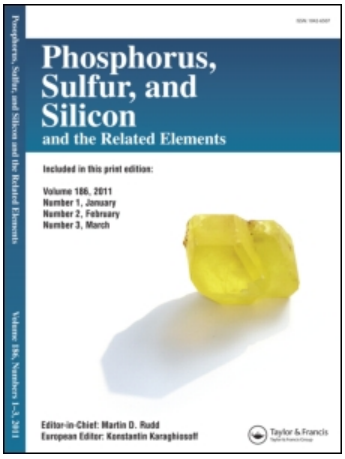

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A Convenient Route to 1,3,4-Thiadiazoles, Thiazolidinone, Thiazoles, Pyridones, Coumarins, Triazolo[5,1-c]triazines, and Pyrazolo[5,1-c]triazines Incorporating Pyrazolone Moiety and Their Use as Antimicrobial Agents

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*Condensation of 4-acetyl-5-methyl-2-phenyl-2,4-dihydropyrazol-3-one (**1**) with hydrazine derivatives (**2a–d**) afforded hydrazone derivatives (**3a–d**), which reacted with alkyl halides **4a–c** to give bis(alkylthio)methylene derivatives (**5a–e**). Also, **3a,b** reacted with hydrazonyl halides **6a–d** to give 1,3,4-thiadiazole (**7a–d**). Cyclization of **3c** with ethyl bromoacetate and haloketones gave thiazolidinone and thiazole derivatives (**8, 10a,b**) respectively. Treatment of hydrazone (**3d**) with benzylidine malononitrile **13a,b** gave pyridine (**14a,b**). In addition, cyclocondensation of **3d** with phenolic aldehydes furnished coumarin derivatives (**16a–c**). Coupling of **3d** with heterocyclic diazonium salts gave triazol[5,1-c]triazine (**20**) and pyrazolo[5,1-c]triazine (**22**). Some of the prepared products showed potent antimicrobial activity.*

Keywords Pyrazolone; pyrazolotriazine; pyridine; thiadiazole; thiazole; triazolotriazine

INTRODUCTION

Heterocyclic compounds containing the pyrazolone[1,2] moiety are known to exhibit potent fungicidal activity,[3–6] and, as a result of which, the present study incorporates the synthesis of some new compounds having a pyrazolone ring. It has also been noted that pyrazolone and its derivatives possess significant fungicidal activity against the rice blast pathogen *Pyricularia oryzae* and the brown leaf spot pathogen *Helminthosporium oryzae*.[7–12]

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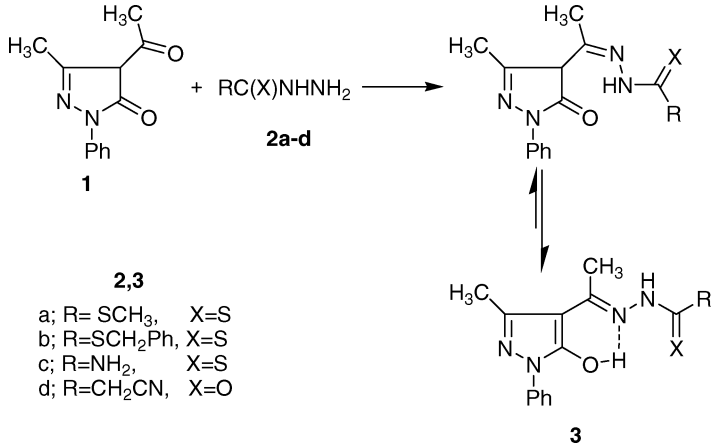
RESULTS AND DISCUSSION

On the basis of the fungicidal activity of heterocyclic compounds containing the pyrazolone[1–4] moiety, it was thought of interest to synthesize heterocyclic compounds (**3–22**) containing this ring system. Condensation of 4-acetyl-5-methyl-2-phenyl-2,4-dihydropyrazol-3-one (**1**)[2] with hydrazine derivatives[14]**2a–d** in hot ethanol afforded hydrazone derivatives **3a–d**, which formed as hydroxyl pyrazole (enol form) and gave characteristic colorations with alcoholic ($FeCl_3$) solution and were soluble in alkali. The ^{1}H NMR of **3b** revealed two singlet signals at δ 2.43 and 2.61 ppm due to two methyl protons at the 4 and 3 positions, a singlet at 4.58 due to the methylene of benzylthio group, in addition to aromatic protons the region 7.22–7.92 ppm and a broad singlet signal at 11.66 ppm due to (NH and enolic OH) (Scheme 1).

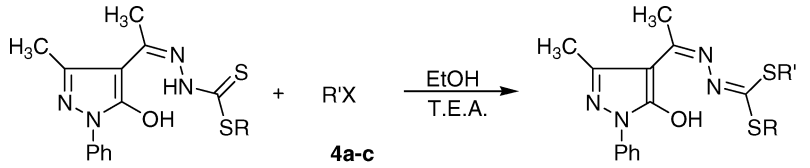


SCHEME 1

Treatment of **3a**,**b** with alkyl halides **4a–c** gave the corresponding bis alkylthio derivatives **5a**,**b**, respectively. Also, alkylation of **3a**,**b** with ethylbromoacetate **4c** afforded the corresponding methylthio (benzylthio) ethoxycarbonylmethyl thiomethylene derivatives **5d**,**e** respectively (Scheme 2).

^{1}H NMR spectrum for compounds **5a–e** showed a broad absorption signal corresponding to the bonded OH proton resonating at δ 14.15–14.19 ppm.

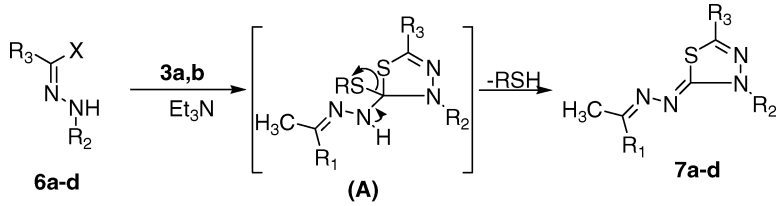
Interaction of alkyl dithioester (**3a**,**b**) with hydrazonyl halides **6a–d**[14,16] in ethanol containing triethylamine at reflux temperatures gave 4,5-dihydro-1,3,4-thiadiazoles (**7a–d**) (Scheme 3). The above results showed that the formation of **7** takes place through the elimination



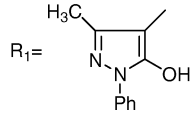
a; R'=CH_3, X=I
b; R'=CH_2Ph, X=Cl
c; R'=CH_2COOEt, X=Br

a; R=R'=CH_3
b; R=R'=CH_2Ph
c; R=CH_3, R'=CH_2Ph
d; R=CH_3, R'=CH_2COOEt
e; R=CH_2Ph, R'=CH_2COOEt

