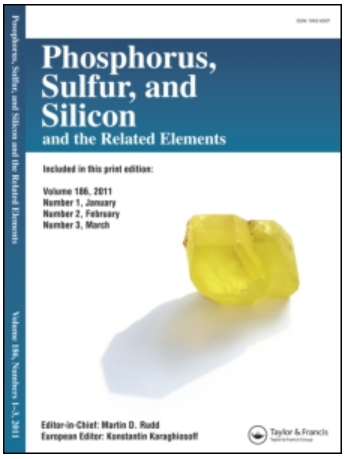

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New Approaches for the Synthesis of 1,3,4-Thiadiazole and 1,2,4-Triazole Derivatives with Antimicrobial Activity

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New Approaches for the Synthesis of 1,3,4-Thiadiazole and 1,2,4-Triazole Derivatives with Antimicrobial Activity

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*The thiosemicarbazide derivatives **3a** and **3b** were cyclized in the presence of concentrated sulfuric acid to give the 5-cyanomethyl-1,3,4-thiadiazole derivatives **4a** and **4b**, respectively. The latter products were used for many heterocyclic transformations to form coumarin, 1,3,4-thiadiazolo[4,5-a]pyridine, and 5-thiophenylthiophene. In addition, compound **3b** underwent cyclization in NaOH (2 N) solution to give the 1,2,4-triazole derivative **16**. The reactivity of the latter product towards some chemical reagents was studied. The antimicrobial activities of the newly synthesized products were measured and showed high activities.*

Keywords Antimicrobial; coumarin; thiadiazole; triazole

INTRODUCTION

The cyclization of suitable linear compounds is one of the most common and popular methods for preparing heterocyclic compounds. Asymmetrical ureas have been cyclized to produce several heterocycles such as 1,3,4-thiadiazoles, 1,2,4-triazoles, and 1,3,5-triazines. 2,4-Disubstituted semicarbazones have been proposed as dipeptide isoesters[2] and could be a new class of urea peptide mimetics. The possible biological properties of semi- and thiosemicarbazone derivatives make it attractive to study the chemical reactivity of these compounds. For instance, Kabashima et al. demonstrated that the reaction of α-halocarbonyl compounds with alkyl- and arylidenephenylthiosemicarbazones gave 1,2,4-triazoline and

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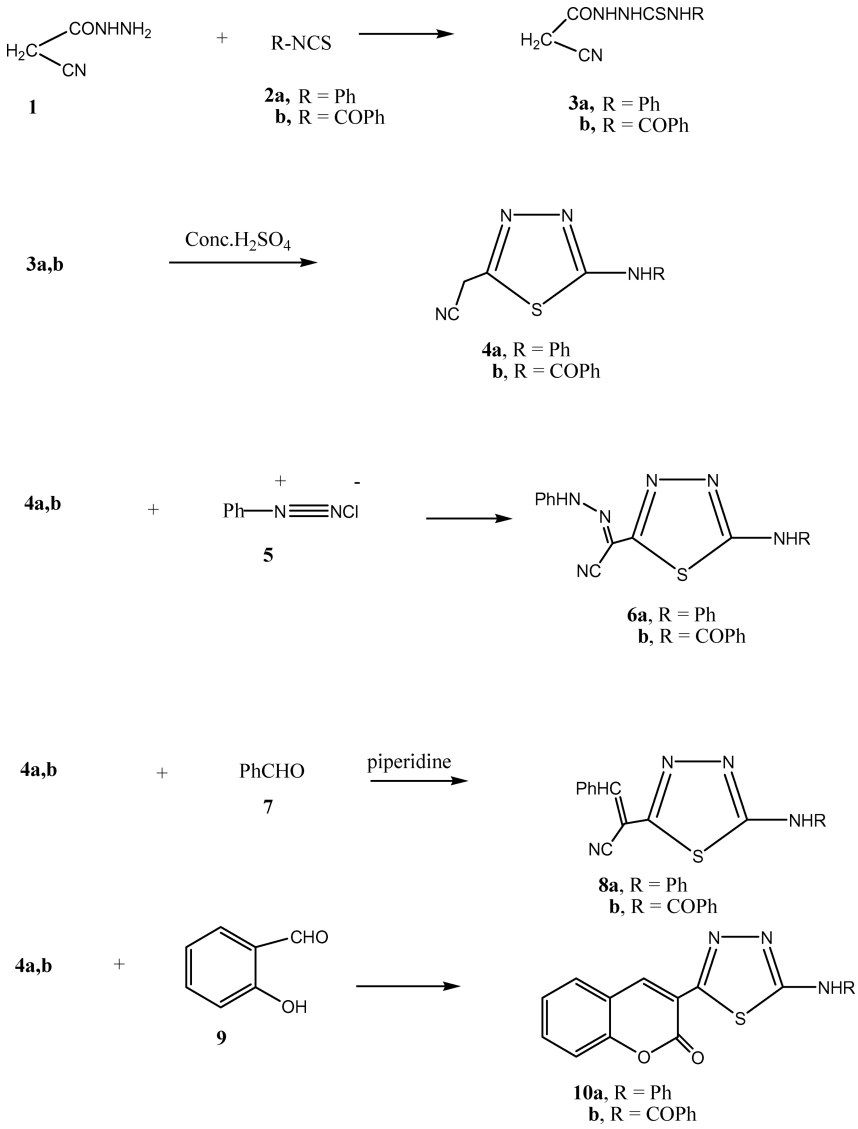
1,2,4-dithiazolidines.[3] 2,4-Disubstituted thiosemicarbazides were cyclized to 1,2,4-triazoline-3-thiones and 1,3,4-thiadiazolines when treated with acyl isothiocyanates.[4] Oxidative cyclization of substituted aldehyde thiosemicarbazones, induced by different metallic salts, led to 1,2,4-triazoline derivatives.[5–9] Alternatively, the interaction of thiosemicarbazide and dithiocarbazate derivatives with some π-acceptors such as propanedinitrile and benzoquinone, as well as naphthoquinone, afforded thiazines, thiadiazines, thiadiazoles, indazoles, pyridazines, oxathiadiazoles, and various fused heterocyclic compounds possible via a single electron transfer before the ring closure step.[10–14]

