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SYNTHESIS OF SOME NEW THIAZOLES AND PYRAZOLO[1,5-*a*]PYRIMIDINES CONTAINING AN ANTIPYRINE MOIETY

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Ethyl 2-{2-[4-(2,3-dimethyl-5-oxo-1-phenyl-3-(pyrazolin-4-yl)]-2-cyano-1-(phenylamino) vinylthio}-acetate, 2-[4-(2,3-dimethyl-5-oxo-1-phenyl-(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-2-(4-oxo-3-phenyl-(1,3-thiazoilidin-2-ylidene))ethanenitrile, 2-[4-(2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-2-(4-methyl-3-phenyl(1,3-thiazolin-2-ylidene)) ethanenitrile, 2-(5-acetyl-4-methyl-3-phenyl(1,3-thiazolin-2-ylidene))-2-[4-(2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]ethanenitrile, and ethyl 2-(cyano (4-(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)methylene)-2, 3-dihydro-4-methyl-3-phenylthiazole-5-carboxylate were synthesized by treatment of 2-(4-(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)-3-mercapto-3-(phenylamino)-acrylonitrile with appropriate halo ketones or halo esters. Also, 4-{2-[5, 7-dimethyl-2-(phenylamino)(7a-hydropyrazolo[1,5-a]pyrimidin-3-yl](1,-thiazol-4-yl)}-2, 3-dimethyl-1-phenyl-3-pyrazolin-5-one derivatives were synthesized via reaction of 4-{2-[5-amino-3-(phenylamino)pyrazolin-4-yl](1,3-thiazol-2-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one with β-diketone or β-keto ester. All synthesized compound were established by elemental analysis, spectral data, and alternative synthesis whenever possible.

Keywords: Antipyrine; coumarine; pyrazoles; pyrazolo[1,5-*a*]pyrimidines; thiazoles

INTRODUCTION

Broad spectra of bioactive antipyrine derivatives have been investigated and diverse bioactivities such as analgesic,[1,2] anti-inflammatory,[3] antimicrobial,[4–6] and anticancer[7] activity have been reported. Also, a large number of thiazole derivatives have been found to exhibit pharmacological activity.[8–13] As an extension of our study[14–18] and as a part of our program aiming at the synthesis of different thiazoles for medicines, we report herein the synthesis of some new thiazoles and pyrazolo[1,5-*a*]pyrimidines containing an antipyrine moiety.

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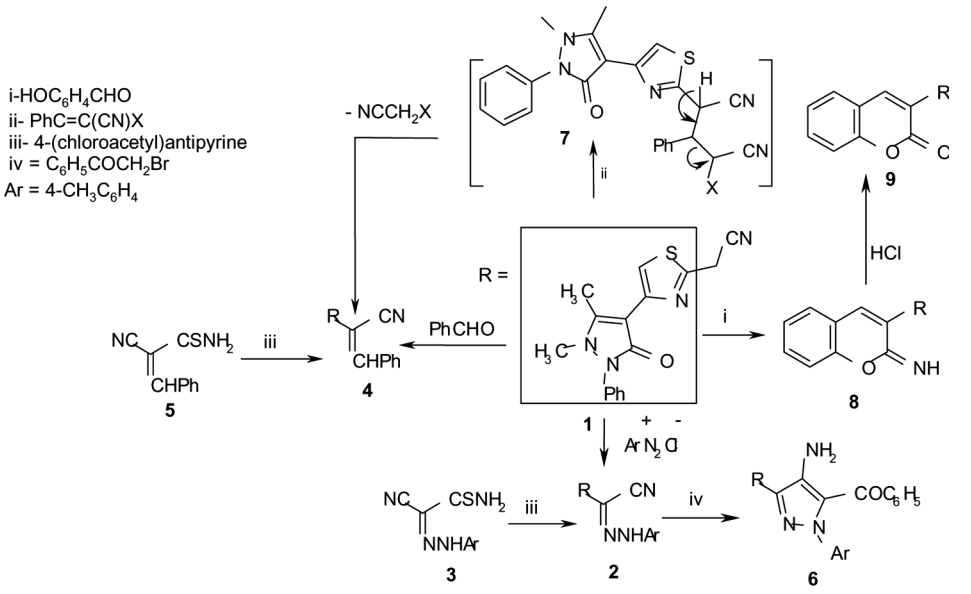
RESULTS AND DISCUSSION

Treatment of 2-[4-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-1,3-thiazol-2-yl]ethanenitrile[19] (**1**) with the appropriate of 4-methylbenzenediazonium chloride, benzaldehyde, or salicylaldehyde to give [4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)thiazol-2-yl]-(N′-4-tolylhydrazino)-acetonitrile (**2**), [4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)thiazol-2-yl]-3-phenylacrylonitrile (**4**) and 4-[2-(2-imino-2H-chromen-3-yl)-thiazol-4-yl]-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (**8**), respectively. Compound **8** was converted to 3-[4-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-1,3-thiazol-2-yl]-2H-chromen-2-one (**9**) by hydrolysis with hydrochloric acid (Scheme 1).