SCHEME 2



a; R_2=C_6H_5, R_3=$COCH_3$, X=Cl
b; R_2=o-$CH_3C_6H_4$, R_3=COOEt, X=Cl
c; R_2=p-ClC_6H_4, R_3=COOEt, X=Br
d; R_2=C_6H_5, R_3=C_6H_5CO, X=Br



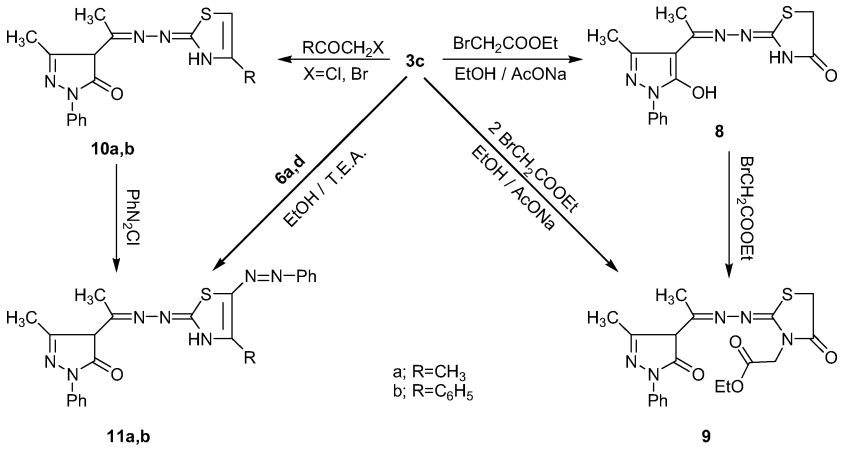
SCHEME 3

of alkyl mercaptan from the cyclic intermediate (**A**) (Scheme 3). The structures of **7** were deduced from their spectral data and elemental analysis.

Compounds **7a–d** are soluble in NaOH solution and give coloration with alcoholic $FeCl_3$. The ^1H NMR spectrum for **7a** exhibited three singlet signals at δ 2.43, 2.51, and 2.63 ppm due to $3CH_3$ groups at position 4, 3 and on the thiadiazole ring, and aromatic multiplets at 7.18–7.98 ppm.

The behavior of the thiocarbamoyl functional group in compound **3c** towards some α-halocarbonyl reagents was investigated. Thus, compound **3c**, when treated with one equivalent of ethyl bromoacetate in boiling ethanol in the presence of fused sodium acetate,

underwent a cyclization thus giving the thiazolidinone derivative **8.** However, **3c** reacted with two moles of ethyl bromoacetate to give N-ethoxycarbonylthiazolidinone derivative **9**, which was obtained from treatment of **8** with ethyl bromoacetate (Scheme 4). The ^{1}H NMR of **8** revealed two singlet signals at 2.30 and 2.48 ppm due to $2CH_3$ at position 4, 3 and one singlet at 3.66 ppm due to CH_2 of thiazolidinone, in addition to aromatic multiplets and NH at 7.02–8.07 and a broad peak from OH at 13.8 ppm.



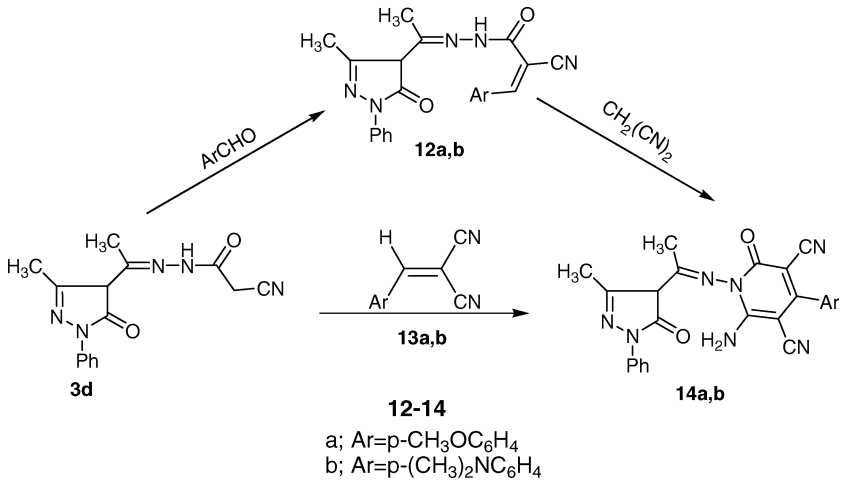
SCHEME 4

Interaction of **3c** with haloketones in ethanol at reflux temperature in the presence of fused sodium acetate afforded thiazole derivatives **10a**,**b**, which, when subjected to coupling reaction with benzene diazonium chloride in ethanol/sodium acetate, gave phenylazothiazole derivatives**11a**,**b**. The latter compounds were prepared directly from the cyclocondensation reaction of **3c** with hydrazonyl halides **6a**,**d** in ethanol/triethylamine under reflux (Scheme 4).

Also the reactivity of **3d** towards some electrophilic reagents was studied. Thus, condensation of **3d** with aromatic aldehydes in hot ethanol/piperidine furnished the novel acrylonitriles (**12a**,**b**) (Scheme 5).

Treatment of the latter compounds with malononitrile in ethanol/piperidine furnished the aminopyridine derivatives **14a**,**b** (Scheme 5). The IR spectrum of **14a** revealed ν (NH_2) at 3320, υ (CN) at 2188, and υ (CO) 1660 cm^{-1}, while the mass spectra of **14a**,**b** showed the corresponding molecular ion peaks at m/e 479 and 492, respectively.

Further support for the proposed structure **14** comes from their independent synthesis through the addition of acetonitrile derivative **3d**



