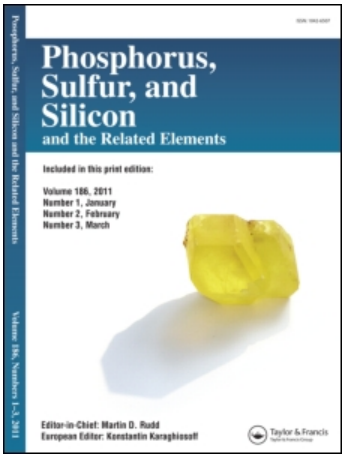

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New Synthetic Routes to 1,3,4-Thiadiazole Derivatives

A. A. Elagamey[a]; F. M. A. El-Taweel[a]; R. A. N. Abu El-Enein[a]
[a] Department of Chemistry, New Damietta, Arab Republic of Egypt

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New Synthetic Routes to 1,3,4-Thiadiazole Derivatives

A. A. Elagamey
F. M. A. El-Taweel
R. A. N. Abu El-Enein
Department of Chemistry, New Damietta,
Arab Republic of Egypt

*Different new 1,3,4-thiadiazolopyridine derivatives (**6**, **8**, **20**, **28**, and **42**) were synthesized from 5-cyanomethyl-1,3-4-thiadiazole (**1**) and activated nitriles. Also, spiro indolono-thiadiazolopyridine (**12**) was obtained from the reaction of (**1**) with 2-(2-oxoindolin-3-ylidene)malononitrile (**10**). Other heterocyclic derivatives at position-5 in the thiadiazole ring were obtained for possible use as antimicrobial agents.*

Keywords 1,3,4-Thiadiazoles; actived nitriles; thiadiazolopyridine; pyridine; furo[2,3-*b*]indole; pyridazine

INTRODUCTION

Alkylazoles are versatile reagents, which have been extensively utilized for the synthesis of polyfunctionally substituted aromatic and heteroaromatic systems.[1–11] These aromatic and heteroaromatic[2] systems are interesting as potential biodegradable agrochemicals,[4,11] pharmaceuticals, and intermediates[4] in the dye industry.[12–14]

In general, thiadiazole derivatives have been reported to be biologically versatile compounds having antimicrobial,[15–25] mutagenic,[16] anticonvulsant,[23,26] cytotoxicity,[22,27] antiviral,[27,28] antiinflammatory,[29–31] antihelicobacterpylori,[32] anti-tuberculosis,[33] antiimmobility[34] and anticancer.[35]

In continuation of our studies, the utility of *N*-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide (**1**), the arylidenenitriles **2**, and active methylene nitriles **3** as excellent precursors is reported. The present work has resulted in the formation of novel 1,3,4-thiadiazolopyridine and 2-substitued 1,3,4-thiadiazole derivatives of expected potential biological importance.

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Address correspondence to A. A. Elagamey, New Damietta, Department of Chemistry, Faculty of Science, A. R. Egypt. E-mail: r_elagamey@yahoo.com

RESULTS AND DISCUSSION

It has been found that (**1**) reacted readily with arylidenemalononitriles **2a,b,d** in ethanolic/piperidine to yield thiadiazolo[3,2-*a*]pyridines (**6a–c**) via hydrogen elimination. ^{1}H NMR spectra of the reaction products revealed no signals at $\delta \approx 4.5$–5.0 ppm for one proton linked to an sp^3 carbon corresponding to pyridine H-4 protons.[36] The oxidation of dihydroazines by arylidene malononitriles has been observed.[37] Thus, structure **6** was established for the reaction products. The formation of **6** was assumed to proceed *via* a Michael type addition of the active methylene group in **1** to the activated double bonds in the arylidenenitriles **2** to give Michael adducts **4**, which readily cyclized to **5** and dehydrogenated to afford **6**. Compound **6a** was also prepared from the reaction of (**9**) with malononitrile using the same reaction conditions.

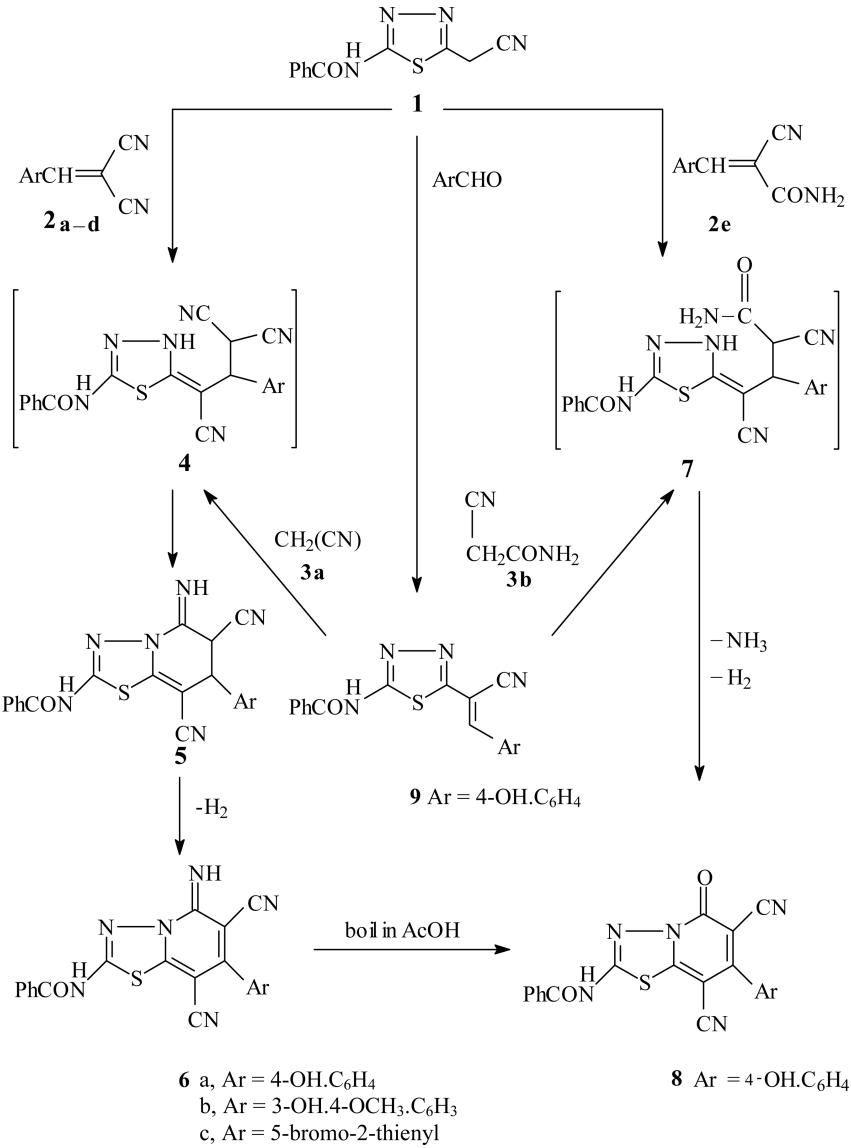
Similarly, compound **1** reacted with **2e** in ethanol/piperdine to yield (**8**) *via* ammonia and hydrogen elimination. The same product **8** was also obtained by reacting (**9**) with cyanoacetamide (**3b**). Compound **8** could be directly obtained from boiling **6a** in glacial acetic acid (Scheme 1).

Also, compound **1** reacted with (**10**) in ethanol catalyzed by piperdine to afford compound (**12**). Structure **12** was establised for the reaction product based on the analytical and spectral data, which is in good agreement with structure **12** (cf. Experimental section).

