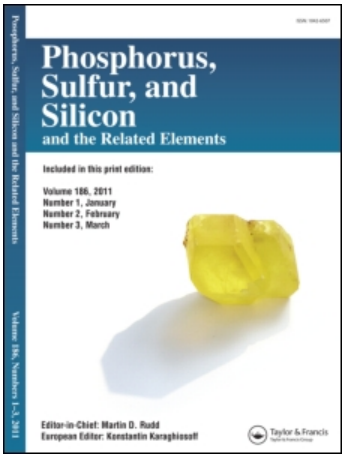

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Utility of 2-[4-Benzo[*d*]furan-2,1,3-thiazol-2-yl)] Ethane-Nitrile in Synthesis of Thiazole, Coumarin, Thiphene, and Thiadiazoline Derivatives

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Utility of 2-[4-Benzo[*d*]furan-2,1,3-thiazol-2-yl)] Ethane-Nitrile in Synthesis of Thiazole, Coumarin, Thiphene, and Thiadiazoline Derivatives

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Coumarine, thiazole, thiophene and 2,3-dihydro-1,3,4-thiadiazole derivatives were synthesized from 2-[4-(4-methyl-2-phenyl-1,3-thiazol.-5-yl)-1,3-thiazol-2-yl]ethanenitrile and salicylaldehyde, chloroacetone, ethyl chloroacetate, or hydrazonoyl halides, respectively.

Keywords 2,3-Dihydro-1,3,4-thiadiazole; coumarin; hydrazonoyl halides; thiazole; thiophene

INTRODUCTION

Thiazoles are widely used as accelerators in rubber vulcanization and as antioxidants.[1,2] A large number of dyes are derived from thiazololium salts. Benzothiazolium salts have been synthesized and many of them have been used in silver photography, essentially as sensitizing dyes.[3] Other derivatives exhibited the phenomenon of photochromism. It this article, I report the synthesis of some new biologically active thiazoles containing different moites such as coumarin, thiophene, and thiadiazoline.

RESULTS AND DISCUSSION

2-bromoacetylbenzo(d)furanethan-1-one (**1**) was reacted with cyanothioacetamide in ethanol to yield the corresponding 2-[4-benzofuryl)-1,3-thiazol-2-yl] ethanenitrile (**3**). Structure **3** was confirmed on the basis of elemental analysis and IR, ^{1}H-NMR, and chemical transformation. Its ^{1}HNMR spectrum showed signals at $\delta = 4.17$ (s, 2H, CH_2CN), 7.34

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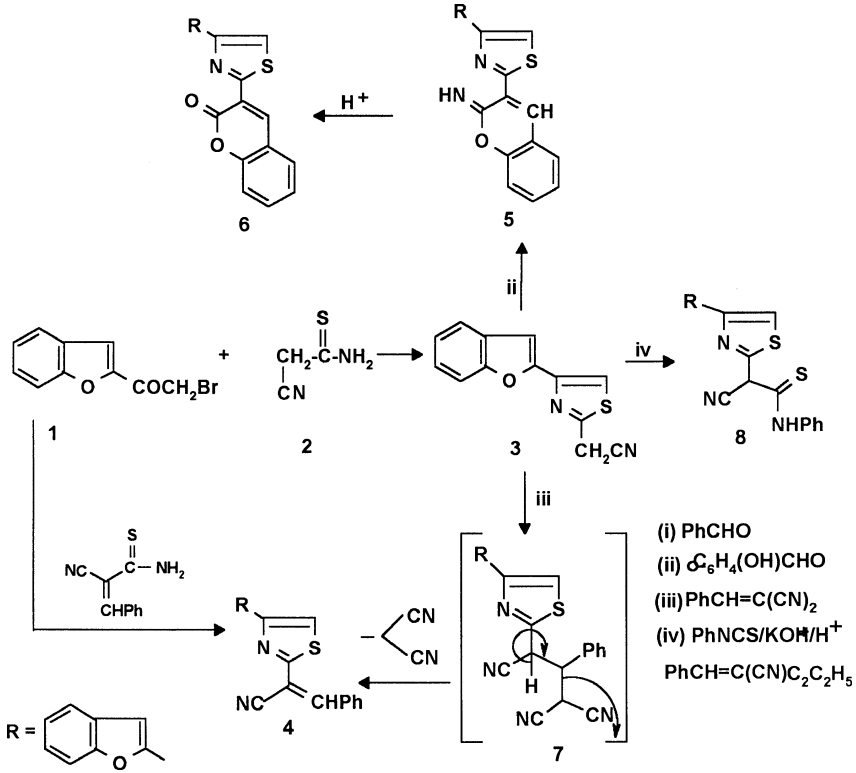
(s, 1H, thiazole (CH), and 7.42–7.97 (m, 5H, Ar-H). IR (cm^{-1}) revealed bands at 2923 (C—H) and 2219 (CN).