Structures **2** and **4** were elucidated by elemental analysis, spectral data, alternative synthetic routes, and chemical transformation. ^{1}H NMR spectrum of **2** showed signals at $\delta = 2.42$ (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 7.26–7.52 (m, 10H, ArH's and NH proton) and 8.16 (s, 1H, thiazole H-5). Its infrared (IR) spectra revealed bands at 3417 (NH), 2206 (CN), 1681 (CO), 1620 (C=N). Thus, treatment of 4-(chloroacetyl)antipyrine with 2-cyano-2-(4-tolyhydrazono)thioacetamide (**3**) and 2-cyano-3-phenylthioacrylamide (**5**) in boiling acetic acid gave products identical in all respects (mp, mixed mp, and spectra) to **2** and **4,** respectively. Compound **2** reacted with ω-bromoacetophenone in boiling *N,N*-dimethylformamide containing potassium carbonate and triethylamine to give 4-{2-[4-amino-1-(4-methylphenyl)-5-phenylcarbonyl)pyrazol-3-yl](1,3-thiazol-4-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**6**). Structure **6** was confirmed by elemental analysis and spectral data. IR spectrum of **6** revealed bands at 3463, 3355 (NH_2), 1681 (CO), and 1600 (C=C). Its ^{1}H NMR showed signals at $\delta = 2.42$ (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 6.23 (s, br., 2H, NH_2), 7.21–7.52 (m, 14H, ArH's), and 8.05 (s, 1H,

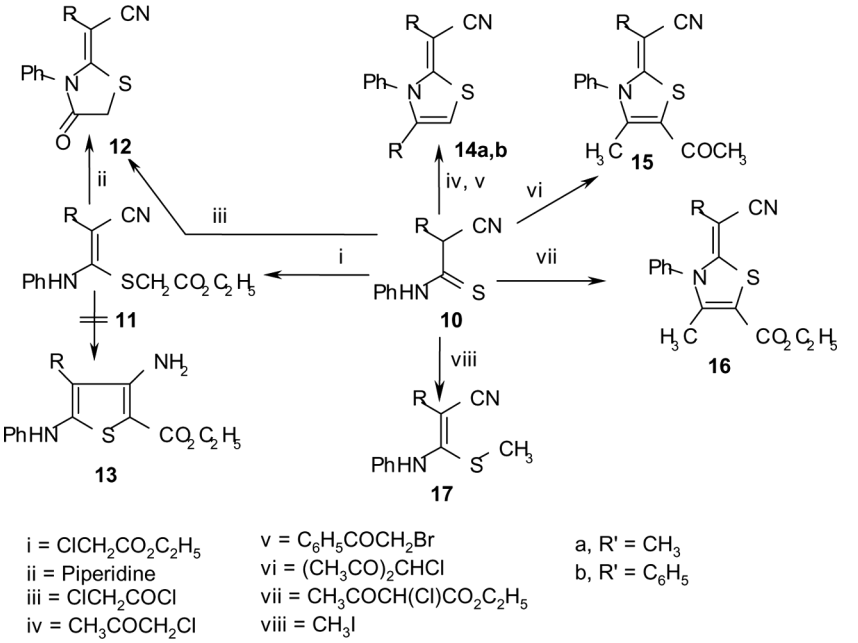


Scheme 1. Synthesis of 4-aminopyrazoles **6** and 4-substituted coumarine **9**.

thiazole H-5). Meanwhile, compound **1** reacted with either (phenylmethylene)-methane-1,1-dicarbonitrile or ethyl 2-cyano-3-phenylprop-2-enoate in boiling ethanol containing a catalytic amount of piperidine to yield **4**. The reaction that takes place is 1,4-Michael addition followed by a tautomerization to form the intermediate **7**, which readily loses one molecule of malononitrile or ethyl cyanoacetate.

Treatment of thioamide **10**, synthesized via reaction of **1** with phenyl isothiocyanate in the presence of potassium hydroxide, with ethyl chloroacetate in the presence of potassium hydroxide gives ethyl 2-{2-[4-(2,3-dimethyl-5-oxo-1-phenyl-3-(pyrazolin-4-yl)]-2-cyano-1-(phenylamino)vinylthio}acetate (**11**) (Scheme 2). Compound **11** was elucidated by elemental analysis, spectra, and chemical transformation. ^{1}H NMR spectrum of **11** showed signals at $\delta = 1.24$ (t, 3H, $CH_2\mathbf{CH_3}$), 2.55 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 3.32 (s, 2H SCH_2), 4.13 (q, 2H, $\mathbf{CH_2}CH_3$), 7.27–7.52 (m, 11H, ArH's and NH proton), and 8.09 (s, 1H, thiazole H-5). IR spectrum reveled bands at 3182 (NH), 2198 (CN), 1726 (CO), 1654 (C=N), 1593 (C=C). Compound **11**, when boiled with ethanol containing catalytic amounts of piperidine, gave 2-[4-(2,3-dimethyl-5-oxo-1-phenyl-(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-2-(4-oxo-3-phenyl-(1,3-thiazoilidin-2-ylidene))ethanenitrile (**12**). Treatment of **10** with chloroacetylchloride in *N,N*-dimethylformamide containing potassium hydroxide gave a product identical in all respects (mp, mixed mp., spectra) with **12**.

