Synthesis and Antioxidant Activity of Some New Thiazolyl–Pyrazolone Derivatives

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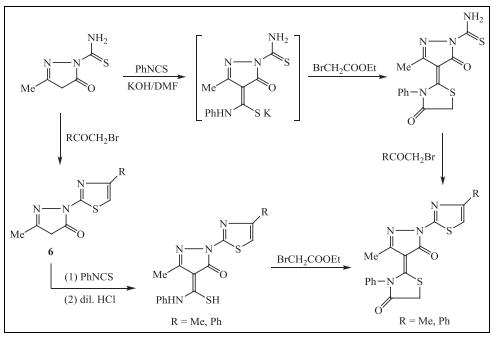

3-Methyl-1-thiocarbamoyl-2-pyrazolin-5-one has been utilized as a core for the synthesis of some 1-(thiazol-2-yl)-pyrazolin-5-one derivatives through diazo-coupling reaction and/or Knoevenagel condensation followed by heterocyclization with some α-halogenated reagents such as bromoacetone, phenacyl bromide, and ethyl bromoacetate. Base prompted addition of the core compound to an equimolar amount of phenyl isothiocyanate furnished 3-methyl-4-phenylthiocarbamoyl-1-thiocarbamoyl-2-pyrazolin-5-one which undergoes heterocyclization with α-halogenated reagents at the more reactive phenylthiocarbamoyl moiety to afford the corresponding 4-(thiazol-2-yl)-1-thiocarbamoyl-2-pyrazolin-5-ones. The new synthesized thiazolyl–pyrazolone compounds were evaluated for their potential antioxidant activity by using (ABTS Radical Cation Decolorization Assay).

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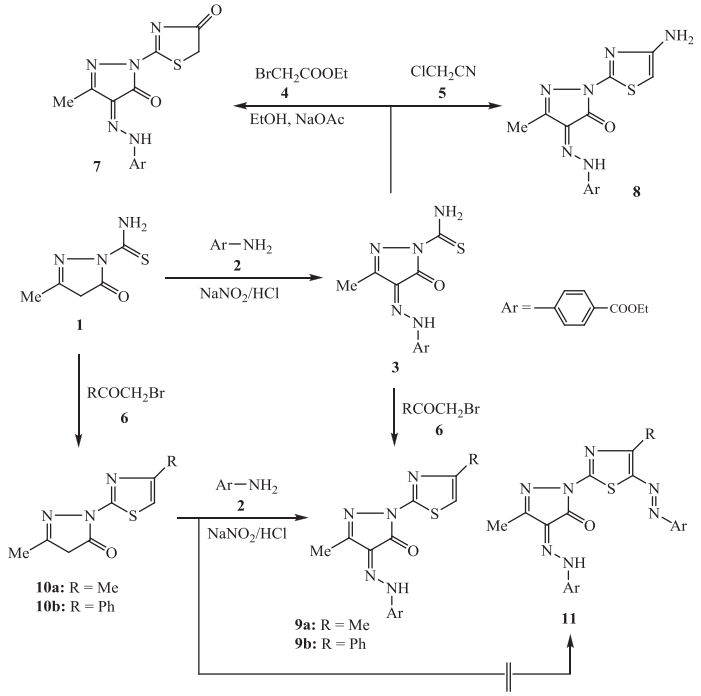
INTRODUCTION

The synthesis of various heterocyclic compounds having more than one heteroatom with structural and functional novelty has been increased in the recent years. The wide variety of these heterocycles have been explored for developing pharmaceutically important molecules like chalcones and their derivatives like pyrazoles and thiazoles. Pyrazole derivatives have gained great interest because of their pharmacological activities such as antidepressant [1], antioxidant [2], antiinflammatory [3], anticancer [4], antiviral [5], antibacterial [6], and antifungal [7] properties. Pyrazole derivatives containing thiazole ring have attracted the researchers because of their varied biological activities [8–12]. Therefore, several methods have been reported for the synthesis of thiazolyl–pyrazole derivatives [13,14]. In the literature, pyrazole derivatives are of interest principally for antioxidant properties because of the presence of conjugated π-system, which delocalize after donation of hydrogen atom and stabilize the antioxidant molecule; activity is also related to the concentration and type of substituent present [15]. In the present study, we report on the synthesis of some new thiazolyl–pyrazolone derivatives, their characterization by spectral data (IR, ^{1}H NMR and MS) and evaluation of their antioxidant properties that revealed interesting results by using (ABTS Radical Cation Decolorization Assay).