Compound **3** reacted with both benzaldehyde and salicylaldehyde to give the corresponding substituted acrylonitrile **4** and the substituted coumarin **5**, respectively (Scheme 1). Structures **4** and **5** were established on the basis of elemental analysis and spectral data. The IR (cm^{-1}) spectrum revealed bands at 3057 (CH arom.), 2924 (CH aliph), 2191 (CN), and 1519 (C=C). ^{1}H NMR (δ ppm) spectrum of **4** showed signals at $\delta = 7.26$–7.99 (m, 10H, ArH's) and 8.23 (s, 1H, CH=).

^{1}HNMR spectrum of **5** (DMSO-d_6) showed signals at $\delta = 7.22$–7.82 (m, 10H, ArH's) and 9.12 (br., 1H, NH). Its IR (cm^{-1}) spectrum revealed bands at 3309 (NH), 3050 (CH arom), 2921 (CH aliph), and 1658 (C=N).

Compound **5** was converted to coumarin derivative **6** by treatment with hydrochloric acid. IR spectrum of compound **6** revealed bands at 3080 (CH arom.), 2921 (CH aliph), 1720 (CO), and 1604 (C=N).



SCHEME 1

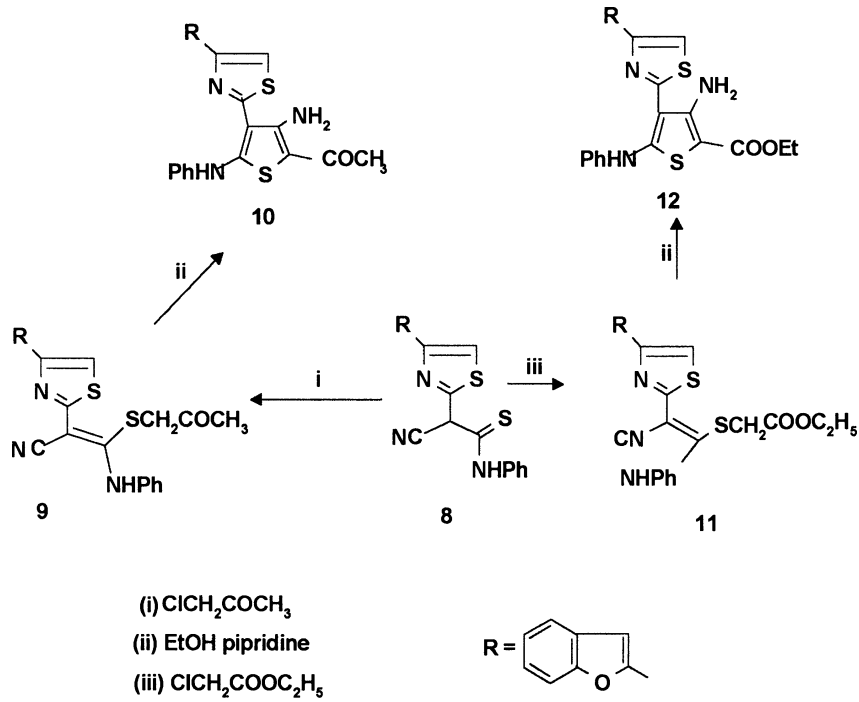
α-substituted cinnamonitrile reacted with **3** in ethanol containing a catalytic amount of piperidine gave a product identical in all respects (m.p., mixed m.p., and spectra) with **4**. The formation of **4** can be explained by the addition of cinnamonitrile to **3** via the Micheal addition to give the adduct intermediate **7** followed by elimination of malononitrile (or ethyl cyanoacetate), respectively, to give final product **4** (Scheme 1).