Analogously, treatment of **10** with either chloroacetone or ω-bromoacetophenone in *N,N*-dimethylformamide containing potassium hydroxide gave 2-(4-(2, 3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1*H*-pyrazol-4-yl)thiazol-2-yl)-2-(4-methyl-3-phenylthiazol-2(3*H*)-ylidene)acetonitrile (**14a**) and 2-(4-(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1*H*-pyrazol-4-yl)thiazol-2-yl)-2-(3,4-diphenylthiazol-2(3*H*)-ylidene)

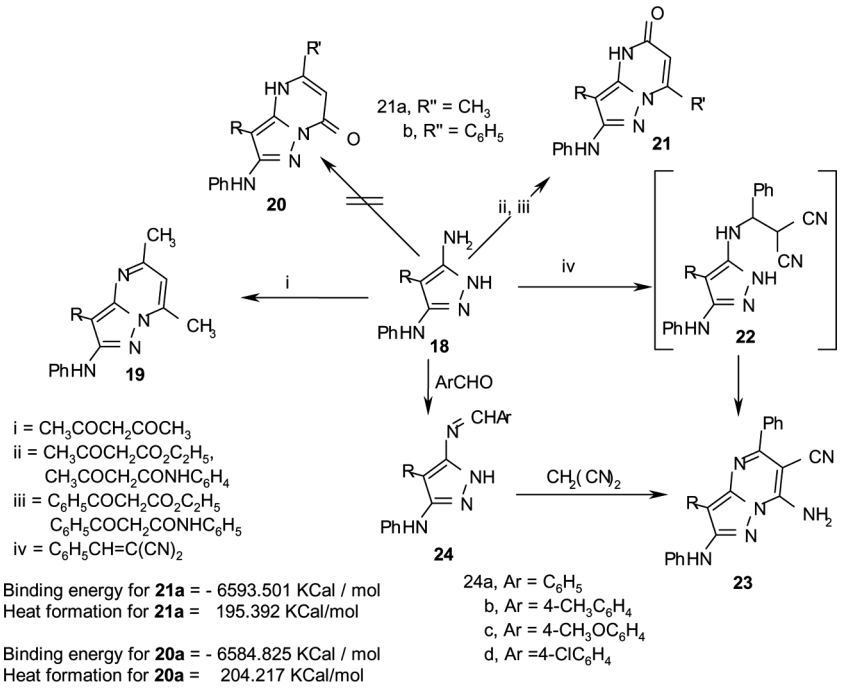


Scheme 2. Synthesis of some thiazoles **12**, **14**–**16**.

acetonitrile (**14b**), respectively. Structures **14a** and **14b** were elucidated by elemental analysis and spectral data (cf. Experimental section).

Also, compound **10** reacted with either 3-chloro-2,4-pentanedione, ethyl 2-chloro-3-oxobutanoate, or iodomethane in *N,N*-dimethylformamide containing potassium hydroxide to afford 2-(5-acetyl-4-methyl-3-phenyl(1,3-thiazolin-2-ylidene))-2-[4-(2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]ethanenitrile (**15**), ethyl 2-(cyano(4-(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1*H*-pyrazol-4-yl)thiazol-2-yl)methylene)-2,3-dihydro-4-methyl-3-phenylthiazole-5-carboxylate (**16**), and 2-[4-(2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-3-methylthio-3-(phenylamino)prop-2-enenitrile (**17**), respectively. Structures **15** and **16** were confirmed by elemental analysis and spectral data. Thus, ^{1}H NMR spectrum of **15** showed signals at $\delta = 2.28$ (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 7.25–7.66 (m, 10H, ArH's), and 8.03 (s, 1H, thiazole 5-H). Its IR revealed bands at 2187 (CN), 1656 (CO), 1633 (C=N), and 1587 (C=C).^{1}H NMR spectrum of **16** showed signals at $\delta = 1.41$ (t, 3H, $CH_2\mathbf{CH_3}$), 2.10 (s, 3H, CH_3), 2.96 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 4.35 (q, 2H, $\mathbf{CH_2}CH_3$), 7.25–6.67 (m, 10H, ArH's), and 8.02 (s, 1H, thiazole H-5). Its IR revealed bands at 2183 (CN), 1705, 1658 (CO's), and 1596 (C=C).

Treatment of **17** with hydrazine hydrate in boiling ethanol gave 4-{2-[5-amino-3-(phenylamino)pyrazolin-4-yl](1,3-thiazol-2-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**18**) (Scheme 3). Structure **18** was elucidated by elemental analysis, spectral data, and chemical transformation. Thus, **18** reacted with 2,4-pentanedione



Scheme 3. Synthesis of some pyrazolo[1,5-*a*]pyrimidines **19**, **21**, and **23**.

in boiling acetic acid to give 4-{2-[5,7-dimethyl-2-(phenylamino)(7a-hydropyrazolo[1,5-a]pyrimidin-3-yl](1,-thiazol-4-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**19**). Structure **19** was confirmed on the basis of elemental analysis and spectral data. Thus, ^{1}H NMR spectrum of **19** showed signals at $\delta = 2.56$ (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 6.12 (s, 1H, pyrimidine H-5), 7.0–7.95 (m, 11H, ArH's and thiazole H-5), and 9.75 (s, 1H, NH). Its IR spectrum revealed bands at 3301 (NH), 1639 (C=N), and 1602 (C=C).

