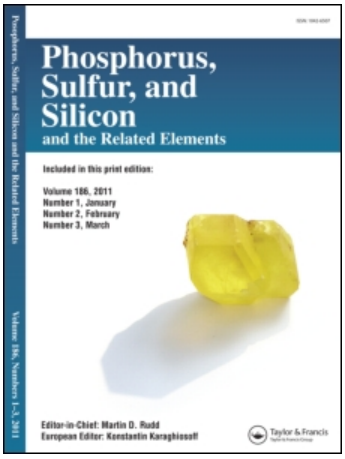

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THE USES OF 4-PHENYL-3-THIOSEMICARBAZIDE IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESIS OF THIAZOLE, PYRAZOLE AND 1,3,4-THIADIAZINE DERIVATIVES

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4-Phenyl-3-thiosemicarbazide derivatives **1a–c** react with phenacylbromide, 3-bromoacetylcoumarin and monochloroacetic acid to afford thiazole derivatives **3a–c**, **8a–c** and **12a–c** respectively. Reaction of **1a** with ethyl acetoacetate afford the condensated product **17**. Reaction of **3a–c** and **8a–c** with aromatic diazonium salts afford the 5-arylazothiazole derivatives **5a–f** and **9a–f** respectively. Most of the synthesized products show high fungicidal and bactericidal activities.

Key words: Heterocycles; thiadiazines; thiazoles; pyrazoles; phenyl thiosemicarbazide.

INTRODUCTION

Thiosemicarbazides are versatile reagents which have been recently used as synthetic intermediates for heterocyclic compounds which have many applications as anticancer, antimicrobial, antitubercular and antibacterial[1–4] reagents. Recently we were involved in a series of reactions which showed the utility of 4-phenyl-3-thiosemicarbazide,[5] as a precursor for thiazole, pyrazole, pyridine and their fused derivatives. In continuation to our previous work we report here the utility of the title reagent to form thiazole, pyrazole and 1,3,4-thiadiazine derivatives together with their uses for formation of arylazo derivatives. Most of the synthesized products were screened biologically and showed high activities.

RESULTS AND DISCUSSION

The 4-aryl-3-thiosemicarbazide derivatives **1a–c** react with phenacyl bromide in refluxing ethanol and the presence of a catalytic amount of triethylamine to afford the thiazole derivatives **3a–c**. The structures of the latter products were established based on analytical and spectral data. Thus ^{1}H NMR spectrum of **3a** showed a D_2O exchangeable singlet at δ = 3.38 ppm for NH_2 group, a singlet at δ = 6.89 ppm for thiazole H-5, a multiplet at δ = 7.28–7.84 ppm for two C_6H_5 groups. Reaction of **3a–c** with aryldiazonium salts **4a,b** afforded the arylazo derivatives

