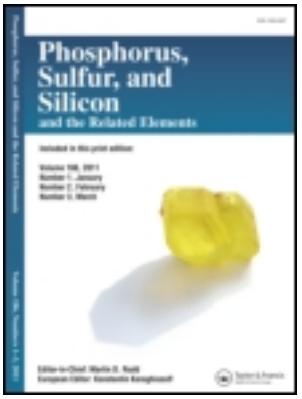


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis and Antibacterial Activity of Some New S-Triazole Derivatives

Abd El-Badih A. G. Ghattas [a], Hassan M. Moustafa [a], Elsayed A. A. Hassanein [a] & Bahgat R. M. Hussein [a]

[a] Chemistry Department, Faculty of Science, Sohag University, Sohag, Egypt

Accepted author version posted online: 09 May 2012.Version of record first published: 10 Sep 2012.

To cite this article: Abd El-Badih A. G. Ghattas, Hassan M. Moustafa, Elsayed A. A. Hassanein & Bahgat R. M. Hussein (2012): Synthesis and Antibacterial Activity of Some New S-Triazole Derivatives, Phosphorus, Sulfur, and Silicon and the Related Elements, 187:12, 1469-1481

To link to this article: http://dx.doi.org/10.1080/10426507.2012.690118

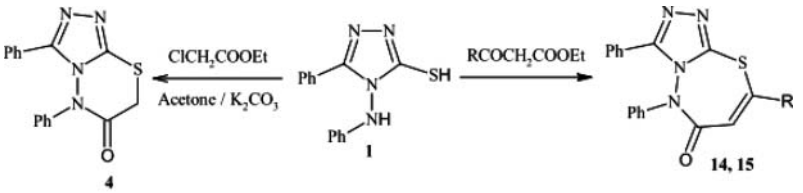
Phosphorus, Sulfur, and Silicon, 187:1469–1481, 2012

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2012.690118

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME NEW S-TRIAZOLE DERIVATIVES

Abd El-Badih A. G. Ghattas, Hassan M. Moustafa, Elsayed A. A. Hassanein, and Bahgat R. M. Hussein
Chemistry Department, Faculty of Science, Sohag University, Sohag, Egypt

GRAPHICAL ABSTRACT



Abstract *Alkylation of 4-anilino-5-phenyl-4H-1,2,4-triazole-3-thiol (**1**) with some halo compounds yielded the corresponding sulfides **2a–f**. Some sulfides **2e,f** were cyclized to give triazolothiadiazines **3** and **4**. Triazolothiadiazoles **5** and **6** were prepared through the reaction of compound **1** with carbon disulfide or ethyl orthoformate, respectively. Treatment of compound **1** with ethyl chloroformate or phenyl isothiocyanate yielded triazolo-thiadiazole and triazole **9** and **10**, respectively. Reaction of compound **1** with Lawesson's reagent gave triazolothiadiazaphosphole derivative **11**. Also, compound **1** underwent cyclocondensation reactions with some bidentate reagents to give triazolothiazines **4**, **12**, and **13**. Triazolo-thiazepines and triaziepine **14–16** were synthesized via the reaction of compound **1** with β-ketoesters or ethyl cyanoacetate. Tricyclic systems **19** and **20** were prepared through the reaction of compound **4** with the appropriate reagent. Some synthesized compounds were tested for antibacterial activity.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Lawesson's reagent; s-triazole; triazolothiadiazine; triazolothiadiazepines

INTRODUCTION

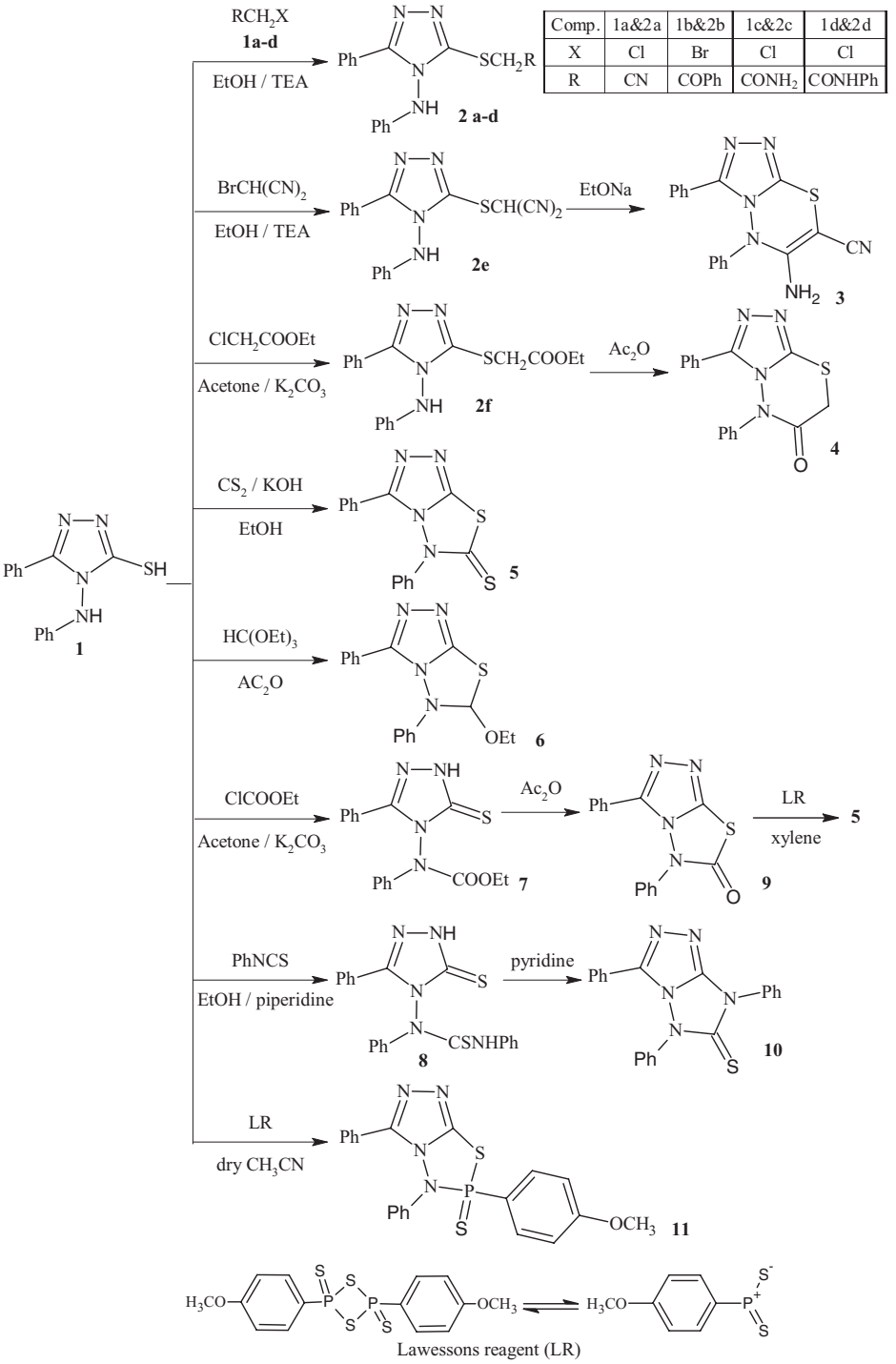
Heterocycles bearing a symmetrical triazole ring are reported to show a broad spectrum of biological activities such as antifungal,[1–3] antibacterial,[4,5] anti-inflammatory,[6,7]

