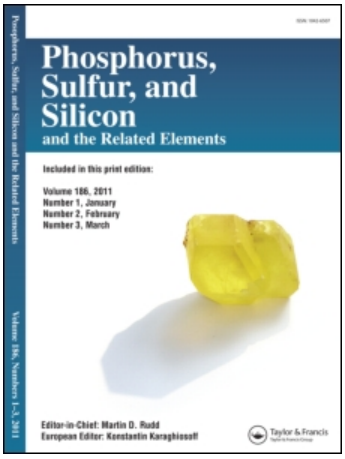

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

2-[4-(2-Thienyl)-1,3-thiazol-2-yl]ethanenitrile in Heterocyclic Synthesis of Biological Interist

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To cite this Article Abdelhamid, Abdou O. and Al-Atoom, Ali A.(2005) '2-[4-(2-Thienyl)-1,3-thiazol-2-yl]ethanenitrile in Heterocyclic Synthesis of Biological Interist', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 7, 1629 — 1646
To link to this Article: DOI: 10.1080/104265090885048
URL: http://dx.doi.org/10.1080/104265090885048

Phosphorus, Sulfur, and Silicon, 180:1629–1646, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090885048

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2-[4-(2-Thienyl)-1,3-thiazol-2-yl]ethanenitrile in Heterocyclic Synthesis of Biological Interist

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*Thiazolylacetonitrile was used in the synthesis of coumarin, pyrazolo[4,3-*d*]pyrimidines, 1,3,4-thiadiazolines, aminothiophenes, and thiazoles in a good yields. Also, pyrazolo[4,5-*d*]triazolino[4,5-*a*]pyrimidines, pyrazolo[4,5-*d*]thiazolino[3,2-*a*]pyrimidines, and pyrazolo[4,5-*d*]tetrazolino[1,5-*a*]pyrimidines were synthesized from pyrazolo[4,5-*d*]pyrimidine. Structures of the newly synthesized were elucidated by elemental analysis, spectral data, and alternative synthesis routes whenever possible. Some synthesized compounds were tested for their antimicrobial activity.*

Keywords 1,3,4-thiadiazolines; Pyrazolo[4,3-*d*]pyrimidines; pyrazolo[4,5-*d*]-triazolino-[4,5-*a*]pyrimidines; pyrazolo[4,5-*d*]thiazolino[3,2-*a*]pyrimidines; pyrazolo-[4,5-*d*]tetrazolino[1,5-*a*]pyrimidines

INTRODUCTION

A large number of thiazole derivatives has been found to exhibit pharmacological activity.[1,2] They also were used as an anthelmintic,[3] fungicidal,[4] and antifungal activity, inhibiting in vivo the growth of Xanthomonas oryzae,[5] and ingredient of herbicides.[6] As an extension of our study[7–9] and as a part of our program aiming at the synthesis of different thiadiazoles, we report herein the utility of 2-[4-(2-thienyl)-1,3-thiazol-2-yl]ethanenitrile in heterocyclic synthesis.

RESULTS AND DISCUSSION

2-bromo-1-(2-thienyl)ethan-1-one[10] (**1**) reacted with cyanothioacetamide (**2**) in ethanol under reflux to give 2-[4-(2-thienyl)-1,3-thiazol-2-yl]ethanenitrile (**3**). Structure **3** was confirmed by elemental analysis,

Received June 23, 2004; accepted August 2, 2004.
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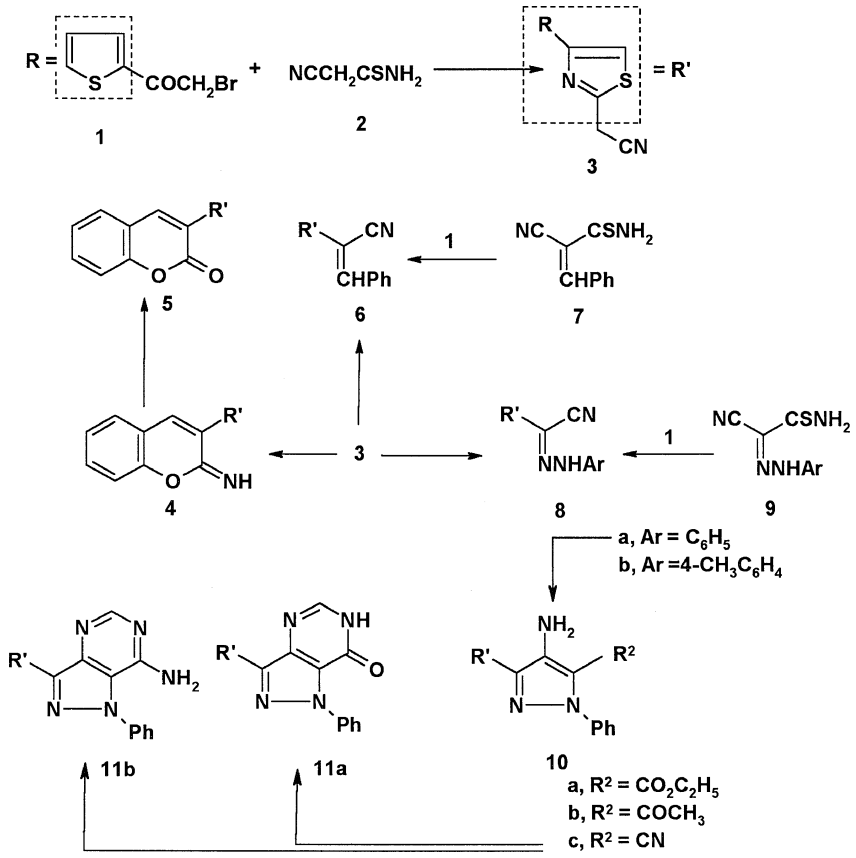
spectral data, and chemical transformation. ^{1}H NMR (δ ppm) spectrum showed signals at $\delta = 4.15$ (s, 2H, CH_2CN), 7.06–7.46 (m, 4H, thiazole C-5 and thiophene). Its IR (cm^{-1}) revealed bands at 3101 (C—H), 2198 (CN), and 1620 (C=C).