RESULTS AND DISCUSION

In this work, we use the thiosemicarbazide derivatives **3a** and **3b**, which were synthesized according to the literature procedure[15,16] in the synthesis of potentially biologically active 1,3,4-thiadiazole and 1,2,4-triazole derivatives. Therefore, compounds **3a** and **3b** underwent cyclization in the presence of concentrated sulfuric acid to give the 5-cyanomethyl-1,3,4-thiadiazole derivatives **4a** and **4b**, respectively. The assignment of the structures of compounds **4a**,**b** was based on analytical and spectroscopic data. Thus, the ^{1}H NMR spectrum of compound **4a** showed the presence of a singlet at δ 4.68 ppm for the CH_2 group, a multiplet at δ 7.26–7.33 ppm corresponding to the phenyl protons, and a singlet at δ 8.69 ppm for the NH group.

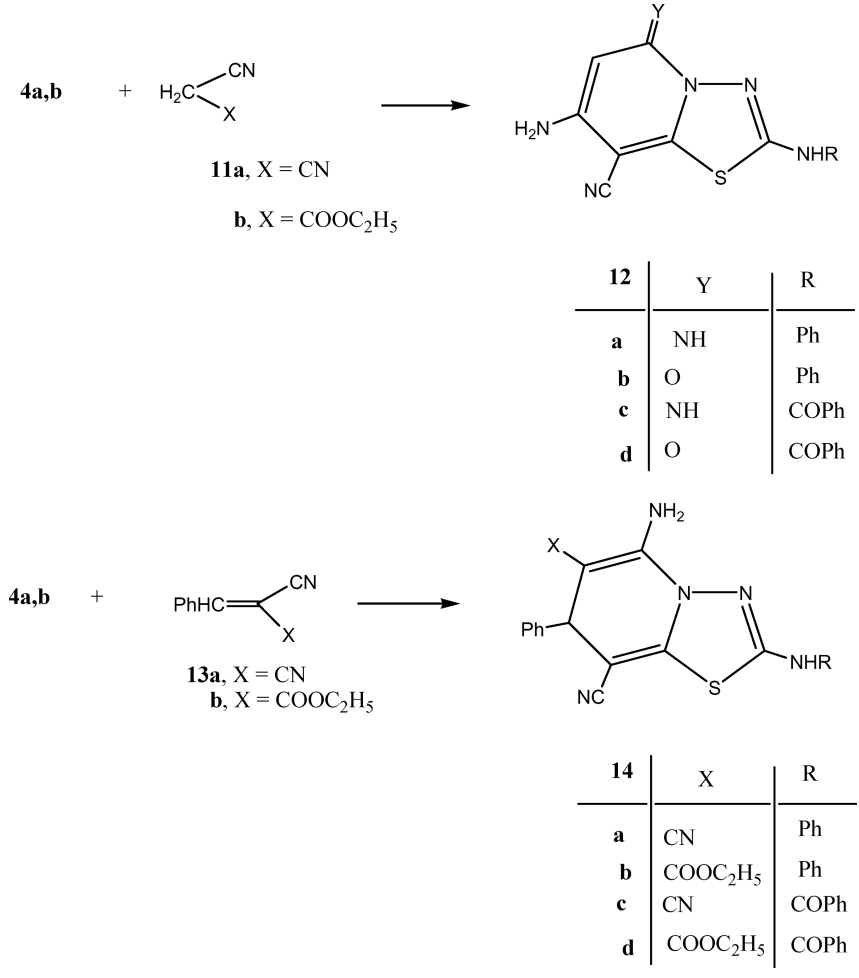
The reaction of compounds **4a** or **4b** with benzenediazonium chloride (**5**) in ethanol/sodium hydroxide solution at 0–5°C gave the phenyl hydrazone derivatives **6a** and **6b**, respectively. The reaction of compounds **4a** and **4b** with benzaldehyde (**7**) gave the benzal derivatives **8a** and **8b**, respectively. In addition, the reaction of compounds **4a** and **4b** with salicylaldehyde (**9**) gave the coumarin derivatives **10a** and **10b**, respectively. Formation of coumarins from the reaction of cyanomethylene reagents with salicylaldehyde has been reported previously in the literature.[17,18] The analytical and spectroscopic data of **8a**,**b** and **10a**,**b** were in agreement with the proposed structures. Thus the ^{1}H NMR spectrum **10a** a singlet at δ 6.69 ppm corresponding to coumarin H-4, a multiplet at δ 7.31–7.44 ppm for aromatic protons and a singlet at δ 8.35 ppm (D_2O exchangeable) for an NH group (Scheme 1).



SCHEME 1

The reaction of compounds **4a** and **4b** with either malononitrile (**11a**) or ethyl cyanoacetate (**11b**) afforded the 1,3,4-thiadiazolo[4,5-a]pyridine derivatives **12a–d**, respectively. The structures of the latter products were established based on analytical and spectroscopic data. On the other hand, the reaction of compound **4a** and **4b** with

the cinnamonitrile derivatives **13a** and **13b** resulted in the formation of the 7-phenyl-1,3,4-thiadiazolo[4,5-a]pyridine derivatives **14a–d**, respectively. The obtained analytical and spectral data are in agreement with the proposed structures. Thus, the ^{1}H NMR spectrum of **14a** showed the presence of a singlet at δ 4.68 ppm corresponding to NH_2 group, a singlet at δ 5.36 for pyridine H-4, a multiplet at δ 7.29–7.38 ppm for aromatic protons, and a singlet at δ 8.36 (D_2O exchangeable) corresponding to an NH group (Scheme 2).