Received 13 March 2012; accepted 28 April 2012.
The authors are grateful to the Chemistry Department, Faculty of Science, Sohag University, Egypt for both supporting and facilitating this study. Also, we extend our thanks to Dr. Rehab Moustafa Mohamed and Ms. Dalia Ahmed Abd El Raheem from the Botany Department, Faculty of Science, Sohag University, Egypt for evaluation of bacterial inhibiting effects.
Address correspondence to Bahgat R. M. Hussein, Chemistry Department, Faculty of Science, Sohag University, Sohag 82524, Egypt. E-mail: bahgat.ramadan@yahoo.com

antimicrobial,[8] and antituberculosis activity.[9] Among the 1,2,4-triazole derivatives, the mercapto- and the thiono-1,2,4-triazole ring systems have been studied and so far a variety of antitumor properties have been reported for a large number of these compounds.[10,11] s-Triazoles are also applied in medicine as follows: alprazolam (tranquilizer), estazolam (hypnotic, sedative, tranquilizer, etc.), rilmazafon (hypnotic, anxiolytic, used in the case of neurotic insomnia, etc.), benatradin (diuretic), trapidil (hypotensive), trazodon (antidepressant, anxiolytic, etc.), etoperidone (antidepressant), nefazodone (antidepressant, 5-HT_2 A-antagonist, etc.), anastrozole, letrozole, vorozole (antineoplastics, nonsteroidal competitive aromatase inhibitors, etc.), ribavirin (the potent antiviral N-nucleoside), fluconazole, itraconazole, and terconazole (the powerful azole antifungal agents).[3,12–15] In view of these findings and in continuation of our work in the same field,[16–22] we report herein the synthesis of some new s-triazole derivatives and evaluate them for antibacterial activity.

RESULTS AND DISCUSSION

4-Anilino-5-phenyl-4*H*-1,2,4-triazole-3-thiol (**1**)[23] reacted with halo compounds, namely chloroacetonitrile, phenacyl bromide, chloroacetamide, N-phenyl chloroacetamide, bromomalononitrile, and ethyl chloroacetate, to give the corresponding sulfides, namely 4-anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl-thioacetonitrile (**2a**), 2-(4-anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio-1-phenylethanone (**2b**), 2-(4-anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl)thioacetamide (**2c**), 2-(4-anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio-N-phenylacetamide (**2d**), 4-anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl-thiomalononitrile (**2e**), and ethyl (4-anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl)thioacetate (**2f**), respectively (cf. Scheme 1). The structure of these compounds was characterized on the basis of their elemental and spectroscopic analyses (cf. Experimental section). The IR spectra of compounds **2a–f** showed the absence of an absorption band corresponding to (NH) in triazole ring, while exhibiting characteristic absorption bands corresponding to (CH) aliphatic groups at 2936–2923, (C≡N) 2249 (**2a**); (C=O) 1673 (**2b**); (NH_2) 3333 and 3180, (C=O) 1687 (**2c**), (C=O) 1672 (**2d**); (C≡N) 2210 (**2e**), and (C=O) 1720 (**2f**), respectively. The ^{1}H NMR spectrum of compound **2f** showed multiplet signals at 7.97–7.55 ppm for aromatic protons + (NH) proton, singlet signal at 4.29 ppm for S-CH_2 protons, quartet signals at 4.18–4.11 ppm for CH_2 protons, and triplet signals at 1.20–1.16 ppm for CH_3 protons. Cyclization reaction of compounds **2e** and **2f** yielded 6-amino-3,5-diphenyl-5*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-7-carbonitrile (**3**) and 3,5-diphenyl-5*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazin-6(7H)-one (**4**), respectively. The IR spectra of compounds **3** and **4** showed the absence of absorption bands corresponding to (NH) in triazole ring and (NH) anilino group, while exhibiting characteristic absorption bands corresponding to (NH_2) at 3331 and 3202, (C≡N) 2199 (**3**), and (C=O) 1742 (**4**). The mass spectra (MS) of compounds **3** and **4** showed the molecular ion peaks at *m/z* 330 ($M^+ - 2$, 29.4%) and 308.25 (M^+, 0.58%), respectively. 3,5-Diphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole-6(5H)-thione (**5**) and 6-ethoxy-3,5-diphenyl-5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (**6**) were prepared via the reaction of compound **1** with carbon disulfide and/or ethyl orthoformate, respectively (cf. Scheme 1). The structure of these compounds was characterized on the basis of their elemental and spectroscopic analyses (cf. Experimental section). MS of compound **5** showed the molecular ion peak at *m/z* 310 (M^+, 8.86%), ^{1}H NMR spectrum of compound **6** showed multiplet signals at 7.98–7.55 ppm for aromatic protons, quartet signals at 3.33–3.29 ppm for CH_2 protons, and triplet signals at 1.44–1.39 ppm for CH_3 protons.