Compound **3** reacted with each of salicylaldehyde and benzaldehyde to give 3-(4-(2-thienyl)-1,3-thiaozl-2-yl)-2H-chromen-2-imine (**4**) and (2E)-2-(4-(2-thienyl)(1,3-thiazol-2-yl))-3-phenylprop-2-enenitrile (**6**), respectively (Scheme 1). Structures of **4** and **6** were established on the basis of elemental analysis, spectral data, chemical transformation, and alternative synthesis. ^{1}H NMR spectrum of **4** showed signals at δ =6.68–7.41 (m, 9H) and 8.42 (s, 1H). Its IR (cm^{-1}) spectrum revealed bands at 3150 (NH), 3057 (CH), and 1559 (C=C). ^{13}C NMR spectrum of **4** showed signals at $\delta = 115, 116, 121, 124, 125, 127, 128, 129, 130, 136,$



SCHEME 1

143, 154, 163, and 164. Also, compound **4** was converted to coumarin derivative **5** by hydrochloric acid and its IR spectrum revealed bands at 3039 (CH), 1708 (CO), and 1539 (C=C) (no bands at region 3400–3150 due to the absence of NH group). ^{1}H NMR (δ ppm) spectrum of **6** showed one signal at δ =7.00–7.41 (m, ArH's). Its IR (cm^{-1}) spectrum revealed bands at 3057 (CH), 2191 (CN), and 1595 (C=C). Thus, 2-(aminothioxomethyl)-3-phenylprop-2-enenitrile[11] (**7**) reacted with 2-bromo-1-(2-thienyl)ethan-1-one[9] (**1**) in boiling ethanol to give a product identical in all respects (mp., mixed mp., and spectra) with **6**.

Treatment of **3** with the appropriate arenediazonium chlorides in ethanolic sodium acetate solution at 0°C afforded (2E)-3-aza-3-(arylamino)-2-(4-(2-thienyl)-1,3-thiazol-2-yl)prop-2-enenitrile **8a** and **8b**. Structure **8** was confirmed by elemental analysis, spectral data, alternative route, and chemical transformation. ^{1}H NMR spectrum of **8b** showed signals at δ = 2.35 (s, 3H), 7.11–7.424 (m, 8H) and 14.06 (s, br., 1H). Its ^{13}C NMR showed signals at δ = 24, 116, 119, 123, 125, 127, 129, 130, 136, 140, 143, and 155.

On the other hand, treatment the appropriate (2E)-2-aminothioxomethyl-3aza-3-(arylamino)prop-2-enenitrile[12] **9a**,**b** with **1** in boiling ethanol under reflux afford products identical in all respects (mp., mixed mp. and spectra) with **8a** and **8b**, respectively.

Compound **8a** reacted with each of ethyl chloroacetate, chloroacetone, and chloroacetonitrile in boiling *N*,*N*-dimethylformamide solution containing potassium carbonate. Triethylamine afforded ethyl 4-amino-1-phenyl-3-(4-(2-thienyl)(1,3-thiazol-2-yl)pyrazole-5-carboxylate (**10a**), 1-[4-amino-1-phenyl-3-(4-(2-thienyl)(1,3-thiazol-2-yl)pyrazol-5-yl]ethane-1-one (**10b**), and 4-amino-1-phenyl-3-(4-(2-thienyl)-1,3-thiazol-2-yl)pyrazole-5-carbonitrile (**10c**), respectively. Structures **10a–c** were elucidated on the basis on elemental analysis and spectral data. ^{1}H NMR spectrum of **10a** showed signals at δ = 1.20 (t, 3H), 4.24 (q, 2H), 5.87 (s, br., 2H) and 7.07–7.48 (m, 9H). ^{1}H NMR spectrum of **10b** showed signals at δ = 2.55 (s, 3H), 5.39 (s, br., 2H) and 7.00–7.57 (m, 9H). IR spectrum of **10b** revealed bands at 3471, 3352 (NH2), 3097 (CH), 1631 (CO), and 1581 (C=C). IR spectrum of **10c** revealed bands at 3444 (NH_2), 3352 (CH), 2215 (CN), and 1598 (C=C). Compound **10c** reacted with each formic acid or formamide to give 1-phenyl-3-(4-(2-thienyl)(1,3-thiazol-2-yl))-6-hydropyrazolo[4,5-*d*]pyrimidine-7-one (**11a**) and 1-phenyl-3-(4-(2-thienyl)(1,3-thiazol-2-yl))-6-hydropyrazolo[4,5-*d*]pyrimidine-7-ylamine (**11b**), respectively (Scheme 1 and Tables II and III).

Moreover, treatment of **3** with each of phenyl isothiocyanate or carbon disulfide followed with iodomethane gave 3-(phenylamino)-2-(4-(2-thienyl)(1,3-thiazol-2-yl))-3-thioxopropanenitrile (**12**), and

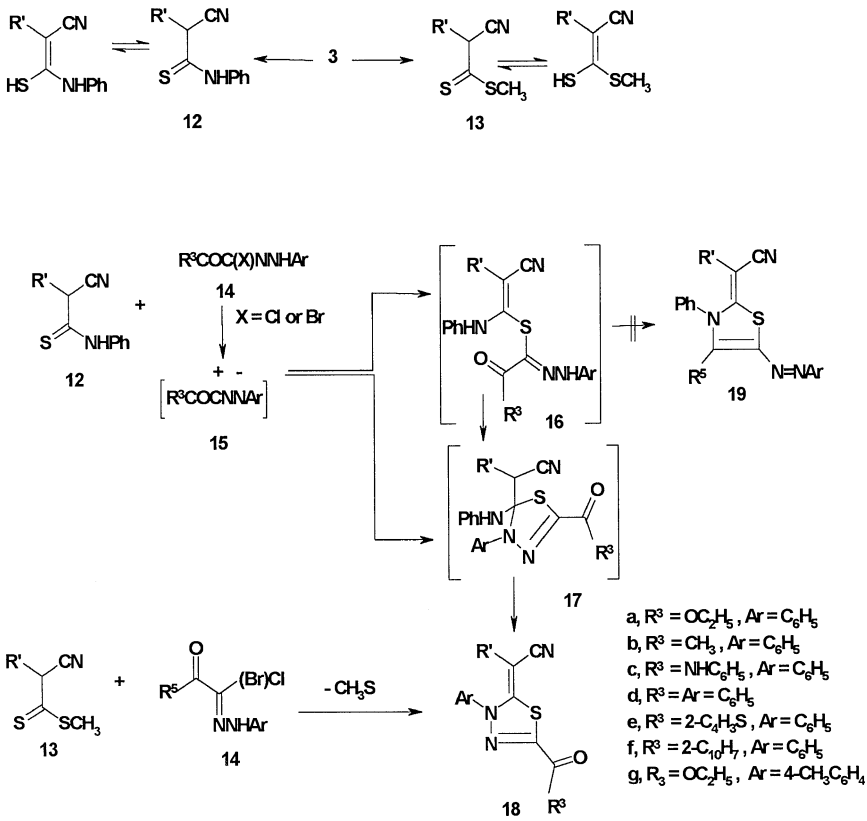
TABLE I Response of Various Microorganisms to Some Synthesized Compounds in Vitro (Culture). W: Low Activity (1–5 mm) (+); M: Moderate Activity (6–10 mm) (++); S: High Activity (11–15 mm) (+++); I: Inhibitor