Compound **1** condensed with 2,3-indolinedione (**13**) to yield a product with the molecular formula $C_{19}H_{11}N_5SO_2$ ($M^+ = 373$ m/z). The IR spectrum indicated clearly that the reaction product is **15** based on the IR spectrum, which revealed the absence of signals due to the cyano function. Thus, was **15** established as a reaction product. Compound **15** was assumed to be formed *via* the initial condensation of 2,3-indolinedione **13** with the active methylene group in **1** to give the ylidenic intermediate **14**, which readily cyclized to yield the final isolable product **15**.

Similarly, compound **1** reacted with 1,2-dihydro-2,3-dimethyl-4-nitroso-1-phenylpyrazol-5-one (**16**) to yield a product resulting from the elimination of water from the reactants. Structure **17** was established for the reaction product on the basis of their IR and ^{1}H NMR spectra (cf. Experimental section).

It has been reported that a mixture of aliphatic aldehydes and active methylene nitriles can be utilized as a synthetic equivalent of alkylidenemalononitriles.[36,38] By this method, different heterocycles can be prepared. Thus, the mixture formaldehyde and malononitrile as a synthetic equivalent of **18** reacted with compound **1** in refluxing ethanol/piperidene to afford **20**. Compound **20** was suggested to be



SCHEME 1

formed through the first addition of the active methylene in **1** to the π-deficient center in **18** to give the adducts **19**. These were cyclized to yield **20**. The formation of **20** is in accordance with the previously reported formation of similar systems.[8]

Similarly, compound **1** reacted with a mixture of formaldehyde and 2-amino-1,1,3-tricyanopropene (**22a**) or diethyl 2-amino-1-cyanopropene-1,3-dicarboxylate (**22b)** in ethanol and in the presence of piperidine as a catalyst to afford (**24a)** and (**24b**), respectively. Structure **24** was established from analytical and spectral data (cf. Experimental section). Compounds **24a**,**b** were proposed to be obtained through first the condensation of **1** with formaldehyde to give the intermediate **21**, which added on the active methylene in **22a**,**b** to give the intermediates **23**. The latter cyclized to yield **24a**,**b** (Scheme 3).

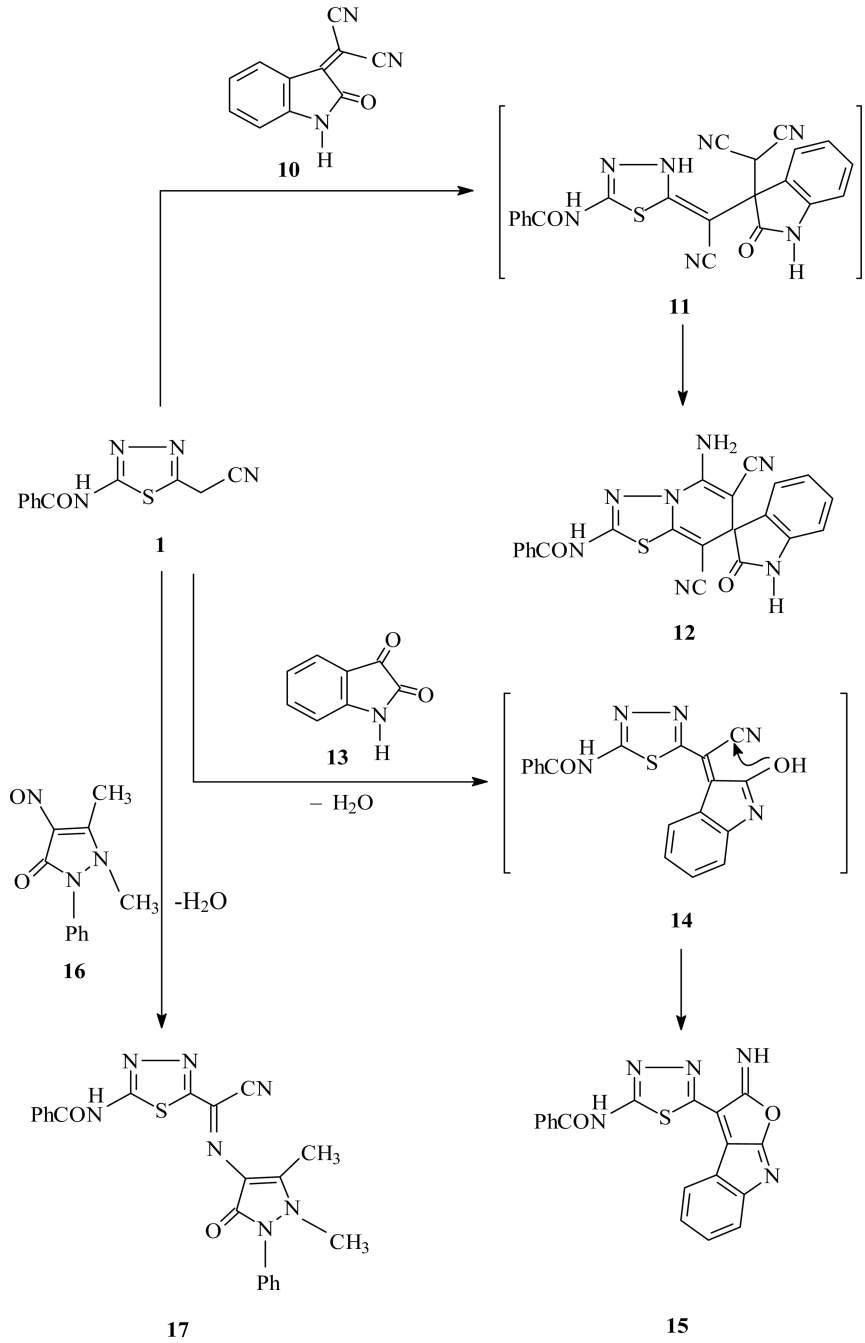
The cyclocondensation of compound **1** with ketenedithioacetal **25** resulted in the formation of a product with thiomethanol elimination. Thiadiadiazol[3,2-*a*]pyridine **28** was suggested as a reaction product. Structure **28** was supported from its IR spectrum and elemental analysis. The formation of **28** was suggested to be found *via* the addition of the active methylene group in **1** to give the adduct **26**. The latter eliminated thiomethanol to give the intermediate **27**, which cyclized to **28** (Scheme 4).

Also, compound **1** reacted with cyanothioformanilide (**29**) in ethanol catalyzed by piperidine to yield **31**. The IR spectrum of **31** showed the presence of an amino group and the absence of cyano functions. Compound **31** was thought to be formed *via* the sequence demonstrated in Scheme 4.