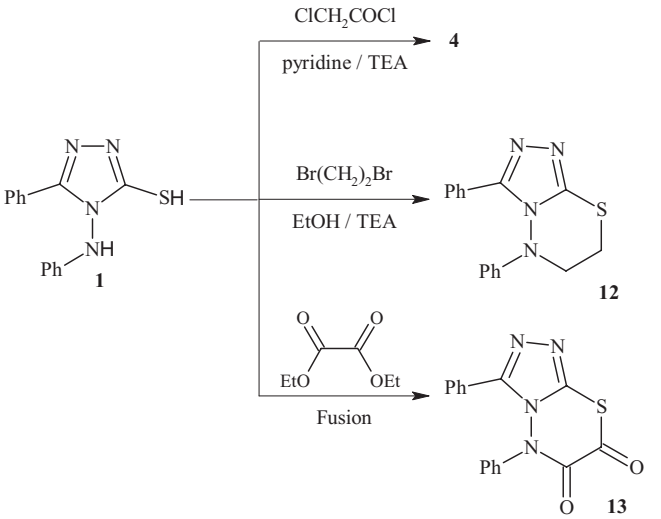


Comp.	1a&2a	1b&2b	1c&2c	1d&2d
X	Cl	Br	Cl	Cl
R	CN	COPh	$CONH_2$	CONHPh

Scheme 1

Treatment of compound **1** with ethyl chloroformate in acetone containing anhydrous potassium carbonate or phenyl isothiocyanate in ethanol containing few drops of piperidine, gave ethyl(3-mercapto-5-phenyl-4*H*-1,2,4-triazol-4-yl)phenylcarbamate (**7**) and 1-(3-mercapto-5-phenyl-4*H*-1,2,4-triazol-4-yl)-1,3-diphenylthiourea (**8**), respectively. Compounds **7** and **8** were cyclized to give 3,5-diphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-6(5*H*)-one (**9**) and 3,5,7-triphenyl-5*H*-1,2,4-triazolo[4,3-b]-1,2,4-triazole-6(7*H*)-thione (**10**), respectively. Thiation of compound **9** by using Lawesson's reagent in xylene yielded the corresponding triazolo[3,4-b]thiadiazole derivative **5**, (cf. Scheme 1). The structure of these compounds was characterized on the basis of their elemental and spectroscopic analyses (cf. *Experimental*), MS of compounds **8**–**10** showed the molecular ion peaks at *m/z* 403.45(M^+, 0.32%), 294.4 (M^+, 0.03%), and 369.5 (M^+, 0.45%), respectively. The IR spectra of compounds **7** and **9** showed the absence of absorption bands corresponding to (NH) anilino group, while exhibiting characteristic absorption bands corresponding to ($C{=}O_{ester}$) group at 1762 (**7**) and ($C{=}O_{amidic}$) at 1747 (**9**). ^{1}H NMR spectrum of compound **7** showed multiplet signals at 7.93–7.59 for aromatic protons, quartet signals at 4.49–4.42 ppm for CH_2 protons, and triplet signals at 1.38–1.33 ppm for CH_3 protons (ethyl group). Treatment of compound **1** with Lawesson's reagent in dry acetonitrile yielded 2-(4-methoxyphenyl)-1,6-diphenyl-1,2-dihydro-1,2,4-triazolo[4,3-d]-1,3,4,2-thiadiazaphosphole-2-sulfide (**11**) (cf. Scheme 1). The structure of this compound was characterized on the basis of its elemental and spectroscopic analyses (cf. *Experimental*). ^{1}H NMR spectrum of compound **11** showed multiplet signals at 7.62–6.99 ppm for aromatic protons and singlet signal at 3.80 ppm for CH_3 protons. MS of compound **11** showed the molecular ion peak at *m/z* 436 (M^+, 15.37%).

Cyclization of compound **1** with chloroacetyl chloride, 1,2-dibromoethane, and diethyl oxalate yielded 3,5-diphenyl-5*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazin-6(7*H*)-one (**4**), 3,5-diphenyl-6,7-dihydro-5*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (**12**), and 3,5-diphenyl-5*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-6,7-dione (**13**), respectively (cf. Scheme 2). The structure of these compounds was determined on the basis of their elemental and spectroscopic analyses (cf. *Experimental*). ^{1}H NMR spectrum of compound

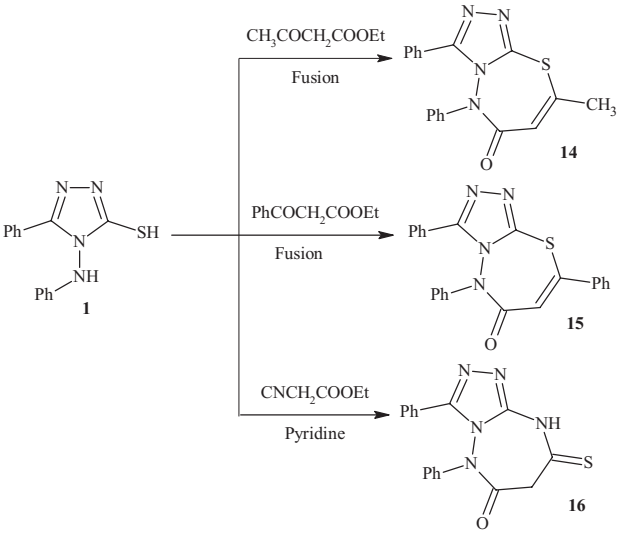


Scheme 2

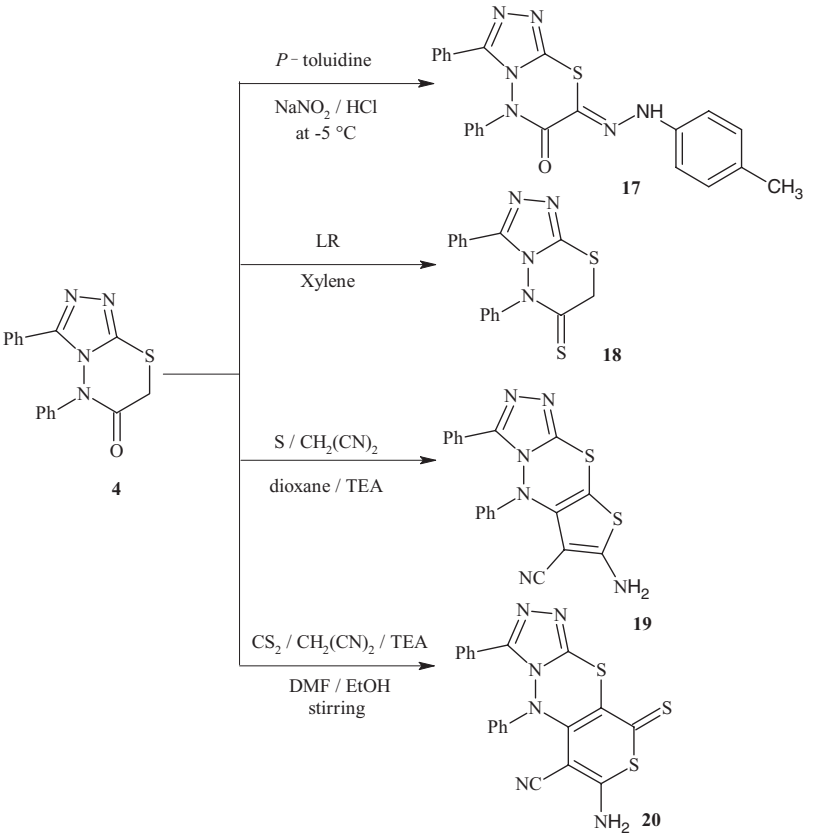
12 showed multiplet signals at 7.97–7.55 ppm for aromatic protons, triplet signals at 3.81–3.76 ppm for N-CH_2 protons, and triplet signals at 2.53–2.89 ppm for S-CH_2 protons. The IR spectrum of compound **13** showed the absence of absorption band corresponding to (NH) in triazole ring and (NH) anilino group, while exhibiting a characteristic absorption broad band corresponding to (C=O) groups at 1688 (**13**). MS of compound **13** showed the molecular ion peak at *m*/*z* 322 (M^+, 1.42%).