	Diameter of the Zone of Inhibition				
Comp. no.	Staplyococcus aureus (ATCC25923)	Streptococcus pyogenes ATCC19615	Pseudomonas syringae PV phasealicola	Aspergillus niger	Fusarium oxysporum
5	M	—	W	—	—
10a	W	—	M	—	—
10b	—	M	W	—	—
10c	M	—	W	—	—
18a	—	W	—	—	—
18d	—	—	M	—	—
18e	—	W	—	—	—
20	M	—	—	—	—
24b	—	—	W	—	—
332	—	—	M	—	—
34	M	W	—	—	—

3-methylthio-2-(4-(2-thienyl) (1,3-thiazol-2-yl))-3-thioxopropanenitrile (**13**), respectively (Scheme 2). Structures **12** and **13** were confirmed on the basis of elemental analysis, spectral data, and chemical transformation. Thus, ^{13}C NMR of **13** showed signals at $\delta = 23$, 56, 115, 116, 126, 127, 128, 140, 143, 166, and 230 ppm. Treatment of *C*-ethoxycarbonoyl-*N*-phenylhydrazonoyl chloride (**14a**) with **12** in ethanolic triethylamine solution afforded one isolable product according to *tlc* and spectral data. Thus, ^{1}H NMR spectrum showed signals at $\delta = 1.46$ (t, 3H), 4.50 (q, 2H) and 7.09–7.63 (m, 9H). ^{13}C NMR showed signals at δ = 14, 61, 89, 115, 116, 119, 125, 128, 129, 130, 140, 143, 146, 149, 153, 154, and 161 ppm. Its IR spectrum revealed bands at 3101 (CH), 2183 (CN), 1712 (CO), and 1542 (C=C). The product was formulated as ethyl 2-[cyano(4-(2-thienyl)(1,3-thiazol-2-yl)methylene]-3-phenyl-1,3,4-thiadiazolin-5-carboxylate (**18a**).

Also, compound **13** reacted with **14a** in ethanolic triethylamine to give an identical product (mp., mixed mp. and spectra) with **18a**. On the above data the structure **19** was ruled out (Scheme 2).

Two possible pathways can account for the formation of **18a**: (First) 1,3-addition of the thiol tautomer **12** to the nitrilium imide **15a**, (which prepared in situ by treatment of hydrazonoyl chloride **14a** with triethylamine), can give the thiohydrazonate ester **16a**, which undergoes nucleophilic cyclization to yield **17a**, which affords **18a** by loss of aniline.



SCHEME 2

Second, 1,3-cycloaddition of the nitrilium imide **15a** to the C=S of **17a** can give **18a** directly (cf. Scheme 2).

Similarly, the appropriate hydrazonoyl halides **14b–g** reacted with each of thioanilide **12** or carbodithioate **13** gave the corresponding 2,3-dihydro-1,3,4-thiadiazoles **18b–g**, respectively (Scheme 2).

Treatment of amino ester **10a** with ammonium thiocyanate in acetic acid under reflux afforded 1-phenyl-3-(4-(2-thienyl)(1,3-thiazol-2-yl))-5-thioxo-4,6-dihydropyrazolo[4,5-*d*]pyrimidine-7-one (**20**). Methylation of **20** with iodomethane in presence of sodium ethoxide gave 5-methylthio-1-phenyl-3-(4-(2-thienyl)(1,3-thiazol-2-yl))-6-hydropyrazolo[4,5-*d*]pyrimidine-7-one (**21**). ^{1}H NMR spectrum of **21** showed signals at $\delta = 3.70$ (s, 3H) and 6.06–7.81 (m, 10H). Its IR spectrum revealed bands at 3355 (NH), 3101 (CH), 1712 (CO), and 1585 (C=C). ^{13}C NMR spectrum of **21** showed signals at $\delta = 13$,

TABLE II Characterization Data of the Newly Synthesized Compounds

Compd. no.	m.p. °C solvent	Yield (%) color	Mol. formula mol. wt	% Analyses calcd./found			
				C	H	N	S
3	49–51	75	$C_9H_6N_2S_2$	52.40	2.93	13.58	31.09
	EtOH	Brown	206.30	52.50	2.80	13.70	31.10
4	189–91	72	$C_{16}H_{10}N_2OS_2$	61.91	3.25	9.03	20.66
	Dioxan	Pale brown	310.40	61.82	3.53	9.16	20.52
5	174–76	80	$C_{16}H_9NO_2S_2$	61.72	2.91	4.50	20.59
	EtOH	Pale brown	311.38	61.80	2.88	4.42	20.48
6	90–92	85	$C_{16}H_{10}N_2S_2$	62.28	3.42	9.52	21.78
	EtOH	Yellow	294.40	62.43	3.29	9.36	21.60
8a	183–85	80	$C_{15}H_{10}N_4S_2$	58.04	3.25	18.05	20.66
	AcOH	Yellow	310.40	58.13	3.18	17.98	20.72
8b	185–87	68	$C_{16}H_{12}N_4S_2$	59.23	3.73	17.27	19.77
	AcOH	Yellow	324.43	59.11	3.68	17.15	19.64
10a	108–10	84	$C_{19}H_{16}N_4O_2S_2$	57.56	4.07	14.13	16.17
	EtOH	Yellow	396.49	57.39	4.00	14.22	16.25
10b	180–82	58	$C_{18}H_{14}N_4OS_2$	58.99	3.85	15.29	18.35
	AcOH	Yellow	366.47	59.08	3.77	15.19	18.27
10c	140–42	67	$C_{17}H_{11}N_5S_2$	58.43	3.17	20.04	18.35
	AcOH	Olive	349.44	58.31	3.28	20.15	18.20
11a	252–58	70	$C_{18}H_{11}N_5OS_2$	57.28	2.94	18.55	16.99
	AcOH	Yellow	377.45	57.42	3.07	18.37	17.10
11b	259–62	60	$C_{18}H_{12}N_6S_2$	57.43	3.21	22.32	17.03
	AcOH	Olive	376.46	57.26	3.13	22.42	17.21
12	178–79	65	$C_{16}H_{11}N_3S_3$	56.28	3.25	12.31	28.17
	AcOH	Brown	341.48	56.41	3.13	12.50	28.33
13	210–12	50	$C_{11}H_8N_2S_4$	44.57	2.72	9.45	43.26
	DMF	Yellow	296.46	44.40	2.88	9.62	43.41
18a	245–47	74	$C_{20}H_{14}N_4O_2S_3$	54.78	3.22	12.78	21.93
	AcOH	Reddish Red	438.55	54.80	3.13	12.67	22.01
18b	304–306	65	$C_{19}H_{12}N_4OS_3$	55.86	2.96	13.71	23.55
	DMF	Orange	408.53	55.72	2.90	13.58	23.35
18c	264–66	55	$C_{24}H_{15}N_5OS_3$	59.36	3.11	14.42	19.81
	DMF	Reddish Red	485.61	59.30	3.23	14.33	19.68
18d	267–68	70	$C_{24}H_{14}N_4OS_3$	61.25	3.00	11.91	20.47
	DMF	Orange Red	470.60	61.10	3.10	12.02	20.59
18e	285–87	75	$C_{22}H_{12}N_4OS_4$	55.44	2.54	11.76	26.91
	DMF	Reddish Red	476.62	55.36	2.56	11.84	26.79
18f	289–291	80	$C_{28}H_{16}N_4OS_3$	64.59	3.10	11.76	26.91
	DMF	Brown	520.66	64.63	3.25	11.61	27.00
18g	235–37	82	$C_{21}H_{16}N_4O_2S_2$	55.73	3.56	12.38	21.25
	AcOH	Yellow	452.58	55.69	3.40	12.50	21.05
20	>330	85	$C_{18}H_{11}N_5OS_3$	52.79	2.71	17.10	23.49
	Dioxan	Yellow	409.51	52.66	2.84	16.95	23.37
21	207–10	72	$C_{19}H_{13}N_5OS_3$	53.88	3.09	16.54	22.71
	Dioxan	Yellow	423.53	54.01	3.20	16.65	22.61