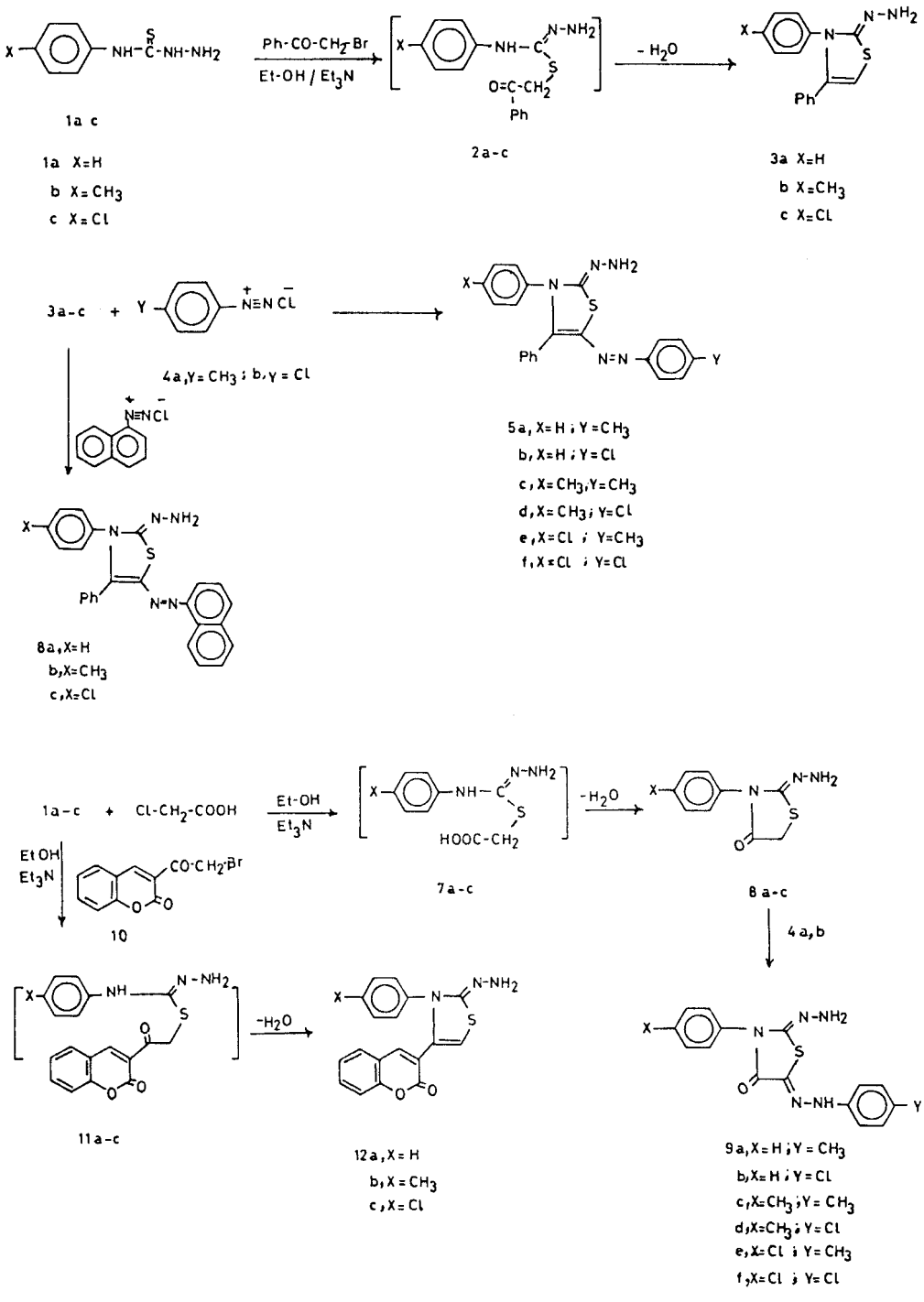

Chart (1)