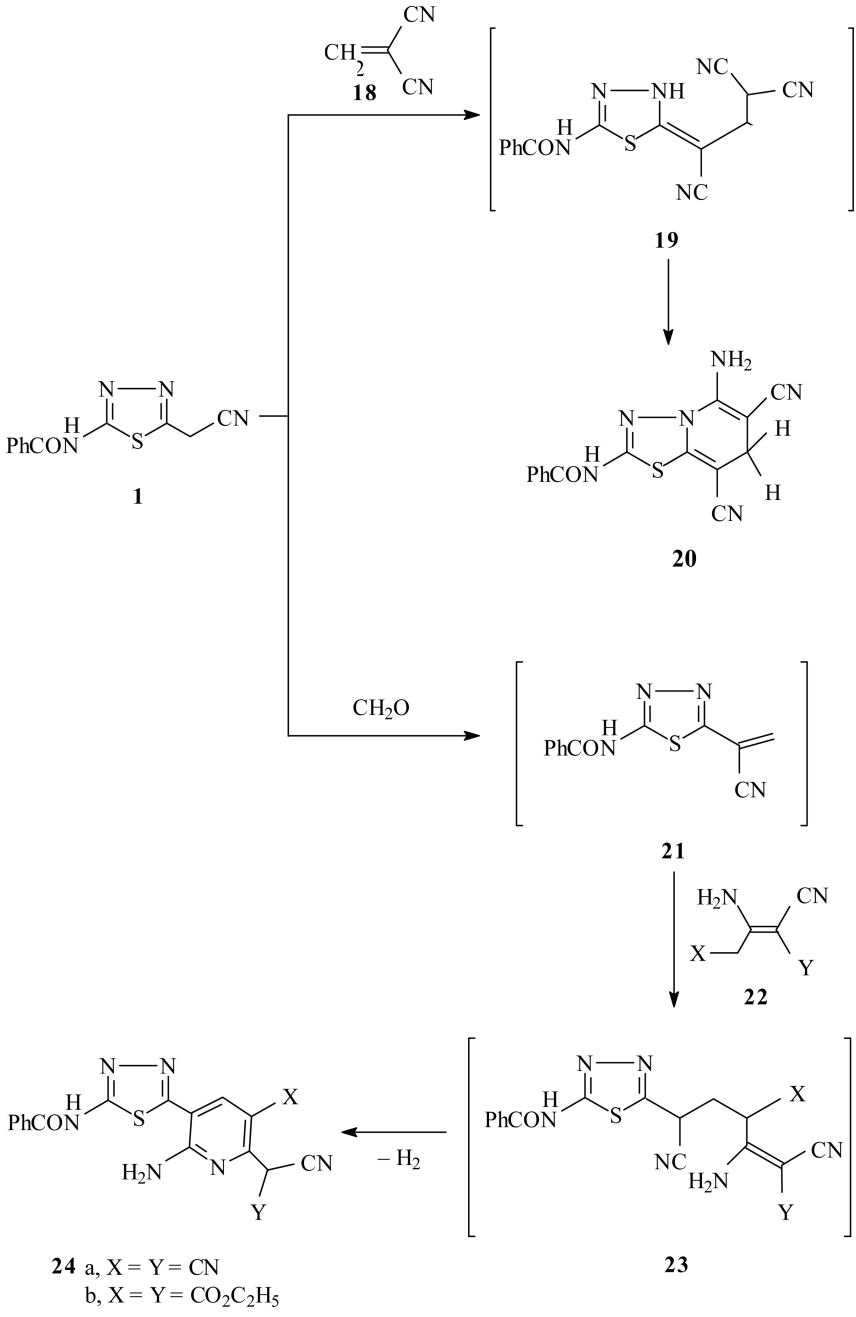
N-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide (**1**) reacted with mercaptoacetic acid (**32**) in dry pyridine to give **33**. This compound reacted readily with the arylidenemalononitriles **2a,b** in refluxing dry pyridine to yield (1:1) adducts. Acyclic structures **34** were ruled out by an ^{1}H NMR spectrum of **35**, which revealed in addition to the aromatic protons, the presence of a signal at $\delta = 3.96$ ppm for the CH_2 group and a signal at $\delta = 4.64$ ppm for pyran H-4. Thus, pyrano[2,3-*d*]thiazole structure **35** was established as reaction products. The formation of **35** was proposed to proceed *via* the Michael type addition of the active methylene group in the thiazole derivatives **33** to the activated double bond in **2a,b** to give Michael adducts **34**, which readily cyclized to yield **35**.

Also, compound **33** reacted with ethyl arylidenecyanoacetate (**2f**) in refluxing dry pyridine to yield **37** rather **38** as established by the IR spectrum, which showed an absorption band at $\upsilon = 2219$ cm^{-1} corresponding to the cyano group (Scheme 5).

Recently, it has been reported that enaminonitriles were extensively used as starting material for the synthesis of a variety of heteroaromatic systems.[36,38–47] In continuation to our studies on the chemistry of enaminonitriles, the utility of compound **1** as a starting component for the synthesis of 1,3,4-thiadiazolopyridines is reported. Thus, the