8-Methyl-3,5-diphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepin-6(5*H*)-one (**14**), 3,5, 8-triphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepin-6(5*H*)-one (**15**), and 3,5-diphenyl-8-thioxo-8,9-dihydro-5*H*-1,2,4-triazolo[4,3-b]-1,2,4-triazepin-6(7*H*)-one (**16**) were synthesized by reaction of compound **1** with ethyl acetoacetate, ethyl benzoylacetate, and ethyl cyanoacetate, respectively (cf. Scheme 3). The structure of these compounds was characterized on the basis of their elemental and spectroscopic analyses (cf. Experimental section). The IR spectra of compounds **14**–**16** showed the absence of absorption bands corresponding to (NH) in triazole ring and (NH) anilino group, while exhibiting characteristic absorption bands corresponding to (C=O) at 1735 (**14**), (C=O) 1754 (**15**), (NH) 3135, (C=O) at 1697, and (C=S) at 1176 (**16**). ^{1}H NMR spectrum of compound **14** showed multiplet signals at 7.78–7.39 ppm for aromatic protons, singlet signal at 5.92 ppm for CH proton, and singlet signal at 2.42 ppm for CH_3 proton; ^{1}H NMR spectrum of compound **15** showed multiplet signals at 7.92–7.54 ppm for aromatic protons + CH proton; ^{1}H NMR spectrum of compound **16** showed broad singlet signal at 14.71 ppm NH proton, multiplet signals at 7.90–7.55 ppm for aromatic protons, and singlet signal at 3.42 ppm for CH_2 protons.

Compound **4** coupled with *p*-toluenediazonium chloride to give 3,5-diphenyl-5*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-6,7-dione-7-(*p*-tolyl)hydrazone (**17**). Thiation of compound **4** with LR gave 3,5-diphenyl-5*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-6(7*H*)-thione (**18**). Polyfused heterocyclic compounds: 7-amino-3,5-diphenyl-5*H*-thieno[3,2-e]-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-6-carbonitrile (**19**) and 7-amino-3, 5-diphenyl-9-thioxo-5,9-dihydrothio-pyrano[4,3-e]-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-6-carbonitrile (**20**) were synthesized by reaction of compound **4** with a mixture of elemental sulfur and malononitrile or carbon disulfide and malononitrile, respectively



Scheme 3



Scheme 4

(cf. Scheme 4). The structure of these compounds was determined on the basis of their elemental and spectroscopic analyses (cf. *Experimental*). The IR spectrum of compound **17** showed absorption bands corresponding to (NH) at 3140 and (C═O) at 1750, while IR spectra of compounds **18**–**20** showed the absence of absorption band corresponding to (C═O), while exhibiting characteristic absorption bands corresponding to (C═S) at 1147 (**18**), (NH_2) at 3328 and 3208, and (C≡N) at 2202 (**19**), (NH_2) at 3316 and 3186, and (C≡N) at 2204.9 (**20**). MS of compounds **17**–**20** showed molecular ion peaks at *m*/*z* 426.1 (M^+, 0.86%), 324.3 (M^+, 0.02%), 388.7 (M^+, 1.35%), and 432.55 (M^+, 0.67%), respectively.

Antibacterial Activity

The compounds were dissolved in dimethyl sulfoxide (DMSO). In order to ensure that the solvent had no effect on bacterial growth or enzymatic activity, negative control tests were performed using DMSO at the same concentrations. The inhibitory effect of compounds **1**, **2a**, **2c**–**f**, **3**, **4**, **6**–**8**, **10**, **11**, **14**–**17**, and **20** in in vitro growth of broad spectrum of bacteria representing one species of Gram positive bacteria, namely *Bacillus cereus* and two species of Gram negative bacteria, namely *Pseudomonas aeruginosa* and *Escherichia coli*

was evaluated using the agar diffusion method (cup and plate method)[24] by measuring the zone of inhibition on agar plates at three different concentrations 10,000 ppm, 30,000 ppm, and 50,000 ppm. DMSO was used as solvent control. The results are summarized in Table S1. (Table S1 is available online in Supplemental Materials.)

EXPERIMENTAL

Melting points (mp) were uncorrected and were determined by Kofeler melting point apparatus. The infrared (IR) (cm^{-1}) spectra were recorded (KBr disc) on a Nicolet 710 Fourier transform infrared (FT-IR) spectrophotometer. ^1H NMR (DMSO-d_6) spectra were recorded at 300 MHz on a Varian Gemini NMR spectrometer at Cairo University, and the chemical shift was expressed in δ-value (ppm) using tetramethylsilane (TMS) as an internal reference. Elemental analyses were carried out in an elemental analyzer at 240 °C. The MS were performed on Micromass 7070 E spectrometer operating at 70 eV, using direct inlet. Selected ^1H NMR spectra are presented in Figures S1–S5. (Figures S1–S5. are available online in Supplemental Materials.)

General Procedure for Synthesis of Sulfides 2a–e

To a solution of compound **1** (0.5 g, 1.86 mmol) in ethanol (30 mL) and triethylamine (1.86 mmol), chloroacetonitrile, phenacyl bromide, chloroacetamide N-phenyl chloroacetamide, and/or bromomalononitrile (1.86 mmol) was added. The reaction mixture was refluxed for 3 h, and the solvent was evaporated under reduced pressure. The formed precipitate was collected and recrystallized from ethanol.

4-Anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl-thioacetonitrile (2a). Yield 0.46 g (80%); mp 89–92 °C; IR (ν_{max}, cm^{-1}): 3423 (NH), 3055 (CH_{arom}), 2939 (CH_{aliph}), 2249 (C≡N), 1604 (C=N); ^1H NMR (δ): 10.39 (s, 1H, NH), 8.01–7.58 (m, 10H, H_{arom}), 4.53 (s, 1H, CH_2). *Anal.* calcd. for $C_{16}H_{13}N_5S$ (307.37): C, 62.52; H, 4.26; N, 22.78; S, 10.43%. Found: C, 62.55; H, 4.33; N, 22.67; S, 10.31%.

2-(4-Anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl)thiophenylethanone (2b). Yield 0.45 g (72%); mp 147–149 °C; IR (ν_{max}, cm^{-1}): 3440 (NH), 3070 (CH_{arom}), 2923 (CH_{aliph}), 1673 (C=O), 1594 (C=N); ^1H NMR (δ): 8.09–7.55 (m, 15H, H_{arom}), 5.17 (s, 1H, NH), 5.15 (s, 2H, CH_2). *Anal.* calcd. for $C_{22}H_{18}N_4OS$ (386.46): C, 68.37; H, 4.49; N, 14.5; S, 8.3%. Found: C, 68.22; H, 4.35; N, 14.66; S, 8.38%.