RESULTS AND DISCUSSION

Synthesis and reactions. The key compound 3-methyl-1-thiocarbamoyl-2-pyrazolin-5-one (**1**) was prepared by the reaction of ethyl acetoacetate with thiosemicarbazide according to the previously reported methodology [16]. The reactivity of methylene group in compound **1** was investigated toward the electrophilic diazocoupling reaction with the aromatic diazonium chloride of ethyl 4-amino benzoate (**2**); the reaction proceeded in pyridine to afford the corresponding 4-arylhydrazono-1-thiocarbamoyl-2-pyrazolin-5-one derivative **3** (Scheme 1). The chemical structure of **3** was secured by its correct elemental and spectral analyses. The IR spectrum of **3** showed absorption bands at 3370, 3252, and 3162 cm^{-1} corresponding to the NH_2 and NH groups and revealed the presence of two absorption bands at 1707 and 1691 cm^{-1} corresponding to the two carbonyl groups. The ^{1}H NMR spectrum showed triplet and quartet signals at 1.30 and 4.30 ppm because of ethyl group ($COOCH_2CH_3$), a singlet signal at 2.15 ppm

Scheme 1. Synthesis of 4-(arylhydrazono)-1-(thiazol-2-yl)-2-pyrazolin-5-ones **7**–**10**.



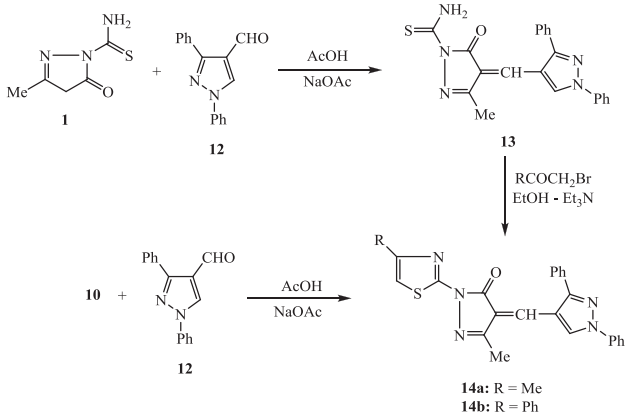
because of methyl protons (CH_3), two doublet signals at 7.55 and 8.00 ppm corresponding to the aromatic protons, in addition to two singlet signals at 9.55 and 11.55 ppm corresponding to the NH_2 and NH groups, respectively.

Heterocyclization of 4-arylhydrazono-1-thiocarbamoyl-2-pyrazolin-5-one derivative **3** with variety of α-halogenated reagents **4–6** was employed to synthesize the target thiazolyl–pyrazole derivatives **7**, **8,** and **9**. Treatment of **3** with ethyl bromoacetate under reflux in ethanol containing sodium acetate for 4 h afforded the corresponding thiazolyl-pyrazol-5-one **7**. The structure of **7** was established on the basis of its elemental analysis and spectral data. The reaction of compound **3** with chloroacetonitrile in ethanol containing a catalytic amount of triethylamine furnished the corresponding 4-aminothiazolyl-pyrazol-5-one **8**. The structure of **8** was confirmed by its correct elemental analysis and spectral data. The IR spectrum exhibited absorption bands at 3374, 3293, and 3166 cm^{-1} corresponding to the NH_2 and NH functions, while the absorption bands at 1701 and 1671 cm^{-1} were attributed to the two carbonyl groups (ester and pyrazole ring). The ^1H NMR spectrum displayed triplet signal at 1.30 ppm because of the protons of methyl group (ester), singlet signal at 2.15 ppm for the protons of methyl group, quartet signal at 4.30 ppm for the protons of methylene group (ester), singlet signal at 7.07 ppm for the proton of thiazole C-5, two doublet signals at 7.60 and 7.98 ppm because of the aromatic protons, and two signals at 8.50 and 11.60 corresponding to the protons of NH_2 and =NNH groups.

In addition, heterocyclization of compound **3** with α-bromoketones 6 (e.g. bromoacetone and phenacyl bromide) is carried out in hot ethanol containing drops of triethylamine to afford the corresponding 4-substitutedthiazolyl-pyrazol-5-one derivatives **9**. The chemical structure of compounds **9a**,**b** was confirmed on the basis of their elemental analysis and spectral data. An attempt to synthesis arylazothiazolyl-arylhydrazonopyrazol-5-one derivatives **11** was failed, 1-thiocarbamoyl-2-pyrazolin-5-one compound **1** was reacted with α-bromoketones **6** (e.g. bromoacetone and phenacyl bromide) to furnish the corresponding thiazol-pyrazol-5-one derivatives **6** which underwent diazocoupling reaction with aromatic diazonium salt gave the corresponding 4-substitutedthiazolyl-pyrazol-5-one derivatives **9** and did not give the arylazothiazolyl-arylhydrazonopyrazol-5-one derivatives **11**.

