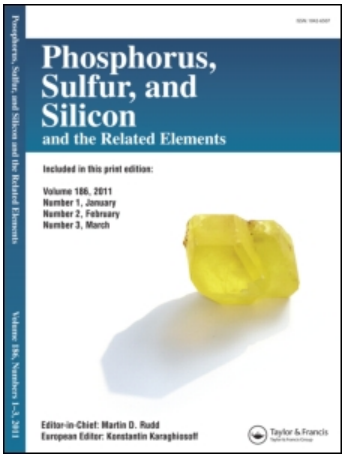


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# Uses of 1-Cyanoacetyl-4-phenyl-3-thiosemicarbazide in Heterocyclic Synthesis: Synthesis of Thiazole, Coumarin, and Pyridine Derivatives with Antimicrobial and Antifungal Activities

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# Uses of 1-Cyanoacetyl-4-phenyl-3-thiosemicarbazide in Heterocyclic Synthesis: Synthesis of Thiazole, Coumarin, and Pyridine Derivatives with Antimicrobial and Antifungal Activities

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*The reaction of cyanoacetyl hydrazine with phenylisothiocyanate gave the thiosemicarbazide **3**. The latter underwent a series of heterocyclization reactions when it reacts with either aromatic aldehydes or α-haloketones, follwed by further reaction of the products with cyanomethylene reagents or hydrazines to give either thiazole, coumarin, or pyridine derivatives. The newly synthesized product showed antimicrobial and antifungal activities.*

**Keywords** Coumarins; pyrazoles; pyridines; thiazoles

## INTRODUCTION

The cyclization of suitable linear compounds is one of the most common and popular methods for preparing heterocyclic compounds. Unsymmetrical ureas have been cyclized to produce several heterocycles such as 1,3,4-thiadiazoles, 1,2,4-triazoles, and 1,3,5-triazines.[1] 2,4-Disubstituted semicarbazones have been proposed as dipeptide

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isosteres[2] and could be a new class of urea peptide mimetics. The possible biological properties of semi- and thiosemicarbazone derivatives make it attractive to study the reactivity of these compounds. $\alpha$-Halocarbonyl compounds were allowed to react with alkyl- and arylidenephenylthiosemicarbazones to give 1,2,4-triazoline and 1,2,4-dithiazolidines.[3] 2,4-Disubstituted thiosemicarbazides were cyclized to 1,2,4-triazoline-3-thiones and 1,3,4-thiadiazolines when treated with acyl isothiocyanates.[4] Oxidative cyclization of substituted aldehyde-thiosemicarbazones, induced by different metallic salts, led to 1,2,4-triazoline derivatives.[5–9] On the other hand, the interaction of thiosemicarbazide and dithiocarbazate derivatives with some $\pi$-acceptors such as propanedinitrile, and benzoquinone as well as naphthoquinone affords thiazines, thiadiazines, thiadiazoles, indazoles, pyridazines, oxathiadiazoles, and various fused heterocyclic compounds possible via a single electron transfer before the ring closure step.[10–14]



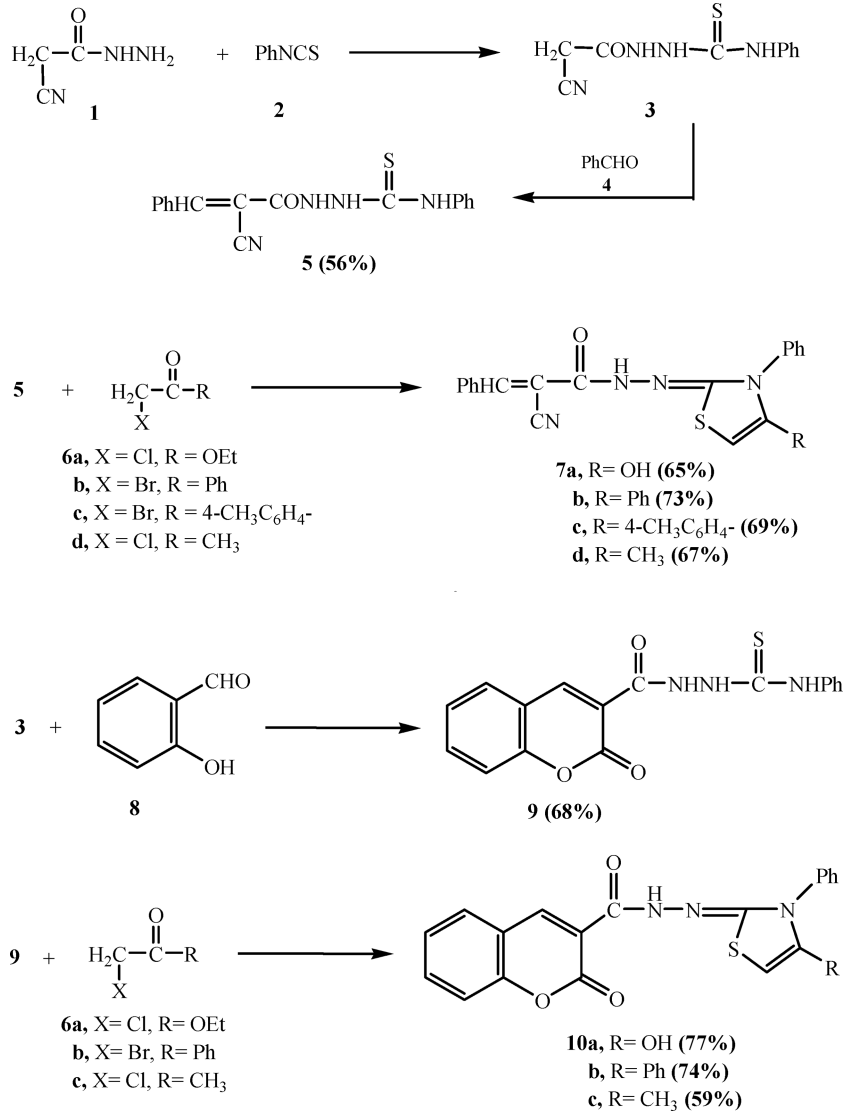
## RESULTS AND DISCUSSION

### Chemistry

We report here the results of our investigations on the reaction of cyanoacetylhydrazine **1** with phenylisothiocyanate (**2**) to give the 1-cyanoacetyl-4-phenylthiosemicarbazide derivative **3**. The reaction has been reported in literature.[15] We report here the uses of compound **3** in heterocyclic synthesis via exploring the scope and limitations of the functional groups present. Thus, the reaction of compound **3** with benzaldehyde (**4**) gave the benzal derivative **5**. Structure of the latter product was based on analytical and spectral data. Thus, $^1$H-NMR showed a singlet at $\delta$ 7.12 corresponding to CH group, a multiplet at $\delta$ 7.41–8.01 corresponding to two $C_6H_5$ groups, and three singlets at $\delta$ 9.76, 10.75, and 10.80 corresponding to three NH groups.