2-(4-Anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl)thioacetamide (2c). Yield 0.73 g (97%); mp 178–180 °C; IR (ν_{max}, cm^{-1}): 3439.5 (NH), 3333 and 3180 (NH_2), 2999 (CH_{arom}), 2933 (CH_{Aliph}), 1687 (C=O); ^1H NMR (δ): 7.98–7.95 and 7.63–7.57 (m, 10H, H_{arom}), 7.79 (brs, 1H, NH), 7.39 (brs, 2H, NH_2), 4.106 (s, 2H, CH_2). *Anal.* calcd. for $C_{16}H_{15}N_5OS$ (325.38): C, 59.06; H, 4.65; N, 21.52; S, 9.85%. Found: C, 59.26; H, 4.75; N, 21.68; S, 9.73%.

2-(4-Anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio-N-phenylacetamide (2d). Yield 0.53 g (88%); mp 148–150 °C; IR (ν_{max}, cm^{-1}): 3420 (2NH), 3058 (CH_{arom}), 2932 (CH_{aliph}), 1672 (C=O), 1609 (C=N); ^1H NMR (δ): 10.45 (s, 1H, NH), 7.96–7.55 (m, 15H, H_{arom} + NH), 4.34 (s, 2H, CH_2); MS (*m/z*, *I*%): M^+ 401.3 (0.02%). *Anal.* calcd. for $C_{22}H_{16}N_5OS$ (401.48): C, 65.81; H, 4.77; N, 17.44; S, 7.99%. Found: C, 65.75; H, 4.82; N, 17.61; S, 7.87%.

4-Anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl-thiomalononitrile (2e). Yield 0.94 g (76%); mp 188–190 °C; IR (ν_{max}, cm^{-1}): 3419 (NH), 3050 (CH_{arom}), 2931 (CH_{aliph}), 2210 (C≡N), 1618 (C=N); ^1H NMR (δ): 14.72 (brs, 1H, NH), 7.90–7.50 (m, 10H, H_{arom} + 1H, CH). *Anal.* calcd. for $C_{17}H_{12}N_6S$ (332.38): C, 61.43; H, 3.64; N, 25.28; S, 9.65%. Found: C, 61.35; H, 3.44; N, 25.39; S, 9.41%.

Synthesis of Ethyl(4-anilino-5-phenyl-4*H*-1,2,4-triazol-3-yl) thioacetate (2f)

A mixture of compound **1** (2 g, 7.46 mmol), ethyl chloroacetate (0.79 mL, 7.46 mmol), and anhydrous potassium carbonate (2.04 g, 14.92 mmol) in dry acetone (40 mL) was refluxed for 8 h on a water bath. The solvent was evaporated and the solid formed was washed with water and crystallized from benzene, yield 1.92 g (72%); mp 71–73 °C; IR (ν_{max}, cm^{-1}): 3303 (NH), 3019 (CH_{arom}), 2927 (CH_{Aliph}), 1744 (C=O), 1605 (C=N); ^1H NMR (δ): 7.97–7.55 (m, 11H, H_{arom} + NH), 4.29 (s, 2H, CH_2), 4.18–4.11 (q, J = 7 Hz, 2H, CH_2), 1.20–1.16 (t, J = 7 Hz, 3H, CH_3). *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, 61.11; H, 5.34; N, 15.64; S, 9.22%.

Synthesis of 6-Amino-3,5-diphenyl-5*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-7-carbonitrile (3)

A suspension of compound **2e** (0.322 g, 1 mmol) in sodium ethoxide solution (0.2 g Na in 30 mL absolute ethanol) was refluxed for 3 h and allowed to cool. The precipitate was collected, washed with water, and recrystallized from ethanol, yield 0.3 g (90%); mp 190 °C; IR (ν_{max}, cm^{-1}): 3331 and 3202 (NH_2), 2199 (C≡N), 1631 (C=N); ^1H NMR (δ): 8.96 (s, 2H, NH_2), 8.10–7.05 (m, 10H, H_{arom}); MS (*m/z*, *I*%): $M^+ - 2$, 330 (29.4%). *Anal.* calcd. for $C_{17}H_{12}N_6S$ (332.38): C, 61.43; H, 3.64; N, 25.28; S, 9.65%. Found: C, 61.45; H, 3.72; N, 25.15; S, 9.52%.

Synthesis of 3,5-Diphenyl-5*H*-1,2,4triazolo[3,4-b]-1,3,4-thiadiazin-6(7*H*)-one (4)

Method A. To a solution of compound **1** (0.7 g, 2.6 mmol) in pyridine (40 mL), chloroacetyl chloride (0.45 mL, 4 mmol) was added. The reaction mixture was refluxed for 3 h and then poured into ice-cold water. The formed precipitate was collected, filtered, and recrystallized from ethanol, yield 0.53 g (66%).

Method B. A solution of compound **2f** (1 g, 2.82 mmol) in acetic anhydride (25 mL) was refluxed for 4 h and then poured into ice-cold water. The formed precipitate was collected, filtered, and recrystallized from ethanol, yield 0.74 g (85%); mp 79–82 °C; IR (ν_{max}, cm^{-1}): 3055.6 (CH_{arom}), 2984–2930 (CH_{aliph}), 1742 (C=O), 1608 (C=N); ^1H NMR (δ): 7.86–7.22 (m, 10H, H_{arom}), 4.42 (s, 2H, CH_2); MS (*m/z*, *I*%): M^+ 308.25 (0.58%). *Anal.* calcd. for $C_{16}H_{12}N_4OS$ (308.35): C, 62.32; H, 3.92; N, 18.17; S, 10.40%. Found: C, 62.11; H, 3.76; N, 18.34; S, 10.27%.

Synthesis of 3,5-Diphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole-6(5*H*)-thione (5)

Method A. A mixture of compound **1** (0.5 g, 1.86 mmol) and potassium hydroxide (0.11 g, 2 mmol) in ethanol (30 mL) was stirred for 0.5 h, then carbon disulfide (22 mL, 3 mmol) was added slowly. The reaction mixture was refluxed until H_2S evolution ceased (12 h), then concentrated and poured into ice-cold water. The precipitate was washed with water, filtered, and recrystallized from ethanol, yield 0.53 g (91%).