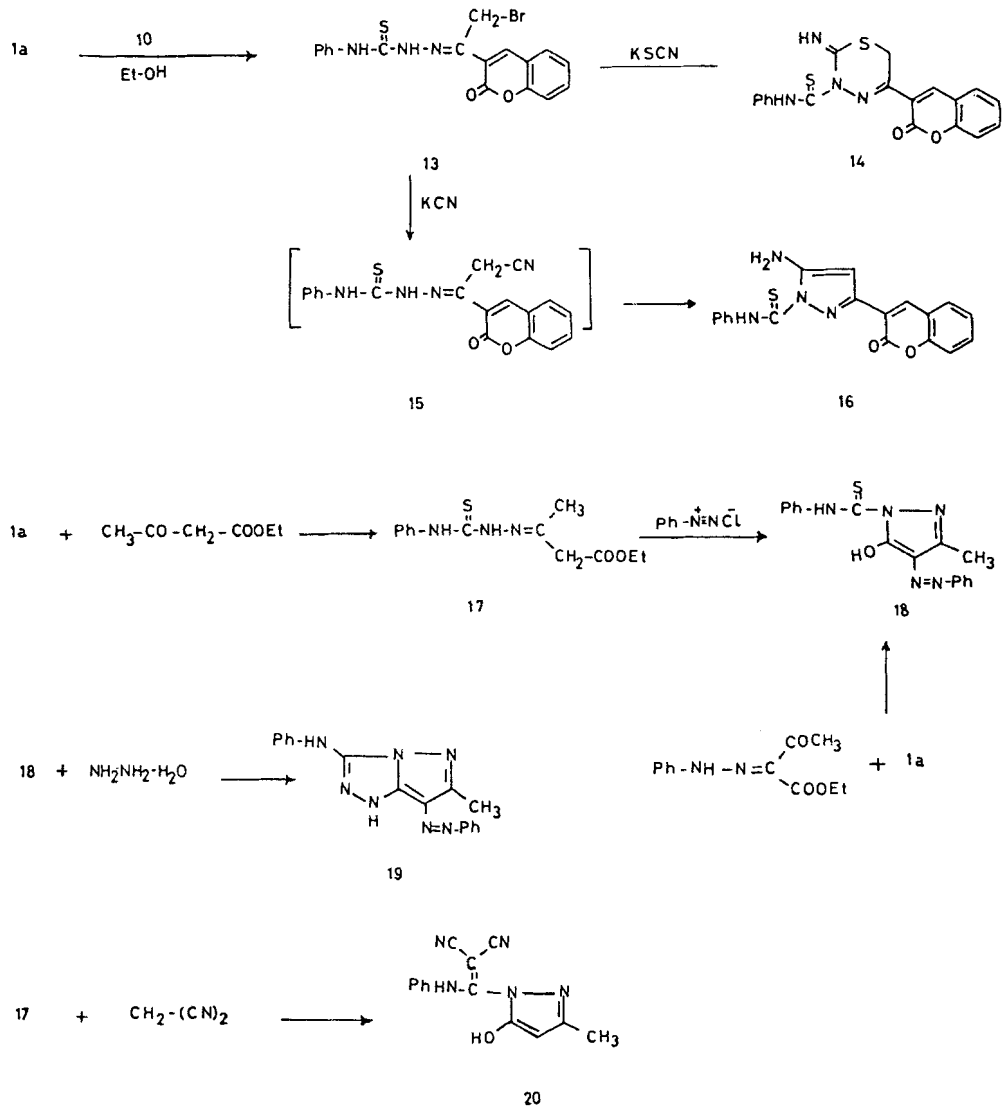

Chart (2)

5a–f. In a similar manner, the reaction of **3a–c** with α-diazonaphthalene salts afforded the corresponding azo derivatives **6a–c**. Structures of **5a–f** and **6a–c** were confirmed based on analytical and spectral data.

Reaction of **1a–c** with monochloroacetic acid afforded the thiazole derivatives **8a–c**.[6] Reaction of **8a–c** with aryldiazonium salts **4a,b** afforded the arylazo derivatives **9a–f**. Reaction of **1a–c** with 3-bromoacetyl coumarin[7] **10** in refluxing ethanol containing a catalytic amount of triethylamine afforded the 4-coumarin-3′-yl-thia-

TABLE I

Physical and analytical data of the newly prepared compounds

Compd. (colour)	solvent	m.p. (°C)	yield (%)	Mol. formula (M. wt.)	Analysis (Calcd./Found) % C	H	N	S
3a	EtOH	166	75	$C_{15}H_{13}N_3S$	67.4	4.9	15.7	11.9
(white)				(267.35)	67.9	5.0	15.9	11.6
3b	EtOH	164	79	$C_{16}H_{15}N_3S$	68.3	5.3	14.9	11.4
(white)				(281.38)	68.3	5.3	15.2	11.1
3c	EtOH	184	81	$C_{15}H_{12}N_3SCl$	59.7	3.9	13.9	10.6
(white)				(301.84)	59.5	4.0	13.6	10.4
8a	MeOH	290-3	69	$C_9H_9N_3SO$	52.1	4.3	20.3	15.4
(yellow)				(207.25)	52.0	4.4	20.0	15.4
8b	MeOH	268-72	75	$C_{10}H_{11}N_3SO$	54.3	4.9	19.0	14.4
(yellow)				(221.32)	54.4	5.0	19.1	14.0
8c	EtOH	180	72	$C_9H_8N_3SOCl$	44.7	3.3	17.3	13.2
(orange)				(241.74)	44.6	3.2	17.5	13.3
5a	dioxane	80	80	$C_{22}H_{19}N_5S$	68.5	4.9	18.16	8.3
(red)				(385.49)	68.7	4.9	18.4	8.2
5b	EtOH	102	84	$C_{21}H_{16}N_5SCl$	62.1	3.9	17.2	7.9
(orange)				(405.95)	61.9	3.5	17.4	8.0
5c	EtOH	99	77	$C_{23}H_{21}N_5S$	69.1	5.3	17.5	8.0
(red)				(399.32)	69.0	5.2	17.4	8.2
5d	dioxane	68	69	$C_{22}H_{18}N_5SCl$	62.9	4.2	16.6	7.6
(red)				(419.62)	62.6	4.2	16.8	7.9
5e	MeOH	82	74	$C_{22}H_{18}N_5SCl$	62.9	4.2	16.6	7.6
(orange)				(419.62)	62.6	4.3	16.5	7.6
5f	MeOH	69	77	$C_{21}H_{15}N_5SCl_2$	57.4	3.4	15.9	7.2
(orange)				(440.34)	57.7	3.5	16.1	7.4
6a	EtOH	82	71	$C_{25}H_{19}N_5S$	71.2	4.5	16.6	7.6
(yellow)				(421.53)	71.4	4.8	16.5	7.5
6b	EtOH	92	64	$C_{26}H_{21}N_5S$	71.7	4.8	16.1	7.3
(yellow)				(435.55)	71.6	4.8	16.0	7.7
6c	dioxane	102	66	$C_{25}H_{18}N_5SCl$	65.8	3.9	15.3	7.0
(orange)				(456.02)	65.5	3.1	15.2	6.7
9a	EtOH	162-4	90	$C_{16}H_{15}N_5SO$	59.0	4.6	21.5	9.8
(orange)				(325.39)	59.2	4.8	21.8	9.7
9b	EtOH	179	87	$C_{15}H_{12}N_5SOCl$	52.1	3.4	20.2	9.2
(red)				(345.88)	51.2	3.0	20.0	9.0
9c	EtOH	250-3	80	$C_{17}H_{17}N_5SO$	60.2	5.0	20.8	9.5
(red)				(339.42)	60.0	4.8	20.6	9.2