Similarly, **18** reacted with either ethyl acetoacetate or ethyl benzoylacetate in acetic acid to afford 3-[4-(2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-7-methyl-2-(phenylamino)-4,6,7,7a-tetrahydropyrazolo[1,5-*a*]-pyrimidin-5-one (**21a**) and 3-[4-(2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-7-phenyl-2-(phenylamino)-4,6,7,7a-tetrahydropyrazolo[1,5-*a*]-pyrimidin-5-one (**21b**), respectively. Structures **21** were elucidated by elemental analysis, spectral data, and alternative synthetic routes. ^{1}H NMR spectrum of **21a** showed signals at $\delta = 2.35$ (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 8.67 (s, 2H, 2 NH), 5.60 (s, 1H, pyrimidine H-5), 6.87–7.450 (m, 10H, ArH's), and 8.01 (s, thiazole H-5). Its IR spectrum revealed bands at 3350 (NH), 1687 (CO), 1643 (C=N), and 1610 (C=C). Molecular orbital calculation (using Hyper-Chem., semi-empirical Method AM1) indicated that the structure **21** is more stable than structure **20**.

Compound **18** reacted with acetoacetanilide or benzoylacetanilide to afford products identical in all aspects (mp, mixed mp, and spectra) to **21a** and **21 b**.

Also, compound **18** reacted with 2-benzylidenemalononitrile in boiling ethanol to afford 7-amino-3-[4-(2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2yl)]-5-phenyl-2(phenylamino)-7a-hydropyrazolo[1,5-*a*]pyrimidine-6-carbonitrile (**23**). The structure of **23** was confirmed by elemental analysis, alternate synthetic route, and spectral data. ^{1}H NMR spectra of **23** showed signals at $\delta = 2.92$ (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 7.25–7.61 (m, 15H, ArH's), 8.00 (s, 1H, thiazol H-5), 8.95 (s, br., 2H, NH_2), 9.75 (s, br., 1H, NH). Thus, treatment of 4-{2-[5-(1-aza-2-phenylvinyl)-3-(phenylamino)pyrazol-4-yl](1,3-thiazol-2-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**24a**), which was prepared via reaction of **18** with benzaldehyde in ethanolic sodium ethoxide, with malononitrile gave a product identical in all respects (mp, mixed mp, and spectra) to **23**.

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu Fourier transform (FT)–IR 8201 PC spectrophotometer. ^{1}H NMR and spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300-MHz spectrometer, and chemical shifts are expressed in δ units using tetramethylsilane (TMS) as an internal reference. Elemental analyses were carried out at the Microanalytical Center of the Cairo University.

[4-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)thiazol-2-yl]-(N′-tolylhydrazino)-acetonitrile (2)

Method A. A solution of the appropriate 4-methylbenzenediazonium chloride (0.01 mol.) was added to a solution of **1** (3.1 g, 0.01 mol) and sodium acetate (1.3 g,

0.01 mol) in ethanol (30 ml) at 0–5 °C while stirring, and the reaction mixture was stirred for 6 h at 0 °C. The resulting solid was collected and recrystallized from acetic acid to give yellow crystals; mp 249–251 °C, yield (92%); IR (cm^{-1}): 3417 (NH), 2206 (CN), 1681 (CO), 1620 (C=N). ^{1}H NMR (CD_3Cl) $\delta = 2.42$ (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 7.26–7.52 (m, 10H, ArH's and NH proton), and 8.16 (s, 1H, thiazole H-5). Anal. calcd. for $C_{23}H_{20}N_6OS$ (428.52): C, 64.47; H, 4.70; N, 19.61; S, 7.48. Found: C, 64.35, H; 4.67; N, 19.52; S, 7.58.

Method B. A mixture of 4-chloroacetylantipyrine (2.6 g, 0.01 mol) and 4-tolylazocyanothioacetamide (2.18 g, 0.01 mol) in ethanol (20 ml) was heated under reflux for 2 h. The resulting solid was collected, washed with boiling water containing sodium acetate, and recrystallized from dimethylformamide to give **2**.

Synthesis of 4 and 8

Method A. An equimolar amount of **1** and either benzaldehyde or salicylaldehde (5 mmol) in 20 ml ethanol containing a catalytic amount of sodium ethoxide was stirred for 2 h. The resulting solid was collected and recrystallized from acetic acid to give **4** and **8,** respectively.

Method B. A mixture of 4-chloroacetylantipyrine (2.6 g, 0.01 mol) and 2-cyano-phenylthioacrylamide (1.88 g, 0.01 mol) in acetic acid (20 ml) was heated under reflux for 2 h. The resulting solid was collected, washed with boiling water containing sodium acetate, and recrystallized from dimethylformamide to give **4**.