SCHEME 2

The reaction of either compound **4a** or **4b** with any of the cyanomethyleno reagents **11a** or **11b** and elemental sulfur gave the 5-thiophenylthiophene derivatives **15a–d** respectively. The reaction was produced in the same way as the reported in Gewald's thiophene synthesis.[19,20]

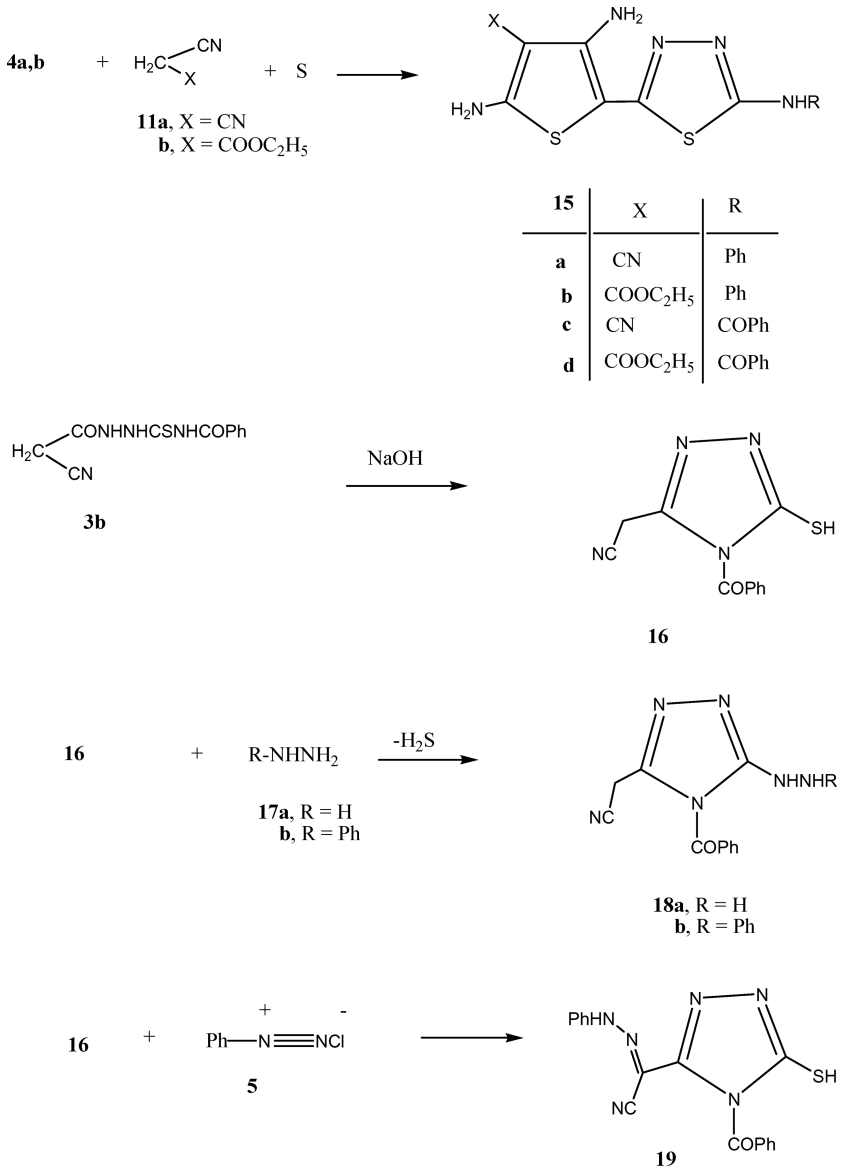
Compound **3b** underwent ready cyclization in sodium hydroxide (2.0 N) solution to give the 1,2,4-triazole derivative **16**. Assignment of the structure of the latter product was based on analytical and spectroscopic data. The ^{1}H NMR spectrum of compound **16** showed the presence of a singlet at δ 4.82 corresponding to the CH_2 group, a broad singlet at δ 5.26 for the SH group, and a multiplet at δ 7.30–7.37 for the phenyl protons. Further confirmation for the structure of compound **16** was obtained through studying its reactivity with some chemical reagents. Thus when compound **16** was allowed to react with hydrazine hydrate (**17a**) and phenylhydrazine (**17b**), the hydrazone derivatives **18a** and **18b**, respectively, were formed. Moreover, the reaction of compound **16** with benzenediazonium chloride **5** gave the phenylhydrazone derivative **19**. The analytical and spectroscopic data of compounds **18a**,**b** and **19** were consistent with the proposed structures (see the Experimental section and Scheme 3).

The reaction of compound **16** with benzaldehyde gave the benzal derivative **20**. Furthermore, the reaction of compound **16** with salicylaldehyde (**9**) gave the 3-(1,2,4-triazol-3-yl)-coumarin derivative **21** (Scheme 4).

