a solution of chloroacetonitrile or chloroacetic acid (0.0055 mol) in absolute EtOH (5 mL) was added dropwise with stirring. The reaction mixture was stirred at room temperature for a further 30 min, followed by refluxing for 1 h. The precipitated KCl was filtered off. The excess solvent was removed from the mixture by evaporation under vacuum and the residue was treated with H_2O. The crude product thus formed was collected by filtration and crystallized from (EtOH) to give **21a,b** as colorless needles.
(5-Phenyl-1,2,4-triazolo-3-yl)thioacetonitrile (21a). Yield: 1.10 g (92%), colorless needles (EtOH), mp 168-170°C. IR (KBr): ν = 3175 (NH), 3090 (C–H arom.), 2885 (C–H aliph.), 2210 (C≡N), 1550 (C=N), 1410 cm^{-1} (C=C). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 4.15 (s, 2H, CH_2), 7.6–8.1 (m, 5 H, H-arom.), 11.6 ppm (s, 1H, NH). Anal. Calcd for $C_{10}H_8N_4S$ (216.26): C, 55.54; H, 3.73; N, 25.91; S, 14.83%. Found: C, 55.44; H, 3.89; N, 25.67; S, 15.01%.
(5-Phenyl-1,2,4-triazolo-3-yl)thioacetic acid (21b). Yield: 1.10 g (91%); colorless needles (EtOH), mp 180-182 °C. Lit. 179 °C[49]. IR (KBr): ν = 3270 (NH), 3100 (C–H arom.), 2992 (C–H aliph.), 1710 (C=O), 1550 (C=N), 1460 cm^{-1} (C=C). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 4.05 (s, 2H, CH_2), 7.2–8.0 (m, 5 H, H-arom.), 11.50 ppm (s, 1H, NH). Anal. Calcd for $C_{10}H_9N_3O_2S$ (235.26): C, 51.05; H, 3.86; N, 17.86; S, 13.63%. Found: C, 50.88; H, 4.12; N, 17.36; S, 13.55%.

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