(Continued on next page)

TABLE II Characterization Data of the Newly Synthesized Compounds *(Continued)*

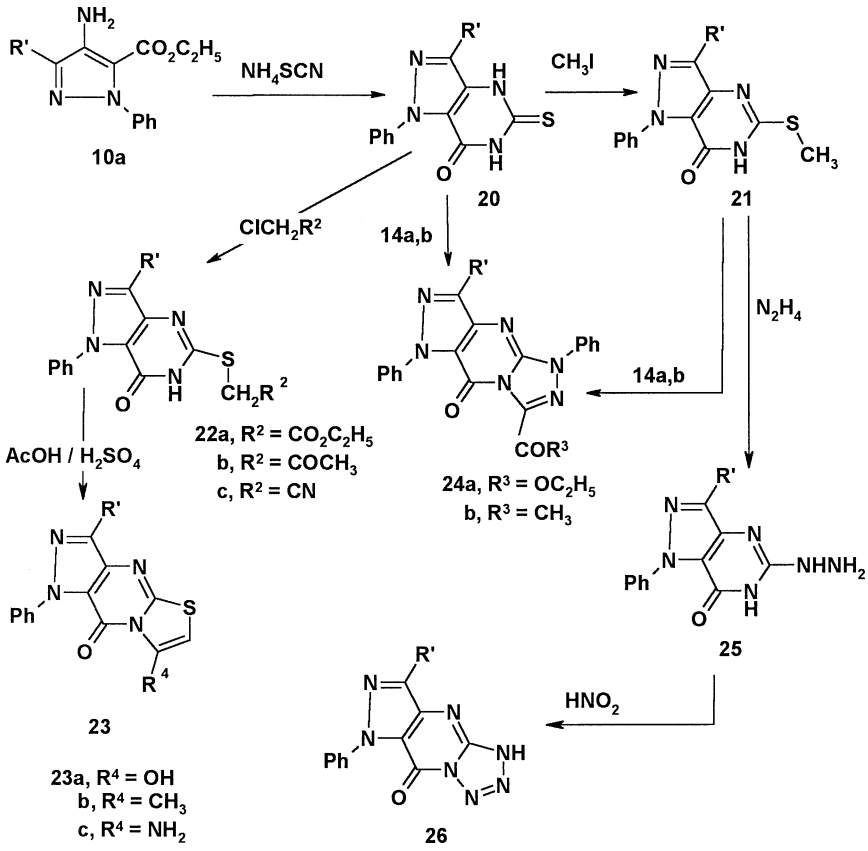
Compd. no.	m.p. °C solvent	Yield (%) color	Mol. formula mol. wt	% Analyses calcd./found C	H	N	S
22a	240–42	68	$C_{22}H_{16}N_5O_3S_3$	53.42	3.26	14.16	19.45
	Dioxan	Colorless	494.61	53.28	3.32	14.26	19.61
22b	250–52	70	$C_{21}H_{14}N_5O_2S_3$	54.29	3.04	15.08	20.71
	Dioxan	Yellow	464.57	54.45	3.13	14.96	20.55
22c	220–22	60	$C_{20}H_{11}N_6OS_3$	53.68	2.48	18.78	21.49
	Dioxan	Yellow	447.54	53.82	2.62	18.93	21.34
23a	>320	45	$C_{20}H_{11}N_5O_2S_3$	53.44	2.47	15.58	21.40
	DMF	Gray	449.54	53.34	2.60	15.44	21.27
23b	>320	70	$C_{21}H_{13}N_5OS_3$	56.36	2.93	15.65	21.49
	DMF	Gray	447.56	56.20	3.02	15.81	21.66
23c	290–92	80	$C_{20}H_{12}N_6OS_3$	53.58	2.67	18.74	21.45
	DMF	Gray	448.36	53.46	2.81	18.58	21.63
24a	220–22	65	$C_{28}H_{19}N_7O_3S_2$	59.46	3.39	17.33	11.34
	AcOH	Yellow	565.64	59.30	3.28	17.23	11.48
24b	254–56	55	$C_{27}H_{17}N_7O_2S_2$	60.55	3.20	18.31	11.97
	AcOH	Yellow	535.61	60.71	3.38	18.16	12.00
25	135–37	75	$C_{18}H_{13}N_7OS_2$	53.06	3.22	24.06	15.74
	EtOH	Yellow	407.48	53.15	3.37	24.18	15.86
26	170–73	70	$C_{18}H_{10}N_8OS_2$	51.66	2.41	26.78	15.32
	EtOH	Yellowish brown	418.46	51.49	2.60	26.90	15.10
27	274–76	85	$C_{16}H_{10}KN_3S_3$	50.63	2.66	11.07	25.34
	EtOH	Pale brown	379.57	50.50	2.51	10.85	25.12
28a	185–87	73	$C_{20}H_{17}N_3O_2S_3$	56.18	4.01	9.83	22.50
	AcOH	Olive	427.57	56.27	4.14	9.74	22.63
28b	234–36	80	$C_{19}H_{15}N_3OS_3$	57.41	3.80	10.57	24.20
	AcOH	Olive	397.54	57.32	3.93	10.67	24.30
28c	255–57	60	$C_{18}H_{12}N_4S_3$	56.82	3.18	14. 72	25.28
	Dioxan	Gold	380.51	56.92	3.33	14.69	25.45
28d	190–92	85	$C_{24}H_{17}N_3OS_3$	62.72	3.73	9.14	20.93
	AcOH	Olive	459.61	62.70	3.71	9.22	21.08
29a	254–55	62	$C_{18}H_{11}N_3OS_3$	56.67	2.91	11.01	25.21
	AcOH	Green	381.50	56.83	3.06	10.92	25.35
29b	251–52	60	$C_{19}H_{13}N_3S_3$	60.13	3.45	11.07	25.35
	Dioxan	Olive	379.53	60.00	3.59	11.24	25.52
29c	261–63	50	$C_{18}H_{12}N_4S_3$	56.82	3.18	14.72	25.28
	AcOH	Brown	380.51	56.91	3.23	14.66	25.11
29d	268–70	45	$C_{24}H_{15}N_3S_3$	65.28	3.42	9.52	21.78
	Dioxan	Olive	441.60	65.38	3.58	9.40	21.91
30a	121–23	35	$C_{20}H_{17}N_3O_2S_3$	56.18	4.01	9.83	22.50
	EtOH	Pale yellow	427.57	56.33	4.18	9.68	22.62
30c	191–92	45	$C_{18}H_{12}N_4S_3$	56.82	3.18	14.72	25.28
	EtOH	Brown	380.51	56.99	3.36	14.85	25.42
30d	136–37	55	$C_{24}H_{17}N_3OS_3$	62.72	3.73	9.14	20.93
	EtOH	Yellowish green	459.61	62.88	3.72	9.06	20.76