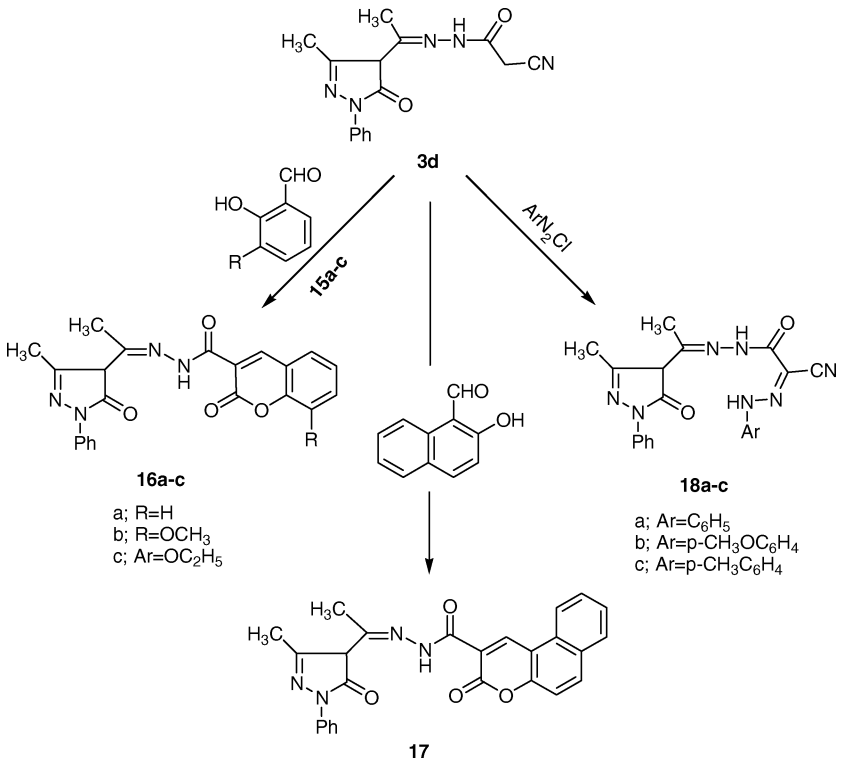
SCHEME 5

to the activated double bond in benzylidene malononitrile derivatives **13a**,**b** under Michael reaction conditions (identical spectral data, mp, and mmp determinations; Scheme 5).

Treatment of **3d** with salicyldehyde derivatives **15a–c** in ethanol/piperidine at reflux temperature afforded the coumarin derivatives **16a–c**; in addition, **3d** condensed with 2-hydroxy-1-naphthaldehyde under the same reaction conditions to give benzo[5,6]coumarin derivative **17** (Scheme 6). The IR spectrum of **16a–c** revealed characteristic carbonyl absorptions at 1710, 1706, and 1700 cm^{-1}, respectively. The ^1H NMR of **16b** revealed three singlet signals at δ 2.46, 2.65, and 4.01 ppm due to $2CH_3$ groups in the pyrazole ring at position 4, 3 and the methoxy group of coumarin ring in addition to aromatic multiples at 6.64–8.01 and a broad OH peak at 14.11 ppm.

Moreover, coupling of **3d** with aryldiazonium salts in ethanolic sodium acetate solution at 0 °C afforded the arylhydrazone derivatives **18a–c** (Scheme 6). The IR spectra of **18b** revealed absorption bands at 3220, 2214, and 1690 cm^{-1} due to NH, CN, and CO groups, respectively, and its ^1H NMR revealed two singlet signals at 2.40 and 2.50 due to $2CH_3$ at position 4, 3 and one singlet signal at 3.76 due to OCH_3 aromatic multiplets at 6.96–8.00, in addition to 2NH at 10.80 and 12.09 ppm.

Coupling of **3d** with the diazotized heterocyclic amines gives excellent building blocks for the synthesis of poly condensed heterocyclic derivatives. Thus, coupling of **3d** with 1,2,4-triazole-3-diazonium



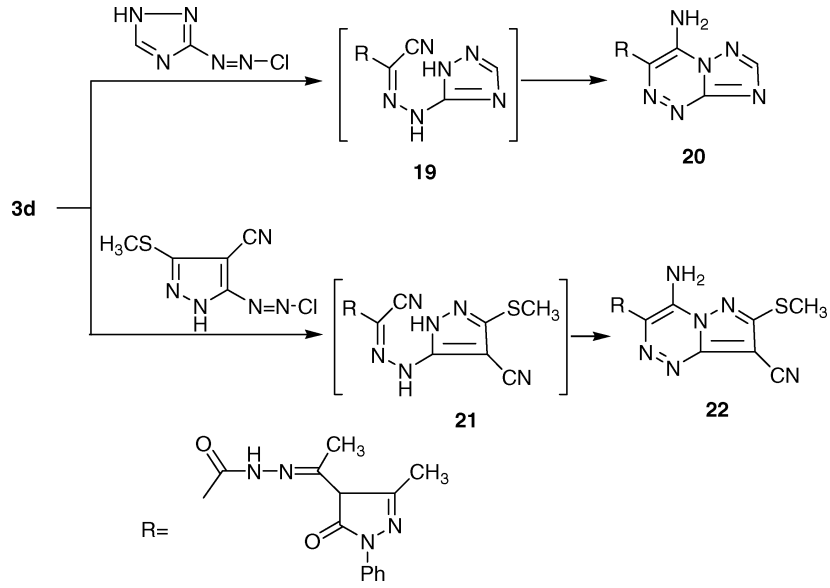
SCHEME 6

chloride gave the 1,2,4-triazolo[5,1-c]-1,2,4-triazine derivative **20** via the nonisolable hydrazone intermediate **19** (Scheme 7).

The IR spectrum of the isolated product showed absorption bands at (3440, 3278, 3140, and 1688 cm^{-1}) due to (NH_2, NH, and CO) functional groups. Its mass spectrum showed the molecular ion peak at (m/e = 392). A similar interaction of **3d** with pyrazole-5-diazonium chloride afforded high yields of the pyrazolo[5,1-c]-1,2,4-triazine **22** via the nonisolable hydrazone intermediate **21** (Scheme 7).

BIOLOGICAL ACTIVITY

Compounds **8**, **9**, and **12b** showed very high activity (IZ > 20 mm) against *Bacillus NCTC* and *Staphylococcus ATCC*, with Citrofloxacin as reference. This activity was expected to occur through the thiazolidinone and benzylidine moieties, and be highly active with Gram-negative bacteria. Compounds **3b**,**10a**, and **18c** showed highly active



SCHEME 7

(IZ 15~20 mm) against *Bacillus NCTC*, *Staphylococcus ATCC*, and *Escherichia coli ATCC*. Compounds **5e**, **5c**, **14**, and **20** showed moderate activity against *Bacillus NCTC*, *Staphylococcus*, *Escherichia coli*, and *Pseudomonas ATCC*. Compound **16c** exhibited less activity with Gram-positive bacteria. However, compounds **3d**, **8**, **9**, **10a**, **12b**, and **18c** exhibited moderate activity against the fungi *Candida albicans*; compound **20** showed less activity, and the remaining compounds showed no inhibition zone with *Candida albicans* (Table I).

The high activity against Gram-negative bacteria was exerted by compounds (**10**, **11**, **14b**) with the thiazolidinone **10**, **11** and cinamonitrile **14b** moieties and **20c** with the acetonitrilehydrazone moiety. The moderate activity against *C. albicans* was exhibited by compounds (**10**, **11**, **14b**) and compounds (**3b**, **12b**) with acetonitrile and thiazole moieties, respectively.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν , cm^{-1}). The ^1H NMR spectra were recorded in DMSO-d_6 at 300 MHz on a Varian Gemini NMR spectrometer (δ , ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 eV.