ANTIMICROBIAL ACTIVITY

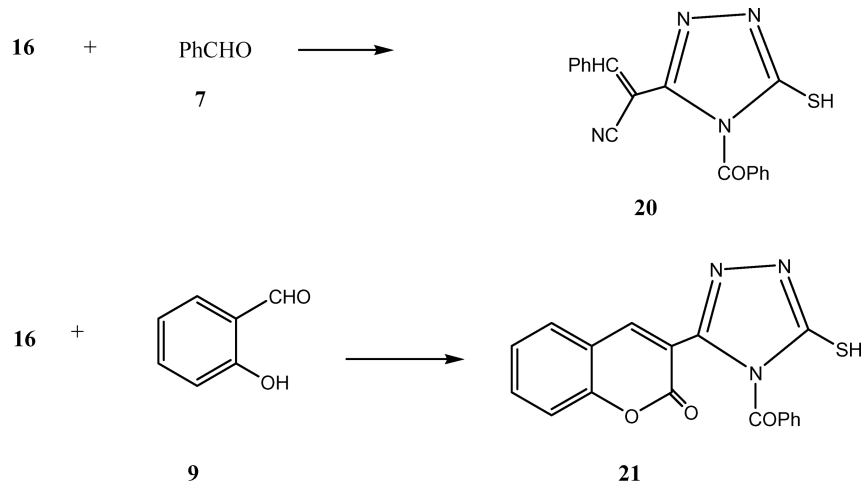
The in vitro antimicrobial activity of the structurally promising 24 heterocyclic derivatives were tested against two strains of Gram-positive bacteria (*Bacillus subtilis* CECT 498 and *Bacillus cereus* CECT 148), two strains of Gram-negative bacteria (*Escherichia coli* ECT 101 and *Pseudomonas aeruginosa*), and*Candida albicans* CECT 1394 as a representative species of fungi. The newly synthesized products were dissolved in aqueous ethanol to give a logarithmic series of concentrations from 2 to 256 mg/L upon tenfold dilution with the growth medium and spore suspension of the test fungi. The toxicity of compounds was determined via pipette additions into the wells of multi-well slides, followed by with 25 μL of the culture medium. The inoculated slides were then incubated at 25 °C until short germ tubes appeared of approximately 50 μm in length (at 0 h).

Five μL volumes of the prepared compound test solutions were added to the inoculated wells, one control well on each slide being treated



SCHEME 3

with solvent only. The slides were then returned to the incubator until germ tubes 400 μm ($\pm$50 μm) long were visible in the control wells. Further growth was arrested by the addition of lactophenol aniline blue to each of the wells. The minimal inhibitory concentration [(MIC)



SCHEME 4

in μg mL^{-1}] was determined using an adaptation of agar streak dilution method based on radial diffusion.[21,22] Under the same conditions, ampicillin (antibacterial) and cycloheximide (antifungal) were used as standards. The MIC was considered to be the lowest concentration of the tested compound (in dimethylformamide) that inhibits growth of bacteria or fungi on the plate (Table I). The diameters of the inhibition zones corresponding to the MICs are also presented in Table I.

It is obvious from Table I that compounds **10b** (N(5-oxo-2H-chromen-3-yl)-1,3,4-thiadiazol-2-yl)benzamide), **12d** (N-(7-amino-8-cyano-5-oxo-5H-[1,3,4-]thiadiazolo[3,2-a]pyridine-2-yl)benzamide), and **15c** (N-(5-(3,5-diamino-4-cyanothiophene-2-yl)-1,3,4-thiadiazol-2-yl)benzamide) are the most active towards *E. coli*, and their activity is higher than that of ampicilin. Alternatively, compounds **4a**, **4b**, **8b**, **12b**, **12d**, and **16** are more active towards *B. Cereus* than ampicilin. Compounds **4a**, **8b**, **12b**, **12d**, and **15a** showed high activity against *B. Subtilis*. Moreover, compounds **6a**, **6b**, **8a**, **10a**, **10b**, **14b**, **15a**, and **15c** showed high activity towards *C. Albicans*, where compounds **10b** and **15b** (both of them with the 2-substituted thiadiazole derivatives) showed the maximum activities. It is clear that compound **8b** (N-(5-(1-cyano-2-phenylvinyl)-1,3,4-thiadiazol-2-yl)benzamide) showed the highest activity towards *E. Coli*, *B. Subtilis*, and *C. Albicans* (Tables II and III).

TABLE I Antimicrobial Activities of the Tested Compounds

	MIC (μgmL^{-1}) (zone of inhibition, mm)			
Compound No.	*E. coli* ECT	*B. cereus* CECT	*B. subtilis* CECT	*C. albicans* CECT
4a	—	22.52 (8)	20.55 (4)	8.65 (4)
4b	—	11.32 (3)	21.01 (8)	18.73 (8)
6a	—	6.05 (15)	16.88 (2)	22.89 (3)
6b	—	12.30 (4)	12.40 (4)	33.23 (6)
8a	—	3.72 (6)	18.22 (8)	16.58 (12)
8b	—	22.38 (8)	24.18 (3)	22.83 (6)
10a	—	20.46 (9)	19.15 (4)	23.64 (6)
10b	12.50 (6)	18.12 (5)	16.45 (6)	100.00
12a	—	0.40 (10)	18.23 (5)	16.42 (2)
12b	—	18.24 (7)	22.01 (8)	4.13 (10)
12c	—	10.05 (6)	0.61 (6)	30.23 (6)
12d	11.34 (4)	12.25 (2)	22.45 (8)	6.18 (4)
14a	—	4.55 (10)	6.25 (15)	24.44 (2)
14b	—	16.22 (3)	18. 32 (8)	10.38 (4)
14c	—	6.22 (6)	14.40 (4)	0.03 (9)
14d	—	0.40 (5)	12.55 (12)	25.36 (8)
15a	—	23.63 (6)	21.15 (4)	50.17
15b	—	26.12 (3)	8.22 (2)	100.00 (5)
15c	14.84	18.32 (5)	10.33 (5)	23.16 (9)
15d	—	0.08 (2)	8.36 (4)	12.42 (2)
16	—	22.33 (5)	12.22 (8)	8.66 (6)
18a	—	6.05 (6)	4.55 (10)	12.34 (7)
18b	—	3.13 (10)	6.13 (4)	12.34 (7)
19	—	12.50 (10)	6.13 (4)	12.50
20	—	0.40 (5)	8.25 (6)	22.82 (8)
21	—	0.05 (9)	14.36 (8)	20.11 (4)
Ampicillin	6.25	3.13	12.50 (10)	—
Cycloheximide	—	—	—	12.50 (6)

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian EM-390 MHz spectrophotometer in DMSO-d_6 as the solvent and TMS as internal reference. Chemical shifts are expressed in δ or ppm. Antibacterial results were recorded by a research group at the Botany Department at Cairo University.