1,3-Diphenyl-1H-pyrazole-4-carbaldehyde (**12**) was synthesized previously [17] by heating of acetophenone phenyl hydrazone with Vilsmer–Haack reagent (DMF-$POCl_3$). The reactivity of our starting material, 3-methyl-1-thiocarbamoyl-2-pyrazolin-5-one (**1**) toward Knoevenagel condensation was also examined. Thus, condensation of equimolar amounts of pyrazolin-5-one compound **1** with 4-formylpyrazole **12** in acetic acid and fused sodium acetate yielded the corresponding condensation product **13** which underwent further heterocyclization reaction with α-bromoketones **6** (namely, bromoacetone and phenacyl bromide) furnished the corresponding thiazolyl–pyrazole derivatives **14**. The chemical structures of **14a**,**b** were confirmed by its spectral data and alternative synthesis from the reaction of thiazolyl-pyrazolin-5-one **10** with 4-formylpyrazole derivative **12** (Scheme 2). The IR spectrum of **14a** revealed the absence of NH_2 function and

Scheme 2. Synthesis of 1-(thiazol-2-yl)-4-[(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-2-pyrazolin-5-ones **14**.



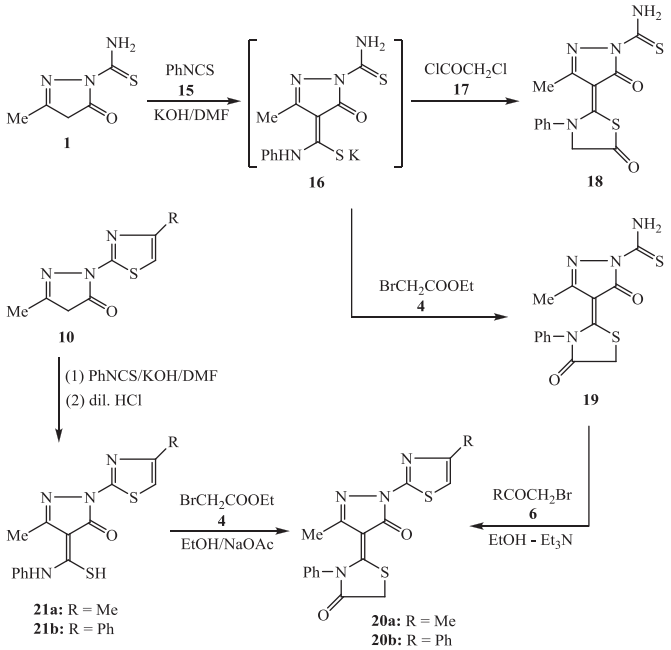
showed absorption band at 1671 cm^{-1} referring to the carbonyl group (C=O). ^{1}H NMR spectrum of **14b** displayed a singlet signal at 2.35 ppm because of the protons of the methyl group (CH_3), a singlet signal at 6.60 ppm because of the methine proton (CH=C), a singlet signal at 7.10 because of the proton of thiazole C-5, and a multiplet signal at the region 7.20–7.85 ppm for the aromatic and the pyrazole C-5 protons.

The base prompted addition of our starting compound **1** to equimolar amount of phenyl isothiocyanate (**15**) in DMF containing potassium hydroxide afforded the corresponding potassium sulfide salt **16** that was not isolated. *In situ* subsequent treatment of the non-isolable potassium salt **16** with chloroacetyl chloride (**17**) at room temperature furnished the corresponding 5-oxothiazolyl-pyrazolin-5-one derivative **18** (Scheme 3). The chemical structure of **18** was inferred from its elemental analysis and spectral data. Thus, its IR spectrum showed absorption bands at 3239 and 3208 cm^{-1} corresponding to the NH_2 function and bands at 1753 and 1657 cm^{-1} referring to the two carbonyl groups and 1591 cm^{-1} for the (C=N) function. The ^{1}H NMR spectrum showed two singlet signals at 2.35 and 4.25 ppm referring to the protons of methyl and methylene groups, a multiplet signal in the region 7.15–7.60 ppm because of the aromatic protons, and a singlet signal at 9.65 ppm for the protons of amino (NH_2) group. The mass spectrum showed the molecular ion peak at $m/z = 332$ corresponding to the molecular weight of the molecular formula $C_{14}H_{12}N_4O_2S_2$.