Method B. A mixture of compound **9** (0.5 g, 1.69 mmol) and Lawesson's reagent (0.34 g, 1.69 mmol) in xylene (30 mL) was refluxed until H_2S ceased (3 h), and the solvent was then evaporated under reduced pressure. The formed precipitate was collected and recrystallized from ethanol, yield 0.34 g (65%); mp 320 °C; IR (ν_{max}, cm^{-1}): 3055 (CH_{arom}), 1616 (C=N), 1107 (C=S); ^1H NMR (δ): 8.31–7.19 (m, 10H, H_{arom}); MS (*m*/*z*, *I*%): M^+ 310 (8.86%). *Anal.* calcd. for $C_{15}H_{10}N_4S_2$ (310.39): C, 58.04; H, 3.25; N, 18.05; S, 20.66%. Found: C, 58.25; H, 3.42; N, 18.12; S, 20.44%.

Synthesis of 6-Ethoxy-3,5-diphenyl-5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadi-azole (6)

To a solution of compound **1** (0.53 g, 2 mmol) in acetic anhydride (20 mL), ethyl orthoformate (0.6 mL, 4 mmol) was added. The reaction mixture was refluxed for 4 h, and the solvent was evaporated under reduced pressure. The precipitate formed was collected and recrystallized from ethanol, yield 0.62 g (96%); mp 215–217 °C; IR (ν_{max}, cm^{-1}): 3049 (CH_{arom}), 2936 (CH_{aliph}), 1622 (C=N); ^1H NMR (δ): 7.98–7.55 (m, 11H, H_{arom} + CH), 3.37–3.29 (q, $J = 7.4$ Hz, 2H, CH_2), 1.44–1.39 (t, $J = 7.38$ Hz, 3H, CH_3). *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, 62.73; H, 4.69; N, 17.06; S, 9.95%.

Synthesis of Ethyl(3-mercapto-5-phenyl-4*H*-1,2,4-triazol-4-yl) phenylcarbamate (7)

A mixture of compound **1** (0.8 g, 2.98 mmol), ethyl choloroformate (0.32 mL, 2.98 mmol), and anhydrous potassium carbonate (1.1 g, 8 mmol) in dry acetone (30 mL) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residual solid was washed with water, filtered, and recrystallized from ethanol, yield 0.95 g (93.5%); mp 126–128 °C; IR (ν_{max}, cm^{-1}): 3151 (NH), 2986 (CH_{arom}), 2936, (CH_{Aliph}), 1762 (C=O), 1622 (C=N), 1198 (C=S); ^1H NMR (δ): 7.93–7.59 (m, 11H, H_{arom} + NH), 4.49–4.42 (q, $J = 7.2$ Hz, 2H, CH_2), 1.38–1.33 (t, $J = 7.2$ Hz, 3H, CH_3). *Anal.* calcd. for $C_{17}H_{16}N_4O_2S$ (340.39): C, 59.98; H, 4.47; N, 16.46; S, 9.42%. Found: C, 59.88; H, 4.35; N, 16.62; S, 9.58%.

Synthesis of 1-(3-Mercapto-5-phenyl-4*H*-1,2,4-triazol-4-yl)-1,3-diphenylthiourea (8)

A mixture of compound **1** (0.5 g, 1.86 mmol), phenyl isothiocyanate (0.22 mL, 1.86 mmol), and few drops of piperidine in ethanol (30 mL) was refluxed for 3 h. The solvent was evaporated under reduced pressure. The formed precipitate was collected and

recrystallized from ethanol, yield 0.69 g (91.6%); mp 98–101 °C; IR (ν_{max}, cm^{-1}): 3421 ($NH_{anilino}$), 3258 (NH), 3044 (CH_{arom}); ^1H NMR (δ): 7.87–7.26 (m, 17H, H_{arom} + 2NH); MS (*m/z*, *I*%): M^+ 403.45 (0.32%). *Anal.* calcd. for $C_{21}H_{17}N_5S_2$ (403.52): C, 62.51; H, 4.25; N, 17.36; S, 15.89%. Found: C, 62.41; H, 4.32; N, 17.56; S, 15.58%.

Synthesis of 3,5-Diphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-6(5*H*)-one (9)

A solution of compound **7** (0.6 g, 1.76 mmol) in acetic anhydride (20 mL) was refluxed for 6 h; the solvent was evaporated under reduced pressure, the formed precipitate was collected and recrystallized from ethanol, yield 0.47 g (90%); mp 142–145 °C; IR (ν_{max}, cm^{-1}): 3077 (CH_{arom}), 1747 (C=O), 1619 (C=N); ^1H NMR (δ): 7.98–7.43 (m, 10H, H_{arom}); MS (*m/z*, *I*%): M^+ 294.4 (0.03%). *Anal.* calcd. for $C_{15}H_{10}N_4OS$ (294.33): C, 61.21; H, 3.42; N, 19.04; S, 10.98%. Found: C, 61.35; H, 3.66; N, 19.24; S, 10.78%.

Synthesis of 3,5,7-Triphenyl-5*H*-1,2,4-triazolo[4,3-b]-1,2,4-triazole-6(7*H*)-thione (10)

A solution of compound **8** (0.5 g, 1.23 mmol) in pyridine (25 mL) was refluxed until H_2S ceased (12 h). The solvent was evaporated under reduced pressure, the formed precipitate was collected and recrystallized from ethanol, yield 0.37 g (82%); mp 193–195 °C; IR (ν_{max}, cm^{-1}): 1176 (C=S); ^1H NMR (δ): 7.69–7.18 (m, 15H, H_{arom}); MS (*m/z*, *I*%): M^+ 369.5 (0.45%). *Anal.* calcd. for $C_{21}H_{15}N_5S$ (369.44): C, 68.27; H, 4.09; N, 18.96; S, 8.68%. Found: C, 68.34; H, 4.22; N, 18.75; S, 8.53%.

Synthesis of 2-(4-Methoxyphenyl)-1,6-diphenyl-1,2-dihydro-1,2,4-triazolo[4,3-d]-1,3,4,2-thiadiazaphosphole 2-sulfide (11)

A mixture of compound **1** (1 g, 3.73 mmol) and Lawesson's reagent (0.75 g, 3.73 mmol) in acetonitrile (30 mL) was refluxed until H_2S ceased (3 h), and the solvent was then evaporated under reduced pressure. The formed precipitate was collected and recrystallized from ethanol, yield 1.43 g (88%); mp 224–226 °C; IR (ν_{max}, cm^{-1}): 3095 (CH_{arom}), 2921 (CH_{aliph}), 1630 (C=N), 690 (P=S); ^1H NMR (δ): 7.62–7.99 (m, 14H, H_{arom}), 3.80 (s, 3H, CH_3); MS (*m/z*, *I*%): M^+ 436 (15.37%). *Anal.* calcd. for $C_{21}H_{17}N_4OPS_2$ (436.48): C, 57.78; H, 3.93; N, 12.84; S, 14.69%. Found: C, 57.66; H, 3.82; N, 12.98; S, 14.41%.