Compound **5** reacts with $\alpha$-haloketones (**6a–d**) to give the thiazole derivatives **7a–d**. The analytical and spectral data are consistent with the proposed structures. As an example, the $^1$H-NMR spectrum of **7a** showed two singlets at $\delta$ 5.77 and 6.25 corresponding to thiazole H-5 and CH=C groups, a multiplet at $\delta$ 6.85–7.83 corresponding to two $C_6H_5$ groups, two singlets at $\delta$ 9.98, 11.07 corresponding to NH and OH groups, respectively. Moreover, $^{13}$C NMR spectrum showed $\delta$ 58 (thiazole C-4), 116.8 (CN), 117.4, 119.5, 122.5, 124.3, 128.9, 129.5, 140.9, 143.2 (aromatic C), 167.5 (C=O), and 180.5 (thiazole C-5). On the other hand, the reaction of compound **3** with salicaldehyde **(8)** gave the coumarin derivative **9**. The reactivity of the latter product towards $\alpha$-halocarbonyl compounds was studied in the

aim of formation of coumarin bearing thiazolyl group with potential biological activities.[16–20] Thus, the reaction of **9** with either ethyl chloroacetate (**6a**), phenacyl bromide (**6b**) or chloroacetone (**6c**) gave the thiazole derivatives **10a–c** (Scheme 1). The reaction of compound **3** with 4-methylphenacyl bromide (**11**) in 1,4-dioxan solution afforded the



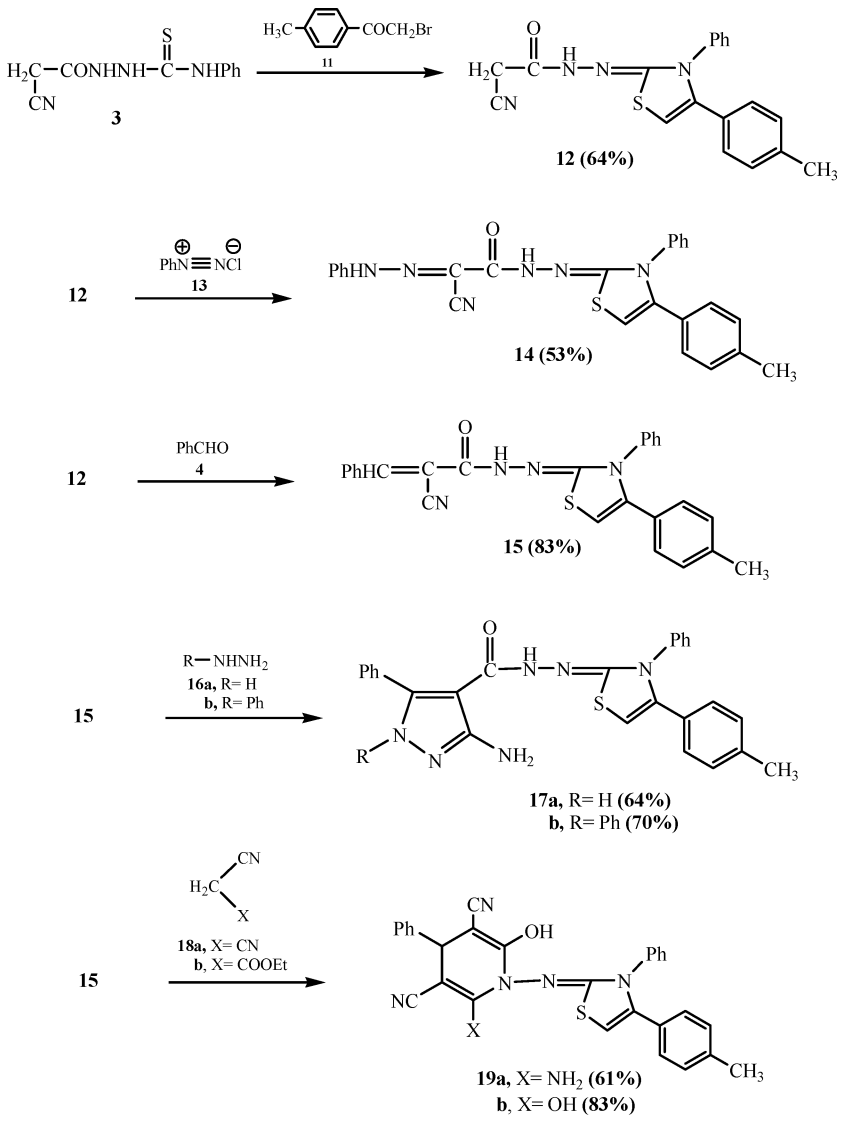

**SCHEME 1**

thiazole derivative **12**. The analytical and spectral data are in agreement with the proposed structure. Thus, $^{1}$H-NMR spectrum of the reaction product showed two singlets at $\delta$ 2.50, 3.80 corresponding to $CH_3$ and $CH_2$ groups, respectively, a singlet at $\delta$ 6.33 corresponding to thiazole H-5, a muliplet at $\delta$ 6.95–7.37 corresponding to $C_6H_5$ and $C_6H_4$, and a singlet at $\delta$ 10.22 Corresponding to NH group. Moreover, the $^{13}$C-NMR showed $\delta$ 25.8 ($CH_3$), 33.6 ($CH_2$), 115.8 (CN), 118.4, 119.5, 120.6, 123.7, 126.8, 129.1, 131.5, 138.2, 140.9 (aromatic C, thiazole C-5), 155.8 (C=N), and 170.9 (C=O).

Compound **12** showed high reactivity towards many chemical reagents. Thus, it reacts with benzenediazonium chloride (**13**) to give the phenylhydrazone derivative **14** for which the analytical and spectral data are in agreement with the proposed structure. On the other hand, with benzaldehyde (**4**), compound **12** gives the benzal derivative **15**. Compound **15** reacts with either hydrazine hydrate (**16a**) or phenylhydrazine (**16b**) to give the pyrazole derivatives **17a** and **17b**, respectively. The $^{1}$H-NMR and $^{13}$C-NMR spectra of **17a** are consistent with the proposed structure (see experimental section). The reaction took place via formation of amidrazone derivatives followed by Michael addition and auto-oxidation. Structures of compounds **17a**,**b** were confirmed on the basis of analytical and spectral data (see experimental section). On the other hand, compound **15** reacts with either malononitrile (**18a**) or ethyl cyanoacetate (**18b**) to give the pyridine derivatives **19a** and **19b**, respectively (Scheme 2). In case of the reaction of compound **15** with malononitrile, a Michael addition took place while in case of the reaction with ethyl cyanoacetate, ethanol liberation took place. Analytical and spectral data are the basis of structures elucidation. Moreover, the reaction of compound **12** with salicaldehyde (**8**) gave the coumarin derivative **20**.

The reaction of compound **12** with 1,3-dicarbonyl compounds was studied in the aim of formation of pyridine derivatives with potential biological activities.[21,22] Thus, it reacted with either acetylacetone (**21a**) or ethyl acetoacetate (**21b**) to give the pyridine derivatives **22a** and **22b**, respectively. Structures of the latter products were based on analytical and spectral data (see Experimental section). On the other hand, the reaction of compound **12** with either malononitrile (**18a**) or ethyl cyanoacetate (**18b**) gave the same pyridine derivative **23** (Scheme 3). The reaction took place via Michael-type addition and hydrolysis of imino group in case of the reaction with malononitrile, whereas a loss of ethanol took place in case of the reaction with ethyl cyanoacetate.

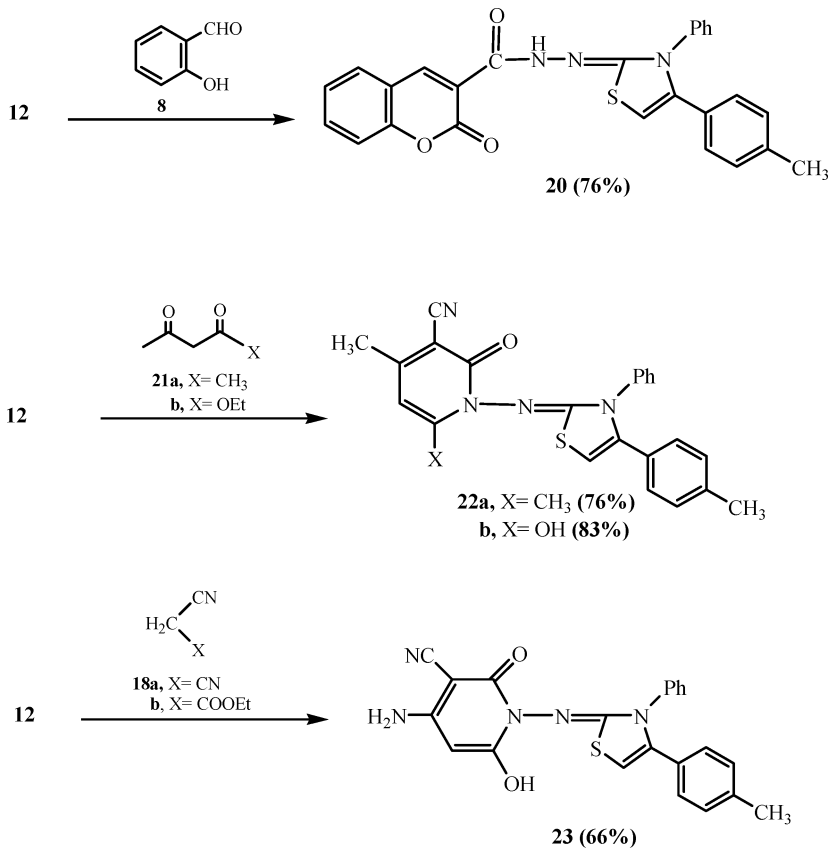
The reaction of compound **3** with both elemental sulfur and phenylisothiocyanate (**2**) gave the thiazole derivative **24**. Elemental analysis,




**SCHEME 2**

IR, and $^1$H-NMR spectrum are in agreement with the proposed structure.