Compound **3** reacted with phenyl isothiocyanate in *N,N*-dimethylformamide containing potassium hydroxide, which acidifies with acetic acid, to afford thioanilide **8** (Scheme 1). Compound **8** was confirmed on the basis of elemental analysis, IR, and ^{1}H-NMR, and chemical transformation. Thus, compound **8** reacted with chloroacetone in the presence of potassium hydroxide to give S-acetonyl derivative **9**. ^{1}H NMR spectrum of **9** showed signals at $\delta = 2.64$ (s, 3H, CH_3), 3.34 (s, 2H, CH_2), 6.86 (s, 1H, CH thiazole) and 7.43–7.94 (m, ArH's and NH). Its IR (cm^{-1}) spectrum revealed bands at 3433 (NH), 2175 (CN), 1705 (CO), and 1600 (C=N).

Compound **9** was converted to thiazole derivative **10** by heating in ethanol containing a catalytic amount of piperidine. ^{1}H NMIR showed signals at $\delta = 2.79$ (s, 3H), 6.49 (s, 1H), 7.02 (s, 1H), and 7.25–7.96 (m, 9H, ArH's). Its IR (cm^{-1}) spectrum revealed bands at 2167 (CN), 1640 (C=N), and 1600 (C=C).

Ethyl chloroacetate reacted with thioanilide derivative **9** in *N,N*-dimethylformamide containing potassium hydroxide at room temperature to give **11**. Compound **11** was confirmed on the basis of elemental analysis and spectral data and converted to aminothiophene **12** by boiling in ethanol containing a catalytic amount of piperidine. ^{1}HNMR (δ ppm) spectrum **11** showed signals at $\delta = 1.22$ (t, 3H, CH_3 ester), 2.66, 3.34 (s, 2H, SCH_2), 4.11 (q, 2H, CH_2CH_3), and 7.22–791 (m, 9H, (s, Ar., 1H, NH). Its IR (cm^{-1}) revealed bands at 3440 (NH), 2923 (CH), 2190 (CN), 1743 (CO), and 1620 (C=N). ^{1}H-NMR (δ ppm) spectrum of **12** showed signals at $\delta = 1.35$ (t, 3H, CH_3 CH2), 4.27 (q, 2H, CH_2), 6.10 (s, 2H, NH_2), 7.19–7.98 (m, 10H, ArH's) and 11.51 (s, br., 1H, NH). Its IR (cm^{-1}) revealed bands at 3394, 3301, 3290 (NH_2, NH), 1710 (CO), 1645 (C=N), and 1600 (C=C).

Treatment of the appropriate hydrazonoyl halides **13a–c** with thioanilide 8 in *N,N*-dimethylformamide containing potassium hydroxide gave a single product (tlc) in each case. IR (cm^{-1}) spectra of the corresponding products showed bands near 2921 (CN) and 1728 and 1689 (CO's) ^{1}H NMR spectrum of **14a** showed signals at $\delta = 1.47$ (t, 3H, CH_3CH_2) 4.49 (q, 2H, CH_2 ester), 7.15 (s, 1H, thiazole and 7.26–8.02 (m, 9H, Ar—H). ^{1}H NMR spectrum of **14b** showed signals at $\delta = 1.47$ (t, 3H, CH_2CH_3), 2.48 (s, 3H, 4/$CH_3C_6H_4$), 4.40 (q, 2H, CH_2CH_3), 7.15 (s, 1H, thiazole C-5), and 7.26–8.02 (m, 9H, ArH). On the above-finding