Synthesis of 3,5-Diphenyl-6,7-dihydro-5*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (12)

To a solution of compound **1** (0.5 g 1.86 mmol) in ethanol (30 mL) and drops of triethylamine, 1,2-dibromoethane (0.14 mL, 1.86 mmol) was added. The reaction mixture was refluxed for 3 h; the solvent was evaporated under reduced pressure. The formed precipitate was collected and recrystallized from ethanol, yield 0.37 g (68%); mp 109–111 °C; IR (ν_{max}, cm^{-1}): 3075 (CH_{arom}), 2927 (CH_{aliph}), 1635 (C=N); ^1H NMR (δ): 7.97–7.55 (m, 10H, H_{arom}), 3.82–3.78 (*t*, J = 6 Hz, 2H, N-CH_2), 2.53–2.49 (*t*, J = 6 Hz, 2H, S-CH_2).

Anal. calcd. for $C_{16}H_{14}N_4S$ (294.37): C, 65.28; H, 4.79; N, 19.03; S, 10.89%. Found: C, 65.15; H, 4.58; N, 19.28; S, 10.76%.

Synthesis of 3,5-Diphenyl-5*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6,7-dione (13)

A mixture of compound **1** (0.5 g, 1.86 mmol) and diethyl oxalate (0.25 mL, 1.86 mmol) was heated for 1.5 h. The reaction mixture was treated with ethanol. The precipitate was collected and recrystallized from ethanol, yield 0.45 g (75%); mp 120–122 °C; IR (ν_{max}, cm^{-1}): 3025 (CH_{arom}), 1688 (2C=O); ^1H NMR (δ): 7.89–7.52 (m, 10H, H_{arom}); MS (*m*/*z*, *I*%): M^+ 322 (1.42%). *Anal.* calcd. for $C_{16}H_{10}N_4O_2S$ (322.34): C, 59.62; H, 3.13; N, 17.38; S, 9.95%. Found: C, 59.51; H, 3.37; N, 17.22; S, 9.84%.

General Procedure for Synthesis of Compounds 14 and 15

To a solution of compound **1** (0.5 g, 1.86 mmol), the appropriated ketoester, namely ethyl acetoacetate and/or ethyl benzoylacetate (1.86 mmol) was added. The reaction mixture was heated for 1 h, then treated with methanol. The precipitate was collected and recrystallized from methanol.

8-Methyl-3,5-diphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepin-6(5*H*)-one (14). Yield 0.56 g (90%); mp 136–138 °C; IR (ν_{max}, cm^{-1}): 3071 (CH_{arom}), 2924 (CH_{aliph}), 1754 (C=O), 1612 (C=N); ^1H NMR (δ): 7.78–7.39 (m, 10H, H_{arom}), 5.92 (s, 1H, CH), 2.42 (s, 3H, CH_3). *Anal.* calcd. for $C_{18}H_{14}N_4OS$ (334.39): C, 64.65; H, 4.22; N, 16.75; S, 9.59%. Found: C, 64.43; H, 4.35; N, 16.66; S, 9.71%.

3,5,8-Triphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepin-6(5*H*)-one (15). Yield 0.64 g (86%); mp 214–217 °C; IR (ν_{max}, cm^{-1}): 3095 (CH_{arom}), 1735 (C=O), 1616 (C=N); ^1H NMR (δ): 7.92–7.54 (m, 16H, H_{arom} + CH). *Anal.* calcd. for $C_{23}H_{16}N_4OS$ (396.46): C, 69.68; H, 4.07; N, 14.13; S, 8.09%. Found: C, 69.56; H, 4.19; N, 14.33; S, 8.12%.

Synthesis of 3,5-Diphenyl-8-thioxo-8,9-dihydro-5*H*-1,2,4-triazolo[4,3-b]-1,2,4-triazepin-6(7*H*)-one (16)

A mixture of compound **1** (0.55 g, 2.05 mmol) and ethyl cyanoacetate (0.23 mL, 2.05 mmol) in dry pyridine (30 mL) was refluxed for 6 h, cooled and then poured into ice-cold water. The formed precipitate was collected, filtered, and recrystallized, yield 0.47 g (69%); mp 217–219 °C (ethanol); IR (ν_{max}, cm^{-1}): 3146 (NH), 3010 (CH_{arom}), 2947 (CH_{aliph}), 1697 (C=O), 1176 (C=S), 1610 (C=N); ^1H NMR (δ): 14.71 (brs, 1H, NH), 7.90–7.55 (m, 10H, H_{arom}), 3.45 (s, 2H, CH_2). *Anal.* calcd. for $C_{17}H_{13}N_5OS$ (335.38): C, 60.88; H, 3.91; N, 20.88; S, 9.56%. Found: C, 60.65; H, 3.82; N, 20.63; S, 9.71%.

Synthesis of 3,5-Diphenyl-5*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-6,7-dione-7-(*p*-tolyl)hydrazone (17)

The freshly prepared *p*-toluenediazonium chloride [from *p*-toluidine (0.54 g, 5 mmol) in conc. HCl (5 mL) and sodium nitrite (0.48 g, 5mmol)] was added slowly over 30 min with stirring to an equivalent solution of compound **4** (1.54 g, 5 mmol) in a solution of 20% NaOH (2 mL) at 0–5 °C. The mixture was kept in an ice bath for 30 min [during this

period the pH was maintained at 8–9], and then neutralized by the addition of acetic acid. The precipitate formed was filtered off and washed with water, recrystallized from ethanol, yield 0.47 g (69%); mp 218–220 °C; IR (ν_{max}, cm^{-1}): 3140 (NH), 3020 (CH_{arom}), 1750 (C=O), 1612 (C=N); MS (*m/z*, *I*%): M^+, 426.1 (0.86%). *Anal.* calcd. for $C_{23}H_{18}N_6OS$ (426.49): C, 64.77; H, 4.25; N, 19.70; S, 7.52%. Found: C, 64.52; H, 4.41; N, 19.87; S, 7.36%.

Synthesis of 3,5-Diphenyl-5*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-6 (7*H*)-thione (18)

A mixture of compound **4** (0.31 g, 1 mmol) and Lawesson's reagent (0.20 g, 1 mmol) in xylene (30 mL) was refluxed for 4 h (until all the H_2S gas was evolved); the solvent was evaporated under reduced pressure, the precipitate formed was collected and recrystallized from ethanol, yield 0.24 g (65%); mp 125–128 °C; IR (ν_{max}, cm^{-1}): 3050 (CH_{arom}), 2930 (CH_{aliph}), 1600 (C=N), 1147 (C=S); MS (*m/z*, *I*%): M^+ 324.3 (0.02%). *Anal.* calcd. for $C_{16}H_{12}N_4S_2$ (324.42): C, 59.23; H, 3.73; N, 17.27; S, 19.77%. Found: C, 59.35; H, 3.68; N, 17.41; S, 19.92%.