On the other hand, *in situ* treatment of the potassium salt **16** with equimolar amount of ethyl bromoacetate (**4**) afforded the isomeric 4-oxothiazolyl-pyrazolin-5-one derivative **19**. The IR spectrum of **19** showed absorption bands at 3247 and 3190 cm^{-1} because of the (NH_2) group and bands at 1743 and 1655 cm^{-1} corresponding to the two carbonyl functions. The ^{1}H NMR spectrum showed a singlet signal at 2.35 ppm referring to the three protons of methyl group, a singlet signal at 4.05 ppm corresponding to the protons of methylene (CH_2) function, a multiplet signal in the region 7.10–7.55 ppm because of the aromatic protons, and a singlet signal at 9.55 ppm for the protons of (NH_2) function. The mass spectrum of the compound showed the molecular ion peak at $m/z = 332$ corresponding to the molecular weight of its formula $C_{14}H_{12}N_4O_2S_2$.

Further heterocyclization of the 4-oxothiazolyl-1-thiocarbamoyl-2-pyrazolin-5-one derivative **19** with α-bromoketone compounds **6** including phenacyl bromide

Scheme 3. Synthesis of 3-methyl-4-(thiazolidin-2-ylidene)-2-pyrazolin-5-ones **18**–**20**.



and bromoacetone was achieved by reflux in hot ethanol and drops of triethylamine as a basic catalyst to furnish the corresponding 4-(4-oxothiazolyl)-1-(4-substitutedthiazolyl)-2-pyrazolin-5-one derivatives **20a** and **20b**. Also the structure of **20** was further confirmed by an independent synthesis via thiocarbamoylation of compound **10** by the reaction with phenyl isothiocyanate in DMF containing solid potassium hydroxide followed by neutralization with dilute HCl to give the corresponding thiazolyl-4-thiocarbamoyl-2-pyrazolin-5-one derivatives **21** which underwent cyclization reaction with ethyl bromoacetate (**4**) by heating in ethanol containing anhydrous sodium acetate to afford the target compounds **20**. The IR spectrum of **20a** (as an example) showed an absorption band at 1718 cm^{-1} because of the (C=O) function of thiazole ring besides one amidic carbonyl absorption band (pyrazole ring) at 1661 cm^{-1}, while the stretching band of (C=N) function absorbed at 1601 cm^{-1}. The ^1H NMR spectrum of the same compound showed two singlet signals at 2.15 and 2.40 ppm referring to the protons of two methyl groups, a singlet signal at 3.95 ppm for the protons of methylene group, a singlet signal at 6.65 ppm for the proton of thiazole C-5, and a multiplet signal in the region 7.15–7.60 ppm for the aromatic protons. The chemical structure of **21** was also established on the basis of elemental analysis and spectral data. The IR spectrum of **21b** (as an example) showed absorption bands at 3106 and 1649 cm^{-1} corresponding to the (NH) and (C=O) functions, respectively. Also ^1H NMR spectrum in $CDCl_3/CF_3COOD$ displayed a singlet signal at 2.15 ppm referring to the protons of methyl group, a singlet signal at 6.65 ppm for the proton of thiazole C-5, and a multiplet signal in the region 6.90–7.65 ppm because of the aromatic protons. The mass spectrum displayed molecular ion peak at 392 (7.6%) corresponding to the molecular weight of the molecular formula $C_{20}H_{16}N_4OS_2$.

Treatment of the non-isolable potassium salt **16** with dilute HCl afforded the corresponding thiocarbamoyl-2-pyrazolin-5-one derivative **22** with new active phenylthiocarbamoyl function group at 4-position for further derivatization (Scheme 4). The chemical structure of **22** was secured by its correct elemental and spectral analyses. The IR spectrum of **22** revealed the presence of absorption bands at 3338, 3241, and 3185 cm^{-1} referring to the NH_2 and NH functions, while the absorption at 1662 cm^{-1} was attributed to the carbonyl group. The ^1H NMR spectrum in $CDCl_3/CF_3COOD$ showed a singlet signal at 2.15 ppm because of the protons of methyl group and a multiplet signal in the region 7.10–7.55 ppm because of the aromatic protons. Treatment of **22**, which has two different thiocarbamoyl moieties, with equimolar amount of α-bromoketone compounds **6** (namely, bromoacetone and phenacyl bromide) in hot ethanol containing triethylamine as a basic catalyst afforded the corresponding 4-(3-phenyl-4-substituted-thiazol-2-ylidene)-1-thiocarbamoyl-2-pyrazolin-5-one derivatives **23**. The formation of thiazole ring proceeds through heterocyclization of the more reactive phenylthiocarbamoyl moiety with α-bromoketone rather than the less reactive thiocarbamoyl moiety.