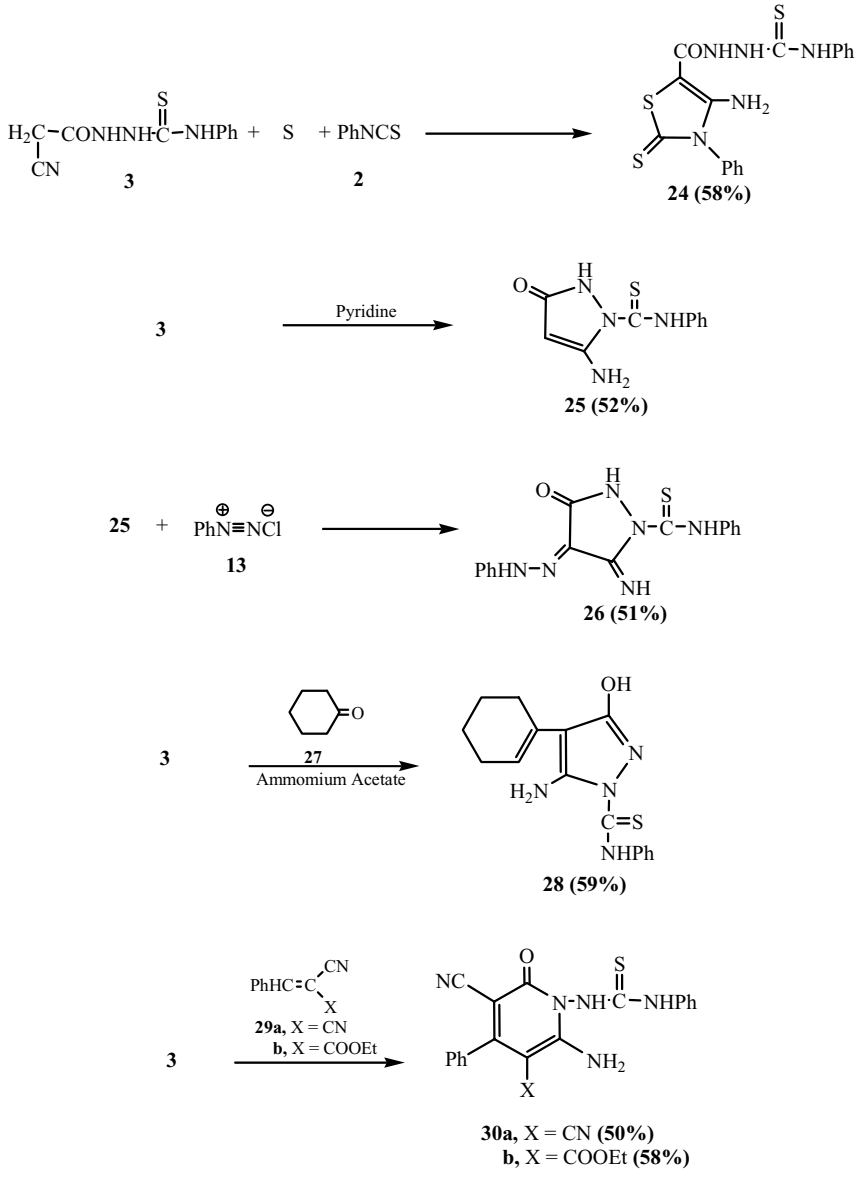
Compound **3** underwent ready cyclization when heated in pyridine solution to give the 5-aminopyrazol-3-one derivative **25**. The IR spectrum of the latter product showed the presence of a C=O group




**SCHEME 3**

stretching at 1703 $cm^{-1}$. Moreover, the $^1$H-NMR showed a singlet at $\delta$ 5.18 corresponding to an $NH_2$ group, a singlet at $\delta$ 6.60 corresponding to pyrazole H-4, a multiplet at $\delta$ 6.90–7.62 corresponding to $C_6H_5$, and two singlets at $\delta$ 10.41 and 10.98 corresponding to two NH groups, respectively. Compound **25** reacts with benzenediazonium chloride (**13**) to give phenyl hydrazone derivative **26**.

The reaction of compound **3** with cyclohexanone (**27**) in the presence of ammonium acetate gave the condensed product **28**. The reaction of compound **3** with either $\alpha$-cyanocinnamonitrile (**29a**) or ethyl $\alpha$-cyanocinnamate (**29b**) took place via Michael addition and oxidation to give the pyridine derivatives **30a** and **30b**, respectively (Scheme 4). The analytical and $^1$H-NMR spectra are the basis of confirming the structures of the latter products (see Experimental section).




**SCHEME 4**

The work in this section shows the uses of thiosemicarbazide derivatives to form thiazole, coumarin, pyrazole, and pyridine derivatives. Such a group of compounds might be difficult to obtain via other reaction routes.

## Microbiology

### *In Vitro Evaluation of Antibacterial and Antifungal Activities*

*Test organisms.* The fungi selected for this study were *Fusarium oxysporum* f.sp. *Lycoperici* (SACC.) SNYDER et HANSEN and *Helminthosporium oryea* (*Cochliobolus miyabeanus*) (ITO and KURIBAYASHI) DPECHSLER ex DASTUR. The former organism, an important plant pathologen causing tomato wilt in Egypt, was isolated from infected tomato plants. The latter organism was isolated from infected rice plants.

The newly synthesized products were dissolved in aqueous ethanol to give a logarithmic series of concentrations from 2 to 256 mg/L upon tenfold dilution with the growth medium and spore suspension of the test fungi. The toxicity of compounds was determined by sporeling bioassay described by Spendley and Ride,[23] which is based on the technique of Skipp and Bailey.[24] A suspension of fungal spores was prepared in water and pipetted into the wells of multiwell slides, followed with 25 $\mu$L of the culture medium. The inoculated slides were then incubated at 25°C until short germ tubes appeared; approximately 50 $\mu$m in length (at 0 h) was calculated. Five $\mu$L volumes of the prepared compound test solutions were added to the inoculated wells, one control well on each slide being treated with solvent only. The slides were then returned to the incubator until germ tubes 400 50+/− $\mu$m long were visible in the control wells. Further growth was arrested by the addition of lactophenol aniline blue to each of the wells. Based on these assays, the percent inhibition of germ-tube growth (with respect to the controls) was plotted against the logarithm of concentration of each compound. From this, the concentrations producing 50% inhibition ($ED_{50}$) and 100% inhibition (MLD) were directly obtained. When the $ED_{50}$ or MLD values exceeded the maximum concentrations of compound used, extrapolation was performed when the last point was within 5% of the $ED_{50}$ or MLD line, otherwise the result was expressed as >256 mg/L.

*Growth.* Since some compounds are lethal at relatively high doses and others at lower doses, comparison of the effect of compound on the growth, sporulation, and nucleic acid synthesis of the test fungi was undertaken at a concentration of 64 mg/L.

A series of conical flasks (250 mL capacity) containing 50 mL Czapek-Dox liquid medium were used for each fungus. Each of three flasks was supplemented with 64 mg/L of each compound. The flasks were inoculated with a 5-mm diameter agar disc cut from the margin of actively growing colonies. The flasks were incubated at 28°C for 7 days after which the produced mycelial felts were collected, washed several times with distilled water, and oven-dried at 80°C to constant mass.