Table I (Continued)

Compd. (colour)	solvent	m.p. (°C)	yield (%)	Mol. formula (M. wt.)	Analysis (Calcd./Found) % C	H	N	S
9d	EtOH	75	79	$C_{16}H_{14}N_5SOCl$	53.4	3.8	19.4	8.8
(orange)				(359.88)	53.1	3.4	19.2	8.5
9e	dioxane	158	82	$C_{16}H_{14}N_5SOCl$	53.4	3.8	19.4	8.8
(orange)				(359.88)	53.1	3.6	19.3	8.7
9f	DMF	105	75	$C_{15}H_{11}N_5SOCl_2$	47.3	2.8	18.4	8.4
(yellow)				(380.40)	47.2	2.7	18.1	8.0
12a	DMF	198	69	$C_{18}H_{13}N_3SO_2$	64.4	3.9	12.5	9.5
(orange)				(335.37)	64.5	4.2	12.4	9.5
12b	DMF	168	71	$C_{19}H_{15}N_3SO_2$	65.3	4.2	12.0	9.1
(orange)				(349.40)	65.2	4.4	12.2	9.4
12c	DMF	215-7	75	$C_{18}H_{12}N_3SO_2Cl$	58.4	3.2	11.3	8.6
(orange)				(369.86)	58.5	3.4	11.0	8.5
13	EtOH	132	63	$C_{18}H_{14}N_3SO_2Br$	51.9	3.3	10.0	7.6
(yellow)				(416.33)	52.0	3.3	10.4	7.3
14	EtOH	201-4	67	$C_{19}H_{14}N_4S_2O_2$	57.8	3.5	14.2	16.2
(yellow)				(394.46)	57.9	3.3	14.4	16.5
16	EtOH	188	69	$C_{19}H_{14}N_4SO_2$	62.9	3.8	15.4	8.8
(yellow)				(362.40)	62.6	3.8	15.0	8.7
19	dioxane	228-30	80	$C_{14}H_{11}N_5O$	63.3	4.1	26.4	
(orange)				(265.27)	63.3	4.5	26.1	
20	dioxane	118	71	$C_{17}H_{15}N_7$	64.3	4.7	30.9	
(yellow)				(317.35)	64.5	4.3	30.8	

zole derivative **12a–c**. Formation of **12a–c** takes place through the intermediate formation of **11a–c**. The structures of **12a–c** were confirmed based on analytical and spectral data. Thus, the ^{1}H NMR spectrum of **12a** revealed the presence of a singlet at δ = 3.89 ppm for NH_2 group, a singlet at δ = 6.55 ppm corresponding for thiazole H-5, a singlet at δ = 6.99–7.0 ppm for coumarin H-4 and a multiplet at δ = 7.32–7.35 corresponding for C_6H_5 and C_6H_4 group. On the other hand, conducting the same reaction of **1a** with **10** in cold ethanol afforded the acyclic product **13**. Formation of **13** takes place in analogy with the reported literature.[6,8] **13** Underwent nucleophilic attack with nucleophilic reagents like potassium cyanide and potassium thiocyanate to afford the 5-coumarin-3′-yl-thiadiazine derivative **14** and the 4-coumarin-3′-yl-pyrazole derivative **16**. The latter product **16** is formed through intermediate formation of the non-isolable intermediate **15**. Structures of **14** and **16** were established based on analytical and spectral data. Thus, ^{1}H NMR spectrum of **14** revealed the presence of a singlet at δ = 3.95 ppm for thiadiazine CH_2, a singlet at δ = 7.08 ppm for coumarin H-4, a multiplet at δ = 7.21–7.39