Moreover, heterocyclization reaction of **23**, which has only one thiocarbamoyl moiety as a single choice, with α-bromoketone compounds was achieved by heating in ethanol containing triethylamine as a basic catalyst to form 3-methyl-4-(4-substituted-3-phenylthiazol-2-ylidene)-1-(4-substituted-thiazol-2-yl)-2-pyrazolin-5-one derivatives **24a–c**. Assignment of these products was based on elemental analyses, spectral data, and an independent synthesis *via* further reaction of thiazolyl-4-thiocarbamoyl-2-pyrazolin-5-one derivatives **21** with bromoacetone and/or phenacyl bromide.

Scheme 4. Synthesis of 3-methyl-4-(thiazol-2-yl)-2-pyrazolin-5-ones **23** and **24**.

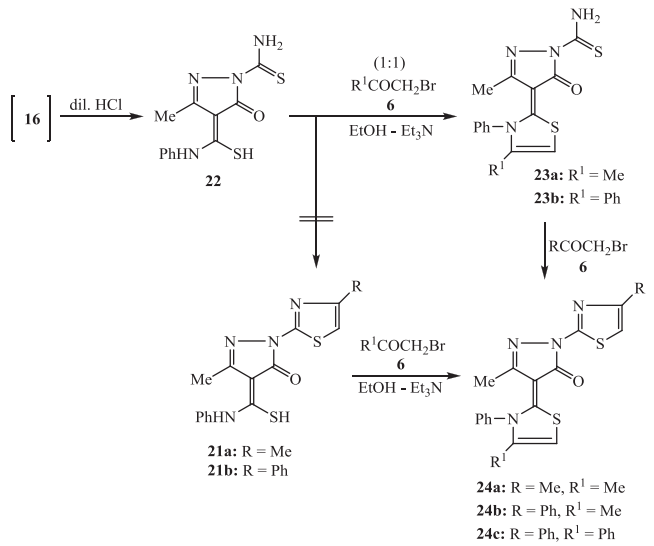


Table 1

Antioxidant activity of the synthesized thiazolyl–pyrazole derivatives.

	ABTS Abs (control) − Abs (test) / Abs (control) × 100	
Method compounds	Absorbance of samples	% inhibition
Control of ABTS	0.510	0%
Ascorbic acid	0.060	88.20%
1	0.408	20.00%
3	0.435	14.70%
7	0.358	29.80%
8	0.379	25.70%
9a	0.216	57.60%
9b	0.225	55.90%
10a	0.177	65.30%
10b	0.058	88.60%
14a	0.182	64.30%
14b	0.110	78.40%
18	0.169	66.90%
19	0.267	47.60%
20a	0.282	44.70%
20b	0.254	50.20%
21a	0.138	72.90%
21b	0.073	85.70%
23a	0.391	23.30%
23b	0.375	26.50%
24a	0.413	19.00%
24b	0.352	31.00%
24c	0.411	19.40%

Antioxidant activity. The newly synthesized thiazolyl–pyrazole compounds **7–10**, **14**, **18–21**, **23,** and **24** (Table 1) were tested for their antioxidant activities by using (ABTS Radical Cation Decolorization Assay) [18,19]. The results (Table 1) indicated that most of the examined compounds (except **1**, **3**, **7**, **8**, **23,** and **24**) exhibited moderate to very strong antioxidant activity. The compounds **10a**, **14b**, **18,** and **21a** displayed strong antioxidant activity. Compounds **10b** and **21b** displayed the best antioxidant property (88.60%) and (85.70%) respectively. Compound **10b** was even more active than the standard inhibitor (L-ascorbic acid 88.20%).

Structure–activity study. The antioxidant potential of thiazolyl–pyrazole compounds is connected with the positioning and forms of substituents on the thiazole and pyrazole rings. The enhancement in antioxidant activity of compounds **10b** and **21b** may be because of the presence of phenyl ring on the thiazole ring and phenylthiocarbamoyl group along with core pyrazolin-5-one moiety. Structure–activity relationship (SAR) points out two major properties of the most active thiazolyl–pyrazoles. 4-Phenyl substitution on the thiazole ring is generally more beneficial than the methyl substitution. The link of thiazolyl ring at position 1 of the pyrazole ring increased the activity whereas at position 4 hindered the activity.

CONCLUSIONS

Nineteen substituted thiazolyl-pyrazolin-5-one derivatives were synthesized from the readily available 3-ethyl-1-thiocarbamoyl-2-pyrazolin-5-one by diazo-coupling reaction, Knoevenagel condensation, or thiocarbamoylation reaction with phenyl isothiocyanate followed by heterocyclization with various α-halogenated reagents such as bromoacetone, phenacyl bromide, and ethyl bromoacetate. Their structures were clearly confirmed by spectroscopy data (IR, ^{1}H NMR, and MS) and elemental analysis. The target compounds were evaluated for their potential antioxidant activity by using ABTS Radical Cation Decolorization Assay. Among the analogue compounds, **10b** and **21b** showed the excellent activity in comparison to the standard inhibitor.