*Sporulation.* Plates of Czapek-Dox agar supplemented with 64 mg/L of each compound were inoculated with a 5-mm diameter agar disc of the used fungus. The plates were then incubated for 7 days at 28°C. A 1-$cm^2$ section was cut from the margin of the colony and transferred to a vial containing 10 mL sterile distilled water. The suspension was spontaneously shaken for 5 min, and the concentration of spores per mL was counted in a hemocytometer. Three plates were used for each treatment.

Most of the tested compounds showed significant toxicity which is dependent on their chemical structure. The toxicity pattern of the compounds toward the two fungi is similar although the levels of compounds that were required to produce $ED_{50}$ and MLD for *Helminthosporium oryzae* were higher than those required for *Fusarium oxyporum f. sp. Lycopersici*.

The effect of all tested compounds on growth, sporulation and nucleic acid synthesis was tested at a concentration of 64 mg/L. Compound **20** allowed good mycelial growth, sporulation and nucleic acid synthesis by the two fungi. This indicates that the two fungi can use the N-containing heterocyclic ring as a nitrogen source. Introducing the benzal moiety to compound **3** gives compound **5**, the latter showed high antimicrobial activities than the first. Comparing compounds **7a**, **7b**, **7c**, and **7d**. One can notice that all of them are thiazole derivatives with different substituted groups. Compound **7d** (with the $CH_3$-group showed the highest activities. However, compounds **10a–c** with a coumarin and thiazole moieties showed reverse activities, where **10a** showed higher activities than **10b** and **10c**. Compound **17b** with the N-Ph group showed higher activities than **17a** (with the N-H group). It is of much interest that **19a** (pyridine with the 2-aminopyridine) showed better activities than **19b** (with the 2-hydroxypyridine). Similarly for compound **22b** (with 2-hydroxypyridine) showed higher activities than **22a** (with 2-methylpyridine).



## EXPERIMENTAL

### Chemistry

All melting points are uncorrected. IR spectra were recorded for (KBr) discs on a Pye Unicam SP-1000 spectrophotometer. $^1$H-NMR and $^{13}$C-NMR spectra were measured on a Varian EM-390-400 MHz in $CD_3SOCD_3$ as solvent using TMS as internal standard, and chemical shifts are expressed as $\delta$ Analytical data; they were obtained from the Microanalytical Data Unit at Cairo University, Giza, Egypt.

**TABLE I Measured Concentrations (mg/L) of Each of the Tested Compounds Producing 50% Inhibition and 100% Inhibition (MLD) of *Fusarium Oxysporum* f. sp. *Lycopersici* and *Helminthosporium Oryzea***

| | *F. Oxysporum* f. sp. *Lycopersici* | | *H. oryzae* | |
|---|---|---|---|---|
| Compound no. | $ED_{50}$ | MLD | $ED_{50}$ | MLD |
| **3** | 18 | 76 | 12 | 78 |
| **5** | 80 | 206 | 73 | 201 |
| **7a** | 11 | 72 | 24 | 68 |
| **7b** | 31 | 80 | 36 | 118 |
| **7c** | 12 | 60 | 36 | 63 |
| **7d** | 20 | 88 | 30 | 112 |
| **9** | 84 | 166 | 70 | 118 |
| **10a** | 90 | 236 | 244 | 78 |
| **10b** | 12 | 88 | 68 | 50 |
| **10c** | 31 | 85 | 36 | 108 |
| **12** | 20 | 88 | 30 | 112 |
| **14** | 88 | 220 | 70 | 250 |
| **15** | 80 | 206 | 73 | 201 |
| **17a** | 14 | 36 | 16 | 44 |
| **17b** | 16 | 87 | 45 | 120 |
| **19a** | 77 | 226 | 68 | 250 |
| **19b** | 18 | 88 | 31 | 102 |
| **20** | 84 | 166 | 70 | 118 |
| **22a** | 28 | 110 | 48 | 108 |
| **22b** | 79 | 196 | 80 | 203 |
| **23** | 84 | 166 | 70 | 118 |
| **24** | 10 | 70 | 15 | 78 |
| **25** | 88 | 230 | 190 | 210 |
| **26** | 80 | 250 | 196 | >256 |
| **28** | 120 | 230 | 110 | 205 |



### *Synthesis of α-Benzalcyanoacetyl-4-phenyl-3-thiosemicarbazide (5)*

To a solution of compound **3** (3.08 g, 0.013 mol) in 1,4-dioxan (100 mL) containing piperidine (1 mL), benzaldehyde (1.39 g, 0.013 mol) was added. The reaction mixture was heated under reflux for 3 h and then poured onto a beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration and dried.

Yellow crystals (from ethanol), 56% yield (2.40 g), m.p. 100°C. IR ($\upsilon$, $cm^{-1}$): 3416-3217 (3NH), 3083 (CH aromatic), 2860 (CH=C), 2260 (CN), 1692 (C=O), 1199 (C=S). $^1$H-NMR ($\delta$, ppm): 7.12 (s, 1H, CH=C), 7.41–8.01 (m, 10H, $2C_6H_5$), 9.76, 10.75, 10.80 (3s, 3H, 3NH). Calc. for

**TABLE II Effect of 64 mg/L of Each Compound on Mycelial Dry Mass, Sporulation and Nucleic Acid Synthesis of *Fusarium Oxysporum* f. sp. *Lycopersici***

| Compound no. | Mycelial dry mass Mg/50 mL | Sporulation spores, $\times 10^{-5}$/mL of culture | DNA | Nucleic acid mg/g dry mass RNA |
|---|---|---|---|---|
| **3** | 168 | 8.4 | 14.5 | 0.18 |
| **5** | 258 | 23.8 | 10.4 | 0.22 |
| **7a** | 144 | 18.6 | 20.8 | 0.23 |
| **7b** | 102 | 23.2 | 10.3 | 0.16 |
| **7c** | 198 | 33.5 | 18.6 | 0.23 |
| **7d** | 226 | 36.6 | 12.5 | 0.33 |
| **9** | 330 | 20.8 | 18.7 | 0.33 |
| **10a** | 225 | 8.9 | 6.3 | 0.84 |
| **10b** | 106 | 20.2 | 6.2 | 0.30 |
| **10c** | 104 | 28.5 | 10.0 | 0.23 |
| **12** | 198 | 33.5 | 18.6 | 0.23 |
| **14** | 256 | 24.6 | 10.8 | 0.34 |
| **15** | 258 | 23.8 | 10.4 | 0.22 |
| **17a** | 102 | 20.3 | 10.7 | 0.16 |
| **17b** | 214 | 23.2 | 10.3 | 0.34 |
| **19a** | 330 | 23.8 | 10.4 | 0.26 |
| **19b** | 258 | 24.8 | 6.3 | 0.38 |
| **20** | 330 | 20.8 | 18.7 | 0.33 |
| **22a** | 168 | 26.4 | 8.5 | 0.10 |
| **22b** | 160 | 20.8 | 12.7 | 0.35 |
| **23** | 220 | 20.6 | 16.8 | 0.38 |
| **24** | 101 | 18.2 | 9.2 | 0.33 |
| **25** | 100 | 10.2 | 6.3 | 0.32 |
| **26** | 136 | 30.2 | 16.0 | 0.32 |
| **28** | 228 | 24.0 | 11.6 | 0.44 |



$C_{17}H_{14}N_4OS$ (322.38): C, 63.33; H, 4.37; N, 17.37; S, 9.94. Found: C, 62.83; H, 4.38; N, 16.87; S, 9.54.

## Reaction of Compound (5) with $\alpha$-Haloketones—General Procedure for the Synthesis of (7a), (7b), (7c), and (7d)

To a solution of compound **5** (1.26 g, $3.90 \times 10^{-3}$ mol) in ethanol (40 mL), either ethyl chloroacetate (0.47 g, $3.90 \times 10^{-3}$ mol), phenacyl bromide (0.77 g, $3.90 \times 10^{-3}$ mol), 4-methylphenacyl bromide (0.83 g, $3.90 \times 10^{-3}$ mol), or chloroacetone (0.36 g, $3.90 \times 10^{-3}$ mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h then poured onto a beaker containing an ice/water mixture, and the pH was adjusted to pH 7 using sodium hydroxide solution. The formed solid product, in each case, was collected by filtration.