TABLE II

I.R. and ^{1}H NMR data of the newly prepared compounds

Compd. No.	I.R. cm^{-1} (selected bands)	^{1}H NMR (δ ppm)
3a	3400-3300 (NH_2), 1640, 1625 (C=N, C=C).	3.38 (s, 2H, NH_2), 6.89 (s, 1H, thiazole H-5), 7.28-7.84 (m, 10H, $2C_6H_5$).
3b	3420-3350 (NH_2), 1650, 1630 (C=N, C=C).	2.12 (s, 3H, CH_3), 3.25 (s, 2H, NH_2), 7.15 (s, 1H, thiazole H-5), 7.38-7.84 (m, 9H, C_6H_5, C_6H_4).
3c	3420-3250 (NH_2), 3050 (CH arom.), 1645 (C=N).	3.25 (s, 2H, NH_2), 7.21 (s, 1H, thiazole H-5), 7.41-7.72 (m, 9H, C_6H_5, C_6H_4).
5a	3420-3340 (NH_2), 1650 (C=N).	2.21 (s, 3H, CH_3), 8.86 (s, 2H, NH_2), 7.31-7.37 (m, 14H, $2C_6H_5$, C_6H_4).
5b	3450-3345 (NH_2), 1645 (C=N).	3.90 (s, 2H, NH_2), 7.33-7.38 (m, 14H, $2C_6H_5$, C_6H_4).
5c	3450-3300 (NH_2), 1645 (C=N).	2.19, 2.20 (2s, 6H, $2CH_3$), 3.84 (s, 2H, NH_2), 7.31-7.38 (m, 13H, C_6H_5, $2C_6H_4$).
5d	3450-3250 (NH_2), 1650 (C=N).	2.18 (s, 3H, CH_3), 3.92 (s, 2H, NH_2), 7.33-7.38 (m, 13H, C_6H_5, $2C_6H_4$).
5e	3450-3280 (NH_2), 3050 (CH arom.), 1640 (C=N).	2.21 (s, 3H, CH_3), 3.92 (s, 2H, NH_2), 7.34-7.38 (m, 13H, C_6H_5, $2C_6H_4$).
5f	3440-3350 (NH_2), 3050 (CH arom.), 1650 (C=N).	3.92 (s, 2H, NH_2), 7.32-7.37 (m, 13H, C_6H_5, $2C_6H_4$).
6a	3450-3320 (NH_2), 1645 (C=N).	3.94 (s, 2H, NH_2), 7.32-7.42 (m, 17H, $2C_6H_5$, C_6H_4, C_6H_3).
6b	3450-3300 (NH_2), 3050 (CH arom.), 1645 (C=N).	2.21 (s, 3H, CH_3), 3.58 (s, 2H, NH_2), 7.33-7.40 (m, 16H, C_6H_5, $2C_6H_4$, C_6H_3).
6c	3450-3300 (NH_2), 3045 (CH arom.), 1650 (C=N).	3.67 (s, 2H, NH_2), 7.34-7.39 (m, 10H, C_6H_5, $2C_6H_4$, C_6H_3).
8a	3450-3320 (NH_2), 1710 (C=O), 1640 (C=N).	3.56 (s, 2H, NH_2), 5.21 (s, 2H, thiazole CH_2), 7.21-7.32 (m, 5H, C_6H_5).
8b	3460-3320 (NH_2), 1700, (C=O), 1645 (C=N).	2.21 (s, 3H, CH_3), 3.79 (s, 2H, NH_2), 5.21 (s, 2H, thiazole CH_2), 7.30-7.35 (m, 4H, C_6H_4).
8c	3460-3200 (NH_2), 1695 (C=O), 1650 (C=N).	3.80 (s, 2H, NH_2), 5.22 (s, 2H, thiazole CH_2), 7.32-7.34 (m, 4H, C_6H_4).
9a	3460-3370 (NH_2), 1700 (C=O), 1640 (C=N).	2.19 (s, 3H, CH_3), 3.92 (s, 2H, NH_2), 7.30-7.36 (m, 9H, C_6H_5, C_6H_4), 8.47 (s, 1H, NH).
9b	3450-3340 (NH_2), 1695 (C=O), 1650 (C=N).	3.87 (s, 2H, NH_2), 7.32-7.38 (m, 9H, C_6H_5, C_6H_4), 8.92 (s, 1H, NH).
9c	3460-3320 (NH_2), 1700 (C=O), 1650 (C=N).	2.19, 2.20 (2s, 6H, $2CH_3$)), 3.95 (s, 2H, NH_2), 7.32-7.38 (m, 9H, C_6H_5, C_6H_4), 9.02 (s, 1H, NH).