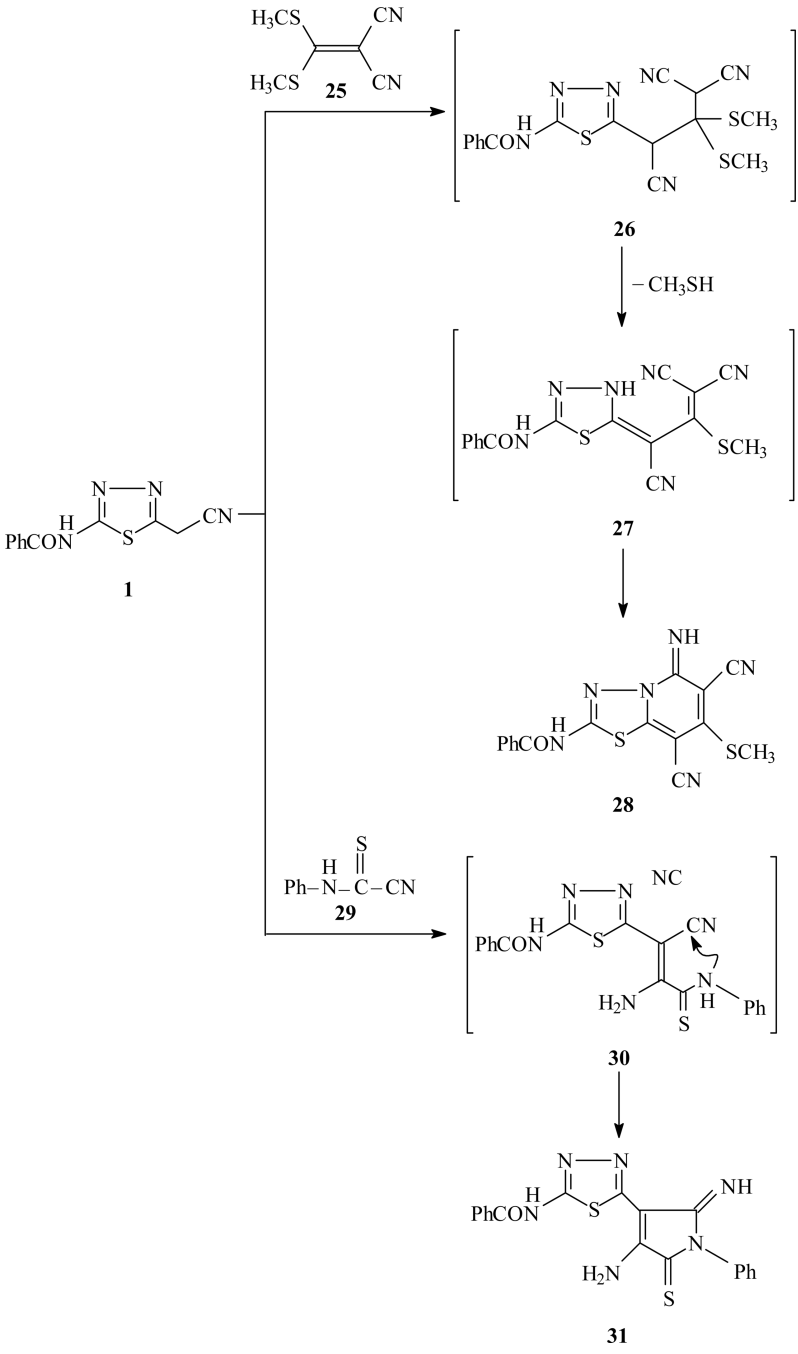


SCHEME 2

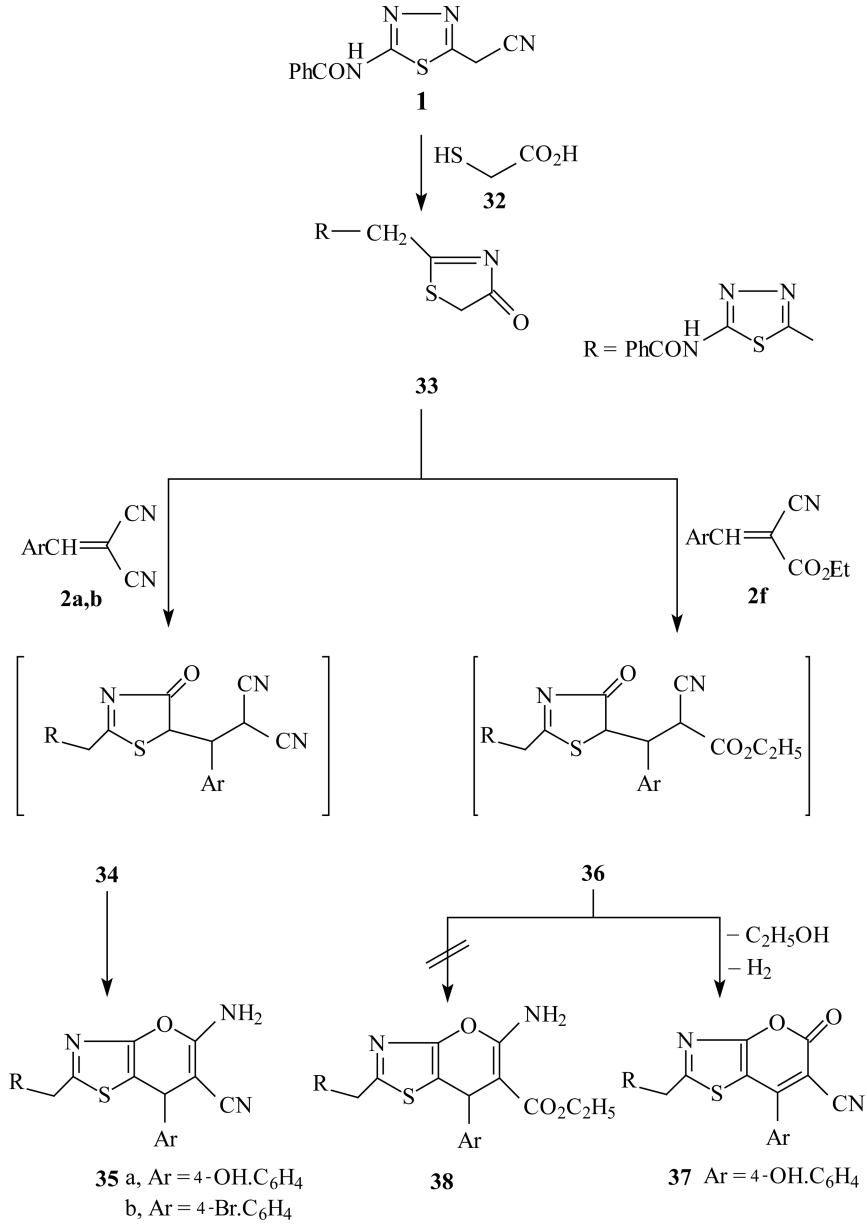


24 a, X = Y = CN
b, X = Y = $CO_2C_2H_5$

SCHEME 3



SCHEME 4



SCHEME 5

treatment of **1** with dimethylformamidedimethylacetal (DMFDMA) in dry xylene at a reflux temperature yielded the propenonitrile **39**. Structure **39** was supported from its ^{1}H-NMR and mass spectra (cf. Experimental section).

The reactivity of **39** toward active hydrogen reagents was investigated. For example, reacting compound **39** with benzoylaminoacetic acid **40** in dry acetic anhydride at a reflux temperature afforded a product *via* dimethylamine and water elimination and furnished a sole product identified as **42**. IR, ^{1}H-NMR, and mass spectra are compatible with structure **42**. This compound is suggested to be formed *via* an initial addition of the active methylene in benzoylaminoacetic acid **40** to the activated double bond in **39** to give the intermediate **41**, which readily cyclized to yield **42**. Compound **42** was also prepared *via* reacting **1** with methyl 2-benzoylamino-3-(*N*, *N*-dimethylamino)propenoate (**43**) *via* dimethylamine and methanol elimination, as shown in Scheme 6.

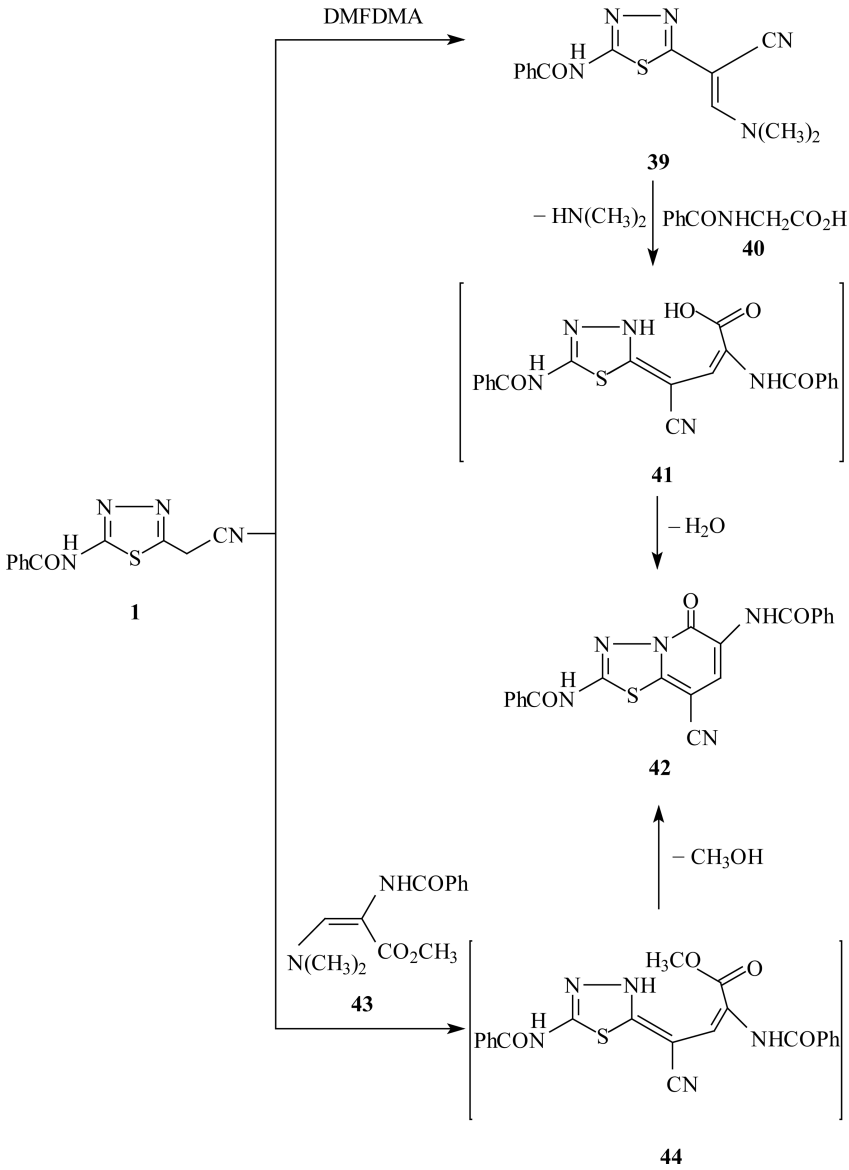
The reactivity of compound **1** toward 2-arylazopropane dinitriles (**45**) and **51** was also studied. Thus, compound **1** was subjected to react with **45** in ethanol containing a few drops of piperidine to give **47**. IR and elemental analysis were compatible with structure **47**. Compound **47** was formed through the first addition of the active methylene group in **1** to the cyano group in **45** to give the intermediate **46**. The later were cyclized into **47a**,**b**.