TABLE I Antibacterial and Antifungal Activities

	Gram-positive		Gram-negative		Unicellular fungi	Filamentous fungi
Comp. No.	*B. subtilis*	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
3b	+++	+++	++	++	++	–
5c	++	++	++	++	–	–
5e	++	++	++	++	–	–
8	++++	++++	+++	+++	++	–
9	++++	+++	+++	+++	++	–
10a	+++	+++	++	++	++	–
12b	++++	++++	+++	+++	++	–
14a	++	++	++	++	–	–
f16c	+	+	–	–	–	–
18c	+++	+++	+++	+++	++	–
20	++	++	++	++	+	–
Citrofloxacin (30 Mg mL^{-1})	++++	++++	+++	+++	–	–

– no inhibition zone.
+ inhibition zone (5–10 mm).
++ inhibition zone (10–15 mm).
+++ inhibition zone (15–20 mm).
++++ inhibition zone (> 20 mm).

Elemental analyses were carried out by the Microanalytical Research Center, Faculty of Science, Cairo University. 4-Acetyl-2-pyrazolin-5-one [2], N′-[1-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)ethylidene]hydrazinecarbodithioic acid methyl ester, acetyl thiosemicarbazone **3c**,[15] and benzylidene malononitrile[17,18] were prepared according to the procedures reported in the literature.

Synthesis of (3b,d)

A mixture of 4-acetylpyrazolone **1** (0.01 mol) and hydrazine derivative **2b** benzylhydrazinecarbodithioate or **2d** cyano acetohydrazide (0.01 mol) in ethanol (50 mL) was refluxed for 1 h, then left to cool. The product was filtered and washed with ethanol several times and finally recrystallized from the proper solvents.

3b: N′-[1-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl) ethylidene]hydrazi-necarbodithioic Acid Benzyl Ester

Yield 84%, recrystallized from benzene, yellow crystals, (mp, 181–183°C), IR (KBr), $\upsilon = 3210$ (NH), 1594 (C=N) cm^{-1}, ^1H NMR ($CDCl_3$),

$\delta = 2.43$ (s, 3H, CH_3 at position-4), 2.61 (s, 3H, CH_3 pyrazolone at position-3), 4.58 (s, 2H, CH_2), 7.22–7.92 (m, 10H, Ar), and 11.66 ppm (br, NH), MF, ($C_{20}H_{20}N_4OS_2$), calculated: C, 60.58; H, 5.08; N, 14.13; Found: C, 60.56; H, 5.00; N, 14.11.

3d: Cyanoacetic Acid [1-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-ethylidene]hydrazide

Yield 78%, recrystallized from ethanol, pale yellow crystals, (mp, 218–220°C), IR (KBr), $\upsilon = 3222$ (NH), 3058 (CH-Ar), 2918 (CH-Al), 2220 (CN), 1656 (CO) cm^{-1}, ^1H NMR (DMSO-d_6)$\delta = 2.34$ (s,3H,CH_3 at position-4), 2.37 (s, 3H, CH_3 pyrazolone at position-3), 3.87 (s, 2H, CH_3), 7.15 (m, 1H, Ar-*p*-H), 7.38 (m, 2H, Ar-*m*-H), 7.94 (d, 2H, Ar-*o*-H), and 11.08 (br,1H, NH) MF. ($C_{14}H_{15}N_5O_2$). Calculated: C, 60.60; H, 5.09; N, 23.56; Found C, 60.57; H, 5.06; N, 23.55.

Synthesis of 5a–e: General Procedure

To a solution of **3a** and/or **3b** (0.01 mol) in ethanol (50 mL), alkylating agent methyl iodide, benzyl chloride, ethyl bromoacetate (0.01 mol), and triethylamine (0.5 mL) were added. The reaction mixture was refluxed for 2 h, and the solid that formed was collected by filtration, washed with ethanol, and recrystallized from the proper solvent.

5a: Yield 72 %, pale yellow crystals from ethanol, mp (195–196°C), IR (KBr) $\upsilon = 3430$ (OH), 2918 (CH-Al.), 1620 (C=N) cm^{-1}, ^1H NMR ($CDCl_3$)$\delta = 2.44$ (s, 3H, CH_3 at position-4), 2.52 (s, 3H, CH_3 pyrazolone at position-5), 2.61 (s,3H, SCH_3), 2.64 (s,3H, SCH_3), 7.15 (m, 1H, Ar-*p*-H), 7.36 (m, 2H, Ar-*m*-H), 8.01 (d, 1H, Ar-*o*-H), 14.18 (br, 1H, OH) MF ($C_{15}H_{18}N_4OS_2$). Calculated: C, 53.87; H, 5.42; N, 16.75; Found C, 53.86; H, 5.40; N, 16.72.

5b: Yield 73%, yellow crystals from ethanol, mp (136–138°C), IR (KBr), $\upsilon = 3438$(OH), 3020 (CH-Ar), 2916 (CH-Al), 1598 (C=N) cm^{-1}, ^1H NMR ($CDCl_3$)$\delta = 2.42$ (s, 3H, CH_3 at position-4), 2.48 (s, 3H, CH_3 of pyrazolone at position-3), 4.25 (s, 2H, SCH_2), 4.30 (s, 2H, SCH_2), 7.14–8.02 (m, 15H, Ar-H) and 14.15 (br, H, OH), MF ($C_{26}H_{26}N_4OS_2$). Calculated: C, 66.64; H, 5.39; N, 11.51, Found: C, 66.62; H, 5.36; N, 11.50.

5c: Yield 73%, yellow crystals from benzene (mp 146–148°C), IR (KBr) $\upsilon = 3428$ (OH), 2924 (CH-Al.), 1616 (C=N) cm^{-1}, ^1H NMR ($CDCl_3$)$\delta = 2.41$ (s, 3H, CH_3 at position-4), 2.45 (s, 3H, CH_3 pyrazolone at position-3), 2.53 (s,3H, SCH_3), 4.31 (s,2H, CH_2), 7.13–8.02 (m, 10H, Ar-H), 14.19 (br, 1H, OH), MF ($C_{21}H_{22}N_4OS_2$). Calculated C, 61.43; H, 5.40; N, 13.65; Found C, 61.40; H, 5.37; N, 13.64.

5d: Yield 68%, pale yellow crystals from ethanol (mp 147–149°C), IR (KBr) υ = 2502 (OH) 2980 (CH-Al), 1730 (CO ester group), 1618 (C=N) cm^{-1}, ^1H NMR ($CDCl_3$)δ = 1.29 (t, 3H, CH_3CH_2), 2.42 (s,3H, CH_3 at position-4), 2.55 (s, 3H, CH_3 of pyrazolone at position-3), 2.66 (s, 3H, SCH_3), 3.81 (s, 2H, SCH_2), 4.23 (q, 2H, CH_3-CH_2), 7.15 (m, 1H, Ar-*p*-H), 7.37 (m, 2H, Ar-*m*-H), 7.98 (d, 2H, Ar-*o*-H), 14.17 (br, 1H, NH), MF ($C_{18}H_{22}N_4O_3S_2$). Calculated: C, 53.18; H, 5.45; N, 13.78, Found: C, 53.16; H, 5.42; N, 13.75.