5-Cyanomethyl-2-phenylamino-1,3,4-thiadiazole (4a) and 2-Benzoylamino- 5-cyanomethyl-1,3,4-thiadiazole (4b)

A suspension of the corresponding thiosemicarbazide either **3a** (2.34 g, 0.01 mol) or **3b** (2.62 g, 0.01 mol) in cold concentrated sulfuric acid

TABLE II Physical and Analytical Data of the Newly Synthesized Products

Compd No.	Yield (%) color	M.p. °C Cryst. solvent	Mol. Formula (Mr)	Calcd/Found (%) C	H	N	S
4a	70 Buff	173–176 Ethanol	$C_{10}H_8N_4S$ (216.26)	55.54 55.62	3.73 4.03	25.91 26.24	14.83 14.71
4b	74 Yellow	262–264 Ethanol	$C_{11}H_8N_4OS$ (244.27)	54.09 53.96	3.30 3.53	22.94 23.31	13.13 13.04
6a	70 Reddish-brown	194–196 Ethanol	$C_{16}H_{12}N_6S$ (320.37)	59.98 60.33	3.78 4.01	26.23 26.52	10.01 9.83
6b	86 Red	252–255 Ethanol	$C_{17}H_{12}N_6OS$ (348.38)	58.61 58.88	3.47 3.26	24.12 24.31	9.20 8.95
8a	62 Yellow	180–183 Ethanol	$C_{17}H_{12}N_4S$ (304.37)	67.08 66.89	3.97 4.08	18.41 18.17	10.53 10.33
8b	50 Yellow	222–224 Ethanol	$C_{18}H_{12}N_4OS$ (332.38)	65.04 64.82	3.64 3.91	16.86 17.04	9.65 9.36
10a	93 Yellow	>300 Ethanol	$C_{17}H_{11}N_3O_2S$ (321.35)	63.54 63.43	3.45 3.66	13.08 12.79	9.98. 10.26
10b	69 Yellow	246–248 Ethanol	$C_{18}H_{11}N_3O_3S$ (349.36)	61.88 62.16	3.17 3.43	12.03 11.89	9.18 9.04
12a	70 Orange	166–169 1,4–dioxan	$C_{13}H_{10}N_6S$ (282.32)	55.30 55.09	3.57 3.69	29.77 29.53	11.36 11.08
12b	66 Yellow	132–135 1,4–Dioxan	$C_{13}H_9N_5OS$ (283.31)	55.11 54.89	3.20 2.93	24.72 24.48	11.32 11. 17
12c	78 Orange	222–225 DMF	$C_{14}H_{10}N_6OS$ (310.33)	54.18 53.87	3.25 3.38	27.08 26.85	10.33 10.61
12d	73 Pale yellow	189–193 1,4–Dioxan	$C_{14}H_9N_5O_2S$ (311.32)	54.01 53.85	2.91 3.27	22.50 22.83	10.30 10.17
14a	70 Pale brown	98–100 Ethanol	$C_{20}H_{14}N_6S$ (370.43)	64.85 64.47	3.81 4.25	22.69 23.05	8.66 8.89
14b	54 Reddish brown	230–233 Ethanol	$C_{22}H_{19}N_5O_2S$ (417.48)	63.29 63.62	4.59 4.31	16.78 17.16	7.68 7.95
14c	60 Reddish brown	98–102 Ethanol	$C_{21}H_{14}N_6OS$ (398.45)	63.30 63.49	3.54 3.76	21.09 20.86	8.05 7.82
14d	78 Reddish brown	230–233 Ethanol	$C_{23}H_{19}N_5O_3S$ (445.50)	62.01 62.17	4.30 4.38	15.72 15.15	7.20 7.27
15a	73 Yellow	258–260 Ethanol	$C_{13}H_{10}N_6S_2$ (314.39)	49.66 49.44	3.21 3.50	26.73 26.53	20.40 20.72
15b	75 Yellow	240–245 Ethanol	$C_{15}H_{15}N_5O_2S_2$ (361.44)	49.84 48.98	4.18 4.33	19.39 19.27	17.74 18.09
15c	64 Brown	>300 Ethanol	$C_{14}H_{10}N_6OS_2$ (342.41)	49.11 49.04	2.94 3.35	24.54 24.48	18.73 19.16
15d	50 Brown	>300 Ethanol	$C_{16}H_{15}N_5O_3S_2$ (389.45)	49.34 49.66	3.88 3.72	17.98 17.81	16.47 16.97
16	57 White	>300 1,4–Dioxan	$C_{11}H_8N_4OS$ (244.27)	54.09 53.85	3.30 3.67	22.94 23.37	13.13 12.84
18a	65 Yellow	282–284 1,4–Dioxan	$C_{11}H_{10}N_6O$ (241.24)	54.54 54.10	4.14 4.48	34.69 34.83	

(Continued on next page)

TABLE II Physical and Analytical Data of the Newly Synthesized Products *(Continued)*

Compd No.	Yield (%) color	M.p. °C Cryst. solvent	Mol. Formula (Mr)	Found/Calcd (%) C	H	N	S
18b	50 Yellow	276–279	$C_{17}H_{14}N_6O$	64.14	4.43	26.40	
		1,4–Dioxan	(318.33)	64.09	4.11	26.32	
19	75 Yellow	280–282	$C_{17}H_{12}N_6OS$	58.61	3.47	24.12	9.20
		Ethanol	(348.38)	58.89	4.11	24.32	9.33
20	50 Pale	226–229	$C_{18}H_{12}N_4OS$	65.04	3.64	16.86	9.65
	brown	Methanol	(332.38)	65.11	3.88	17.17	9.44
21	92 Orange	242–244	$C_{18}H_{11}N_3O_3S$	61.88	3.17	12.03	9.18
		Ethanol	(349.36)	62.26	3.45	12.48	8.76

(28 mL) was stirred for 10 min. Then the mixture, in each case, was allowed to warm to room temperature and stirred for an additional 30 min. The resulting mixture, in each case, was poured onto an ice/water mixture and made alkaline to pH 8 with aqueous ammonia. The solid product formed in each case was collected by filtration.