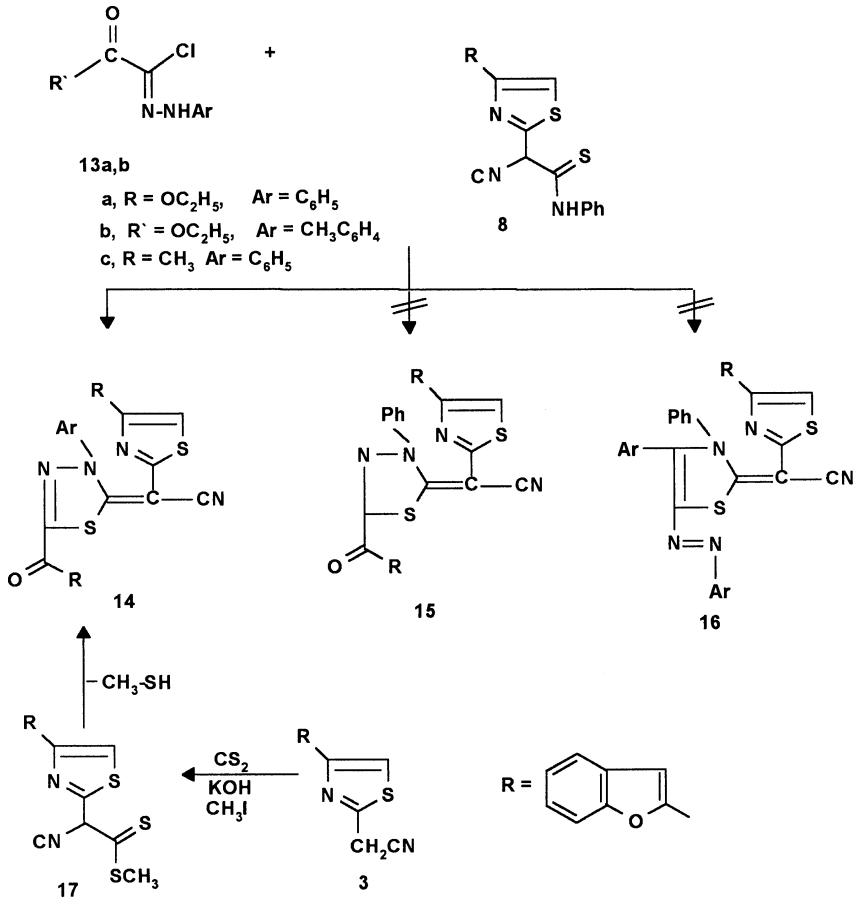
SCHEME 2

structure **15** and **16** were excluded on the results of spectra, elemental analysis and alternative synthesis methods (Scheme 3).

Unequivocal support on structure **14** was obtained from alternative method synthesis. Thus, treatment showed evidence that the reaction of the appropriate hydrazonoyl halides with methyl carbodithioate **17**, which was prepared by treatment of **3** with carbon disulfide in presence of potassium carbon hydroxide and iodomethane, in *N,N*-dimethylformamide containing triethylamine, gave a product identical in all respects (m.p., mixed m.p., and spectra) with **14**.

Two possible pathways can account for the formation of **14**. 1,3-addition of the thiol tautomer **17** to the nitrilium imide **18a** (which was prepared in situ by treatment of thydrazonoyl chloride **17** with triethylamine) can give the thiohydrazonate ester **19**, which undergoes nucleophilic cyclization to yield **20**, which affords **14** by loss of RSH. ii) A1ternatively 1,3-cycloaddition of the nitrilium imide **18** to the C=S of **17** can give **20** directly (Scheme 4).