TABLE II (*Continued*)

Compd. No.	IR (selected bands)	^{1}H NMR (δ ppm)
9d	3460-3325 (NH_2), 1695 (C=O), 1640 (C=N).	2.23 (s, 3H, CH_3), 3.69 (s, 2H, NH_2), 7.32-7.39 (m, 9H, C_6H_5, C_6H_4), 8.87 (s, 1H, NH).
9e	3450-3320 (NH_2), 1690 (C=O), 1645 (C=N).	2.21 (s, 3H, CH_3), 3.76 (s, 2H, NH_2), 7.31-7.35 (m, 9H, C_6H_5, C_6H_4), 8.90 (s, 1H, NH).
9f	3460-3350 (NH_2), 1700 (C=O), 1645 (C=N).	3.89 (s, 2H, NH_2), 7.32-7.37 (m, 8H, $2C_6H_4$), 9.02 (s, 1H, NH).
12a	3450-3350 (NH_2), 1700 (C=O), 1645 (C=N).	3.89 (s, 2H, NH_2), 6.55 (s, 1H, thiazole H-5), 6.99-7.0 (s, 1H, coumarin H-4), 7.32-7.35 (m, 9H, C_6H_5, C_6H_4).
12b	3460-3320 (NH_2), 1700 (C=O), 1645 (C=N).	2.21 (s, 3H, CH_3), 3.88 (s, 2H, NH_2), 6.54 (s, 1H, thiazole H-5), 6.99 (s, 1H, coumarin H-4), 7.31-7.36 (m, 9H, C_6H_5, C_6H_4).
12c	3450-3340 (NH_2), 1695 (C=O), 1650 (C=N).	3.86 (s, 2H, NH_2), 6.60 (s, 1H, thiazole H-5), 6.99 (s, 1H, coumarin H-4), 7.32-7.38 (m, 9H, C_6H_5, C_6H_4).
13	3460-3400 (NH), 1700 (C=O), 1650 (C=N).	3.21 (s, 2H, CH_2), 6.99-7.0 (s, 1H, coumarin H-4), 7.32-7.36 (m, 9H, C_6H_5, C_6H_4), 8.92, 9.21 (2s, 2H, 2NH).
14	3460-3320 (NH), 1695 (C=O), 1655 (C=N).	3.95 (s, 2H, CH_2), 7.08 (s, 1H, coumarin H-4), 7.21-7.39 (m, 9H, C_6H_5, C_6H_4), 8.28, 9.21 (2s, 2H, 2NH).
16	3460-3200 (NH_2, NH), 1700 (C=O), 1650 (C=N).	3.26 (s, 2H, NH_2), 4.62 (s, 1H, pyrazole H-4), 7.18 (s, 1H, coumarin H-4), 7.21-7.39 (m, 9H, (C_6H_5, C_6H_4), 8.92 (s, 1H, NH).
19	3550-3410 (2 NH), 1650 (C=N).	2.12 (s, 3H, CH_3), 7.23-7.34 (m, 10H, $2C_6H_5$), 9.51, 9.85 (2s, 2H, 2NH).
20	3620-3380 (OH, NH), 2225, 2220 (2 CN).	1.58 (s, 3H, CH_3), 4.21 (s, 2H, pyrazole H-4), 7.32-7.35 (m, 5H, C_6H_5), 9.0 (s, 1H, NH), 9.52 (s, 1H, OH).

ppm for C_6H_5 and C_6H_4 and two D_2O exchangeable singlets at δ = 8.28 and 9.21 ppm corresponding to two NH groups. ^{1}H NMR spectrum of **16** revealed the presence of a D_2O exchangeable singlet at δ = 3.26 ppm characteristic for NH_2 group, a singlet at δ = 4.62 ppm for pyrazole H-4, a singlet at δ = 7.18 ppm for coumarin H-4, a multiplet at δ = 7.21–7.39 ppm for C_6H_5 and C_6H_4 and a broad singlet at δ = 8.92 ppm for NH group (D_2O exchangeable).

Reaction of **1a** with ethyl acetoacetate in refluxing ethanol afford the product **17**,[6] the latter reacted with benzene diazonium chloride to afford the phenylazo

TABLE III

In vitro bactericidal and fungicidal activity of some of the newly synthesized compounds

Compd. No.	Staph. albus	Staph. aureus	E. coli
3a	+	+	++
3b	-ve	+	++
3c	+	++	++
8a	+	+	++
8b	+	+	+
8c	++	+	+
13a	+	+	+
13b	+	+	+
13c	+	+	+

Slight effect = +, Moderate effect = ++, Severe eefect = +++

Rating percent control: No effect = 0; slight effect = 10, 20, 30; moderate effect = 40, 50, 60; severe effect = 70, 80, 90; complete effect = 100.