The coupling of **1** with arylidenediazonium chlorides gave the arylhydrazones **48**. Trials to prepare **47** by reacting **48** and malononitriles resulted in the formation of pyridazine **50**. Compound **50** was supported to be formed *via* the addition of the active methylene group in **3a** to give the intermediates **49**. They were cyclized to **50a**,**b** (Scheme 7).

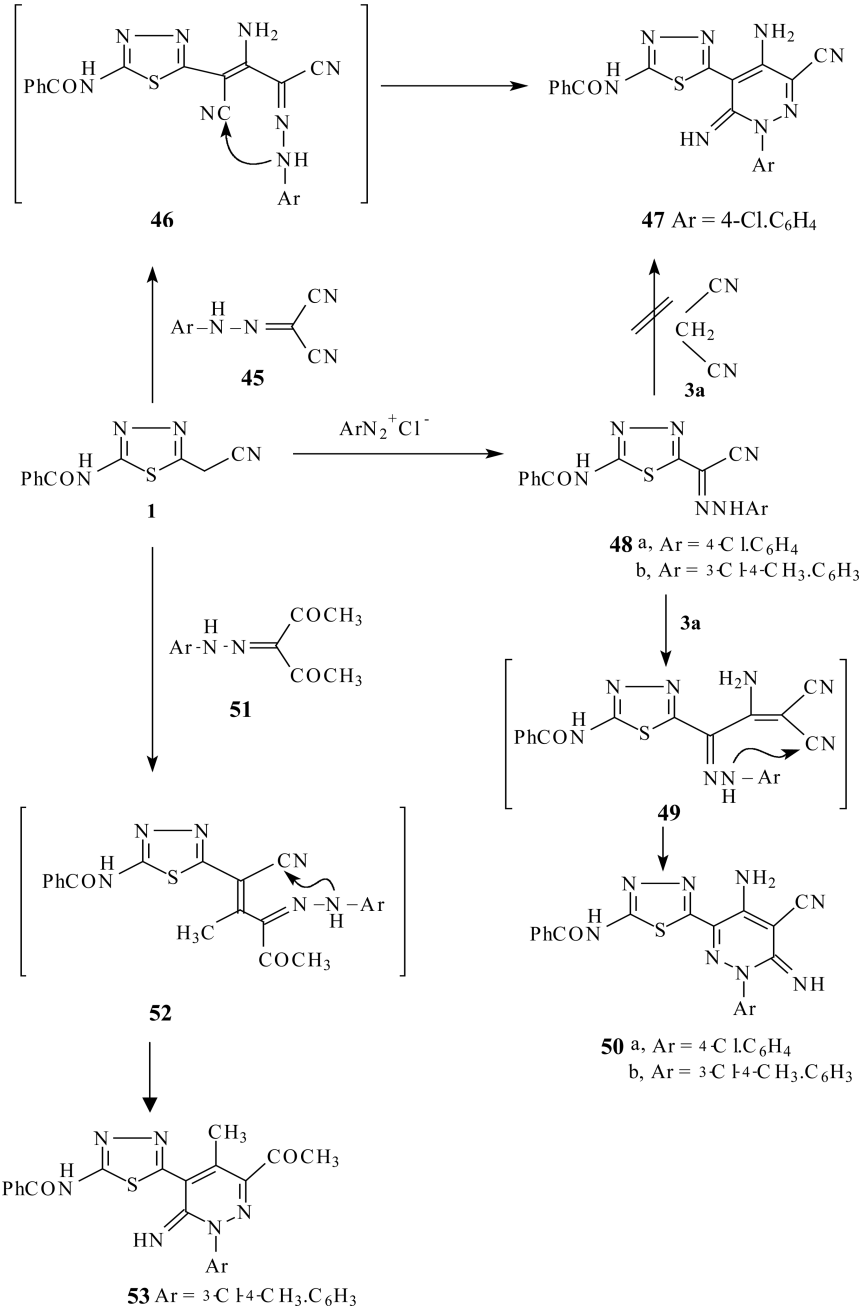
On the other hand, reacting **1** with 3-(3-chloro-4-methylphenylazo)pentan-2,4-dione (**51**) in ethanol and piperidine as a catalyst to yield a product for which structure **53** was established as a reaction product based on IR spectrum, which clearly exihited the presence signals at 3448 cm^{-1} for NH, 1672 cm^{-1} for CO acetyl, and 1654 cm^{-1} for amidic carbonyl. Compound **53** was proposed to be obtained *via* the first condensation of the ketonic carbonyl group in **51** with the active methylene in **1** to give the intermediate **52**, which cyclized to yield **53** (Scheme 7).

BIOLOGICAL ACTIVITIES

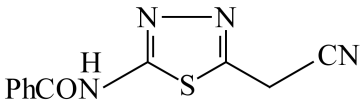
Generally, thiadiazole derivatives have been reported to be biologically versatile compounds as bactericidal, fungicidal, herbicidal, analgesic, and antifungitoxic activity.[48–50]



SCHEME 6



SCHEME 7



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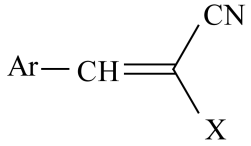
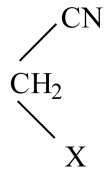


2 a, Ar = 4-OH·C_6H_4, X = CN
b, Ar = 4-Br·C_6H_4, X = CN
c, Ar = 3-OH·4-OCH_3·C_6H_3, X = CN
d, Ar = 5-bromo-2-thienyl, X = CN
e, Ar = 4-OH C_6H_4, X = $CONH_2$
f, Ar = 4-OH C_6H_4, X = $CO_2C_2H_5$



3 a, X = CN
b, X = $CONH_2$

FIGURE 1

MATERIALS AND METHODS

The antimicrobial activities of the novel 1,3,4-thiadiazole derivatives compounds were tested against Gram positive bacterium (*Bacillus Cereus*), Gram negative bacterium (*Escherichia Coli*), and two fungi (*Aspergillus Niger* and *Aspergillus Flavus*). 0.2–0.3 mL of about 1,000 μg mL^{-1} of the different novel 1,3,4-thiadiazole derivatives. Compounds were taken and transferred to a core (10 mm) made in the plate previously inoculated by the tested organisms.

TABLE I Antimicrobial Activities of Some Novel 1,3,4-Thiadiazole Derivatives

Compounds	Tested Organisms			
	E. Coli	*B. Cereus*	*A. Niger*	*A. Flavues*
6c	+	−	−	−
6d	−	+	−	−
9	−	+	−	−
15	+	−	−	−
17	−	+	+	+
20	−	+	−	−
24b	−	−	+	−
35a	−	−	+	+
35b	−	+	−	−
37	−	+	−	−
42	−	+	−	+

−, inactive, +, active.

Bacterial test organisms were grown on nutrient agar while fungi were grown on Dox agar (pH = 7.2), respectively, and incubated at 28–30°C.

Inhibition zones of the test organisms were measured after 24 h for bacteria and 48 h for fungi.

RESULTS

Eleven compounds (**6c**, **6d**, **9**, **15**, **17**, **20**, **24b**, **35a**, **35b**, **37,** and **42**) were tested for antimicrobial activity against two bacterial strains of Gram negative bacterium and Gram-positive bacterium (e.g., *Escherichia Coli* and *Bacillus Cereus* respectively) and two fungal strains of *Aspergillus Niger* and *Aspergillus Flavus*.