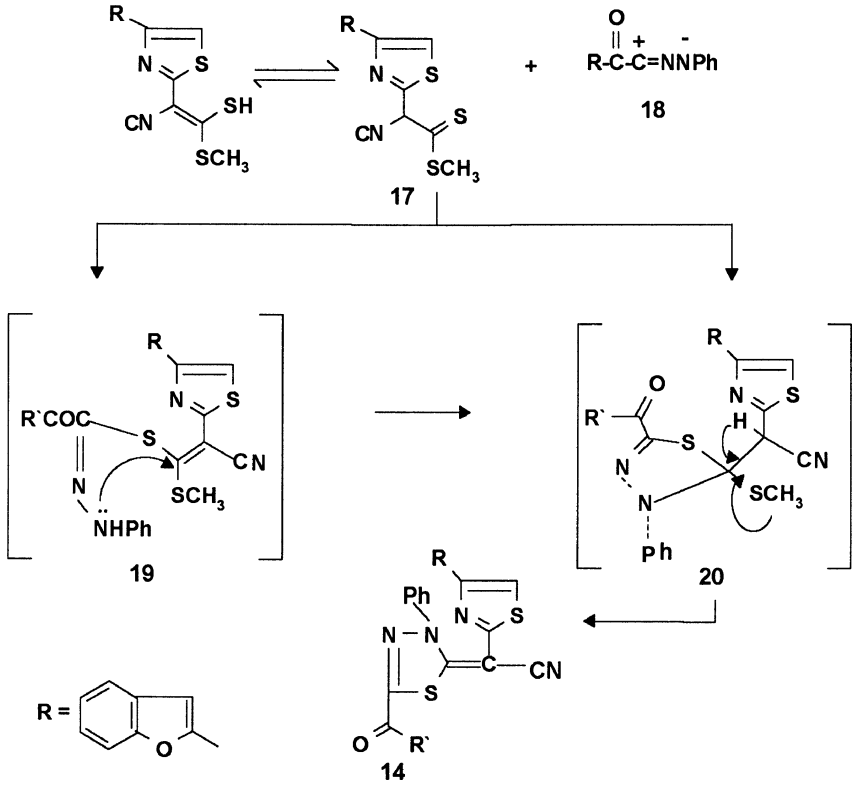
Compound **3** reacted with diazonum chloride and furnished the corresponding **22** that also was obtained via reaction of 2-bromoacetyl



SCHEME 3

benzofuran (1) with phenylazocyanothioacetamide in boiling acetic acid under reflux. Structure 22 was elucidated by elemental analysis and spectra and chemical transformation.

Thus, compound **22** reacted with ethyl chloroacetate or chloroacetone in *N*,*N* dimethylformamide containing potassium carbonate and triethylamine that gave the pyrazoles **23**. ^{1}H NMR (δppm) spectrum of **23a** showed at δ =1.35 (t, 3H), 4.27 (q, 2H), 5.3 (br, 2H, NH_2), 7.2–7,4 (m, 10 H, Ar, H's). Its IR (cm^{-1}) reveled band at 329 (NH_2), 1710 (CO), and 1600 (C=C) ^{1}HNMR spectrum of **23b** showed signals at δ 2.3 (s, 3H, CH_3), 5.5 (s, br, 1H, thiazol C-5), and 7.26–8.02 (m, q, ArH's). Its IR spectrum revealed bonds at 3290 (NH_2), 1710 (CO), 1660 (C=N), and 1600 (C=C).



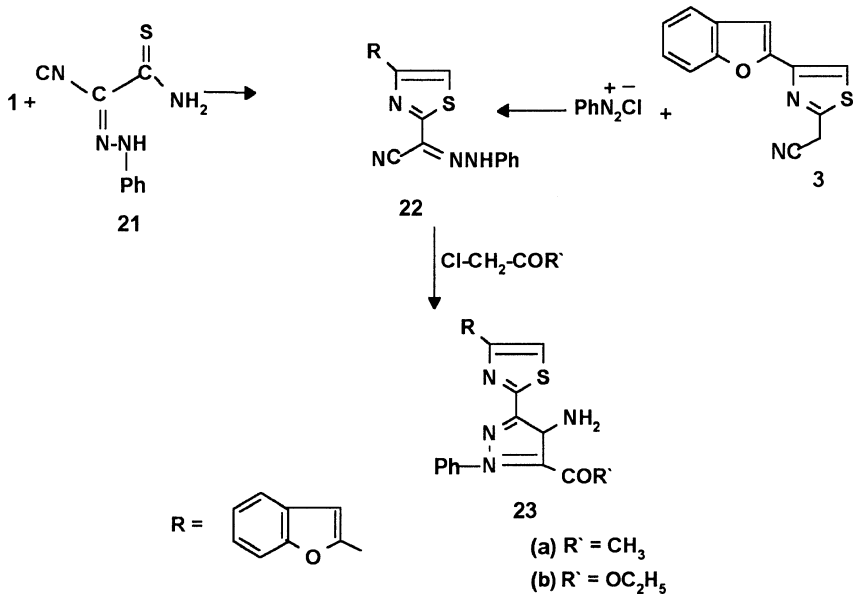
SCHEME 4

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded in $CDC1_3$ and (DMSO-d_6) solutions on a Varian Gemini 300 MHz spectrometer and chemical shifts are expressed in δ units using TMS as an internal reference. Elemental analyses were carried out at the Microanalytical Center of the Cairo University. Hydrazonoyl halides were prepared according to reported methods.[4–9]