5e: Yield 70%, yellow crystals from ethanol, mp (140–142°C), IR (KBr) υ = 3410 (OH), 3050 (CH-Ar), 2912 (CH-Al.), 1726 (CO of ester group), 1590 (C=N) cm^{-1}, ^1H NMR ($CDCl_3$)δ = 1.29 (t, 3H, CH_3-CH_2), 2.42 (s, 3H, CH_3 at position-4), 2.43 (s, 3H, CH_3 of pyrazolone at position-3), 3.75 (s, 2H,SCH_2), 4.23 (q, 2H, CH_3-CH_2), 4.34 (s, 2H, SCH_2), 7.12–8.02 (m, 10H, Ar-H) and 14.18 (br, 1H, OH), MF ($C_{24}H_{26}N_4O_3S_2$). Calculated: C, 59.73; H, 5.43; N, 11.61, Found: C, 59.70; H, 5.41; N, 11.60.

Synthesis of 1,3,4-Thiadiazole (7a–d)

To a mixture of **3a**,**b** (0.01 mol) and appropriate hydrazonyl halide **6a–d** (0.01 mol) in ethanol (50 mL), triethylamine (0.5 mL) was added, and the reaction mixture was refluxed for 2 h. The resulting product was collected by filtration and recrystallized from the proper solvent.

7a: 1-(5-{[1-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl) ethylidene]hydra-zono}-4-phenyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)ethanone

Yield 74%, orange crystals, recrystallized from a mixture of ethanol/benzene, mp 249–251°C, IR (KBr), υ = 3100 (CH-Ar.), 2924 (CH-Al), 1682 (CO of acetyl group) cm^{-1}, ^1H NMR ($CDCl_3$) 2.43 (s, 3H, CH_3 at position-4), 2.51 (s, 3H, CH_3 of pyrazolone at position-3), 2.63 (s, 3H, CH_3CO), 7.18-7.98 (m, 10H, Ar-H), MF ($C_{22}H_{20}N_6O_2S$). Calculated: C, 61.10; H, 4.66; N, 19.43, Found: C, 61.09; H, 4.64; N, 19.41.

7b: 5-{[1-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl) ethylidene]hydra-zono}-4-o-tolyl-4,5-dihydro[1,3,4]thiadiazole-2-carboxylic Acid Ethyl Ester

Yield 69%, yellow crystals, recrystallized from benzene, mp 196–198°C, IR (KBr), υ = 3362 (OH), 3050 (CH-Ar), 2924 (CH-Al), 1710 (CO of ester group) cm^{-1}, ^1H NMR ($CDCl_3$) 1.43 (t, 3H, $\underline{CH_3}$-CH_2), 2.28 (s, 3H, CH_3 of *o*-position), 2.34 (s, 3H, CH_3 at position-4), 2.39 (s, 3H, CH_3 of pyrazolone at position-3), 4.48 (q, 2H, CH_3-$\underline{CH_2}$), 7.16–7.98 (m, 9H,

Ar-H), 13.7 (br, 1H, OH), M.F. ($C_{24}H_{24}N_6O_3S$), Calculated: C, 60.49; H, 5.08; N, 17.64, Found: C, 60.47; H, 5.05; N, 17.61.

7c: 4-(4-Chlorophenyl)-5-{[1-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-ethylidene]hydrazono}-4,5-dihydro[1,3,4] thiadiazole-2-carboxylic Acid Ethyl Ester

Yield 72%, yellow crystals, recrystallized from benzene, mp 254–256°C, IR (KBr), υ = 3090 (CH-Ar.), 2924 (CH-Al), 1742 (CO of ester group) cm^{-1}, ^1H NMR 1.43 (t, 3H, $\underline{CH_3}$-CH_2), 2.44 (s, 3H, CH_3 at position-4), 2.51 (s, 3H, CH_3 of pyrazolone at position-3), 4.46 (q, 2H, CH_3-$\underline{CH_2}$), 7.19–7.96 (m, 9H, Ar-H), MF ($C_{23}H_{21}ClN_6O_3S$). Calculated: C, 55.59; H, 4.26; N, 16.91, Found: C, 55.57; H, 4.24; N, 16.90.

7d: (5-{[1-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)ethylidene]hydra-zono}-4-phenyl-4,5-dihydro[1,3,4] thiadiazol-2-yl)phenylmethanone

Yield 75%, red crystals, recrystallized from a mixture of ethanol/benzene, mp 248–250°C, IR (KBr), υ = 3060 (CH-Ar.), 2925 (CH-Al), 1625 (C=N) cm^{-1}, MS m/z, 495 (M^++1), 494 (M^+) for ($C_{26}H_{22}N_6OS$). Calculated: C, 65.57; H, 4.48; N, 16.99, Found: C, 65.55; H, 4.47; N, 16.97.

Synthesis of (8)

A mixture of **3c** (0.01 mol), ethyl bromoacetate (0.01 mol), and fused sodium acetate (0.02 mol) in ethanol (50 mL) was refluxed for 1 h. The product obtained was collected by filtration, washed with water, and recrystallized from a mixture of DMF/EtOH to give **8** as pale yellow crystals, yield 85%, mp 320–322 °C, IR (KBr), υ = 3432 (OH), 3390 (NH), 3050 (CH-Ar), 2964 (CH-Al), 1620 (CO) cm^{-1}, ^1H-NMR (DMSO-d_6) 2.30 (s, 3H, CH_3 at position-4), 2.48 (s, 3H, CH_3 of pyrazolone at position-3), 3.66 (s, 2H, CH_2), 7.02-8.07 (m, 5H Ar-H and NH) and 13.80 (br, 1H, OH), MF ($C_{15}H_{15}N_5O_2S$), Calculated: C, 54.70; H, 4.59; N, 21.26, Found: C, 54.68; H, 4.57; N, 21.24.

Synthesis of (2-{[1-(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-ethylidene]hydrazono}-4-oxothiazolidin-3-yl) acetic Acid Ethyl Ester (9)

Method A: A mixture of **8** (0.01 mol), fused sodium acetate (0.02 mol), and ethyl bromoacetate (0.01 mol) in ethanol (50 mL) was

refluxed for 1 h. After cooling, the solid that formed was collected and recrystallized from ethanol to give **9** (65% yield), as pale yellow crystals, mp 230–232°C).