5-(α-Phenylhydrazocyanomethyl-2-phenylamino-1,3,4-thiadiazole (6a), 2-Benzoylamino-5-(α-phenylhydrazocyanomethyl-1,3,4-Thiadiazole (6b), and 4-Benzoyl-(a-phenylhydrazocyanomethyl)-3-thioxo-1,2,4-triazole (19)

To a cold solution (0–5°C) of aniline (1.02 g, 1.0 mL, 1.1 equiv.), conc. HCl (1.09 g, 0.92 mL, 3 equiv.) was added. The temperature was maintained at 0–5°C and an aqueous solution of sodium nitrite (0.76 g, 1.1 equiv.) was added dropwise to the aniline solution. The reaction mixture was stirred for 15 min. The clear diazonium salt solution **5** was then added dropwise to a solution of either thiadiazole **4a** (2.16 g, 0.01 mol, 1 equiv.) in ethanol (10 mL), thiadiazole **4b** (2.44 g, 0.01 mol, 1 equiv.) in an ethanol/acetic acid mixture (10:2 mL), or triazole **16** (2.44 g, 0.01 mol) in ethanol/DMF (10:2 mL) containing sodium acetate (4.0 g) at 0–5°C. After the addition of the diazonium salt was complete, the reaction mixture was stirred at room temperature for 2 h and left in the refrigerator overnight. The solid product formed in each case was collected by filtration.

TABLE III Spectral Data of the Newly Synthesized Products

Compd No.	IR (ν/cm-1)	1H NMR (δ ppm) (DMSO-d6)
4a	3465–3341 (NH), 3068 (CH aromatic), 2989 (CH_2), 2227 (CN), 1620 (C═C), 1585 (C═N)	4.68 (s, 2H, CH_2), 7.26–7.33 (m, 5H, C_6H_5), 8.69 (s, 1H, NH)
4b	3455–3337 (NH), 3059 (CH aromatic), 2981 (CH_2), 2224 (CN), 1687 (CO), 1623 (C=C), 1578 (C=N)	4.70 (s, 2H, CH_2), 7.28–7.37 (m, 5H, C_6H_5), 8.85 (s, 1H, NH)
6a	3474–3328 (2 NH), 3055 (CH aromatic), 2224 (CN), 1629 (C=C), 1576 (C=N)	7.31–7.45 (m, 10H, 2 C_6H_5), 8.64, 8.95 (2s, 2H, 2NH)
6b	3465–3317 (2 NH), 3072 (CH aromatic), 2220 (CN), 1685 (CO), 1636 (C=C), 1582 (C=N)	7.27–7.40 (m, 10H, 2 C_6H_5), 8.54, 9.66 (2s, 2H, 2NH)
19	3544–3328 (NH), 3055 (CH aromatic), 2222 (CN), 1687 (C=O), 1638 (C=C), 1577 (C=N)	5.66 (s, br, 1H, SH), 7.29–7.36 (m, 10H, 2 C6H5), 8.61 (s, 1H, NH)
8a	3489–3331 (NH), 3058 (CH aromatic), 2225 (CN), 1643 (C=C), 1582 (C=N)	6.91 (s, 1H, CH=C), 7.30–7.38 (m, 10 H, 2 C_6H_5), 8.73 (s, 1H, NH).
8b	3476–3340 (NH), 3055 (CH aromatic), 2223 (CN), 1685 (CO), 1639 (C=C), 1589 (C=N)	5.82 (s, 1H, CH=C), 6.87 (s, 1H, NH), 7.27–7.40 (m, 10H, 2 C_6H_5)
10a	3458–3339 (NH), 3054 (CH aromatic), 1687 (CO), 1648 (C=C), 1593 (C=N)	6.69 (s, 1H, coumarin H-4), 7.31–7.44 (m, 9H, C_6H_5, C_6H_4), 8.35 (s, 1H, NH)
10b	3473–3329 (NH), 3059 (CH aromatic), 1693, 1688 (2 CO), 1641 (C=C), 1585 (C=N)	6.54 (s, 1H, coumarin H-4), 7.28–7.42 (m, 9H, C_6H_5, C_6H_4), 8.32 (s, 1H, NH)
12a	3450–3328 (NH_2, 2NH), 3046 (CH aromatic), 2220 (CN), 1641 (C=C), 1586 (C=N)	4.66 (s, 2H, NH_2), 7.03–7.36 (m, 6H, C_6H_5, pyridine H-3), 8.68, 9.40 (2s, 2H, NH)
12b	3466–3332 (NH_2, NH), 3048 (CH aromatic), 2221 (CN), 1687 (CO), 1640 (C=C), 1593 (C=N)	4.68 (s, 2H, NH_2), 7.19–7.38 (m, 6H, C_6H_5, pyridine H-3), 8.66 (s, 1H, NH)
12c	3469–3330 (NH_2, 2NH), 3055 (CH aromatic), 2226 (CN), 1689 (CO), 1644(C=C), 1590 (C=N)	4.71 (s, 2H, NH_2), 7.21–7.44 (m, 6H, C_6H_5, pyridine H-3), 8.68, 9.39 (2s, 2H, 2NH)
12d	3485–3341 (NH_2, NH), 3059 (CH aromatic), 2224 (CN), 1692, 1688 (2CO), 1640(C=C), 1588 (C=N)	4.67 (s, 2H, NH_2), 7.23–7.46 (m, 6H, C_6H_5, pyridine H-3), 8.65 (s, 1H, NH)
14a	3477–3332 (NH_2, NH), 3054 (CH aromatic), 2228, 2223 (2 CN), 1656 (C=C), 1588 (C=N)	4.68 (s, 2H, NH_2), 5.36 (s, 1H, pyridine H-4), 7.29–7.38 (m, 10H, $2C_6H_5$), 8.36 (s, 1H, NH)
14b	3469–3343 (NH_2, NH), 3053 (CH aromatic), 2987, 2879 (CH_3, CH_2), 2220 (CN), 1689 (CO), 1654 (C=C), 1587 (C=N)	1.36 (t, 3H, J = 7.09 Hz, CH_3), 4.23 (q, 2H, J = 9.07 Hz, CH_2), 4.67 (s, 2H, NH_2), 5.63 (s, 1H, pyridine H-4), 7.25–7.37 (m, 10H, $2C_6H_5$), 8.59 (s, 1H, NH)