All tested products have antimicrobial activities either against the tested bacteria or the fungi (Table I).

Only two compounds (**6c**, **15**) have antimicrobial activity against *Escherichia Coli*, while seven compounds (**6d**, **9**, **17**, **20**, **35b**, **37,** and **42**) have antimicrobial activity against *Bacillus Cereus*.

On the other hand, three compounds (**17**, **35a** and **42**) showed antimicrobial activity against *Aspergillus Flavus* while three compounds (**17**, **24b**, and **35a**) exhibited antimicrobail activity against *Aspergillus Niger*.

CONCLUSION

It has been found that compounds **17**, **35a**, and **42** are highly active against two bacterial strains of Gram negative bacterium and Gram-positive bacterium (e.g., *Escherichia Coli* and *Bacillus Cereus,*

TABLE I Analytical Data and Physical Characteristics of Novel Compounds

No.	Molecular formula (M. wt.)	M.P. (°C)	Recryst. solvent	Color	Yield (%)	Element analysis (found)		
						C	H	N
6a	$C_{21}H_{12}N_6SO_4$ (412.42)	>300	1,4-Dioxane	Brown	78	61.16 (61.43)	2.90 (3.10)	20.38 (20.33)
6b	$C_{22}H_{14}N_6SO_3$ (442.45)	>300	1,4-Dioxane/DMF	Yellow	75	59.72 (59.67)	3.19 (3.32)	18.99 (18.85)
6c	$C_{19}H_9BrN_6S_2O$ (481.35)	>300	EtOH/DMF	Yellow	75	47.41 (48.00)	1.88 (1.93)	17.46 (17.71)
8	$C_{21}H_{11}N_5SO_3$ (413.41)	>300	EtOH/DMF	Yellow	82	61.01 (61.21)	2.68 (2.56)	16.94 (16.83)
9	$C_{18}H_{12}N_4SO_4$ (348.38)	>300	1,4-Dioxane	Orange	80	62.05 (61.99)	3.47 (4.01)	16.08 (16.31)
12	$C_{22}H_{13}N_7SO_2$ (439.46)	>300	1,4-Dioxane	Red	88	60.13 (60.20)	2.98 (2.89)	22.31 (22.41)
15	$C_{19}H_{11}N_5O_2S$ (373.39) ($M^+ = 373$)	>300	EtOH/DMF	Brown	71	61.12 (60.49)	2.97 (3.15)	18.76 (18.67)
17	$C_{22}H_{17}N_7SO_2$ (462.50)	>300	EtOH/DMF	Red	60	57.13 (57.33)	3.70 (3.81)	21.10 (21.00)
20	$C_{15}H_{10}N_6SO$ (322.35)	>300	1,4-Dioxane	Red	65	55.89 (55.85)	3.13 (3.22)	26.07 (26.13)
24a	$C_{18}H_{10}N_8SO$ (386.39)	>300	1,4-Dioxane/DMF	Orange	82	55.95 (55.91)	2.61 (2.59)	29.00 (28.85)
24b	$C_{22}H_{22}N_6SO_5$ (480.50)	>300	1,4-Dioxane/DMF	Deep red	87	54.99 (54.97)	4.20 (4.00)	17.49 (17.51)
28	$C_{16}H_{10}N_6S_2O$ (366.42)	270–272	EtOH/DMF	Yellow	76	52.44 (52.36)	2.72 (3.01)	22.90 (22.83)
31	$C_{19}H_{14}N_6S_2O$ (406.49)	>300	EtOH	Brown	66	56.14 (56.19)	3.47 (4.01)	20.67 (20.73)
35a	$C_{23}H_{16}S_2O_3$ (488.54)	>300	1,4-Dioxane	Yellow	88	56.33 (56.62)	3.30 (3.37)	17.20 (17.11)
35b	$C_{23}H_{15}BrN_6O_2S_2$ (551.45)	>300	DMF	Yellow	77	50.09 (50.15)	2.74 (2.67)	15.24 (15.11)
37	$C_{23}H_{13}N_5S_2O_4$ (487.51)	>300	DMF	Brown	87	56.66 (56.73)	2.69 (2.81)	14.37 (14.23)
39	$C_{14}H_{13}N_5SO$ (299.35) ($M^+ = 299$)	>300	EtOH	Yellow	65	56.17 (65.00)	4.30 (4.10)	23.34 (23.21)
42	$C_{21}H_{13}N_5SO_3$ (416) ($M^+ = 416$)	280–282	EtOH/1,4-Dioxane	Colorless	65	60.71 (60.34)	3.15 (3.00)	16.86 (16.45)
47	$C_{20}H_{13}ClN_8SO$ (448.89)	252–254	1,4-Dioxane	Brown	82	53.52 (53.60)	2.92 (3.12)	24.96 (24.91)
48a	$C_{17}H_{11}ClN_6SO$ (382.83)	190–192	1,4-Dioxane/H_2O	Yellow	71	53.34 (53.50)	2.90 (3.21)	21.95 (21.87)
48b	$C_{18}H_{13}ClN_6SO$ (397.00)	198–200	1,4-dioxane/H_2O	Yellow	65	54.45 (54.59)	3.30 (3.51)	21.16 (20.96)
50a	$C_{20}H_{13}ClN_8SO$ (448.06)	248–250	1,4-Dioxane/H_2O	Brown	60	53.52 (53.42)	2.92 (3.11)	24.96 (24.85)
50b	$C_{21}H_{15}ClN_8SO$ (462.08)	250–252	1,4-Dioxane	Brown	65	54.49 (54.61)	3.27 (3.41)	24.21 (24.11)
53	$C_{23}H_{19}ClN_6O_2S$ (478.96)	>300	1,4-Dioxane	Yellow	71	57.67 (57.71)	3.99 (4.11)	17.54 (17.43)