Synthesis of 4-Benzo(d) Furan-2-yl Ethanenitrile (3)

A mixture of 2-bromoacetylbenzo(d)furan[10] (1) (2.4 g, 0.1 mmol) and cyanothioacetamide (10.0 g, 0.01 m) in ethanol (25 mL) was refluxed for 2 h. The reaction mixture was poured onto ice-cold water (50 mL)



SCHEME 5

and few drop of ammonium hydroxide (25%) were added. The resulting solid was collected, washed with water, and recrystallized from ethanol to give thiazolylacetonitrile **3** (Table I).

Synthesis of 2-(4-Benzo(d) Furan(1,3-thiazol-2-yl)-3-phenylprop-2-eneitrile (3)

Thiazolylacetonitrile 3 (1.2 g, 5 mmol) and benzaldehyde (3 g, 5.0 g mmol) in ethanol (15 mL) and piperidine (drops) were stirred at room temperature for 2 h. The stirring was continued for 2 h. The resulting solid was collected by filtration, washed with ethanol, and recrystallized from ethanol to give **4** (Table I).

Synthesis of 3-[-4-Benzofuran)-1,3-thiazol-2-yl]-2H-chromen-2-imin (5)

Thiazolylacetonitrile 3 (1.2 g, 5 mmol) and salicyladehded (0.53 mL, 5 mmol) in ethanol (20) containing a catalytic amount of piperidine were stirred at room temperature for 2h. The resulting solid was collected and recrystallized from a mixture of EtOH/DMF to give 5 (Table I).

TABLE I Characterization Data of the Newly Synthesized Compounds

Compound no.	M.P., °C Solvent	Yield % Color	Mol. formula mol. wt	% Analyses, calcd./found C	H	N	S
3	168–170	90	$C_{13}H_8N_2OS$	65.00	3.33	11.66	13.33
	EtOH	Yellow	240.28	65.14	3.00	11.28	13.00
4	145–147	85	$C_2OH_{12}N_2OS$	73.17	3.65	8.53	9.65
	EtOH	Brown	328.39	73.05	3.31	8.30	9.40
5	150	90	$C_2OH_{12}N_2O_2S$	69.76	3.48	8.13	9.30
	EtOH	Yellow	344.39	69.96	3.11	8.32	9.00
6	170–172	90	$C_2OH_{11}NO_3S$	69.56	3.18	4.05	9.27
	dioxans	Yellow	345.37	69.31	3.40	4.22	9.51
7	180	80	$C_{22}OH_{14}N_4OS$	69.10	3.66	14.65	8.37
	EtOH	Yellow	382.43	69.38	3.30	14.25	8.00
8	130–32	70	$C_2OH_{13}N_3OS_2$	64.00	3.46	11.20	17.06
	EtOH	Yellow	375.47	63.90	3.21	11.33	17.33
9	100	40	$C_{23}OH_{19}N_3S_2O_2$	63.74	4.38	9.69	14.78
	Pet.ether	Yellow	433.55	63.50	4.10	9.41	14.51
10	166–70	65	$C_{23}H_{17}N_3S_2O_2$	64.03	3.94	9.74	14.84
	EtOH	Brown	431.53	64.32	3.60	9.51	14.56
11	110°C	40	$C_{24}H_{19}N_3O_3S_2O_3$	62.47	4.12	9.11	13.88
	Pet.ether	Brown	461.56	62.20	4.33	9.00	13.53
12	210-12	70	$C_{24}H_{19}N_3O_3S_2$	62.47	4-12	10.00	13.85
	EtOH/DMF	Brown	461.56	62.25	4.32	9.78	13.61
14a	132–34	55	$C_{24}H_{16}N_4O_3S_2$	61.01	3.38	11.86	13.55
	EtOH	Brown	472.54	61.15	3.18	11.71	13.23
14b	130°C	50	$C_{25}H_{18}N_4S_2O_3$	61.72	3.70	11.52	13.16
	EtOH	Brown	486.47	61.56	3.48	11.35	13.00
14c	145–47	70	$C_{23}H_{14}N_4O_2S_2$	62.44	3.16	12.66	14.47
	EtOH	Brown	442.52	62.21	3.35	12.31	14.19
17	100–2	60	$C_{15}H_{10}N_2OS_3$	54.54	3.03	8.48	29.9
	Pet. ether	Yellow	330.39	54.21	3.30	8.62	29.30
22	150–52	65	$C_{19}H_{12}N_4OS$	66.27	3.48	16.27	9.30
	EtOH	Red	344.97	66.00	3.20	16.00	9.50
23a	180–182	65	$C_{22}H_{17}N_4O_2S$	65.83	4.23	13.96	7.98
	EtOH	Brown	401.38	65.55	4.00	13.65	7.73
23b	210–12	65	$C_{23}H_{19}N_4O_3S$	64.03	4.40	12.99	7.42
	EtOH	Yellow	431.49	64.20	4.12	12.64	7.23