(Continued on next page)

TABLE III Spectral Data of the Newly Synthesized Products *(Continued)*

Compd No.	IR (ν/cm-1)	1H NMR (δ ppm) (DMSO-d6)
14c	3479–3338 (NH_2, NH), 3057 (CH aromatic), 2225, 2222 (2CN), 1705 (CO), 1659 (C=C), 1584 (C=N)	4.64 (s, 2H, NH_2), 5.72 (s, 1H, pyridine H-4), 7.28–7.39 (m, 10H, $2C_6H_5$), 8.63 (s, 1H, NH)
14d	3459–3329 (NH_2, NH), 3059 (CH aromatic), 2229 (CN), 1689, 1684 (2 CO), 1648 (C=C), 1568 (C=N)	1.35 (t, 3H, J = 6.77, CH_3), 4.26 (q, 2H, J = 6.77 Hz, CH_2), 4.57 (s, 2H, NH_2), 5.68 (s, 1H, pyridine H-4), 7.33–7.47 (m, 10H, $2C_6H_5$), 8.60 (s, 1H, NH)
15a	3475–3331 (2NH2, NH), 3053 (CH aromatic), 2219 (CN), 1645 (C=C), 1587 (C=N)	4.47, 5.60 (2s, 4H, $2NH_2$), 7.27–7.39 (m, 5H, C6H5), 8.31 (s, 1H, NH)
15b	3468–3319 ($2NH_2$, NH), 3059 (CH aromatic), 2987, 2855 (CH_3, CH_2), 1680 (CO), 1645 (C=C), 1587 (C=N)	1.14 (t, 3H, J = 7.66 Hz, CH_3), 4.23 (q, 2H, J = 7.66 Hz, CH_2), 4.45, 5.68 (2s, 4H, $2NH_2$), 7.28–7.37 (m, 5H, C_6H_5), 8.44 (s, 1H, NH)
15c	3488–3328 ($2NH_2$, NH), 3066 (CH aromatic), 2221 (CN), 1689 (CO), 1645 (C=C), 1587 (C=N)	4.67, 5.37 (2s, 4H, $2NH_2$), 7.32–7.38 (m, 5H, C_6H_5), 8.48 (s, 1H, NH)
15d	3473–3321 ($2NH_2$, NH), 3056 (CH aromatic), 2980 (CH3), 2877 (CH_2), 1689, 1686 (2 CO), 1642 (C=C), 1581 (C=N)	1.42 (t, 3H, J= 6.62 Hz, CH_3), 4.21 (q, 2H, J = 6.62 Hz, CH_2), 4.60, 5.41 (2s, 4H, $2NH_2$), 7.34–7.48 (m, 5H, C_6H_5), 8.52 (s, 1H, NH)
16	3310 (SH), 3058 (CH aromatic), 1715 (CO), 2897 (CH_2), 1652 (C=C), 1580 (C=N)	4.82 (s, 2H, CH_2), 5.26 (s, br, 1H, SH). 7.30–7.37 (m, 5H, C_6H_5)
18a	3483–3322 (NH_2, NH), 3058 (CH aromatic), 2227 (CN), 1710 (CO), 1651 (C=C), 1590 (C=N)	4.73 (s, 2H, NH_2), 4.85 (s, 2H, CH_2), 7.27–7.40 (m, 5H, C_6H_5), 8.42 (s, 1H, NH)
18b	3483–3322 (2 NH), 3061 (CH aromatic), 2224 (CN), 1713 (CO), 1657 (C=C), 1588 (C=N)	4.84 (s, 2H, CH_2), 7.29–7.38 (m, 10H, $2C_6H_5$), 8.39, 8.68 (2s, 2H, 2NH)
20	3055 (CH aromatic), 2223 (CN), 1688 (CO), 1639 (C=C), 1589 (C=N)	5.83 (s, br, 1H, SH), 6.79 (s, 1H, CH=C), 7.27–7.40 (m, 10H, 2 C_6H_5)
21	3058 (CH aromatic), 1693, 1682 (2 CO), 1652 (C=C), 1578 (C=N)	6.34 (s, 1H, coumarin H-4), 6.61 (s, br, 1H, SH), 7.35–7.41 (m, 9H, C_6H_5, C_6H_4)

3-Phenyl-2-(5-(phenylamino)-1,3,4-thiadiazol-2-yl)acrylonitrile (8a), N-(5-(1-Cyano-2-phenylvinyl)-1,3,4-thiadiazol-2-yl) benzamide (8b), and 2-(4,5-Dihydro-5-thioxo-3H-1,2,4-triazol-3-yl-3-phenylacrylonitrile (20)

To a solution of either **4a** (1.08 g, 0.005 mol), **4b** (1.22 g, 0.005 mol), or **16** (1.22 g, 0.005 mol) in DMF (25 mL) containing piperidine (0.5 mL),

benzaldehyde (0.53 g, 0.51 mL, 0.005 mol) was added. The reaction mixture, in each case, was heated under refluxed for 4 h, and then cooled and poured onto an ice/water mixture. The pH was made acidic using hydrochloric acid. The solid product formed, in each case, was collected by filtration.