Method B: A mixture of **3c** (0.01 mol), ethyl bromoacetate (0.02 mol), and fused sodium acetate (0.02 mol) in ethanol (50 mL) was refluxed for 2 h. After cooling, the obtained product was collected and recrystallized from benzene to give **9** (68% yield), mp, mixed mp with product from procedure (A) gave no depression.

IR (KBr), υ = 3060 (CH-Ar.), 2984 (CH-Al.), 1728 (CO of ester), 1620 (CO of thiazolidinone) cm^{-1}, ^{1}H-NMR ($CDCl_3$) 1.31 (t, 3H, $\underline{CH_3}$-CH_2), 2.43 (s, 3H, CH_3 at position-4), 2.50 (s, 3H, CH_3 of pyrazolone at position-3), 4.06 (s, 2H, CH_2 of thiazolidinone), 4.28 (q, 2H, CH_3-$\underline{CH_2}$), 4.52 (s, 2H, NCH_2), 7.27 (m, 1H, Ar-*p*-H), 7.40 (m, 2H, Ar-*m*-H), 7.98 (d, 2H, Ar-*o*-H), MF ($C_{19}H_{21}N_5O_3S$), Calculated: C, 54.93; H, 5.09; N, 16.86, Found: C, 54.91; H, 5.07; N, 16.83.

Synthesis of 5-Methyl-4-{1-[(4-substituted-3H-thiazol-2-ylidene)hydrazono]-ethyl}-2-phen-yl-2,4-dihydropyrazol-3-one (10a,b)

A mixture of **3c** (0.01 mol) and chloroacetone and/or phenacyl bromide (0.01 mol) in ethanol (40 mL) was refluxed for 1 h. The solid product that formed was collected by filtration and recrystallized from the proper solvent.

10a: 5-Methyl-4-{1-[(4-methyl-3H-thiazol-2-ylidene)hydrazono]ethyl}-2-phen-yl-2,4-dihydropyrazol-3-one

Yield 72%, red crystals, from benzene, mp (270–272°C); IR (KBr), υ = 3396 (OH), 3194 (NH), 3045 (CH-Ar.), 2960 (CH-Al.) cm^{-1}; MS (m/z), 327 (M^+ , 0.32%), 272, 231, 215 (100%) for ($C_{16}H_{17}N_5OS$), Calculated: C, 58.70; H, 5.23; N, 21.39, Found: C, 58.68; H, 5.20; N, 21.37.

10b: 5-Methyl-2-phenyl-4-{1-[(4-phenyl-3H-thiazol-2-ylidene)hydrazono]eth-yl}-2,4-dihydropyrazol-3-one

Yield 70%, red crystals, from benzene, mp (247–250°C), IR (KBr), υ = 3466 (OH), 3250 (NH), 3050 (CH-Ar), 2980 (CH-Al), ^{1}H NMR ($CDCl_3$) 2.45 (s, 3H, CH_3 at position-4), 2.67 (s, 3H, CH_3 of pyrazolone at position-5), 4.60 (br, 1H, NH), 7.17–8.51 (m, 10H, Ar-H) and 14.53 (br, 1H, OH), MF ($C_{21}H_{19}N_5OS$), Calculated: C, 64.76; H, 4.92; N, 17.98, Found: C, 64.75; H, 4.91; N, 17.97.

Syhthesis of 5-Methyl-4-[1-(4-substituted-5-phenylazo-3H-thiazol-2-ylidene-azo)ethyl]-2-phenyl-2,4-dihydropyrazol-3-one (11a,b)

Method A: To a cold solution of **10a**,**b** (0.01 mol) in ethanol containing sodium acetate (3 g), benzene diazonium chloride (0.01 mol) was added, [prepared by diazotization of aniline (0.012 mol) in conc. HCl (6 mL) with sodium nitrite (0.97g in 5 mL H_2O) at 0 °C] portion-wise over (30 min) with constant stirring. After complete addition, the reaction mixture was stirred for a further 1 h at 0 °C. The solid product was filtered off, washed with water, and recrystallized from a mixture of ethanol/benzene to give **11a,b**.

Method B: To a mixture of **3c** (0.01 mol) and the appropriate hydrazonyl halide (**6a**,**d**) (0.01 mol) in ethanol (50 mL), triethylamine (0.5 mL) was added, and the reaction mixture was refluxed for 2 h. The isolated product was collected by filtration and recrystallized to give a product that was identical in mp, mixed mp, and spectra with **11 a**,**b**, respectively, which was obtained from method A.

11a: 5-Methyl-4-[1-(4-methyl-5-phenylazo-3H-thiazol-2-ylidene-azo)ethyl]-2-phenyl-2,4-dihydropyrazol-3-one

Mp 253–255 °C, IR (KBr), $\upsilon = 3150$ (NH), 3020 (CH-Ar.), 2954 (CH-Al.), cm^{-1}, ^1H NMR ($CDCl_3$) 2.45 (s, 3H, CH_3 at position-4), 2.67 (s, 3H, CH_3 of pyrazolone at position-5), 2.72 (s, 3H, CH_3 of thiazole), 7.24–7.98 (m, 11H, Ar-H and NH), MF ($C_{22}H_{21}N_7OS$), Calculated: C, 61.23; H, 4.91; N, 22.72, Found: C, 61.20; H, 4.90; N, 22.71.

11b: 5-Methyl-2-phenyl-4-[1-(4-phenyl-5-phenylazo-3H-thiazol-2-ylideneazo)-ethyl]-2,4-dihydropyrazol-3-one

Mp 220–222°C, IR (KBr), $\upsilon = 3310$ (OH), 3200 (NH), 3058 (CH-Ar.), 2980 (CH-Al.) cm^{-1}, ^1H NMR ($CDCl_3$) 2.44 (s, 3H, CH_3 at position-4), 2.53 (s, 3H, CH_3 of pyrazolone at position-5), 7.19–8.33 (m, 11H, Ar-H and NH), and 14.07 (br, 1H, OH) M.F. ($C_{27}H_{23}N_7OS$), Calculated: C, 65.70; H, 4.70; N, 19.86, Found: C, 65.68; H, 4.69; N, 19.83.

Synthesis of 2-Cyano-3-(substituted)acrylic Acid [1-(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl) ethylidene]hydrazide (12a,b)

To a solution of **3d** (0.01 mol) in ethanol (50 mL), the appropriate aromatic aldehyde was added as well as a few drops of piperidine. The reaction mixture was refluxed for 2 h, then allowed to cool. The precipitate

that formed was filtered off, washed with ethanol, and recrystallized from ethanol to afford the corresponding **12a**,**b**.