Synthesis of 3-[Benzofuran)1,3-thiazol-2-yl]-2H-chromen-2-one (6)

A mixture of 5 (0.5 g 0.01 mmol) and dilute hydrochloric acid (5 mL, 50%) was stirred at room temperature for 1h. The resulting solid was collected and recrystalized from EtOH/DMF to give coumarin derivative **6** (Table I).

Synthesis of 2-[4-(4-Benzo(d)furan(1,3-thiazol-yl)]-3-(phenylamino-sulfanylprop-2-enenitrile (7)

Phenyl isothiocyanate (0.6 mL, 5 mmol) was added to a mixture of thiazolylacetonitril 3 (1.2 g, 5 mmol) and potassium hydroxide (0.33 g. 5 mmol) in N,N-dimethylformarmide (15 mL) and was stirred at room temperature until potassium hydroxide dissolve completely. The reaction mixture was stirred for 1 h. Then the reaction mixture was acidified with acetic acid. The resulting solid was collected and recrystallized from ethanol to give thioanilide **7**.

Synthesis 9,11,14a and 14b 13a–b

Phenyl isothiocyanate (0.6 mL, 5 mmol) was added to a mixture of (5 mmol) in thiazolylacetonitrile **3** (1.2 g, 5 mmol) and potassium hydroxide in *N*,*N*-dimethylformamide (15 mL) while stirring at room temperature until potassium hydroxide disso1ved completely. The reaction mixture was stirred for 30 min. Chloroacetone (0.46 g, 0.4 mL, 5 mmol), ethyl chloroacetate (0.65 g, 0.53 mL, 5 mmol), or appropriate hydrazonoyl halides **12a**,**b** (5 mmol) was added and the reaction mixture was stirred for 3h. The resulting solid was collected and recrystallized from the appropriate solvent to afford **8**,**9** and **14a**,**b**.

Synthesis of Thiazole 9 and Aminothiophene 11

Each of 8 (1.22 g, 2.5 mmol) and 9 (1.3 g, 2.5 mmol) in ethanol (20 mL) containing a catalytic amount of piperidine (3 drops) was refluxed for 30 min. The resulting solid was collected and recrystallized from the appropriate solvent to give thiazole 10 or aminothiophene **11**, respectively (Table I).

Preparation of 2-[4-Benzofuryl(1,2-thazol-2-yl)-3-methyltho-3-thioxo-propenitrile (16)

A mixture of carbon disulfide (0.3 mL, 5 mmol) was added to a mixture of thiazolylacetonitrile **2** (1.2 g, 5 mmol) and potassium hydroxide (0.33 g, 5 mmol) in N,N-dimethylformamide (15 mL) and was stirred at room temperature until potassium hydroxide dissolved completely. The reaction mixture was stirred for 30 min. Iodomethane was then added (0.72 g, 0.32 mL, 5 mmol) and while sttring continued. The resulting solid was collected and recrystallized from DMF to afford **17** (Table I).