7-Amino-5-imino-2-(phenylamino)-*5H*-[1,3,4]thiadiazolo[3,2-a]pyridine-8-carbonitrile (12a), 7-Amino-5-oxo-2-(phenylamino)-*5H*-[1,3,4]thiadiazolo[3,2-a]pyridine-8-carbonitrile (12b), N-(7-Amino-8-cyano-5-imino-5H-[1,3,4-]thiadiazolo[3,2-a]pyridine-2-yl)benzamide (12c), and N-(7-Amino-8-cyano-5-oxo-5H-[1,3,4-]thiadiazolo [3,2-a]pyridine-2-yl)benzamide (12d)

To a solution of either thiadiazole **4a** (2.16 g, 0.01 mol) or thiadiazole **4b** (2.44 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (1.01 g, 1.4 mL, 1.0 equiv.), either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) was added. The reaction mixture in each case was heated under reflux for 3 h then poured onto ice water containing a few drops of hydrochloric acid. The formed solid product, in each case was collected by filtration.

2,4-Diamino-5-(5-phenylamino)-1,3,4-thiadiazol-2-yl)thiophene-3-carbonitrile (15a), Ethyl 2,4-diamino-5-(5-(phenylamino)-1,3,4-thiadiazol-2-yl)thiophene-3-carboxylate (15b), N-(5-(3,5-Diamino-4-cyanothiophene-2-yl)-1,3,4-thiadiazol-2-yl)benzamide (15c), and Ethyl 2,4-Diamino-5-(5-benzamido)-1,3,4-thiazol-2-yl)thiophene-3-carboxylate (15d)

To a solution of either thiadiazole **4a** (2.16 g, 0.01 mol) or thiadiazole **4b** (2.44 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (1.01 g, 1.4 ml, 1.0 equiv.) and elemental sulfur (0.32 g, 0.01 mol), either malononitrile **11a** (0.66 g, 0.01 mol) or ethyl cyanoacetate **11b** (1.13 g, 1.1 ml, 0.01 mol) was added separately. The resulting reaction mixture in each case was heated under reflux for 4 h then poured onto an ice/water mixture, and the pH was made acidic using hydrochloric acid. The formed solid product, in each case, was collected by filtration.

3-(5-Phenylamino-1,3,4-thiadiazol-2-yl)-2H-chromen-2-one (10a), N(5-Oxo-2H-chromen-3-yl)-1,3,4-thiadiazol-2-yl) benzamide (10b), and 3-(4,5-Dihydro-5-thioxo-3H-1,2, 4-triazol-3-yl)-2H-chromen-2-one (21)

To a solution of either thiadiazole **4a** (1.08 g, 0.005 mol), thiadiazole **4b**, (1.22 g, 0.005 mol), or triazole **16** (1.22 g, 0.005 mol) in 1,4-dioxane (25 mL) containing a few drops of piperidine, salicylaldehyde (0.67 g, 0.58 mL, 0.005 mol, 1.1 equiv.) was added. The reaction mixture, in each case, was heated under reflux for 4 h, and then cooled and poured onto an ice/water mixture. Then the pH was made acidic using hydrochloric acid. The solid product formed, in each case, was collected by filtration.

2-(1-Benzoyl-4,5-dihydro-5-thioxo-3H-1,2, 4-triazol-3-yl)acetonitrile (16)

A solution of thiosemicarbazide **3b** (2.62 g, 0.01 mol) in sodium hydroxide (2 N, 28 mL) was refluxed for 3 h. The resulting solution was cooled to room temperature and acidified to pH 3–4 with 37% hydrochloric acid. The solid product formed was collected by filtration.

2(1-Benzoyl-5-hydrazino-1,2,4-Triazol-3-yl)axetonitrile (18a) and 2(1-Benzoyl-5-phenylhydrazino-1,2,4-triazol-3-yl) axetonitrile (18b)

To a solution of triazole **16** (1.22 g, 0.005 mol) in ethanol (25 mL), either hydrazine hydrate (0.25 g, 0.005 mol) or phenylhydrazine (0.54 g, 0.49 mL, 0.005 mol) was added. The reaction mixture, in each case, was heated under reflux for 4 h, and then poured onto an ice/water mixture containing few drops of hydrochloric acid. The solid product formed in each case was collected by filtration.

5-Amino-7-phenyl-2-(phenylamino)-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6,8-dicarbonitrile (14a), Ethyl 5-Amino-8-cyano-7-phenyl-2-(phenylamino)-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carboxylate (14b), N-(5-Amino-6,8-dicyano-7-phenyl-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-2-yl0benzamide (14c), and Ethyl 5-Amino-2-(benzamido)-8-cyano-7-phenyl-7H-[1,3,4] thiadiazolo[3,2-a]pyridine-6-carboxylate (14d)

To a solution of either the thiadiazol**4a** (1.2 g, 0.005 mol) or **4b** (1.08, 0.005 mol) in DMF (30 mL) containing triethylamine (0.5 g, 0.7 ml, 1.0 equiv.), either benzalmalononitrile **13a** (0.77 g, 0.005 mol) or

benzalethyl cyanoacetate **13b** (1.0 g, 0.005 mol) was added separately. The resulting reaction mixture in each case was heated under reflux for 4 h then poured onto an ice/water mixture and the pH was made acidic using hydrochloric acid. The formed solid product, in each case, was collected by filtration.

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