(Continued on next page)

TABLE II Characterization Data of the Newly Synthesized Compounds *(Continued)*

Compd.0 no.	m.p. °C solvent	Yield (%) color	Mol. formula mol. wt	% Analyses calcd./found C	H	N	S
31	143–45	35	$C_{22}H_{19}N_3O_3S_3$	56.27	4.08	8.95	20.48
	EtOH	Yellow	469.61	56.43	4.16	8.82	20.37
32	266–68	60	$C_{22}H_{17}N_3O_2S_3$	58.51	3.97	9.31	21.30
	Dioxan	Olive	451.59	58.62	4.08	9.23	21.41
33	160–63	30	$C_{21}H_{17}N_3O_2S_3$	57.38	3.90	9.56	21.88
	EtOH	Olive	439.58	57.38	4.06	9.71	21.58
34	262–64	60	$C_{21}H_{15}N_3OS_3$	59.83	3.59	10.00	22.82
	Dioxan	Yellow	421.56	59.99	3.75	9.87	22.66

107, 115, 120, 126, 127, 128, 129, 130, 140, 141, 143, 156, 159, and 193 ppm. Compound **20** reacted with each of ethyl chloroacetate, chloroacetone, chloroacetonitrile, or the appropriate hydrazonoyl halides **14a**,**b** to give S-alkyl derivative **22a–c** and 1,3-disubstituted 7-phenyl-5-(4-(2-thienyl(1,3-thiazol-2-yl))-8a-hydopyrazolo[4,5-*d*]1,2,4-triazolino[1,5-*a*]pyrimidine-5-one **24a**,**b**, respectively (Scheme 3). Structure **22** was elucidated by elemental analysis, spectral data, and chemical transformation. Thus, ^{1}H NMR spectra of **22b** showed signals at $\delta = 1.99$ (s, 3H), 3.72 (s, 2H), 5.68 (s, br., 1H) and 7.05–7.86 (m, 9H). ^{13}C NMR spectrum showed signals at $\delta = 18$, 101, 107, 115, 120, 125, 126, 127, 128, 129, 141, 143, 153, and 163 ppm. Compounds **22a–c** were converted to pyrazolo[4,5-*d*]1,3-thiazolino[2,3-*a*]pyrimidin-5-one derivatives **23a–c** by boiling in a mixture of acetic acid and sulfuric acid under reflux. Structures **23a–c** were confirmed by elemental analysis and spectral data (cf. Experimental). Compound **20** reacted with the appropriate hydrazonoyl chlorides **14a**,**b** and triethylamine in boiling chloroform under reflux to give pyrazolo[4,5-*d*]1,2,4-triazolino[4,5-a]pyrimidine-8-one derivatives **24a**,**b**, respectively (Scheme 3). Structure **24** was elucidated by elemental analysis, spectral data and alternative synthesis route. ^{1}H NMR spectrum of **24a** showed signals at $\delta = 1.48$ (t, 3H), 4.58 (q, 2H), 7.06–7.11 (m, 1H), 7.27–7.62 (m, 9H), 7.81–85 (d, 2H) and 8.46–8.50 (d, 2H). Its ^{13}C NMR spectrum showed signals at $\delta = 14$, 62, 107, 115, 116, 118, 120, 125, 126, 127, 128, 129, 139, 141, 143, 146, 154, 158, 159, and 163 ppm. ^{1}H NMR spectrum of **24b** showed signals at $\delta = 2.64$ (s, 3H), 7.10–7.13 (m, 1H), 7.27–7.65 (m, 9H), 7.79–8.31 (d, 2H) and 8.48–8.52 (d, 2H). Its ^{13}C NMR spectrum showed signals at $\delta = 21$, 107, 115, 116, 118, 120, 126, 127, 128, 129, 139, 141, 143, 146, 154, 163, and 194 ppm. Also, treatment of **14a**

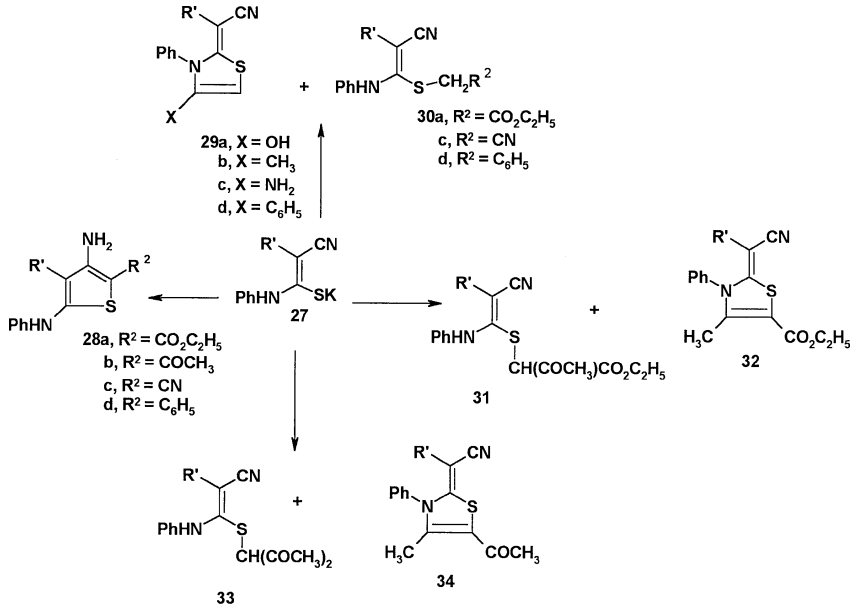


SCHEME 3

with **21** in ethanolic triethylamine afforded an identical product in all respects (mp., mixed mp., and spectra) with **24a**.

Compound **21** reacted with hydrazine hydrate in boiling ethanol under reflux and yielded 5-hydrazino-1-phenyl-3-(4-(2-thienyl)(1,3-thiazol-2-yl))-6-hydropyrazolo-[5,4-d]pyrimidin-7-one (**25**). Compound **25** reacted with nitrous acid to give 7-phenyl-5-(4-(2-thienyl)-(1,3-thiazol-2-yl))-8a-hydro-3H-pyrazolo[4,5-*d*]1,2,3,4-tetrazolino[1,5-*a*]pyrimidin-8-one (**26**) (cf. Scheme 3).