12a: 2-Cyano-3-(4-methoxyphenyl)acrylic Acid [1-(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylidene]hydrazide

Yield 65%, orange crystals, mp 224–226°C, IR (KBr), $\upsilon = 3400$ (OH), 3350 (NH), 3050 (CH-Ar), 2952 (CH-Al), 2212 (CN) cm^{-1}, ^1H NMR ($CDCl_3$), 2.46 (s, 3H, CH_3 at position-4), 2.73 (s, 3H, CH_3 of pyrazolone at position-3), 3.82 (s, 3H, CH_3O), 6.87–8.04 (m, 11H, Ar-H CH of benzylidine and NH) and 13.90 (br, 1H, OH), MF ($C_{23}H_{21}N_5O_3$), Calculated: C, 66.49; H, 5.09; N, 16.86, Found: C, 66.47; H, 5.05; N, 16.83.

12b: 2-Cyano-3-(4-dimethylaminophenyl)acrylic acid [1-(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylidene]hydrazide

Yield 68%, yellow crystals, mp 208–210°C, IR (KBr), $\upsilon = 3420$ (NH), 3050 (CH-Ar), 2942 (CH-Al), 228 (CN) cm^{-1}, ^1H NMR ($CDCl_3$), 2.46 (s, 3H, CH_3 at position-4), 2.71 (s, 3H, CH_3 of pyrazolone at position-3), 3.02 (s, 6H, $N(CH_3)_2$), and 6.62–8.02 (m, 11H, Ar-H, NH and CH of benzylidine). MF ($C_{24}H_{24}N_6O_2$), Calculated: C, 67.27; H, 5.65; N, 19.61, Found: C, 67.25; H, 5.63; N, 19.60.

Synthesis of 6-Amino-4-(4-substitutedphenyl)-1-[1-(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylideneamino]-2-oxo-1,2-dihydropy-ridine-3,5-dicarbonitrile (14a,b)

Method A: To a solution of the appropriate **12a**,**b** (0.01 mol) in ethanol (40 mL), malononitrile (0.01 mol) and few drops of piperidine were added. The reaction mixture was heated under reflux for 2 h, then left to cool. The precipitate was collected by filtration, washed with ethanol, and recrystallized from ethanol/DMF to give the corresponding pyridine-2-one derivatives **14a**,**b**.

Method B: To a solution of **3d** (0.01 mol) in ethanol (40 mL), the appropriate benzylidinemalononitrile (0.01 mol) and few drops of piperidine were added. The reaction mixture was heated under reflux for 2 h, then left to cool to room temperature. The solid product that formed was collected by filtration, washed with ethanol, and then recrystallized from ethanol/DMF to give products identical in all respects (mp, mixed mp, and spectra) with those **14a**,**b** obtained from method A.

14a: 6-Amino-4-(4-methoxyphenyl)-1-[1-(3-methyl-5-oxo-1-phenyl-4,5-dihy-dro-1H-pyrazol-4-yl)ethylideneamino]-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile

Pale yellow crystals, mp >300°C, yield 68%, IR (KBr), υ = 3388, 3320 (NH_2), 3030 (CH-Ar), 2918 (CH-Al), 2188 (CN), 1660 (CO) cm^{-1}. MS (m/z) (M^+ 479) for ($C_{26}H_{21}N_7O_3$), Calculated: C, 65.13; H, 4.41; N, 20.45, Found: C, 65.11; H, 4.40; N, 20.43.

14b: 6-Amino-4-(4-dimethylaminophenyl)-1-[1-(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylideneamino]-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile

Yellow crystals, mp >300°C, yield 72%, IR (KBr), υ = 3390, 3250 (NH_2), 3185 (CH-Ar), 2920 (CH-Al), 2204 (CN). MS (m/z) (M^+ 492) for ($C_{27}H_{24}N_8O_2$), Calculated: C, 65.84; H, 4.91; N, 22.75, Found: C, 65.82; H, 4.90; N, 22.73.

Synthesis of Coumarin Derivatives 16a–c and 17

To a mixture of the appropriate salicyldehyde derivatives **15a–c** and/or 2-hydroxy-1-naphthaldehyde (0.01 mol) and **3d** (0.01 mol) in ethanol (50 mL), a few drops of piperidine were added, and the reaction mixture was heated under reflux temperature for 1 h, then left to cool at room temperature. The obtained solid was collected by filtration and recrystallized from the proper solvent to give **16a–c** and **17**, respectively.

16a: 2-Oxo-2H-chromene-3-carboxylic Acid [1-(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylidene]hydrazide

Yield 76%, red crystals from ethanol, mp 248–250°C), IR (KBr), υ = 3430 (OH), 3346 (NH), 3100 (CH-Ar), 2975 (CH-Al), 1710 (CO of lactone), 1614 (CO) cm^{-1}, ^1H NMR ($CDCl_3$), 2.45 (s, 3H, CH_3 at position-4), 2.64 (s, 3H, CH_3 of pyrazolone at position-3), 6.64–7.99 (m, 10H, Ar-H and NH), 8.76 (s, 1H, coumarin H-4), 14.10 (br, 1H, OH), MF ($C_{22}H_{18}N_4O_4$), Calculated: C, 65.66; H, 4.51; N, 13.92, Found: C, 65.63; H, 4.50; N, 13.90.

16b: 8-Methoxy-2-oxo-2H-chromene-3-carboxylic Acid [1-(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylidene]hydrazide

Yield 78%, orange crystals, from benzene, mp 230–232°C), IR (KBr), υ = 2450 (OH), 3326 (NH), 3100 (CH-Ar), 2926 (CH-Al), 1706 (CO of lactone) cm^{-1}, ^1H NMR ($CDCl_3$) 2.46 (s, 3H, CH_3 at position-4), 2.65 (s, 3H, CH_3 of pyrazolone at position-3), 4.01 (s, 3H, OCH_3), 6.64–8.01

(m, 9H, Ar-H and NH), 8.75 (s, 1H, coumarin H-4), and 14.11 (br, 1H, OH), MF ($C_{23}H_{20}N_4O_5$), Calculated: C, 63.88; H, 4.66; N, 12.96, Found: C, 63.87; H, 4.64; N, 12.94.

16c: 8-Ethoxy-2-oxo-2H-chromene-3-carboxylic acid [1-(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylidene]hydrazide

Yield 74%, orange crystals, from ethanol, mp 240–242°C, IR (KBr), $\upsilon = 3304$ (NH), 3050 (CH-Ar), 2928 (CH-Al), 1700 (CO of lactone) cm^{-1}, ^1H NMR ($CDCl_3$), 1.54 (t, 3H, $\underline{CH_3}$-CH_2), 2.45 (s, 3H, CH_3 at position-4), 2.62 (s, 3H, CH_3 of pyrazolone at position-3), 4.23 (q, 2H, CH_3-$\underline{CH_2}$), 6.70–8.00 (m, 9H, Ar-H and NH), and 8.73 (s, 1H, coumarin H-4), MF ($C_{24}H_{22}N_4O_5$), Calculated: C, 64.57; H, 4.97; N, 12.55, Found: C, 64.55; H, 4.95; N, 12.53.