derivative **18**.[6] The structure of **18** was established based on analytical and spectral data[6] together with its synthesis through another reaction route. Thus, reaction of **17** with phenyl hydrazonoethyl acetoacetate[9] afford the same product **18** (identical m.p. and mixed m.p.). Reaction of **18** with hydrazine hydrate afforded the pyrazolo[3,2-c]triazole derivative **19**. On the other hand, reaction of **17** with malononitrile afforded the pyrazole derivative **20**. Structure of the latter product was established based on IR spectrum which revealed the presence of OH stretching band at 3620–3580 cm^{-1} and two CN groups stretchings at 2225 and 2220 cm^{-1}. ^1H NMR spectrum revealed the presence of a singlet at δ = 1.58 ppm for CH_3, a singlet at δ = 4.21 ppm for pyrazole CH, a multiplet at δ = 7.32–7.35 ppm for C_6H_5, a D_2O exchangeable singlet at δ = 9.0 ppm for NH and a singlet at δ = 9.52 ppm for OH group.

BIOLOGICAL ACTIVITY

The diverse biological activities of thiazoles and their fused derivatives promoted our attention to test and study the biological activities of some newly synthesized products. The bactericidal and antifungal activities were studied. The antibacterial effect was determined using Gutter technique, while the antifungal effect was determined turbidimetric.[10,11] Table III shows that most of the tested compounds had high activity.

EXPERIMENTAL

All melting points are uncorrected, IR spectra were recorded (KBr) on a Paye Unicam SP-1000 spectrophotometer. ^1H NMR spectra were recorded on a Varian EM-300 MHz spectrometer with DMSO as solvent and TMS as internal reference. Chemical shifts are expressed as δ units (ppm). Analytical

data were obtained from the Microanalytical Data Centre at Cairo University, Egypt. Compounds **16** and **18** were prepared according to Reference 6.

3,4-Diphenyl-2-hydrazono-1,3-thiazole (**3a**). *2-Hydrazono-4-phenyl-3-(4'-methylphenyl)-1,3-thiazole* (**3b**). *3-(4'-Chlorophenyl)-2-hydrazono-4-phenyl-1,3-thiazole* (**3c**). *General procedure:* To a solution of each of **1a**, **1b** or **1c** (0.01 mol) in ethanol (30 ml) containing triethylamine, phenacylbromide (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon dilution with water containing few drops of hydrochloric acid was collected by filtration.

2-Hydrazono-3-phenyl-1,3-thiazol-4-one (**8a**). *2-Hydrazono-3-(4'-methylphenyl)-1,3-thiazol-4-one* (**8b**). *3-(4'-chlorophenyl)-2-hydrazono-1,3-thiazol-4-one* (**8c**). *General procedure:* To a solution of each of **1a**, **1b** or **1c** (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml), chloroacetic acid (0.01 mol) was added. The reaction mixture was heated under reflux for 5 h and the solid product formed upon evaporation under vacuum was triturated with diethyl ether and collected by filtration.

Reaction of **3a–c** *and* **6a–c** *with diazonium salts* **4a,b**: *General procedure:* To a cold solution of each of **3a**, **3b**, **3c**, **6a**, **6b** or **6c** (0.01 mol) in ethanol (40 ml) containing sodium acetate (3.0 g) each of the diazonium salts **4a** or **4b** (0.01 mol) [prepared by adding sodium nitrite solution (0.01 mol) to a cold solution of 4-methyl aniline (0.01 mol) or 4-chloroaniline (0.01 mol) containing the appropriate quantity of hydrochloric acid] was added with continuous stirring. The reaction mixture was left at room temperature for 2 h then the formed solid product was collected by filtration.

Reaction of **3a–c** *with α-naphthyldiazonium chloride:* The same experimental procedure described for synthesis of **5a–f** was carried out except for the use of α-naphthyldiazonium chloride instead of **4a,b**.

4-Coumarin-3'-yl-2-hydrazono-3-phenyl-1,3-thiazole (**12a**). *4-Coumarin-3'-yl-2-hydrazono-3-(4''-methylphenyl)-1,3-thiazole* (**12b**). *4-Coumarin-3'-yl-2-hydrazono-3-(4''-chlorophenyl)-1,3-thiazole* (**12c**). *General procedure:* To a solution of each of **1a**, **1b** or **1c** (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml) 3-bromoacetyl coumarin **10** (0.01 mol) was added. The reaction mixture was heated under reflux for 6 h then evaporated in vacuum. The remaining product was triturated with ethyl acetate then collected by filtration.