EXPERIMENTAL

All melting points (uncorrected) were determined on an electrothermal Gallenkamp melting point apparatus. The completion of reaction was checked by thin-layer chromatography using silica gel-G (0.5-mm thickness, petroleum ether and ethyl acetate solvent system). The IR spectra were recorded in KBr disks on a Thermo Scientific Nicolet iS 50 FT-IR spectrometer (not all frequencies are reported).

The NMR spectra were acquired using a Bruker WP 300 spectrometer at 300 MHz using *TMS* as an internal standard and $CDCl_3$ or DMSO-d_6 as solvent. The mass spectra were performed using a Shimadzu Qp-2010 mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Unit, Cairo University, Giza, Egypt; the results were in satisfactory agreement with the calculated values. Antioxidant activities were carried out at Drugs Department, Faculty of Pharmacy, Mansoura University, Egypt.

Synthesis of 4-(4-ethoxycarbonyl-phenylhydrazono)-3-methyl-1-thiocarbamoyl-2-pyrazolin-5-one (3). In a 100-mL conical flask, a well-stirred solution of ethyl 4-amino benzoate (**2**, 0.01 mol, 1.65 g) in 3.0-mL concentrated hydrochloric acid (3.0 mL) and 2.0-mL H_2O was cooled in an ice-bath at 0–5°C and then diazotized with a solution of $NaNO_2$ (0.7 g in 10-mL H_2O). The freshly prepared diazonium solution was added dropwise to a well-stirred cold solution of the pyrazolin-5-one compound **1** (0.01 mol, 1.57 g) in 15-mL pyridine. The reaction mixture was allowed to stir at 0–5°C for 2 h until complete coupling reaction was achieved. The reaction mixture was diluted with cold water, and the solid product that deposited was collected by filtration, washed with cold water, dried, and recrystallized from ethanol.

Orange crystals, yield 77%; mp 242–244°C; R_f value: 0.62 petroleum ether:ethyl acetate (5:1); IR ($\bar{\nu}$/cm^{-1}): 3370, 3252, 3162, (NH_2 and NH), 1707 (C=O, ester), 1691 (C=O, ring), 1606 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 1.30 (t, 3H, CH_3, J = 7.15 Hz), 2.15 (s, 3H, CH_3), 4.30 (q, 2H, CH_2, J = 7.15 Hz), 7.55 (d, 2H, Ar—H), 8.00 (d, 2H, Ar—H), 9.55 (s, 2H, NH_2), 11.55 (s, 1H, =NNH); MS (EI, 70 eV): *m/z* (%) = 333 (19.6), 304 (30.2), 266 (45.6), 246 (77.8), 190 (65.4), 172 (29.2), 133 (18.6), 91 (100), 77 (36.5). *Anal*. Calcd. for $C_{14}H_{15}N_5O_3S$ (333.09): C, 50.44; H, 4.54; N, 21.01. Found: C, 50.37; H, 4.48; N, 21.05.

Synthesis of 4-(4-ethoxycarbonyl-phenylhydrazono)-1-(4,5-dihydro-4-oxothiazol-2-yl)-3-methyl-1H-pyrazol-5(4H)-one (7). A mixture of the 1-thiocarbamoyl-2-pyrazolin-5-one derivative **3** (0.005 mol, 1.66 g), ethyl bromoacetate (0.005 mol, 0.55 mL), and 0.5-g anhydrous sodium acetate in absolute ethanol (25 mL) was refluxed for 4 h. The reaction mixture was allowed to cool at room temperature, poured into cooled water, and neutralized by dilute HCl. The solid that formed after neutralization was collected by filtration, dried, and recrystallized from ethanol.

Red crystals, yield 82%, mp 201–203°C; R_f value: 0.44 petroleum ether:ethyl acetate (3:1); IR ($\bar{\nu}$/cm^{-1}): 3174 (=NNH), 1741 (C=O, thiazole ring), 1704 (C=O, ester), 1665 (C=O, pyrazole ring), 1610 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 1.30 (t, 3H, CH_3, J = 7.15 Hz), 2.15 (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 4.30 (q, 2H, CH_2, J = 7.15 Hz), 7.58 (d, 2H, Ar—H), 7.98 (d, 2H, Ar—H), 11.35 (s, 1H, =NNH); MS (EI, 70 eV): *m/z* (%) = 373 (21.6), 320 (21.8), 289 (21.2), 223 (30.4), 200 (26.3), 179 (18.7), 133 (47.6), 91 (88.3), 80 (100), 64 (64.7), 55 (28.8). *Anal*. Calcd. for $C_{16}H_{15}N_5O_4S$ (373.08): C, 51.47; H, 4.05; N, 18.76. Found: C, 51.62; H, 4.14; N, 18.68.