### α-Benzalcyanoacetyl-4-(4-hydroxy-3-phenylthiazol-2-ylidieno)-hydrazone (7a)

Pale green crystals (from ethanol), yield 65 % (0.93 g), m.p.118°C. IR ($\upsilon$, $cm^{-1}$): 3525–3190 (OH, NH), 3060 (CH aromatic), 2213 (CN), 1695 (C=O), 1670 (C=N), 1640 (C=C). $^1$H-NMR ($\delta$, ppm): 5.77 (s, 1H, thiazole H-5), 6.25 (s, 1H, CH=C), 6.85–7.83 (m, 10H, $2C_6H_5$), 9.98 (s, 1H, NH), 11.07 (s, 1H, OH). $^{13}$C-NMR (DMSO): 58 (thiazole C-4), 116.8 (CN), 117.4, 119.5, 122.5, 124.3, 128.9, 129.5, 140.9, 143.2 (aromatic C), 167.5 (C=O), 180.5 (thiazole C-5). Calc. for $C_{19}H_{14}N_4O_2S$ (362.40): C, 62.97; H, 3.89; N, 15.45; S, 8.84. Found: C, 63.48; H, 4.30; N, 14.94; S, 8.42.

### α-Benzalcyanoacetyl-4-(3,4-diphenylthiazol-2-ylidieno)hydrazone (7b)

Yellow crystals (from ethanol), 73% yield (1.22 g), m.p. 127°C. IR ($\upsilon$, $cm^{-1}$): 3300–3240 (NH), 3057 (CH aromatic), 2241 (CN), 1683 (C=O). $^1$H-NMR ($\delta$, ppm): 4.61 (s, 1H, thiazole H-5), 6.47 (s, 1H, CH=C), 6.67–8.18 (m, 15H, $3C_6H_5$), 9.22 (s, 1H, NH). Calc. for $C_{25}H_{18}N_4OS$ (422.50): C, 71.07; H, 4.29; N, 13.26; S, 7.58. Found: C, 70.56; H, 4.52; N, 13.66; S, 8.00.

### α-Benzalcyanoacetyl-4-(4-methylphenyl-3-phenylthiazol-2-ylidieno)hydrazone (7c)

Buff crystals (from ethanol), 69% yield (1.19 g), m.p. 82°C. IR ($\upsilon$, $cm^{-1)}$: 3340–3225 (NH), 3060 (CH aromatic), 2923 ($CH_3$), 2240 (CN), 1727 (C=O). $^1$H-NMR ($\delta$, ppm): 3.37 (s, 3H, $CH_3$), 4.89 (s, 1H, thiazole H-5), 6.39 (s, 1H, CH=C), 6.64–8.16 (m, 14H, $2C_6H_5$, $C_6H_4$), 11.14 (s, 1H, NH). Calc. for $C_{26}H_{20}N_4OS$ (436.53): C, 71.53; H, 4.61; N, 12.83; S, 7.34. Found: C, 71.10; H, 5.08; N, 12.35; S, 7.33.

### α-Benzalcyanoacetyl-4-(4-methyl-3-phenylthiazol-2-ylidieno)-hydrazone (7d)

Green crystals (from ethanol), 67% yield (0.95 g), m.p. 136°C. IR ($\upsilon$, $cm^{-1}$): 3350–3293 (NH), 3062 (CH aromatic), 2928 ($CH_3$), 2220 (CN), 1684 (C=O). $^1$H-NMR ($\delta$, ppm): 3.39 (s, 3H, $CH_3$), 4.50 (s, 1H, thiazole H-5), 6.05 (s, 1H, CH=C), 6.85–8.09 (m, 10H, $2C_6H_5$), 9.97 (s, 1H, NH). Calc. for $C_{20}H_{16}N_4OS$ (360.43): C, 66.64; H, 4.47; N, 15.54; S, 8.89. Found: C, 66.16; H, 4.96; N, 15.05; S, 9.38.

### Synthesis of 1-Coumarin-3-oyl-4-phenyl-3-thiosemicarbazide (9)

To a solution of compound **3** (3.00 g, 0.012 mol) in 1,4-dioxan (70 mL) containing piperidine (1 mL), salicaldehyde (1.56 g, 0.012 mol) was added. The reaction mixture was heated under reflux for 4 h and

then poured into a beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration and dried.

Orange crystals (from 1,4-dioxan), 68% yield (3.00 g), m.p. 240°C. IR ($\upsilon$, $cm^{-1}$): 3450–3191(3NH), 3049 (CH aromatic), 1701, 1680 (2C=O), 1195 (C=S). $^1$H-NMR ($\delta$, ppm): 6.96 (s, 1H, coumarin H-4), 7.32–8.99 (m, 9H, $C_6H_5$, $C_6H_4$), 9.76, 11.18, 11.80 (3s, 3H, 3NH). $^{13}$C-NMR (DMSO): $\delta$ 114.2, 118.4, 120.9, 121.4, 123.7, 128.5, 133.6, 136.4 (aromatic C), 156.4 (C=O), 172.5 (C=S). Calc. for $C_{17}H_{13}N_3O_3S$ (339.37): C, 60.16; H, 3.86; N, 12.38; S, 9.44. Found: C, 59.67; H, 4.21; N, 11.89; S, 8.89.

## Reaction of Compound (9) with $\alpha$-Haloketones—General Procedure for the Synthesis of (10a), (10b), and (10c)

To a solution of compound **9** (0.54 g, $1.59 \times 10^{-3}$ mol) in dimethylformamide (30 mL), either ethyl chloroacetate (0.19 g, $1.59 \times 10^{-3}$ mol), phenacyl bromide (0.31 g, $1.59 \times 10^{-3}$ mol), or chloroacetone (0.14 g, $1.59 \times 10^{-3}$ mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h and then poured into a beaker containing an ice/water mixture, and the pH was adjusted to pH 7 using sodium hydroxide solution. The formed solid product, in each case, was collected by filtration and dried.

### *1-Coumarin-3-oyl-3-(4-hydroxy-3-phenyl-2-ylidienothiazolo)-hydrazide (10a)*

Yellow crystals (from dioxan), 77% yield (0.47 g), m.p. 180°C. IR ($\upsilon$, $cm^{-1}$): 3550–3283 (OH, NH), 3055 (CH aromatic), 1750, 1701 (2C=O). $^1$H-NMR ($\delta$, ppm): 4.81 (s, 1H, thiazole H-5), 6.93 (s, 1H, coumarin H-4), 7.37–8.03 (m, 9H, $C_6H_5$, $C_6H_4$), 11.14 (s, 1H, NH), 11.89 (s, 1H, OH). Calc. for $C_{19}H_{13}N_3O_4S$ (379.39): C, 60.15; H, 3.45; N, 11.07; S, 8.45. Found: C, 60.64; H, 3.93; N, 11.56; S, 7.99.

### *1-Coumarin-3-oyl-3-(3,4-diphenyl-2-ylidienothiazolo)-hydrazide (10b)*

Brown crystals (from 1,4-dioxan), 74% yield (0.52 g), m.p. 136°C. IR ($\upsilon$, $cm^{-1}$): 3400–3300 (NH), 3056 (CH aromatic), 1740, 1699 (2C=O). $^1$H-NMR ($\delta$, ppm): 5.60 (s, 1H, thiazole H-5), 6.93 (s, 1H, coumarin H-4), 7.30–8.91 (m, 14H, $2C_6H_5$, $C_6H_4$), 11.13 (s, 1H, NH). Calc. for $C_{25}H_{17}N_3O_3S$ (439.49): C, 68.32; H, 3.89; N, 9.56; S, 7.29. Found: C, 68.81; H, 4.29; N, 9.08; S, 6.94.