[4-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)thiazol-2-yl]-3-phenylacrylonitrile (4)

This compound was obtained as pale yellow crystals (AcOH), mp 195 °C, yield (78%); IR (cm^{-1}): 2216 (CN), 1662 (CO), 1600 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 2.44$ (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 6.95–7.99 (m, 10H, ArH's), 8.07 (s, 1H, thiazole H-5), 8.74 (s, 1H, CH=). Anal. calcd. for $C_{23}H_{18}N_4OS$ (398.49): C, 69.33; H, 4.55; N, 14.06; S, 8.05. Found: C, 69.22, H; 4.45; N, 13.85; S, 8.11.

4-[2-(2-Imino-2H-chromen-3-yl)-thiazol-4-yl]-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one (8)

This compound was obtained as pale-yellow crystals (DMF); mp 240–242 °C, yield (76%); IR (cm^{-1}): 3240 (NH), 1662 (CO), 1643 (C=N), 1596 (C=C). ^{1}H NMR (CD_3Cl) $\delta = 2.44$ (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 6.95–7.99 (m, 10H, ArH's), 8.07 (s, 1H, thiazole H-5), 9.25 (s, br., 1H, NH). Anal. calcd. for $C_{23}H_{18}N_4O_2S$ (414.49): C, 66.65; H, 4.38; N, 13.52; S, 7.74. Found: C, 66.56, H; 4.35; N, 13.42; S, 7.82.

3-[4-(2,3-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-1,3-thiazol-2-yl]-2H-chromen-2-one (9)

A mixture of **8** (1 g, 0.0025 mol) and hydrochloric acid (10 ml, 3 M) was warmed with stirring for 30 min. The resulting solid was collected, washed with

water, and recrystallized from ethanol to give pale-yellow crystals (EtOH); mp 260–262 °C, yield (67%); IR (cm^{-1}): 1702, 1662 (CO's), 1643 (C=N), 1589 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 2.44 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 6.95–7.99 (m, 10H, ArH's), 8.07 (s, 1H, thiazole H-5). Anal. calcd. for $C_{23}H_{17}N_3O_3S$ (415.47): C, 66.49; H, 4.12; N, 10.11; S,7.72. Found: C, 66.52, H; 4.12; N, 10.21; S, 7.65.

4-{2-[4-Amino-1-(4-methylphenyl)-5-phenylcarbonyl)pyrazol-3-yl](1,3-thiazol-4-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (6)

A mixture of 2 (4.27 g, 0.01 mol) and ω-bromoacetophenone (0.01 mol) in DMF (20 ml) containing anhydrous potassium carbonate (0.01 mol) was refluxed in an oil bath at 130 °C for 3 h. The mixture was cooled, triethylamine (1 ml) was added, and the mixture was refluxed for 1 h at 90 °C. Then the reaction mixture was poured into an ice-water mixture (100 ml). The resulting solid was collected and recrystallized from proper solvent to give pale-yellow crystals (AcOH); mp 238–240 °C, yield (69%); IR (cm^{-1}): 3463, 3355 (NH_2), 1681 (CO), 1600 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 2.42 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 6.23 (s, br., 2H, NH_2), 7.21–7.52 (m, 14H, ArH's), 8.05 (s, 1H, thiazole H-5). Anal. calcd. for $C_{31}H_{26}N_6O_2S$ (546.66): C, 8.11; H, 4.79; N, 15.37; S,5.87. Found: C, 68.14, H; 4.87; N, 15.42; S, 5.76.

Ethyl 2-{2-[4-(2,3-Dimethyl-5-oxo-1-phenyl-3-(pyrazolin-4-yl)]-2-cyano-1-(phenyl-amino)vinylthio}acetate (11)

A mixture of **10** (4.45 g, 10 mmol) and potassium hydroxide (0.6 g, 10 mmol) in *N,N*-dimethylformamide (20 mL) was stirred for 2 h at room temperature. Ethyl chloroacetate (10 mmol) was added, and stirring was continued for 2 h. The resulting solid was collected and recrystallized with acetic acid to give pale-yellow crystals (EtOH); mp 230–232 °C, yield (60%); IR (cm^{-1}): 3182 (NH), 2198 (CN), 1726 (CO), 1654 (C=N), 1593 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 1.24 (t, 3H, CH_2CH_3), 2.55 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 3.32 (s, 2H SCH_2), 4.13 (q, 2H, CH_2CH_3), 7.27–7.52 (m, 11H, ArH's and NH proton) and 8.09 (s, 1H, thiazole H-5). Anal. calcd. for $C_{27}H_{25}N_5O_3S_2$ (531.66): C, 61.13; H, 4.74; N, 13.17; S, 12.06. Found: C, 61.13, H; 4.85; N, 13.00; S, 12.10.