Synthesis of 7-Amino-3,5-diphenyl-5*H*-thieno[3,2-e][1,2,4]triazolo [3,4-b][1,3,4]thia-diazine-6-carbonitrile (19)

To a stirred solution of compound **4** (1.1 g, 3.57 mmol) in dry dioxane (20 mL), sulfur (0.11 g, 3.57 mmol) and drops of triethylamine were added. The reaction mixture was refluxed for 1 h and then malononitrile (0.23 mL, 3.57 mmol) was added. The reaction mixture was refluxed for 4 h, and after cooling, the solid precipitate was filtered off, washed with water, and recrystallized from benzene, yield 1.24 g (90%); mp 91–93 °C; IR (ν_{max}, cm^{-1}): 3328 and 3208 (NH_2), 2984 (CH_{arom}), 2202 (C≡N), 1627 (C=N); MS (*m/z*, *I*%): M^+ 388.7 (1.35%). *Anal.* calcd. for $C_{19}H_{12}N_6S_2$ (388.4): C, 58.74; H, 3.11; N, 21.63; S, 16.51%. Found: C, 58.51; H, 3.32; N, 21.53; S, 16.46%.

Synthesis of 7-Amino-3,5-diphenyl-9-thioxo-5,9-dihydrothiopyrano[4,3-e]-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine-6-carbonitrile (20)

To a solution of compound **4** (0.308 g, 1 mmol) in ethanol (20 mL), carbon disulfide (0.38 mL, 5 mmol) and triethylamine (0.5 mL) were added. The reaction mixture was stirred at room temperature for 2 h, and malononitrile (0.066 g, 1 mmol) and dimethylformamide (1 mL) were added. The reaction mixture was refluxed for 4 h. After cooling, the reaction mixture was poured into water and HCl (100:5 v/v), and the solid product was filtered off, washed with water, and recrystallized from chloroform, yield 1.24 g (90%); mp 90–93 °C; IR (ν_{max}, cm^{-1}): 3316 and 3186 (NH_2), 2204 (C≡N), 1632 (C=N); MS (*m/z*, *I*%): M^+ 432.55 (0.67%). *Anal.* calcd. for $C_{20}H_{12}N_6S_3$ (432.54): C, 55.54; H, 2.80; N, 19.43; S, 22.24%. Found: C, 55.38; H, 2.95; N, 19.61; S, 22.13%.

REFERENCES

1. Ghorab, M. M.; El-Sharief, A. M. Sh.; Ammar, Y. A.; Mohamed, Sh. I. *IL Farmaco* **2000,** 55, 354-361.
2. Kokil, R. G. *Lett. Drug Des. Discov.* **2010,** 7, 46-49.

3. Sztanke, K.; Tuzimski, T.; Rzymowska, J.; Pasternak, K.; Szerszen, M. K. *Eur. J. Med. Chem.* **2008,** 43, 404-419.
4. Nath, M.; Sulaxna; Song, X.; Eng, G.; Kumar, A. *Spectrochim. Acta Part A* **2008,** 70, 766-774.
5. Ezabadi, R. I.; Camoutsis, C.; Zoumpoulakis, P.; Geronikaki, A.; Sokovic, M.; Glamocilija, J. *Bioorg. Med. Chem.* **2008,** 16, 1150-1161.
6. Husain, A.; Naseer, Md. A. *Med. Chem. Res.* **2011,** 20, 47-54.
7. Kumar, H.; Javed, A. S.; Khan, A. S.; Amir, M. *Eur. J. Med. Chem.* **2008,** 43, 2688-2698.
8. Kaplancıklı, Z. A.; Turan-Zitouni, G.; Özdemir, A.; Revial, G. *Eur. J. Med. Chem.* **2008,** 43, 155-159.
9. Jadhav, G. R.; Shaikh, M. U.; Kale, R. P.; Shiradka, M. R.; Gill, C. H. *Eur. J. Med. Chem.* **2009,** 44, 2930-2935.
10. Al-Soud, Y. A.; Al-Dweri, M. N.; Al-Masoudi, N. A. *II Farmaco* **2004,** 59(10), 775-783.
11. Mavrova, A. Ts.; Wesselinova, D.; Tsenov, Y. A.; Denkova. P. *Eur. J. Med. Chem.* **2009,** 44, 63-69.
12. Khalil, N. S. A. M. *Eur. J. Med. Chem.* **2010,** 45, 5265-5277.
13. Sadana, K. A.; Mirza, Y.; Aneja, K. R.; Prakash, O. *Eur. J. Med. Chem.* **2003,** 38, 533-536.
14. Shields, P.; Vu, C. B.; Peng, B.; Kumaravel, G.; Jin, X.; Phadke, D.; Wang, J.; Engber, T.; Ayyub, E.; Petter, R. C. *Bioorg. Med. Chem. Lett.* **2004,** 14, 4835-4838.
15. Yao, G.; Haque, S.; Sha, L.; Kumaravel, G.; Wang, J.; Engber, T. M.; Whalley, E. T.; Conlon, P. R.; Chang, H., Kiesman, W. F.; Petter, R. C. *Bioorg. Med. Chem. Lett.* **2005,** 15(3), 511-515.
16. Ghattas, A. B. A. G.; Abdel-Rahman, M.; El-Wassaimy, M. T.; El-Saraf, G. A. *Rev. Roum. Chim.* **1989,** 34, 1987-1993.
17. Ghattas, A. B. A. G.; El-Saraf, G. A. *Sulfur Lett*. **1989,** 8, 261-274.
18. El-Wassaimy, M. T.; Abdel-Rahman, M.; Ghattas, A. B. A. G.; Abd Allah, O. A. *Phosphorus Sulfur Silicon* **1992,** 70, 99-108.
19. Abdel-Rahman, M. A.; Ghattas, A. B. A. G.; El-Saraf, G. A.; Khodiary, A. *Phosphorus Sulfur Silicon* **1993,** 85, 183-192.
20. Moustafa, H. M. *Synth. Commun.* **2001,** 31(1), 97-109.
21. Ghattas, A. B. A. G.; Moustafa, H. M.; Abd Allah, O. A.; Amer, A. A. *Synth. Commun.* **2001,** 31(16), 57-66.
22. Ghattas, A. B. A. G.; Abd Allah, O. A.; Moustafa, H. M.; Amer, A. A. *Eygpt J. Chem.* **2003,** 46, 297-311.
23. Chande, M. S.; Bahandari, J. D.; Joshi, V. R. *Indian J. Chem.* **1993,** 32B, 1218-1228.
24. Barry, A. L. *The Antimicrobial Susceptibility Test, Principles and Practices*; Illus Lea and Febiger: Philadeliphia, PA, **1976**; p. 180.