### *1-Coumarin-3-oyl-3-(4-methyl-3-phenyl-2-ylidienothiazolo)hydrazide (10c)*

Buff crystals (from 1,4-dioxan), 59% yield (0.36 g), m.p. 152 °C. IR ($\upsilon$, $cm^{-1}$): 3480–3420 (NH), 3056 (CH aromatic), 2925 ($CH_3$), 1730,

1702 (2C=O). $^1$H-NMR ($\delta$, ppm): 3.56 (s, 3H, $CH_3$), 6.12 (s, 1H, thiazole H-5), 6.97 (s, 1H, coumarin H-4), 7.36-8.21 (m, 9H, $C_6H_5$, $C_6H_4$), 11.11 (s, 1H, NH). Calc. for $C_{20}H_{15}N_3O_3S$ (377.42): C, 63.64; H, 4.00; N, 11.13; S, 8.49. Found: C, 63.21; H, 4.49; N, 10.72; S, 7.97.

### *Synthesis of 1-N-Cyanoacetylhydrazono-4-(4-methylphenyl-3-phenyl)-thiazole (12)*

To a solution of compound **3** (6.09 g, 0.026 mol) in 1,4-dioxan (70 mL), 4-methylphenacyl bromide (5.54 g, 0.026 mol) was added. The reaction mixture was heated under reflux for 3 h and then poured into a beaker containing an ice/water mixture, and the pH was adjusted to pH 7 using sodium hydroxide solution. The formed solid product was collected by filtration and dried.

Buff crystals (from ethanol), 64% yield (5.88 g), m.p. 160°C. IR ($\upsilon$, $cm^{-1}$): 3490–3438 (NH), 3113 (CH aromatic), 2918 ($CH_3$), 2255 (CN), 1729 (C=O). $^1$H-NMR ($\delta$, ppm): 2.50 (s, 3H, $CH_3$), 3.80 (s, 2H, $CH_2$), 6.33 (s, 1H, thiazole H-5), 6.95-7.37 (m, 9H, $C_6H_5$, $C_6H_4$), 10.22 (s, 1H, NH). $^{13}$C-NMR (DMSO): $\delta$ 25.8 ($CH_3$), 33.6 ($CH_2$), 115.8 (CN), 118.4, 119.5, 120.6, 123.7, 126.8, 129.1, 131.5, 138.2, 140.9 (aromatic C, thiazole C-5), 155.8 (C=N), 170.9 (C=O). Calc. for $C_{19}H_{16}N_4OS$ (348.42)**:** C, 65.49; H, 4.62; N, 16.08; S, 9.20. Found: C, 65.29; H, 4.91; N, 15.59; S, 9.69.



### Synthesis of $\alpha$-Phenylhydrazonocyanoacetyl-4-(4-methylphenyl-3-phenyl-2-ylidienothiazolo)hydrazone (14)

To a cold (0–5°C) solution of compound **12** (1.01 g, $2.89 \times 10^{-3}$ mol) in ethanol (50 mL) containing sodium hydroxide solution (10 mL, 10%) and a solution of benzenediazonium chloride (**13**) ($2.89 \times 10^{-3}$ mol) [which was prepared by dissolving sodium nitrite (0.40 g, $4.30 \times 10^{-3}$ mol) in water, 2 mL was added to a cold solution of aniline (0.27 g, $2.89 \times 10^{-3}$ mol) containing the appropriate amount of hydrochloric acid and with continuous stirring] was added with continuous stirring. The reaction mixture was stirred at room temperature for 3 h, and the formed solid product was collected by filtration and dried.

Reddish brown crystals (from 1,4-dioxan), 53% yield (0.70 g), m.p. 142°C. IR ($\upsilon$, $cm^{-1}$): 3450–3184 (2NH), 3109 (CH aromatic), 2919 ($CH_3$), 2214 (CN), 1737 (C=O). $^1$H-NMR ($\delta$, ppm): 3.32 (s, 3H, $CH_3$), 6.35 (s, 1H, thiazole H-5), 6.98-8.27 (m, 14H, $2C_6H_5$, $C_6H_4$), 10.50, 11.01 (2s, 2H, 2NH). Calc. for $C_{25}H_{20}N_6OS$ (452.53)**:** C, 66.35; H, 4.45; N, 18.57; S, 7.08. Found: C, 66.92; H, 4.95; N, 18.00; S, 7.59.

### *Synthesis of α-Benzalcyanoacetylhydrazino-4-(4-methylphenyl-3-phenyl-2-ylidieno)thiazole (15)*

To a solution of compound **12** (1.43 g, $4.11 \times 10^{-3}$ mol) in ethanol (25 mL) containing piperidine (0.5 mL), benzaldehyde (**4**) (0.43 g, $4.11 \times 10^{-3}$ mol) was added. The reaction mixture was heated under reflux for 3 h and then poured into a beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration and dried.

Yellow crystals (from ethanol), 83% yield (1.50 g), m.p. 100°C. IR ($\upsilon$, $cm^{-1}$): 3350–3295 (NH), 3056 (CH aromatic), 2922 ($CH_3$), 2218 (CN), 1748 (C=O). $^1$H-NMR ($\delta$, ppm): 3.30 (s, 3H, $CH_3$), 6.21 (s, 1H, thiazole H-5), 6.91–7.96 (m, 15H, CH=C, $2C_6H_5$, $C_6H_4$), 10.72 (s, 1H, NH). Calc. for $C_{26}H_{20}N_4OS$ (436.53): C, 71.53; H, 4.61; N, 12.83; S, 7.34. Found: C, 71.32; H, 5.08; N, 12.30; S, 6.85.



## Reaction of Compound (15) with Either Hydrazine Hydrate or Phenyl Hydrazine—General Procedure for the Synthesis of (17a) and (17b)

To a solution of compound **15** (0.70 g, $1.60 \times 10^{-3}$ mol) in ethanol (25 mL), either hydrazine hydrate (0.08 g, $1.60 \times 10^{-3}$ mol) or phenyl hydrazine (0.17 g, $1.60 \times 10^{-3}$ mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h and then poured onto a beaker containing an ice/water mixture. The formed solid product, in each case, was collected by filtration and dried.

### *3-Phenyl-4-(4-methylphenyl)-2-ylidieno(3-amino-5-phenylpyrazol-4-carbohydrazino)thiazole (17a)*

Pale brown crystals (from ethanol), 64% yield (0.48 g), m.p. 170°C. IR ($\upsilon/cm^{-1}$): 3500–3396 ($NH_2$, 2NH), 3058 (CH aromatic), 2923 ($CH_3$), 1700 (C=O). $^1$H-NMR ($\delta$, ppm): 3.29 (s, 3H, $CH_3$), 4.10 (s, 2H, $NH_2$), 6.12 (s, 1H, thiazole H-5), 6.23-8.42 (m, 14H, $2C_6H_5$, $C_6H_4$), 9.40, 10.19 (2s, 2H, 2NH). $^{13}$C-NMR (DMSO): $\delta$ 26.6 ($CH_3$), 106.8, 11.7, 118.9, 119.4, 120.7, 121.7, 124.7, 133.6, 136.2, 138.9, 140.4, 141.7, 146.8 (aromatic C, thiazole C, pyrazole C), 155.9, 156.6 (2 C=N), 169.8 (C=O). Calc. for $C_{26}H_{22}N_6OS$ (466.56)**:** C, 66.69; H, 4.75; N, 18.01; S, 6.87. Found: C, 66.23; H, 5.24; N, 17.73; S, 7.39.

### *3-Phenyl-4-(4-methylphenyl)-2-ylidieno(3-amino-1,5-diphenylpyrazol-4-carbohydrazino)thiazole (17b)*

Buff crystals (from ethanol), 70% yield (0.61 g), m.p. 126°C. IR ($\upsilon$, $cm^{-1}$): 3400–3285 ($NH_2$, NH), 3055 (CH aromatic), 2922 ($CH_3$), 1700 (C=O). $^1$H-NMR ($\delta$, ppm): 3.26 (s, 3H, $CH_3$), 4.13 (s, 2H, $NH_2$), 6.02

(s, 1H, thiazole H-5), 6.36–8.06 (m, 19H, $3C_6H_5$, $C_6H_4$), 10.37 (s, 1H, NH). Calc. for $C_{32}H_{26}N_6OS$ (542.66): C, 70.82; H, 4.82; N, 15.48; S, 5.90. Found: C, 70.54, H, 4.68; N, 14.99; S, 6.21.