Finally, treatment of potassium salt of 3-(phenylamino-3-sulfanyl-2-4-(2-thienyl)(1,3-thiazol-2-yl))prop-2-enenitrile (**27**), which prepared via reaction of phenyl isothiocyanate and **3** in potassium ethoxide solution, with each of ethyl chloroacetate, chloroacetone, chloroacetonitrile, or phenacyl bromide in ethanol afforded [3-amino-2-substituted



SCHEME 4

5-(phenylamino)(4-(4-thienyl)(1,3-thiazol)(2-thienyl)(1,3-thiazol-2-yl) thiophenes] **28a–d**, respectively (Scheme 4). Structure **28** was elucidated by elemental analysis and spectral data. Thus, ^{1}H NMR spectra of **28a** showed signals at $\delta = 1.36$ (t, 3H), 4.28 (q, 2H), 5.10 (s, br., 2H), 7.09–7.48 (m, 9H) and 11.80 (s, br., 1H). Its ^{13}C NMR showed signals at $\delta = 14$, 61, 115, 116, 118, 122, 126, 127, 128, 130, 131, 140, 143, 144, 153, and 160 ppm. Whereas, each of ethyl 2-chloro-3-oxoprpanoate and 3-chloropentan-2,4-dione was reacted by a similar route to give aminothiophenes **28a** and **28b**, respectively.

In contrast, compound **3** reacted with phenyl isothiocyanate in *N*,*N*-dimethylformamide containing potassium hydroxide and followed by ethyl chloroactate afforded thiazole **29a** and S-alkyl **30a**. ^{1}H NMR spectra of **29a** showed signals at $\delta = 3.99$ (s, 2H,C-2 thiazole), and 7.09–7.63 (m, 9H, ArH's). ^{1}H NMR spectra of **30a** showed signals at $\delta = 1.22$ (t, 3H), 3.35 (s, 2H), 4.10 (q, 2H), 7.03–7.05 (m, 1H), 7.07–7.50 (m, 8H) and 12.52 (s, br., 1H). Similarly, **3** reacted with chloroacetyl chloride by the same route and gave a product identical in all respects (mp., mixed mp., and spectra) with **29a** (Scheme 4).

Compound **27** reacted with each of chloroactone, phenacylbromide, chloroacetonitrile, ethyl 3-chloro-2-oxopropanoiate, or 3-chloropentan-2,4-dione in *N*,*N*-dimethylformamide and gave, in each case, S-alkyl

and thiazole derivatives **29b–d**, **32**, and **34**, respectively (Scheme 4). Boiling S-alkyl derivatives **30c**,**d**, **31**, and **33** in ethanol containing a catalytical amount of piperidine afforded corresponding thiophene amines **28a–c**.

Biological Activities

The tested microorganisms were gram +ve bacteria [Staphylococcus aureus (ATCC25923) and Streptococcus pyogenes (ATCC19615)] and gram −ve bacteria (pseudomonas syrinagae PV phasealicola). In addition to 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 on two concenterations (100, 200 μg/mL) that were dissolved in $CHCl_3$. The tests were carried out using the filter paper and hole plate method.[13]

Studies on the biological activity of compounds, **5**, **10a**, **10b**, **10c**, **18a**, **18b**, **18d**, **18e**, **20**, **24a**, **24b**, **32**, and **34** led to the fact that these compounds have a weak-to-moderate biological activity against of the tested bacteria in Table I. All the tested compounds showed negative antifungal activities.

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and were uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer and chemical shifts were expressed in δ units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analysis were carried out at the Microanalytical Center of the Cairo University. 2-Bromoacetylthiopene[9] and hydrazonoyl halides[14–20] **14a–g** were prepared as previously reported.

2-[4-(2-Thienyl)-1,3-thiazol-2-yl] Ethanenitrile 3

A mixture of 2-Bromoacetylthiophene (**1**), (20.5 g, 100 mmol) and cyanothioacetamide (10 g, 100 mmol) in ethanol (25 mL) was refluxed for 2 h. The reaction mixture was poured onto ice-cold water (50 mL) and added 5 drops of conc. ammonium hydroxide (25%). The resulting solid was collected, washed with water, and recrystallized from ethanol to give thiazolylacetonitrile **3** (Tables II and III).

TABLE III Spectra of Some Newly Synthesized Compound

Comp. no.	Spectral data
5	^{13}CNMR: 121, 125, 126, 127, 128, 129, 130, 136, 143, 150, 154, 163, and 164
6	IR: 3093 (CH), 2210 (CN), and 1554 (C═C).
8a	^{1}HNMR: 7.11-7.47 (m, 9H, ArH's), and 14.06 (s, br. NH). IR: 3101 (CH), 2214 (CN), 1596 (C═C).
8b	IR: 3448 (NH), 3119 (CH), 2217 (CN), and 1595 (C═C).
10a	^{13}CNMR: 14, 61, 115, 120, 123, 126, 127, 128, 129, 130, 136, 140, 143, 160, and 162. IR: 3458, 3339 (NH_2), 3092 (CH), 1709 (CO), and 1593 (C═C).
10b	^{13}CNMR: 27, 115, 120, 125, 126, 127, 128, 129, 130, 133, 140, 143, 162, and 196.
10c	^{13}CNMR: 114, 115, 120, 125, 129, 130, 133, 139, 140, 143, and 162.
11a	IR: 3097 (CH), 1697 (CO), 1600 (C═C).
11b	IR: 3467 (NH_2), 3085 (CH), 1608 (C═C).
12	^{1}HNMR: 2.25 (s, 3H, SCH_3), 7.03–7.50 (m, 9H, ArH's), and 12.53 (s, br., NH). IR: 3421, 3359 (NH), 3062 (CH), 2183 (CN), and 1523 (C═C).
13	IR: 3089 (CH), 2202 (CN), 1594 (C═C).
18b	^{1}HNMR: 2.64 (s, 3H, CH_3), and 7.09–7.67 (m, 9H, ArH's). ^{13}CNMR: 23, 89, 115, 116, 118, 126, 127, 128, 130, 140, 146, 149, 153, 154, and 194. IR: 3092(CH), 2194(CN), 1678 (CO), and 1595 (C═C) .
18c	IR: 3386 (NH), 3062 (CH), 2191 (CN), 1674 (CO), and 1582 (C═C).
18d	IR: 3099 (CH), 2189 (CN), 1676 (CO), and 1584 (C═C).
18e	IR: 3102 (CH), 2192 (CN), 1671 (CO), and 1607 (C═N).
18f	IR: 3102 (CH), 2191 (CN), 1672 (CO), 1622 (C═N).
18g	^{1}HNMR: 1.49 (t, 2H, CH_2CH_3), 2.48 (s, 3H, CH_3), 4.5 (q, 2H, CH_2CH_3), and 7.08–7.50 (m, 8H, ArH's). IR: 3094 (CH), 2188 (CN), 1730 (CO).
20	IR: 3355 (NH), 3101 (CH), 1712 (CO), and 1523 (C═C).
21	IR: 3457 (NH), 3112 (CH), 1691 (CO), and 1593 (C═C).
22a	IR: 3448 (NH), 3097 (CH), 1741 (CO), and 1679 (CO).
22b	IR: 3382 (NH), 3089 (CH), 1678 (CO), and 1569 (C═C).
22c	^{1}HNMR: 3.71 (s, 2H, CH_2CN), and 7.26–7.49 (m, 10H, ArH's), IR: 3446 (NH), 3101 (CH), 2247 (CN), 1685 (CO), and 1575 (C═C).
23a	IR: 3095 (CH), 1682 (CO), 1573 (C═C).
23b	IR: 3101 (CH), 1654 (CO), and 1596 (C═C).
23c	IR: 3494, 3371 (NH_2), 3070 (CH), 1708 (CO), and 1589 (C═C).
24a	IR: 3099 (CH), 1720 (CO), 1583 (C═C).
24b	IR: 3101 (CH), 1710 (CO), 1609 (C═C).
25	IR: 3423, 3338 (NH_2), 3097 (CH), 1641 (CO), and 1597 (C═C).
26	IR: 3367 (NH), 3101 (CH), 1689 (CO), and 1596 (C═C).
28a	IR: 3441, 3394 (NH_2), 3101 (CH), 1720 (CO), and 1573 (C═C).
28b	^{1}HNMR: 2.33 (s, 3H, CH_3), 7.10–7.48 (m, 11H, ArH's and NH_2), and 11.99 (s, br., NH). IR: 3433, 3317 (NH_2), 3101 (CH), 1658 (CO), and 1596 (C═C).
28c	IR: 3438, 3349 (NH2), 3100 (CH), 2179 (CN), and 1566(C═C).
28d	IR: 3420, 3238 (NH_2), 3053 (CH), 1592 (CO), 1559 (C═C).