TABLE II Spectral Data of Newly Synthesized Compounds

Compound No.	IR (cm^{-1})	^1H NMR (δH)
6a	3367, 3132 (OH, NH), 2220 (conjugated CN), 1669 (CO amide)	Insoluble in commonly used ^1H NMR solvents
6b	3526 (OH), 2924 (NH), 2220 (conjugated CN), 1644 (CO)	3.86 (3H, OCH_3), 6.96–8.17 (9H, 8H, aromatic and 1H, NH), 10.28 (IH, NH), 13.32 (1H, OH)
6c	3447 (NH), 2220 (conjugated CN), 1622 (CO)	7.46–8.12 (8H, 7H aromatic and 1H, NH), 8.47 (1H, NH)
8	3667 (OH), 3367 (NH), 2230 (conjugated CN), 1672, 1627 (CO)	6.92–8.13 (10H, 9H, aromatic and 1NH), 10.57 (1H, OH)
9	3156, 3130 (OH, NH), 2202 (conjugated CN), 1668 (amide CO)	6.9–8.2 (m, 10H, 9H aromatic and 1H ylidenic proton), 10.6 (1H, NH), 13.3 (1H, OH)
12	3460, 3400 (NH_2,NH), 2230 (conjugated CN), 1709, 1660 (CO)	6.96–8.32 (10H, aromatic and 1NH), 13.55 (s, 2H, NH_2), 11.30 (s, 1H, NH)
15	3195 (NH), 1705 (CO), 1614 (C═NH)	Insoluble in commonly used ^1H—NMR solvents
17	3310 (NH), 2208 (conjugated CN), 1660 (CO, antipyrinyl), 1654 (CO, amidic)	2.4 (s, 3H, CH_3), 3.3 (s, 3H, N—CH_3), 7.3–8.2 (m, 10H aromatic), 3.3 (s, 1H, NH)
20	3306 (NH), 2230 (conjugated CN), 1636, 1616 (CO)	3.8 (s, 2H, pyridine H-4), 7.49–8.77 (7H, 5H aromatic and 2H, NH_2), 9.8 (1H, NH)
24a	3462–3160 (NH_2,NH), 2260–2198 (3 CN conjugated and unconjugated CN), 1654 (CO)	4.63 (s, 1H, CH), 7.51–8.11 (m, 7H, 6H, aromatic and 1H, NH), 13.16 (br, 2H, NH_2)
24b	3460–3158 (NH_2,NH), 1720 (CO, ester), 1660 (CO, amide)	1.05 (t, 3H, CH_3), 1.3 (t, 3H, CH_3), 2.8–3.3 (m, 4H, two CH_2), 5.2 (s, 1H, CH), 7.53–8.18 (m, 7H, 6H, aromatic and 1H, NH), 8.9 (s, 2H, NH_2)
28	3650–3220 (NH), 2202, 2195 (two conjugated CN), 1654 (CO)	Insoluble in commonly used ^1H—NMR solvents
31	3478–3218 (NH_2,NH), 1668 (CO, amide), 1600 (C═S)	7.45-8.21 (m, 12H, 10 aromatic and 2H, 2NH), 13.09 (br, 2H, NH_2)
35a	3440–3341 (NH_2, NH), 3199 (OH), 2195 (conjugated CN), 1686 (CO)	3.96 (s, 2H, CH_2) 4.64 (s, 1H, pyran H-4), 6.36–8.13 (m, 9H, aromatic), 10.32 (s, 1H, NH), 11.43 (s, 1H, OH), 12.92 (br, 2H, NH_2)
35b	3420–3370 (NH_2), 3159 (NH), 3193 (conjugated CN), 1680 (CO)	Insoluble in commonly used ^1H-NMR solvents
37	3225–3150 (OH), 2219 (conjugated CN), 1720 (CO), 1664 (CO)	3.95 (s, 2H, CH_2), 6.94–8.61 (m, 10H, 9H, aromatic and 1H, OH), 10.76 (br, 1H, NH)
39	3149 (NH), 2181 (conjugated CN), 1666 (CO)	3.2 (s, 3H, CH_3), 3.3 (s, 3H, CH_3), 7.4–8.2 (m, 6H, aromatic), 12.91 (s, 1H, NH)
42	3390–3212 (NH), 2219 (conjugated CN), 1673 (CO), 1637 (CO)	Insoluble in commonly used ^1H—NMR solvents
47	3400–3200 (NH_2, NH), 1700 (CO), 1650 (CO amidic)	3.36 (s, 2H, NH_2), 3.55 (s, 1H, NH), 7.32–7.50 (m, 9H, aromatic), 7.67 (s, 1H, NH).
48a	3398, 3165 (NH), 2215 (conjugated CN), 1668 (CO)	Insoluble in commonly used ^1H—NMR solvents
48b	3422, 3163 (NH), 2215 (conjugated CN), 1669 (CO)	2.37 (s, 3H, CH_3), 4.62 (s, 1H, NH) 7.29–8.15 (m, 9H, aromatic and NH)
50a	3400, 3395 (NH_2, NH); 2195 (conjugated CN); 1650 (CO)	Insoluble in commonly used ^1H—NMR solvents
50b	3400, 3381 (NH_2, NH), 2197 (conjugated CN), 1670 (CO)	2.97 (s, 3H, CH_3), 3.37 (s, 2H, NH_2), 7.42–8.00 (m, 9H, aromatic and NH), 8.12 (s, 1H, NH)
53	3420, 3480, 3448 (NH, C═NH), 1718, 1676 (CO)	2.41 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), 7.39–7.62 (m, 9H, aromatic and 1NH), 13.85 (s, 1H, NH)

respectively) and two fungal strains *Aspergillus Niger* and *Aspergillus Flavus,* in comparison to other synthesized derivatives.

The activity may be attributed to the presence of antipyrinyl, bromide, and bifunctional benzamide groups attached to the thiadiazolyl rings.

EXPERIMENTAL

All melting points are uncorrected and were measured on Griffin & George MBF 010T (London) apparatus. Recorded yields correspond to the pure products. IR (KBr) spectra were recorded on a perkin Elmer SP-880 spectrophotometer, and ^{1}H-NMR spectra were measured on a Varian 270 MHz spectrometer in DMSO-d_6 as a solvent and TMS as an internal standard (Chemical shifts are reported in δ units ppm.). Mass spectra were measured on GS/MS INCOL XL finningan MAT. Microanalysis was performed on a LECOCHN-932 and carried out in the Microanalytical Data Units at Cairo and Mansoura Universities.

N-(6,8-Dicyano-7-aryl-5-imino-5*H*-[1,3,4]thiadiazolo [3,2-*a*]pyridin-2-yl)benzamides (6a–c)

Method A

*From **1** and cinnamonitriles, preparation of (**6a–c**).* Equimolecular amounts of **1** (2.44 g, 10 mmoles) and the appropriate cinnamonitriles **2a–c** were refluxed in absolute ethanol (50 mL) and in the presence of piperidine (0.1 mL) for 3 h. The solid products so formed were filtered, recrystallized, and identified as **6a–c**.

Method B

*From **2a**,**b** and malononitrile, preparation of (**6a**,**b**).* To a suspension of **2a**,**b** (10 mmoles) and malononitrile (0.66 g, 10 mmoles) in ethanol (50 mL) containing a catalytic amount of piperidine, 0.1 mL was added. The reaction mixture was refluxed for 5 h. The product so formed was collected by filtration and recrystallized, and compounds **6a**,**b** formed by this method were found identical (m.p., mixed m.p., and IR) with those obtained by Method A.

N-(6,8-Dicyano-7-(4-hydroxyphenyl)-5-oxo-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridin-2-yl]benzamide (8)

Method A

*From **1** and cinnamonitrile **2**, the preparation of (**8**).* Equimolecular amounts of **1** (2.44 g, 10 mmoles) and the appropriate cinnamonitrile

2e (1.88 g, 10 mmoles) were refluxed in absolute ethanol (50 mL) in the presence of piperidine (0.1 mL) for 3 h. The solid products so formed were filtered, recrystallized, and identified as **8**.

Method B

*From **9a** and cyanoacetamide **3b**, the preparation of (**8**).* To a suspension of **9** (3.49 g, 10 mmoles) and cyanoacetamide **3b** (0.84 g, 10 mmoles) in ethanol (50 mL), a catalytic amount of piperidine (0.1 mL) was added. The reaction mixture was refluxed for 5 h. The product so formed was collected by filtration, recrystallized, and identified as **8**.

Method C

A suspension of **6a** (4.13 g, 10 mmoles) in glacial acetic acid was refluxed for 2 h. The solvent was removed invacuo, and the remaining residue was dissolved in hot ethanol. The solid product obtained was collected by filtration, recryalized, and identified as **8**.

N-[5-(1-Cyano-2-(4-hydroxyphenyl)vinyl-1,3,4-thiadiazol-2-yl]benzamides (9)

Compound **1** (2.44 g, 10 mmoles) in ethanol (50 mL) was treated with ρ-hydroxybenzaldehyde (1.22 g, 10 mmoles) and a few drops of piperidine. The mixture was refluxed for 2 h, and then the solvent was concentrated and allowed to stand at r.t. for *ca*. 12 h. The product was collected by filtration and purified by recrystalization from the proper solvents and identified as (**9**).