2-[4-(2,3-Dimethyl-5-oxo-1-phenyl-(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-2-(4-oxo-3-phenyl-(1,3-thiazoilidin-2-ylidene))ethanenitrile (12)

Method A. A solution of **11** (2.65 g, 5 mmol) in ethanol (20 mL) containing piperidine (0.3 mL) was heated under reflux for 2 h. After cooling, the resulting solid was collected by filtration and recrystallized from *N,N*-dimethylformamide to give pale-yellow crystals (DMF); mp 255–257 °C, yield (62%); IR (cm^{-1}): 2166 (CN), 1662 (CO), 1618 (C=N), 1590 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 2.49 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 3.68 (s, 2H, CH_2 thiazoline), 7.13–7.60 (m, 10H, ArH's), 8.07 (s, 1H, thiazole H-5). Anal. calcd. for $C_{25}H_{19}N_5O_2S_2$ (485.59): C, 61.84; H, 3.94; N, 14.42; S,13.21. Found: C, 61.76, H; 4.10; N, 14.32; S, 13.22.

Method B. A mixture of **10** (4.45 g, 10 mmol) and potassium hydroxide (0.6 g, 10 mmol) in *N,N*-dimethylformamide (20 mL) was stirred for 2 h at room temperature. Chloroacetyl chloride (10 mmol) was added, and stirring continued for 2 h. The resulting solid was collected and recrystallized with *N,N*-dimethylformamide to give **12.**

Synthesis of 14a,b and 15–17

A mixture of **10** (4.45 g, 0.01 mol) and potassium hydroxide (0.6 g, 0.01 mol) in *N,N*-dimethylformamide (20 mL) was stirred for 2 h at room temperature. Chloroacetone, ω-bromoacetophenone, 3-chloro-2,4-pentandione, ethyl 2-chloro-3-oxobutanoate, or iodomethane (0.01 mol each) was added, and stirring was continued for 2 h. The resulting solid was collected and recrystallized from the proper solvent to give **14a**, **14b**, **15**, **16**, or **17**, respectively.

2-[4-(2,3-Dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-2-(4-methyl-3-phenyl(1,3-thiazolin-2-ylidene))ethanenitrile (14a). This compound was obtained as pale yellow crystals (AcOH); mp 312–14 °C, yield (60%); IR (cm^{-1}): 2186 (CN), 1654 (C=N), 1593 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 1.90$ (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 6.52–7.60 (m, 10H, ArH's), 7.92 (s, 2H, 2 thiazole H-5). Anal. calcd. for $C_{26}H_{21}N_5OS_2$ (483.62): C, 64.57; H, 4.38; N, 14.48; S, 13.26. Found: C, 64.74, H; 4.26; N, 14.35; S, 13.42.

2-[4-(2,3-Dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-2-(3,4-diphenyl(1,3-thiadiazolin-2- ylidene)ethanenitrile (14b). This compound was obtained as pale yellow crystals (AcOH); mp 310–312 °C, yield (60%); IR (cm^{-1}): IR: 2173 (CN), 1651 (C=N), 1614, 1593 (C=C).^{1}H NMR $(CD_3)_2SO$ $\delta = 2.93$ (s, 3H, CH_3), 3.19 (s, 3H, CH_3), 6.54–7.47 (m, 15H, ArH's), 7.95 (s, 2H, 2 thiazole H-5). Anal. calcd. for $C_{31}H_{23}N_5OS_2$ (545.69): C, 68.23; H, 4.25; N, 12.83; S, 11.75. Found: C, 68.41, H; 4.12; N, 12.74; S, 11.53.

2-(5-Acetyl-4-methyl-3-phenyl(1,3-thiazolin-2-ylidene))-2-[4-(2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]ethanenitrile (15). This compound was obtained as pale yellow crystals (AcOH); mp 346–349 °C, yield (62%); IR (cm^{-1}): IR: 2187 (CN), 1656 (CO), 1633 (C=N), 1587 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 2.28$ (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 7.25–7.66 (m, 10H, ArH's), 8.03 (s, 1H, thiazole 5-H) Anal. calcd. for $C_{28}H_{23}N_5OS_2$ (525.66): C, 63.98; H, 4.41; N, 13.32; S, 12.20. Found: C, 63.34, H; 4.34; N, 13.25; S, 12.10.

Ethyl 2-{[4-(2,3-Dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]cyano-methylene}-4-methyl-3-phenyl-1,3-thiazoline-5-carboxylate (16). This compound was obtained as pale yellow crystals (AcOH); mp 307–309 °C, yield (63%); IR (cm^{-1}): 2183 (CN), 1705, 1658 (CO's), 1596 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 1.41$ (t, 3H, $CH_2\mathbf{CH_3}$), 2.10 (s, 3H, CH_3), 2.96 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 4.35 (q, 2H, $\mathbf{CH_2}CH_3$), 7.25–6.67 (m, 10H, ArH's), 8.02 (s, 1H, thiazole H-5). Anal. calcd. for $C_{28}H_{23}N_5O_4S_2$ (557.66): C, 60.31; H, 4.16; N, 12.56; S, 11.50. Found: C, 60.32, H; 4.00; N, 12.67; S, 11.42.