(Continued on next page)

TABLE III Spectra of Some Newly Synthesized Compound *(Continued)*

Comp. no.	Spectral data
29a	IR: 3096 (CH), 2197 (CN), 1728, 1631 (CO), and 1594 (C═C).
29b	^{1}HNMR: 1.92 (s, 3H, CH_3), 6.38 (s, 1H, thiazol), and 7.04–7.65 (m, 9H, ArH's).
	^{13}C NMR: 19, 80, 109, 115, 116, 118, 119, 126, 128, 130, 140, 141, 143, 153, and 160.
	IR: 3093 (CH), 2167 (CN), 1596 (C═C).
29c	^{1}HNMR: 7.12–7.69 (m, 10H, ArH's), 8.3 (s, br., 1H), and 10.15 (s, br., 1H).
	IR: 3290 (NH), 3093 (CH), 2183 (CN), and 1593 (C═C).
33	IR: 3390 (NH), 2100 (CH), 2184 (CN), 1708 (CO), and 1571 (C═C).
34	IR: 3093 (CH), 2175 (CN), 1666 (CO), and 1573 (C═C).

3-(4-(2-Thienyl)-1,3-thiaozl-2-yl)-2H-chromen-2-imine (4) and (2E)-2-(4-(2-thienyl)(1,3-thiazol-2-yl))-3-phenylprop-2-enenitrile (6)

Method A: Thiazolylacetonitrile **3** (1.03 g, 5 mmol) and salicylaldehyde or benzaldehyde (5 mmol) in ethanol (20) containing catalytic amount of piperidine were stirred at room temperature for 2 h. The resulting solid was collected and recrystallized to give **4** and **6**, respectively (Tables II and III).

Method B: Equimolar amounts of 2-(aminothioxomethyl)-3-phenyl-prop-2-enenitrile and **1** (5 mmol) in ethanol (15 mL) was boiled under reflux for 2 h. The resulting solid was collected and crystallized and gave the identical product (mp., mixed mp, and spectra) with **6**.

3(4-(Thienyl)-1,3-thiazol-2-yl)-2H-chromen-2-one (5)

A mixture of **4** (0.5 g) and hydrochloric acid (5 mL, 6 M) was stirred at room temperature for 1 h. The resulting solid was collected and recrystallized from ethanol to give substituted coumarin **5** (Tables II and III).

(2E)-3-aza-3-(arylamino)-2-(4-(2-thienyl)1,3 Thiazol-2-yl) Prop-2-enentitrile 8a,b

Method A: The appropriate arenediazonium chlorides (5 mmol) was added dropwise to a cold ethanol solution, containing thiazolyacetonitrile **3** (1.03 g, 5 mmol) and sodium acetate (1 g), (50 mL) at 0–5°C while stirring. The mixture was stirred for 3 h at 0–5°C. The resulting solid was collected and crystallized from dioxan to give **8a**,**b** (Tables II and III).

Method B: A mixture of the appropriate (2E)-2-aminothioxomethyl)-3aza)-3-(arylamino)prop-2-enenitrile **9a**,**b** and **1** (5 mmol each) in acetic acid (30 mL) was boiled under reflux for 2 h. The resulting solid, which formed after cooling, was collected and crystallized from acetic acid to afford a product identical in all respects (mp., mixed mp., and spectra) with products obtained in method A.

Aminopyrazoles 10a–c

Equimolar amounts of **8a** and the appropriate of ethyl chloroacetate and chloroacetone, or chloroacetonitrile (5 mmol) in *N*,*N*-dimethylformamide (30 mL) containing potassium carbonate anhydrous (1.5 g) was heated under reflux at 110–120°C for 2 h. The reaction mixture was cooled at room temperature and triethylamine (1 mL) was added dropwise while stirring. The reaction mixture was boiled at 90°C for 1 h and poured onto ice-cold water (100 mL). The resulting solid was collected and recrystallized to give aminopyrazoles **10a–c** (Tables II and III).

Pyrazolo[3,4-*d*]pyrimidines 11a and 11b

Aminopyrazole **10c** (1.25 g, 5 mmol) and formic acid (10 mL, 99%) or formamide (2 mL) in *N*,*N*-dimethylformamide (10 mL) was heated under reflux for 5 h then poured onto on ice-cold water (50 ml). The resulting solid was collected and crystallized to afford **11a** and **11b**, respectively (Tables II and III).

3-(Phenylamino)-2-(4-(2-thienyl)(1,3-thiazol-2-yl))-3-thioxopropanenitrile (12)

Phenyl isothiocyanate (0.65 g (0.6 ml), 5 mmol) was added to a mixture of thiazolylacetonitrile **3** (1.03 g, 5 mmol) and potassium hydroxide (0.28 g, 5 mmol) in *N*,*N*-dimethylformamide (15 mL) while stirring at room temperature until potassium hydroxide dissolve completely, and the reaction mixture continued stirring for 1 h. The reaction mixture was poured onto water (30 mL) and acidified with acetic acid. The resulting solid was collected and recrystallized from acetic acid to give **12** (Tables II and III).