(Alternative Method): Synthesis of 2,3-Dihydro-1,3,4-thiadiazoles Derivatives 14a,b

A mixture of 17 (0.2 g, 5 mmol), the appropriate hydrazonyl chloride **13a**,**b** and triethylamine (0.5 mL, 5 mmol) in *N*,*N*-dimethylformamide (15 mL), while stirring at room temperature for 2h. The resulting solid was collected and then crystallized from an appropriate solvent to give a product identical in all respects (m.p., mixed m.p., and spectra) with **14a–b** which was obtained before.

Synthesis of 3-Aza-2-(4-benzofuran)1,3-(thizaol 2-yl)-3-phenyl-amino) prop-2-enenitrile (22)

Method A

Benzenediazonium chloride (5 mmol), which was prepared by diazotized aniline (0.45 g, 5 mmol), hydrochloric acid (3 mL, 6 M), and sodium nitrite (0.35 g, 5 mmol in 5 mL H_2O) at 0°C, was added dropwise to a solution of **3** (1.2 g, 5 mmol) in pyridine (20 mL) while stirring at 0°C. The reaction mixture was stirred for 3h, then the resulting solid was collected and crystallized from dioxan to affor **22**.

Method B

A mixture of an equimolar amount of 2-bromoacetylfuran and 1-cyano-1-phenylhydrazothioacetamide (5 mmol) in acetic acid (20 mL) was refluxed for 2 h. The reaction mixture was poured onto ice water, and the resulting solid was collected and crystallized from dioxan to give a product identical in all respects (m.p., mixed m.p., and spectra) with **22**, which was obtained in method A.

Synthesis of 3-Thiazol 2-(4-Benzofuran)1,-2-yl)-3-amino Pyrazole 23a,b

A mixture of compound **22** (1.72 g, 5 mmol) and the appropriate chloroactone or ethyl chloroacetate (5 mmol) in *N*,*N*,-dimethyl formamide (20 mL) containing K_2CO_3 (2 g) was refluxed for 2 h at 120°C; then the reaction mixture was cold and triethylamine (5 mmol) was added. The reaction mixture was boiled under reflux at 90°C for 1 h, was allowed to cool, and was pured onto ice (120 g). The solid product was collected and recrystallized from ethanol to give **23a**,**b**.

BIOLOGICAL ACTIVITIES OF SYNTHESIZED COMPOUNDS

The tested microorganisms were gram-positive bacteria (*Staphylococcus aureus*) [ATCC25923] and *Streptococcus pyogenes* [ATCC19615]

TABLE II Response of Various Microorganisms to Some Synthesized Compounds In Vitro (Culture). W: low activity (l–5 mm) (+); M: moderate activity (6–10 mm) (++); S: high activity (11–15 mm) (+++); I: Inhibitor

	Diameter of the Zone of Inhibition				
Compound no.	*Staphylococcus aureus* (ATCC25923)	*Streptococcus pyogenes* ATCC19615	*Pseudomonas syringae* PV phasealicola	*Aspergillus niger*	*Fusarium oxysporum*
3	M	—	W	—	—
5	W	W	M	—	—
6	M	M	W	—	—
8	W	W	W	—	—
9	W	—	—	—	—
11	W	M	W	—	—
12	—	—	—	—	—
14	M	—	W	—	—
17	M	W	—	—	—

and gram-negative bacteria (*pseudomonas syrinagae PV* phasealicola). In addition, some fungal–plant pathogens (*Aspergillus Niger* and *Fusarium Oxysporum*) were tested. Sensitivity of the selected microorganisms to some synthesized compounds were determined in vitro culture to two concentrations (100, 200 μg/mL) that were dissolved in $CHCl_3$. The tests were carried out using the filter paper and hole-plate method.[11]

Studies on the biological activity of compounds **3**, **9**, **11**, **12**, and **14** led to the fact that these compounds have a moderate biological activity against the tested bacteria but no effect on the *Aspergillus niger*. It also has been observed through the results in Table II that the compounds 5, 6, 8, and 17 have a strong effect on bacteria. All the tested compounds showed no antifungal activities.

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