## Reaction of Compound (15) with Cyanomethylene Reagents—Genaral Procedure for the Synthesis of (19a) and (19b)

To a solution of compound **15** (0.51 g, $1.16 \times 10^{-3}$ mol) in ethanol (20 mL) containing triethylamine (0.5 mL), either malononitrile (0.07 g, $1.16 \times 10^{-3}$ mol) or ethyl cyanoacetate (0.13 g, $1.16 \times 10^{-3}$ mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h and then poured into a beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product, in each case, was collected by filtration and dried.



### *1-N-(2-Amino-3,5-dicyano-4[H]-4-phenyl-6-hydroxy)pyrido-3-phen-yl-4-(4-methylphenyl)-2-ylidienoaminothiazole (19a)*

Buff crystals (from ethanol), 61% yield (0.36 g), m.p. 120°C. IR ($\upsilon$, $cm^{-1}$): 3600–3452 (OH, $NH_2$), 2970 ($CH_3$), 2240, 2210 (2CN). $^1$H-NMR ($\delta$, ppm): 3.29 (s, 3H, $CH_3$), 4.42 (s, 2H, $NH_2$), 5.82 (s, 1H, thiazole H-5), 6.22 (s, 1H, pyridine H-4), 6.56–8.02 (m, 14H, $2C_6H_5$, $C_6H_4$), 11.55 (s, 1H, OH). $^{13}$C-NMR (DMS): $\delta$25.3 ($CH_3$), 44.8 (pyridine C-4), 118.0, 118.6 (2 CN), 116.7, 119.5, 119.0, 121.5, 124.6, 127.1, 129.7, 136.4, 139.7, 144.5 (aromatic C, thiazole C, pyridine C-3, C-5, C-6), 155.6 (C=N), 185.8 (pyridine C-2). Calc. for $C_{29}H_{22}N_6OS$ (502.59): C, 69.30; H, 4.41; N, 16.72; S, 6.37. Found: C, 68.82; H, 3.82; N, 16.23; S, 6.86.

### *1-N-(2,6-Dihydroxy-3,5-dicyano-4[H]-4-phenyl)pyrido-3-phenyl-4-(4-methylphenyl)-2-ylidienoaminothiazole (19b)*

Buff crystals (from ethanol), 83% yield (0.49 g), m.p. 86°C. R ($\upsilon$, $cm^{-1}$): 3550–3446 (2OH), 3058 (CH, aromatic), 2980 ($CH_3$), 2200, 2210 (2CN). $^1$H-NMR ($\delta$, ppm): 3.40 (s, 3H, $CH_3$), 5.72 (s, 1H, thiazole H-5), 6.43 (s, 1H, pyridine H-4), 7.04–7.84 (m, 14H, $2C_6H_5$, $C_6H_4$), 11.50, 11.53 (2s, 2H, 2OH). Calc. for $C_{29}H_{21}N_5O_2S$ (503.58): C, 69.16; H, 4.20; N, 13.90; S, 6.36. Found: C, 69.68; H, 4.69; N, 13.45; S, 6.81.

## Synthesis of 1-Coumarin-3-oyl-3-(3-phenyl-4-(4-methylphenyl)-2-ylidieno)-hydrazinothiazole (20)

To a solution of compound **12** (1.00 g, $2.87 \times 10^{-3}$ mol) in ethanol (30 mL) containing piperidine (0.5 mL), salicaldehyde (0.35 g, $2.87 \times 10^{-3}$ mol)

was added. The reaction mixture was heated under reflux for 3 h then poured into a beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration and dried.

Brick red crystals (from 1,4-dioxan), 76% yield (1.00 g), m.p. 120°C. IR ($\upsilon$, $cm^{-1}$): 3345–3315 (NH), 3057 (CH aromatic), 2925 ($CH_3$), 1696, 1740 (2C=O). $^1$H-NMR ($\delta$, ppm): 3.30 (s, 3H, $CH_3$), 6.05 (s, 1H, thiazole H-5), 6.65–8.34 (m, 14H, coumarin H-4, $C_6H_5$, $2C_6H_4$), 9.40 (s, 1H, NH). Calc. for $C_{26}H_{19}N_3O_3S$ (453.51): C, 68.85; H, 4.22; N, 9.26; S, 7.06. Found: C, 68.56; H, 4.64; N, 8.82; S, 6.99.

## Reaction of Compound (12) with $\beta$-Ketoesters—General Procedure for the Synthesis of (22a) and (22b)



To a solution of compound **12** (1.22 g, $3.50 \times 10^{-3}$ mol) in ethanol (30 mL) containing piperidine (1 mL), either acetylacetone (0.35 g, $3.50 \times 10^{-3}$ mol) or ethyl acetoacetate (0.45 g, $3.50 \times 10^{-3}$ mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h and then poured into a beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product, in each case, was collected by filtration and dried.

### *1-N-(5-Cyano-2,4-dimethyl-3[H]-6-oxo)pyrido-3-phenyl-4-(4-methyl-phenyl-2-ylidienoaminothiazole (22a)*

Buff crystals (from ethanol), 76% yield (1.11 g), m.p. 100°C. IR ($\upsilon$, $cm^{-1}$): 3056 (CH aromatic), 3029, 2922, 2858 ($3CH_3$), 2221 (CN), 1683 (C=O). $^1$H-NMR ($\delta$, ppm): 2.40, 2.50, 3.30 (3s, 9H, $3CH_3$), 6.47 (s, 1H, thiazole H-5), 6.58 (s, 1H, pyridine H-3), 6.90–7.83 (m, 9H, $C_6H_5$, $C_6H_4$). Calc. for $C_{24}H_{20}N_4OS$ (412.51): C, 69.88; H, 4.88; N, 13.58; S, 7.77. Found: C, 69.68; H, 5.32; N, 13.10; S, 7.29.

### *1-N-(5-Cyano-4-methyl-3[H]-2-hydroxy-6-oxo)pyrido-3-phenyl-4-(4-methylphenyl)-2-ylidienoaminothiazole (22b)*

Buff crystals (from ethanol), 83% yield (1.22 g), m.p. 146°C. IR ($\upsilon$, $cm^{-1}$): 3550–3434 (OH), 3111 (CH aromatic), 3027, 2921 ($2CH_3$), 2256 (CN), 1728 (C=O). $^1$H-NMR ($\delta$, ppm): 2.50, 3.34 (2s, 6H, $2CH_3$), 6.34 (s, 1H, thiazole H-5), 6.47 (s, 1H, pyridine H-3), 6.95-7.37 (m, 9H, $C_6H_5$, $C_6H_4$), 11.25 (s, 1H, OH). Calc. for $C_{23}H_{18}N_4O_2S$ (414.48): C, 66.64; H, 4.37; N, 13.51; S, 7.73. Found: C, 67.12; H, 4.89; N, 13.99; S, 7.24.

## Synthesis of 1-N-(4-Amino-5-cyano-3[H]-2-hydroxy-6-oxo)-pyrido-3-phenyl-4-(4-methylphenyl)-2-ylidienoaminothiazole (23)

To a solution of compound **12** (1.30 g, $3.73 \times 10^{-3}$ mol) in ethanol (25 mL) containing triethylamine (0.5 mL), either malononitrile (0.24 g, $3.73 \times 10^{-3}$ mol) or ethyl cyanoacetate (0.42 g, $3.73 \times 10^{-3}$ mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h and then poured onto a beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product, in each case, was collected by filtration and dried.