Synthesis of thiazolyl-pyrazolin-5-one derivatives 8 and 9.

Method (A): A mixture of the 1-thiocarbamoyl-2-pyrazolin-5-one derivative **3** (0.005 mol, 1.66 g), appropriate α-halogenated reagents, chloroacetonitrile bromoacetone and/or phenacyl bromide, (0.005 mol), and 0.5-mL triethylamine was refluxed in 20-mL ethanol–DMF mixture (2:1) for 6 h. The reaction mixture was poured into cooled water, and the resulting precipitate was collected by filtration, washed several times with water, and crystallized from EtOH–DMF mixture (5:1). to afford **8**, **9a**, and/or **9b**.

Method (B): A well-stirred solution of ethyl 4-aminobenzoate (**2**, 0.005 mol, 0.82 g) in 1.5-mL concentrated HCl and 3-mL water was cooled in an ice-bath at 0–5°C and diazotized with a solution of 0.35-g $NaNO_2$ in 5-mL H_2O. Then, the freshly cold diazonium solution was added dropwise to a well-stirred cold solution of compound **10** (0.005 mol) in 25-mL pyridine. The reaction mixture was stirred for 2 h until complete coupling reaction was achieved. The solid product which deposited was collected by filtration, washed with cold water, and recrystallized from a mixture of EtOH:DMF (5:1) to give **9a** and **9b**.

4-(4-Ethoxycarbonyl-phenylhydrazono)-3-methyl-1-(4-aminothiazol-2-yl)-2-pyrazolin-5-one (8). Yellowish green crystals, yield 79%, mp 210–212°C; R_f value: 0.68 petroleum ether:ethyl acetate (3:1); IR ($\bar{\nu}$/cm^{-1}): 3374, 3293, 3166 (NH_2 and NH), 1701 (C=O, ester), 1671 (C=O, ring), 1608 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 1.30 (t, 3H, CH_3, J = 7.15 Hz), 2.15 (s, 3H, CH_3), 4.30 (q, 2H, CH_2, J = 7.15 Hz), 7.07 (s, 1H, thiazole H-5), 7.60 (d, 2H, Ar—H), 7.98 (d, 2H, Ar—H), 8.50 (s, 2H, NH_2), 11.60 (s, 1H, =NNH); MS (EI, 70 eV): *m/z* (%) = 372 (11.6), 274 (49.8), 229 (11.6), 165 (24.8), 137 (9.8), 125 (100), 108 (12.6), 97 (28.6). *Anal*. Calcd. for $C_{16}H_{16}N_6O_3S$ (372.10): C, 51.60; H, 4.33; N, 22.57. Found: C, 51.76; H, 4.40; N, 22.67.

4-(4-Ethoxycarbonyl-phenylhydrazono)-3-methyl-1-(4-methylthiazol-2-yl)--2-pyrazolin-5-one (9a). Orange crystals, yield 75%, mp 184–186°C; R_f value: 0.52 petroleum ether:ethyl acetate (3:1); IR ($\bar{\nu}$/cm^{-1}): 3228 (NH), 1714 (C=O, ester) 1671 (C=O, ring), 1608 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 1.30 (t, 3H, CH_3, J = 7.15 Hz), 2.15 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.30 (q, 2H, CH_2, J = 7.15 Hz), 7.52 (s, 1H, thiazole H-5), 7.59 (d, 2H, Ar—H), 7.99 (d, 2H, Ar—H), 11.56 (s, 1H, =NNH); MS (EI, 70 eV): *m/z* (%) = 371 (19.5), 345(20.8), 329 (31.5), 311 (40.7), 253 (100), 236 (64.3), 133 (26.8), 107 (34.1), 93 (61.2), 77 (66.2). *Anal*. Calcd. for $C_{17}H_{17}N_5O_3S$ (371.11): C, 54.97; H, 4.61; N, 18.86. Found: C, 54.86; H, 4.68; N, 18.95.