The Preparation of *N*-[5-Amino-6,8-dicyano-7-((1,3-dihydro-2*H*-indol-2-on)spiro)-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridin-2-yl]benzamide (12)

To a mixture of **1** (2.44 g, 10 mmoles) and 2-(2-oxoindolin-3-ylidene) malononitrile (**10**) (1.95 g, 10 mmoles) in ethanol (50 mL), few drops of piperidine were added. The reaction mixture was refluxed for 4 h and cooled, and the formed precipitate was collected by filtration and recrystallized.

N-(5-(2-Imino-2*H*-furo[2,3-*b*]indol-3-yl)-1,3,4-thiadiazol-2-yl)benz-amide (15)

To a mixture of (2.44 g, 10 mmoles) **1** and (1.47 g, 10 mmoles) of 2,3-indolinedione (**13**) in ethanol (50 mL), a catalytic amount of piperidine

(0.2 mL) was added. The reaction mixture was refluxed for 2 h, and the solid product deposited was filtered off and recrystallized.

The Preparation of*N*-(5-(2,5-Dihydro-2,3-dimethyl-5-oxo-1-phenyl-1*H*-pyarazol-4-ylimino)(cyano)methyl)1,3,4-thiadiazol-2-yl)benzamide (17)

A suspension of **1** (2.44 g, 10 mmoles) and 1,2-dihydro-2,3-dimethyl-4-nitroso-1-phenylpyrazol-5-one (**16**) (2.17 g, 10 mmoles) in ethanol (50 mL) containing 2 drops of piperidine was refluxed for 30 min. The precipitate formed was collected by filtration and recrystallized.

The Preparation of*N*-(5-Amino-6,8-dicyano–7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridin-2-yl)benzamide (20)

To a suspension of **1** (2.44 g, 10 mmoles), malononitrile (0.66 g, 10 mmoles) and formaldehyde 40% (0.9 g, 30 mmoles) in ethanol (50 mL), a catalytic amount of piperidine (0.1 mL) was added. The reaction mixture was refluxed for 5 h, and the products, so formed, were collected by filtration, recrystallized, and identified as **20**.

The Preparation of*N*-(5-(2-Amino-5-cyano-6-(dicyanomethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)benzamide (24a) and ethyl 2-(ethoxycarbonyl) (cyano)methyl)-6-amino-5-(5-(benzamido)-1,3,4-thiadiazol-2-yl) pyridine-3-carboxylate (24b)

A mixture of 2-amino-1,1,3-tricyanopropene (**22a**) (1.32 g, 10 mmoles) or diethyl 2-amino-1-cyanopropene-1,3-dicarboxylate (**22b**) (2.26 g, 10 mmoles), **1** (2.44 g, 10 mmoles), and formaldehyde 40% (0.9 g, 30 mmoles) in ethanol (30 mL) containing 0.1 mL of piperidine was heated under refluxed for 5 h. The products, so formed, were collected by filtration, recrystallized, and identified as **24a**,**b**.

N-(6,8-Dicyano-5-imino-7-(methythio)-5*H*-[1,3,4]thiadiazolo[3,2-*a*] pyridin-2-yl)benzamide (28)

A mixture of [bis(methylsulfonyl)methylene]malononitrile (**25**) (1.70 g, 10 mmoles) and **1** (2.44 g, 10 mmoles) in ethanol (50 mL) and a catalytic

amount (0.1 mL) of piperidine was refluxed for 3 h. The formed solid was collected by filtration and recrystallized.

N-(5-(4-Amino-2,5-dihydro-2-imino-1-phenyl-5-thioxo-1*H*-pyrrol-3-yl)-1,3,4-thiadiazol-2-yl)benzamide (31)

To a suspension of **1** (2.44 g, 10 mmoles) in ethanol (50 mL) were added (1.62 g, 10 mmoles) 1-cyanothioformanilide (**29**) and (0.1 mL) triethylamine. The reaction mixture was heated at a reflux temperature for 2 h, and the product obtained was filtered and recrystallized.

The General procedure for the preparation of *N*-(5-((5-Amino-6-cyano-7-(aryl)-7*H*-pyrano[2,3-*d*]thiazol-2-yl)methyl-1,3,4-thiadiazol-2-yl)benz-amide (35a,b) and *N*-(5-(6-cyano-7-(4-hydroxyphenyl)5-oxo-5*H*-pyrano [2,3-*d*]thiazol-2-yl)methyl-1,3,4-thiadiazol-2-yl)benzamide (37)

Equimolecular amounts (3.0 g, 10 mmoles) of **33** with the appropriate cinnamonitrile **2a**,**b** (10 mmoles) were refluxed in dry pyridine (30 mL) for 3 h. The solvent was removed in vacuo, and the product was triturated with ethanol. The solid products so formed were washed several times with ethanol and then recrystallized and identified as **35a**,**b** and **37**, respectively.

The Preparation of 2-(5-Benzoylamino-1,3,4-thiadiazol-2-yl)-1-(*N,N*-diamino)propenonitrile (39)

Dimethylformamide dimethylacetal (1.19 g, 10 mmoles) was added to **1** (2.44 g, 10 mmoles) in dry xylene (50 mL), and the reaction mixture was refluxed for 6 h. The removal of solvent under reduced pressure yielded the crude product, which was recrystallized.

The Preparation of *N*-(8-Cyano-6-benzoylamino-5-oxo-5*H*-[1,3,4]thiadia-zolo[3,2-*a*]pyridin-2-yl)benzamide (42)

A mixture of **1** (2.44 g, 10 mmoles) and methyl β-(*N*, *N*-dimethylamino)-α-benzoylaminopropenoate (**43**) (2.48 g, 10 mmoles) in glacial acetic acid were refluxed for 6 h, then the solvent was concentrated to its half volume and then left to cool to r.t. The precipitate was collected by filtration and recrystallized.

The General procedure for the preparation of *N*-(5-(5-Amino-2-(aryl)-6-cyano-2,3-dihydro-3-imino-pyridazin-4-yl)-1,3,4-thiadiazol-2-yl)benzamide (47a,b) and *N*-(5-(2-(3-chloro-4-methylphenyl)-6-acetyl-2,3-dihydro-3-imino-5-methylpyridazin-4-yl)-1,3,4-thiadia-zol-2-yl)benzamide (53)

A solution of **1** (2.44 g, 10 mmoles) in ethanol (50 mL) was treated with **45** or **51** (0.01 mol) and a few drops of piperidine. The reaction mixture was reflux for 3 h and then left to cool to r. t. The solids formed were collected by filtration, recrystallized, and identified **47a,b** and **53,** respectively.

The Preparation of *N*-5-[(Arylhydrazano)cyanomethyl]-2-ylbenzamide (48a,b)

To a well-stirred and cold solution of **1** (2.44 g, 10 mmoles) in ethanol (50 mL) containing sodium acetate trihydrate (2.5 g) was added diazonium salt soltution prepared from 10 mmoles of the hydrochloride salt of the amine used and sodium nitrite solution (0.7 g, in 20 H_2O) at such a rate that the temperature was kept below 5° C. After the complete addition, the mixture was stirred for 15 min and left overnight in a refrigerator. The crude product was filtered, washed with dilute cold ethanol, dried, and recrystallized as **48a,b**.

N-(5-(4-Amino-1-(aryl)-5-cyano-1,6-dihydro-6-imino-pyridazin-3-yl)-1, 3,4-thiadiazol-2-yl)benzamide (50a,b)

A solution of **48** (10 mmoles) in ethanol (50 mL) was treated with **3a** (0.66 g, 10 mmoles) and few drops of piperidine. The reaction mixture was reflux for 3 h and then left to cool to r.t. The solid formed was collected by filtration, recrystallized, and identified as (**50a**,**b**).

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