Pale brown crystals (from ethanol), 66% yield (1.03 g), m.p. 100°C. IR ($\upsilon$, $cm^{-1}$): 3600–3433 (OH, $NH_2$), 3114 (CH aromatic), 2921 ($CH_3$), 2257 (CN), 1729 (C=O). $^1$H-NMR ($\delta$, ppm): 2.50 (s, 3H, $CH_3$), 3.64 (s, 2H, $NH_2$), 6.34 (s, 1H, thiazole H-5), 6.47 (s, 1H, pyridine H-3), 6.96–7.37 (m, 9H, $C_6H_5$, $C_6H_4$), 11.29 (s, 1H, OH). Calc. for $C_{22}H_{17}N_5O_2S$ (415.47): C, 63.60; H, 4.12; N, 16.85; S, 7.71. Found: C, 63.08; H, 4.18; N, 17.35; S, 7.36.

## Synthesis of 3-Amino-4-phenyl-5-thioxo-2-oyl-(3-phenylthiouryl)-thiazole (24)

To a solution of compound **3** (1.50 g, $6.41 \times 10^{-3}$mol) in ethanol (100 mL) containing triethylamine (1 mL), elemental sulfur (0.20 g, $6.41 \times 10^{-3}$mol) and phenylisothiocyanate (0.86 g, $6.41 \times 10^{-3}$ mol) were added. The reaction mixture was heated under reflux for 4 h and then poured into a beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration and dried.

Pale brown crystals (from 1,4-dioxan), 58% yield (1.50 g), m.p. 122°C. IR ($\upsilon$, $cm^{-1}$): 3375–3205 ($NH_2$, 3NH), 3033 (CH aromatic), 1699 (C=O), 1210, 1193 (2C=S). $^1$H-NMR ($\delta$, ppm): 4.47 (s, 2H, $NH_2$), 6.80–7.93 (m, 10H, $2C_6H_5$), 9.79, 11.06, 12.62 (3s, 3H, 3NH). Calc. for $C_{17}H_{15}N_5OS_3$ (401.52): C, 50.85; H, 3.76; N, 17.44; S, 23.95. Found: C, 51.35; H, 3.82; N, 16.95; S, 23.56.

## Synthesis of 5-Amino-3-oxo-4[H]-1-(2-phenylthioamido)-pyrazole (25)

A solution of compound **3** (1.00 g, $4.27 \times 10^{-3}$ mol) in pyridine (10 mL) was heated under reflux for 3 h and then poured into a beaker containing ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration and dried.

Buff crystals (from ethanol), 52% yield (0.52 g), m.p. 218°C. IR ($\upsilon$, $cm^{-1}$): 3574–3189 ($NH_2$, 2NH), 3033 (CH aromatic), 1703 (C=O), 1203 (C=S). $^1$H-NMR ($\delta$, ppm): 5.18 (s, 2H, $NH_2$), 6.60 (s, 1H, pyrazole H-4), 6.90–7.62 (m, 5H, $C_6H_5$), 10.41, 10.98 (2s, 2H, 2NH). Calc. for $C_{10}H_{10}N_4OS$ (234.27): C, 51.26; H, 4.30; N, 23.91; S, 13.68. Found: C, 51.36; H, 4.53; N, 23.69; S, 13.67.

## Synthesis of 5-Imino-4-Phenylhydrazono-3-oxo-2[H]-1-phenylthio-amidopyrazole (26)

To a cold solution (0–5°C) of compound **25** (0.38 g, $1.62 \times 10^{-3}$ mol) in ethanol (50 mL) containing sodium hydroxide solution (10 mL, 10%) and a solution of benzenediazonium chloride ($1.62 \times^{-3}$ mol) [which was prepared by dissolving sodium nitrite (0.16 g, $2.43 \times 10^{-3}$ mol) in water, 2 mL was added to a cold solution of aniline (0.15 g, $1.62 \times 10^{-3}$ mol) containing the appropriate amount of hydrochloric acid and with continuous stirring] was added with continuous stirring. The formed solid product was collected by filtration and dried.

Brick red crystals (from dimethylformamide), 51% yield (0.28 g), m.p. 220°C. IR ($\upsilon$, $cm^{-1}$): 3350–3165 (4NH), 3032 (CH aromatic), 1699 (C=O), 1191 (C=S). $^1$H-NMR ($\delta$, ppm): 6.94–7.82 (m, 10H, $2C_6H_5$), 9.88, 10.71, 11.50, 11.63 (4s, 4H, 4NH). Calc. for $C_{16}H_{14}N_6OS$ (338.38): C, 56.79; H, 4.17; N, 24.83; S, 9.47. Found: C, 56.60; H, 4.54; N, 24.38; S, 10.01.



## Synthesis of 5-Amino-4-cyclohexen-1-yl-3-hydroxy-1-(2-phenylthio-amido) pyrazole (28)

To a mixture of compound **3** (1.02 g, $4.35 \times 10^{-3}$ mol) and cyclohexanone (0.41 g, $4.35 \times 10^{-3}$ mol), ammonium acetate (0.33 g, $4.35 \times 10^{-3}$ mol) was added. The reaction mixture was heated in oil bath at 140°C for 1 h and then left to cool. The semisolid formed was triturated with ethanol (40 mL), and the formed solid product was collected by filtration and dried.

Yellowish brown crystals (from ethanol), 59% yield (0.82 g), m.p. 62°C. IR ($\upsilon$, $cm^{-1}$): 3563–3196 (OH, $NH_2$, NH), 1670 (C=N). $^1$H-NMR ($\delta$, ppm): 1.54–2.04 (2m, 8H, $4CH_2$), 3.36 (s, 2H, $NH_2$), 7.30–7.56 (m, 6H, $C_6H_5$, cyclohexene H-2), 8.00 (s, 1H, NH), 9.95 (s, 1H, OH). Calc. for $C_{16}H_{18}N_4OS$ (314.40): C, 61.12; H, 5.77; N, 17.81; S, 10.19. Found: C, 61.64; H, 6.22; N, 17.35; S, 9.70.

## Reaction of Compound (3) with Either $\alpha$-Cyanocinnamonitrile (29a) or Ethyl $\alpha$-Cyanocinnamate (29b)—General Procedure for the Synthesis of Compounds (30a) and (30b)

To a solution of compound **3** (1.11 g, $4.73 \times 10^{-3}$mol) in 1,4-dioxan (50 mL) containing triethylamine (0.5 mL), either $\alpha$-cyanocinnamonitrile (0.73 g, $4.73 \times 10^{-3}$mol) or ethyl $\alpha$-cyanocinnamate (0.95 g, $4.73 \times 10^{-3}$ mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h and then poured into a beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product, in each case, was collected by filtration and dried.

### *6-Amino-3,5-dicyano-2-oxo-4-phenyl-1-(2-phenylthiouryl)pyridine (30a)*

Yellow crystals (from ethanol), 50% yield (0.92 g), m.p. over 300°C. IR ($\upsilon$, $cm^{-1}$): 3445–3237 ($NH_2$, 2NH), 3045 (CH aromatic), 2223, 2220 (2CN), 1688 (C=O).$^1$H-NMR ($\delta$, ppm): 3.58 (s, 2H, $NH_2$), 7.19–7.99 (m, 10H, $2C_6H_5$), 9.62, 10.38 (2s, 2H, 2NH). Calc. for $C_{20}H_{14}N_6OS$ (386.43): C, 62.16; H, 3.65; N, 21.74; S, 8.29. Found: C, 62.68; H, 4.12; N, 21.15; S, 7.89.

### *Ethyl-6-amino-3-cyano-2-oxo-4-phenyl-1-(2-phenylthiouryl)pyridine-5-carboxylate (30b)*

Orange crystals (from ethanol), 58% yield (1.20 g), m.p. 264°C. IR ($\upsilon$, $cm^{-1}$): 3550–3177 ($NH_2$, 2NH), 3058 (CH aromatic), 2207 (CN), 1733, 1699 (2C=O). $^1$H-NMR ($\delta$, ppm): 1.29 (t, 3H, $CH_3$), 3.58 (s, 2H, $NH_2$), 4.42 (q, 2H, $CH_2$), 6.65–7.99 (m, 10H, $2C_6H_5$), 9.62, 10.36 (2s, 2H, 2NH). Calc. for $C_{22}H_{19}N_5O_3S$ (433.48): C, 60.95; H, 4.41; N, 16.15; S, 7.39. Found: C, 60.46; H, 4.92; N, 16.66; S, 7.48.

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