17: 3-Oxo-3H-benzo[f]chromene-2-carboxylic Acid [1-(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylidene]hydrazide

Yield 80%, red crystals, from dioxane, mp 215–216°C, IR (KBr), $\upsilon =$ 3348 (NH), 3062 (CH-Ar), 2960 (CH-Al), 1708 (CO of lactone) cm^{-1}, ^1H NMR (DMSO-d_6), 2.48 (s, 3H, CH_3 at position-4), 2.71 (s, 3H, CH_3 of pyrazolone), 7.14–8.64 (m, 12H, Ar-H and NH), and 9.77 (s, 1H benzocoumarin H-4), MF ($C_{26}H_{20}N_4O_4$), Calculated: C, 69.02; H, 4.46; N, 12.38, Found: C, 69.00; H, 4.44; N, 12.36.

Synthesis of Cyano(aryl-hydrazono)acetic Acid [1-(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylidene]hydrazide (18a–c)

To a stirred solution of **3d** (0.01 mol) in ethanol (50 mL) and sodium acetate (3 g), the appropriate aryldiazonium salt (0.01 mol) was added [prepared by diazotization of 0.01 mol of aromatic amine (0.012 mol) in concentrated HCl (6 mL) with sodium nitrite (0.97 g) in 5mL H_2O) at 0°C] portion wise over 30 min with constant stirring after complete addition. The reaction mixture was stirred for a further 1 h at 0 °C, the solid product was filtered off, washed with water, dried, and recrystallized from the proper solvent.

18a: Cyano(phenyl-hydrazono)acetic Acid [1-(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylidene]hydrazide

Yield 82%, pale yellow crystals, from ethanol/benzene, mp 271–273°C, IR (KBr), $\upsilon = 3230$ (NH), 3068 (CH-Ar), 2980 (CH-Al), 2216 (CN),

1692 (CO)cm^{-1}, MS 401 (M^+ 56%), 402 (M^++1) 14.4%, 199 (88.4), 77 (100) for ($C_{23}H_{18}N_7O_2$), Calculated: C, 62.83; H, 4.77; N, 24.42, Found: C, 62.80; H, 4.75; N, 24.40.

18b: Cyano[(4-methoxyphenyl)hydrazono]acetic Acid [1-(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylidene]hydrazide

Yield 85%, yellow crystals, from ethanol/benzene, mp 240–242 °C, IR (KBr), υ = 3220 (NH), 3076 (CH-Ar), 2960 (CH-Al), 2214 (CN), 1690 (CO) cm^{-1}, ^{1}H NMR (DMSO-d_6), 2.40 (s, 3H, CH_3 at position-4), 2.50 (s, 3H, CH_3 of pyrazolone), 3.76 (s, 3H, OCH_3), 6.96–8.00 (m, 9H, Ar-H), 10.80 (s, 1H, NH), 12.09 (s, 1H, NH of hydrazo), MF ($C_{22}H_{21}N_7O_3$), Calculated: C, 61.24; H, 4.91; N, 22.73, Found: C, 61.22; H, 4.90; N, 22.71.

18c: Cyano-(p-tolylhydrazono)acetic Acid [1-(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylidene]hydrazide

Yield 75%, pale yellow crystals, from ethanol/DMF, mp (262–264 °C), IR (KBr), υ = 3230 (NH), 3072 (CH-Ar), 2950 (CH-Al), 2216 (CN), 1690 (CO) cm^{-1}, ^{1}H NMR (DMSO-d_6), 2.29 (s, 3H, CH_3 *p*-substituted), 2.36 (s, 3H, CH_3 at position-4), 2.43 (s, 3H, CH_3 of pyrazolone), 7.13–7.99 (m, 9H, Ar-H), 10.82 (s, 1H, NH), and 12.08 (s, 1H, NH hydrazone), MF ($C_{22}H_{21}N_7O_2$), Calculated: C, 63.60; H, 5.09; N, 23.60, Found: C, 63.58; H, 5.07; N, 23.57.

Synthesis of 4-Amino[1,2,4]triazolo[5,1-c][1,2,4]triazine-3-carboxylic Acid [1-(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)ethylidene]hydrazide (20) and 4-Amino-8-cyano-7-methylsulfanylpyrazolo[5,1-c][1,2,4]triazine-3-carboxylic Acid [1-(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-ethylidene]hydrazide (22)

General procedure: To a stirred cold solution of **3d** (0.01 mol) in pyridine (25 mL), the triazole and/or pyrazole diazonium salt (0.01 mol) was added portion wise over a period of 30 min. The reaction mixture was kept in an icebox overnight, then diluted with water. The solid that precipitated was filtered off, washed with water, and recrystallized from the proper solvent.

20: Yield 63%, brown crystals from DMF, mp >300°C, IR (KBr), υ = 3450, 3278, 3140 (NH_2, NH), 1688 (CO), MS 393 (M^++1) 23%, 392 (M^+, 100%), for ($C_{17}H_{16}N_{10}O_2$), Calculated: C, 52.04; H, 4.11; N, 35.70, Found: C, 52.02; H, 4.10; N, 35.68.

22: Yield (60%), brown crystals, from ethanol/benzene, mp >300°C), IR (KBr), υ = 3460, 3280, 3136 (NH_2, NH), 2224 (CN), 1664 (CO), MS, 448 (M^+, 100%), for ($C_{20}H_{18}N_9O_2S$), Calculated: C, 51.94; H, 3.92; N, 30.29, Found: C, 51.92; H, 3.91; N, 30.27.

ANTIMICROBIAL ACTIVITY

Most of new prepared compounds have been tested for their antimicrobial using citrofloxacin (30 μg mL^{-1}) as a reference compound. The compounds were tested against Gram-positive bacteria (*Bacillus subtilis NCTC* 10400, *Staphylococcus aureus ATCC* 25923), Gram-negative bacteria (*Escherichia coli ATCC* 25922, *Pseudomonas aeruginosa ATCC* 10415), and fungi (*Candida albicans TMRU* 3669, *Asperigillus nlger ATCC* 6265) by the agar diffusion technique. The tested compounds were dissolved in N,N-dimethylformamide to obtain a solution of 1000 μ g mL^{-1}. The bacteria and fungi cultures were maintained on nutrient agar and Czapek–Dox agar media, respectively. DMF showed no inhibition zones. The agar media were incubated with different microorganisms. After 24 h of incubation at 30 °C for bacteria and 48 h of incubation at 28 °C for fungi, the diameter of inhibition zone (mm) was measured. The minimal inhibitory concentration (MIC) of the active compounds was measured by a twofold serial dilution method.[19] The results are illustrated in Table I.

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