3'-Bromoacetyl coumarin-4'-phenyl-3'-thiosemicarbazone (**13**). Equimolar amounts of **1a** (0.01 mol) and **10** (0.01 mol) in absolute ethanol (50 ml) was heated under reflux for 1 h. The solid product formed upon dilution with water was collected by filtration.

5-Coumarin-3'-yl-2-imino-3-phenylthiocarbamido-1,3,4-thiadiazine (**14**). *5-Amino-3-coumarin-3'-yl-1-phenylthiocarbamido-pyrazole* (**16**). *General procedure:* To a solution of **13** (0.01 mol) in ethanol (30 ml) each of potassium thiocyanate (0.01 mol) or potassium cyanide (0.01 mol) in 10 ml water was added. The temperature of the reaction mixture was kept at 60°C for 1 h. The solid product formed upon pouring the reaction mixture into ice/water mixture containing few drops of hydrochloric acid (till pH = 6) was collected by filtration.

3-Hydroxy-4-phenylazo-2-phenylthiocarbamido-5-methylpyrazole (**18**).

Method (A): To a cold solution of **17** (0.01 mol) in ethanol (50 ml) containing sodium acetate (6 g) a cold solution of benzenediazonium chloride was added. The solid product formed on standing for 1 h was collected by filtration, washed several times with cold water.

Method (B): Equimolar amounts of **1a** (0.01 mol) and phenylhydrazonoethyl acetoacetate (0.01 mol) in absolute ethanol (50 ml) was heated under reflux for 5 h. The solid product formed during heating was collected by filtration.

1-Phenylamino-4-phenylazo-5-methylpyrazolo[3,2-c]triazole (**19**). To a solution of **18** (0.01 mol) in ethanol (40 ml) hydrazine hydrate (0.01 mol) was added. The reaction mixture was heated under reflux for 6 h then evaporated in vacuum. The remaining product was triturated with diethyl ether then collected by filtration.

1-(1',1'-dicyano-2'-phenylaminovinyl)-5-hydroxy-3-methylpyrazole (**20**). To a solution of **17** (0.01 mol) in ethanol (40 ml) containing triethylamine (1 ml) malononitrile (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon dilution with water containing few drops of hydrochloric acid was collected by filtration.

Procedure of biological tests: The newly synthesized compounds were tested against the specified microorganism as 400 μg/ml (w/v) solution in sterile DMSO. A solution of the tested compound (0.1 mol) was poured aseptically in a well of g diameter made by a borer in the seeded agar medium. After pipetting the same volume in wells of all tested microorganisms, plates were incubated after 37°C for 24 h. The activities were expressed as inhibition zones (mm diameter, clear areas) as antibacterial and

antifungal effect, were measured to the nearest 0.5 mm. The least concentration which showed inhibitory effect on any specific microorganism was considered as the minimum inhibitory concentration (MIC) which was determined using Streptomycin and Mycostatin as the references.

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REFERENCES

1. A. F. Bradburg and D. G. Smyth, *Eur. J. Biovhem.*, **169,** 579 (1987).
2. Y. K. Srivastava, R. B. Bhandari and B. L. Verma, *Orient. J. Chem.*, **3,** 128 (1987).
3. M. Okawara, R. Kato, N. Yasuda, T. Yamasaki and M. Furukawa, *J. Chem. Res. S*, **8,** 254 (1987).
4. Z. Leng, A. Tao, Z. Xie, X. Gu, L. Jin and R. Wang, *Daxue Xuebao*, **21,** 295 (1990); *Chem. Abstr.*, **114,** 185376 (1991).
5. H. K. Shukla, N. C. Desia, R. R. Astik and K. A. Thaker, *J. Indian Chem. Soc.*, **61,** 168 (1984).
6. R. M. Mohareb, H. Z. Shams and S. I. Aziz, *Sulfur Letters*, **13,** 101 (1991).
7. H. Hartmann, *J. Prakt. Chem.*, **4,** 551 (1983).
8. Y. Tomita, S. Kabashima, T. Okaware, T. Yamasaki and M. Furukawa, *J. Heterocycl. Chem.*, **27,** 707 (1990).
9. V. Meyer, *Chem. Ber.*, **10,** 2075 (1877).
10. Y. Gutter and Z. Pflanzenkr, *Pflanzenscutz*, **89,** 332 (1982), *Chem. Abstr.*, **97,** 143345 (1982).
11. A. Shachnai, Y. Gutter, M. N. Schiffmann and A. Dinoor, *Bull. Merkaz Volcani, Minhol, HaMerchkar Hachaklai* (bet Dogan, Isr.), **189,** 64 (1978), *Chem. Abstr.*, **97,** 143345 (1982).