2-[4-(2,3-Dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-3-methylthio-3-(phenylamino)prop-2-enenitrile (17). This compound was obtained as pale-yellow crystals (DMF); mp 252–254 °C, yield (65%); IR (cm^{-1}): 3320 (NH), 2186 (CN), 1654 (C=N), 1593 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 2.19$ (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.14 (s, 3H, CH_3), 7.25–7.49 (m, 11H, ArH's, NH), 8.04 (s, 1H, thiazole H-5). Anal. calcd. for $C_{24}H_{21}N_5OS_2$ (459.60): C, 62.72; H, 4.61; N, 15.24; S, 13.95. Found: C, 60.55, H; 4.52; N, 15.20; S, 13.58.

4-{2-[5-Amino-3-(phenylamino)pyrazolin-4-yl](1,3-thiazol-2-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (18)

A mixture of **17** (4.6 g, 0.01 mol) and hydrazine hydrate (1 ml, 99%) in ethanol (20 ml) was heated for 6 h. The resulting solid was collected and recrystallized from *N,N*-dimethylformamide to give colorless crystals (AcOH); mp 284–286 °C, yield (75%); IR (cm^{-1}): 3396, 3334, 3139 (NH, NH_2), 1653 (CO), 1585 (C=C).^{1}H NMR $(CD_3)_2SO$ $\delta = 2.82$ (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 5.81 (s, br., 2H, NH_2), 6.76 (t, 1H), 7.20–7.81 (m, 10H, ArH's), 8.52 (s, 1H, thiazole H-5), 11.24 (s, br., 1H, NH). Anal. calcd. for $C_{23}H_{21}N_7OS$ (443.53): C, 62.29; H, 4.77; N, 22.11; S,7.23. Found: C, 62.32, H; 4.87; N, 22.18; S, 7.32.

Synthesis of 19, 21a, and 21b

A mixture of **18** (4.43 g, 0.01 mol) and the appropriate 2,4-pentanedione, ethyl 3-oxobutanoate (or acetoacetanilide), or ethyl benzoylacetate (0.01 mol) in acetic acid (20 ml) was boiled under refluxed for 3 h. The resulting solid was collected and recrystallized from acetic acid to give **19, 21a,** and **21b**, respectively.

4-{2-[5,7-Dimethyl-2-(phenylamino)(7a-hydropyrazolo[1,5-a]pyrimidin-3-yl](1,-thiazol-4-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (19). This compound was obtained as buff crystals (AcOH); mp 298–300 °C, yield (69%); IR (cm^{-1}): IR: 3301 (NH), 1639 (C=N) and 1602 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ 2.56 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 6.12 (s, 1H, pyrimidine H-5), 7.0–7.95 (m, 11H, ArH's and thiazole H-5) and 9.75 (s, 1H, NH). Anal. calcd. for $C_{28}H_{25}N_7OS$ (507.62): C, 66.25; H, 4.96; N, 19.31; S, 6.32. Found: C, 66.45, H; 4.85; N, 19.21; S, 6.24.

3-[4-(2,3-Dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-7-methyl-2-(phenylamino)-4,6,7,7a-tetrahydropyrazolo[1,5-a]-pyrimidin-5-one (21a). This compound was obtained as buff crystals (AcOH); mp 310–314 °C, yield (72%); IR (cm^{-1}): 3350 (NH), 1687 (CO), 1643 (C=N) and 1610 (C=C). ^{1}H NMR $(CD_3)_2SO$ $\delta = 2.35$ (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 8.67 (s, 2H, 2 NH), 5.60 (s, 1H, pyrimidine H-5), 6.87–7.450 (m, 10H, ArH's), 8.01 (s, thiazole H-5). Anal. calcd. for $C_{28}H_{25}N_7OS$ (507.62): C, 66.25; H, 4.96; N, 19.31; S, 6.32. Found: C, 66.45, H; 4.85; N, 19.21; S, 6.24.

3-[4-(2,3-Dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2-yl)]-7-phenyl-2-(phenylamino)-4,6,7,7a-tetrahydropyrazolo[1,5-a]-pyrimidin-5-one (21b). This compound was obtained as buff crystals (AcOH), mp > 350 °C, yield

(68%); IR (cm^{-1}): 3432 (NH), 1684 (C=O), 1620 (C=N), 1600 (C=C). ^1H NMR $(CD_3)_2SO$ $\delta = 2.96$ (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 6.28 (s, 1H), 7.25–7.60 (m, 15H, ArH's), 7.92 (s, 1H, thiazole H-5), 9.21 (s, 1H, br., NH), 9.42 (s, 1H, br., NH). Anal. calcd. for $C_{32}H_{25}N_7O_2S$ (571.67): C, 67.23; H, 4.41; N, 17.15; S, 6.61. Found: C, 67.34, H; 4.34; N, 17.00; S, 5.45.