Synthesis of 3-Methythio-2-(4-(2-thienyl)(1,3-thiazol-2-yl)-3-thioxopropane-nitrile 13

A mixture of thiazolylacetonitrile **3** (1.03 g, 5 mmol), potassium hydroxide (0.28 g (5 mmol) and carbon disulfide (0.39 g, (0.29 mL), 5 mmol) in

N,*N*,-dimethylformamide (15 mL) was stirred for 6 h at room temperature. Iodometane (0.71 g, 5 mmol) was added dropwise to the above mixture and stirred for 1 h. The resulting solid was collected and crystallized from acetic acid to give **13** (Tables II and III).

2,3-Dihydro-1,3,4-thiadiazoles 18a–g

Method A: Phenyl isothiocyanate (0.65 g, (0.65 mL), 5 mmol) was added to a mixture of thiazolylacetonitrile (1.03 g, 5 mmol) **2** and potassium hydroxide (0.28 g, 5 mmol) in *N*,*N*-dimethylformamide (15 mL) while stirring at room temperature until potassium hydroxide dissolve completely and the reaction mixture was continued stirring for further 30 min. The appropriate hydrazonoyl halides **14a–g (**5 mmol) was added and stirring was continued for 3 h. The resulting solid was collected and recrystallized from the appropriate solvent to afford **18a–g** (Tables II and III).

Method B: Triethylamine (0.5 g, (0.75 mL), 5 mmol) was added dropwise to a mixture of the appropriate hydrazonoyl halides **14a–g** and **13** (1.9 g, 5 mmol) in ethanol (20 mL) while stirring. Stirring was continued for 1 h and the resulting solid was collected and crystallized and gave identical products in all respects (mp., mixed mp., and spectra) with those obtained in method A.

5-Thio-1,4,5,6-tetrahydropyrazolo[4,3-*d*]pyrimidin-7-one (20)

Equimolar amounts of aminopyrazole **10a** and ammonium thiocyanate (5 mmol) in acetic acid (10 mL) were heated under reflux for 5 h, then poured onto ice-cold water. The resulting solid was collected and crystallized to give **20** (Tables II and II).

S-Alkyl Derivatives 21 and 22a–c

1-phenyl-3-(4-thiophen-2-ylthiazol-2-yl)-5-thio-1,4,5,6-tetrahydropyrazolo-[4,3-*d*]pyrimidin-7-one (**20**) (2.04 g, 5 mmol) potassium hydroxide (0.28 g, 5 mmol) in *N*,*N*-dimethylformamide (15 mL) was stirred at room temperature for 6 h. The appropriate iodomethane, ethyl chloroacetate, chloroacetone, or chloroacetonitrile (5 mmol) was added dropwise while stirring and stirred was continued for 2 h. The resulting solid, which formed after dilution with water, was collected and crystallized to give **21** and **22a–c**, respectively (Tables II and III).

Pyrazolo[4,5-*d*]1,3-thiazolino[3.2-*a*]pyrmidin-8-one 23a–c

An appropriate **22a–c** (0.5 g) in a mixture of glacial acetic acid (10 mL) and sulfuric acid (3 mL, 18 M) was heated under reflux for 6 h, then

poured onto ice-cold water (30 mL). The resulting solid was collected and crystallized to give **23a–c**, respectively (Tables II and III).

Pyrazolo[4,5-*d*]1,2,4-triazolino[4,5-*a*]pyrimidin-8-one 24a,b

Equimolar amounts of **21**, **14a**, or **14b** and sodium ethoxide (5 mmol, each) in ethanol (20 mL) was boiled under reflux for 3 h. The resulting solid was collected and crystallized to give **24a** and **24b**, respectively (Tables II and III).

5-Hydrazino-6-pyrazolo[4,5-*d*]pyrimidine-7-one 25

A mixture of **21** (2.12 g, 5 mmol) and hydrazine hydrate (1 mL, 99%) in ethanol (20 mL) was heated under reflux for 3 h. The resulting solid, which formed after cooling, was collected, washed, and crystallized to give **25** (Table I).

Synthesis of 7-Pheny1-5-(4-(2-thienyl) (1,3-thiazol-2-yl)-8a-hydro-3H-pyrazolo-[4,5-*d*]1,2,3,4-tetrazolino[1,5-a] Pyrimidin-8-one 26

Saturated sodium nitrite solution was added to a cold mixture of **25** (1 g) in glacial acetic acid (20 mL) while stirring. The reaction mixture was kept at 0°C for 1 h and the resulting solid was collected and crystallized to give **26** (Tables II and III).

Potassium Salt of 3-(Phenylamino-3-sulfanyl-2-4-(2-thienyl)(1,3-thiazol-2-yl))prop-2-enenitrile (27)

Potassium ethoxide (5 mmol) was added dropwise to a mixture of thiazolylacetonitrile **3** (1.03 g, 5 mmol) and phenyl isothiocyanate (0.65 g, (0.6 mL), 5 mmol) in (10 mL) absolute ethanol at room temperature. Diethyl ether (30 mL) was added to the reaction mixture to complete precipitation and the resulting solid was collected and crystallized from ethanol to give **27** (Table I).

S-Alkyl 30a,c,d, 31, 33 and Thiazole Derivatives 29a–b, 32 and 34

Phenyl isothiocyanate (0.6 mL, 5 mmol) was added to mixture of thiazolylacetonitrile **3** (1.03 g, 5 mmol) and potassium hydroxide (0.28, 5 mmol) in *N*,*N* dimethylformamide (15 mL) while stirring

at room temperature until potassium hydroxid dissolve completely. The reaction mixture continued stirring for further 30 min, then we added the appropriate ethyl chloroacetate, chloroacetonitrile, phenacylbromide, 3-chloropentan-2,4-dione or ethyl 2-chloro-3-oxopropanoate (5 mmol each) while continuously stirring 1 hr. The resulting solid was collected and crystallized to give S-alkyl **30a**,**c**,**d**, **31**, and **33**, and thiazole derivatives **29a–d**, **32**, and **34**, respectively (Tables II and III).

3-Amino Thiophene derivatives 28a–d

Method A: The appropriate S-alkyl derivatives **30a–d** (5 mmol) in ethanol (15 mL) containing catalytic amount of piperidine was heated under reflux for 30 min. The resulting solid was collected and crystallized to give **28a–d** (Tables II and III).

Method B: Potassium ethoxide (5 mmol) was added dropwise to a mixture of thiazolylacetonitrile **3** (1.03 g, 5 mmol) and phenyl isothiocyanate (0.65 g, (0.6 mL), 5 mmol) in (10 mL) absolute ethanol at room temperature. The resulting solid was collected and crystallized to give **28a–d**.

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