7-Amino-3-[4-(2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))(1,3-thiazol-2yl)]-5-phenyl-2(Phenylamino)-7a-Hydropyrazolo[1,5-*a*] pyrimidine-6-carbonitrile (23)

A mixture of **18** (2.2 g, 0.005 mol) and α-cyanocinnaminitrile (0.8 g, 0.005 mol) in ethanol (20 ml) containing a catalytic amount of piperidine (four to six drops) was refluxed for 4 h. The resulting solid was collected and recrystallized from *N,N*-dimethylformamide to give as yellow crystals (DMF); mp 365–367 °C, yield (65%); IR (cm^{-1}): 3396, 3334, 3139 (NH, NH_2), 1653 (CO), 1585 (C=C). ^1H NMR $(CD_3)_2SO$ $\delta = 2.92$ (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 7.25–7.61 (m, 15H, ArH's), 8.00 (s, 1H, thiazol H-5), 8.95 (s, br., 2H, NH_2), 9.75 (s, br., 1H, NH). Anal. calcd. for $C_{33}H_{25}N_9OS$ (571.67): C, 66.54; H, 4.23; N, 21.16; S,5.38. Found: C, 66.45, H; 4.12; N, 21.00; S, 5.45.

4-{2-[5-(1-Aza-2-arylvinyl)-3-(phenylamino)pyrazol-4-yl](1,3-thiazol-2-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (24a–d)

Sodium ethoxide (0.11 g-atom sodium metal) in ethanol (5 ml) was added portionwise while stirring to a mixture containing the appropriate benzaldehyde; 4-methylbenzaldehyde, 4-methoxybenzaldehyde, or 4-chlorobenzaldehyde (0.05 mol); and **18** (2.22 g, mol) for 30 min. The reaction mixture was stirred for 2 h, and then the resulting solid was collected and recrystallized from acetic acid to give **24a–d**, respectively.

4-{2-[5-(1-Aza-2-phenylvinyl)-3-(phenylamino)pyrazol-4-yl](1,3-thiazol-2-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (24a). This compound was obtained as orange crystals (AcOH); mp 255–257 °C, yield (72%); IR (cm^{-1}): 3432 (NH), 1684 (C=O), 1600 (C=C). ^1H NMR $(CD_3)_2SO$ $\delta = 2.81$ (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 6.92–7.99 (m, 16 H, ArH's and thiazole H-5), 8.07 (s, 1H, N=CH), 8.78 (s, 1H, NH) and 9.16 (s, 1H, NH). Anal. calcd. for $C_{30}H_{25}N_7OS$ (531.64): C, 67.78; H, 4.74; N, 18.62; S, 6.03. Found: C, 67.87, H; 4.65; N, 18.62; S, 5.88.

4-{2-[5-(1-Aza-2-(4-methylphenylvinyl)-3-(phenylamino)pyrazol-4-yl](1,3-thiazol-2-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (24b). This compound was obtained as yellow crystals (AcOH); mp 226–228 °C, yield (70%); IR (cm^{-1}): 3432 (NH), 1684 (C=O), 1600 (C=C). ^1H NMR $(CD_3)_2SO$ $\delta = 2.32$ (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 6.92–7.99 (m, 15 H, ArH's and thiazole H-5), 8.07 (s, 1H, N=CH), 8.78 (s, 1H, NH), and 9.16 (s, 1H, NH). Anal. calcd. for $C_{31}H_{27}N_7OS$ (545.67): C, 68.34; H, 4.99; N, 17.97; S, 5.88. Found: C, 68.34, H; 5.12; N, 17.85; S, 6.06.

4-{2-[5-(1-Aza-2-(4-methoxyphenylvinyl)-3-(phenylamino)pyrazol-4-yl](1,3-thiazol-2-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (24c). This compound was obtained as yellow crystals (AcOH); mp 245–248 °C, yield (78%); IR (cm^{-1}): 3432 (NH), 1684 (C=O), 1600 (C=C). ^1H NMR $(CD_3)_2SO$ $\delta = 2.81$ (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.92–7.99 (m, 15 H, ArH's and thiazole H-5), 8.07 (s, 1H, N=CH), 8.78 (s, 1H, NH) and 9.16 (s, 1H, NH). Anal. calcd. for $C_{31}H_{27}N_7O_2S$ (561.67): C, 66.29; H, 4.85; N, 17.46; S, 5.71. Found: C, 66.38, H; 4.92; N, 17.64; S, 5.65.

4-{2-[5-(1-Aza-2-(4-chlorophenylvinyl)-3-(phenylamino)pyrazol-4-yl](1,3-thiazol-2-yl)}-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (24d). This compound was obtained as pale-brown crystals (AcOH); mp 235–237 °C, yield (78%); IR (cm^{-1}): 3432 (NH), 1684 (C=O), 1600 (C=C). ^1H NMR $(CD_3)_2SO$ $\delta = 2.81$ (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 6.92–7.99 (m, 15 H, ArH's and thiazole H-5), 8.07 (s, 1H, N=CH), 8.78 (s, 1H, NH) and 9.16 (s, 1H, NH). Anal. calcd. for $C_{30}H_{24}ClN_7OS$ (566.09): C, 63.65; H, 4.27; N, 17.32; S, 5.66. Found: C, 63.45, H; 4.32; N, 17.45; S, 5.76.

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