4-(4-Ethoxycarbonyl-phenylhydrazono)-3-methyl-1-(4-phenylthiazol-2-yl)--2-pyrazolin-5-one (9b). Red powder, yield 66%, mp 195–197°C; R_f value: 0.46 petroleum ether:ethyl acetate (3:1); IR ($\bar{\nu}$/cm^{-1}): 3118 (NH), 1715 (C=O, ester), 1667 (C=O, ring), 1608 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 1.30 (t, 3H, CH_3, J = 7.15 Hz), 2.15 (s, 3H, CH_3), 4.35 (q, 2H, CH_2, J = 7.15 Hz), 7.15 (s, 1H, thiazole H-5), 7.25–8.00 (m, 9H, Ar—H), 11.25 (s, 1H, =NNH); MS (EI, 70 eV): *m/z* (%) = 433 (13.5), 420(17.7), 407 (26.4), 392 (44.7), 381 (15.6), 372 (23.3), 344 (25.8), 311 (33.4), 258 (100), 243 (42.2), 200 (56.5), 174(35.8), 149 (28.5), 134 (19.7), 102 (18.3), 91 (38.7), 77 (24.7). *Anal*. Calcd. for $C_{22}H_{19}N_5O_3S$ (433.12): C, 60.96; H, 4.42; N, 16.16. Found: C, 61.12; H, 4.53; N, 16.05.

Synthesis of 3-methyl-1-(4-substituted-thiazol-2-yl)-2-pyrazolin-5-ones (10). A mixture of the pyrazolin-5-one compound **1** (0.01 mol, 1.57 g) and bromoacetone and/or phenacyl bromide (0.01 mol) in absolute ethanol (25 mL) containing five drops of triethylamine was refluxed for 2 h. The reaction mixture was allowed to cool at room temperature and the solid that formed was collected by filtration, dried, and recrystallized from ethanol.

3-Methyl-1-(4-methyl-thiazol-2-yl)-2-pyrazolin-5-one (10a). White crystals, yield 61%, mp 202–204°C; R_f value: 0.46 petroleum ether:ethyl acetate (5:1); IR ($\bar{\nu}$/cm^{-1}): 1646 (C=O), 1594 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 2.15 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.85 (s, 2H, CH_2), 6.72 (s, 1H, thiazole H-5); MS (EI, 70 eV): *m/z* (%) = 195 (8.4), 181 (22.8), 173 (15.5), 167 (41.7), 155 (59.3), 139 (6.3), 114 (37.8), 91 (100), 83 (23.3), 65 (40.2). *Anal*. Calcd. for $C_8H_9N_3OS$ (195.05): C, 49.21; H, 4.65; N, 21.52. Found: C, 49.08; H, 4.72; N, 21.61.

3-Methyl-1-(4-phenyl-thiazol-2-yl)-2-pyrazolin-5-one (10b). White crystals, yield 72%, mp 188–189°C (Lit. mp 190–191°C) [20].

Synthesis of 4-[(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-3-methyl-1-thiocarbamoyl-2-pyrazolin-5-one (13). A mixture of compound **1** (0.003 mol, 0.47 g) and 4-formylpyrazole **12** (0.003 mol, 0.75 g) in 15-mL glacial acetic acid containing fused sodium acetate (1.0 g) was refluxed for 2 h. The reaction mixture was allowed to cool at room temperature and then poured into ice water. The resulting precipitated solid was collected by filtration, dried, and crystallized from ethanol. The isolated product was tested by TLC, one spot, R_f = 0.47, petroleum ether: ethyl acetate (3:1).

Yellow crystals, yield 70%, mp 171–173°C; R_f value: 0.34 petroleum ether:ethyl acetate (5:1); IR ($\bar{\nu}$/cm^{-1}): 3240, 3120 (NH_2), 1674 (C=O), 1599 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 2.35 (s, 3H, CH_3), 6.45 (s, 1H, HC=C), 7.25–7.77 (m, 11H, Ar—H and pyrazole H-5), 9.48 (s, 2H, NH_2); MS (EI, 70 eV): *m/z* (%) = 387 (20.4), 374 (44.8), 259 (14.5), 250 (16.9), 177 (30.2), 129 (62.3), 93 (61.8), 77 (84.1), 69 (95.3), 55 (100). *Anal*. Calcd. for $C_{21}H_{17}N_5OS$ (387.12): C, 65.10; H, 4.42; N, 18.08. Found: C, 65.26; H, 4.49; N, 18.17.

Synthesis of 4-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-3-methyl-1-(4-substituted-thiazol-2-yl)-2-pyrazolin-5-one (14).

Method (A): To a mixture of compound **13** (0.002 mol, 0.77 g) and bromoacetone or phenacyl bromide (0.002 mol) in absolute ethanol (20 mL), few drops of triethylamine were added as a catalyst. The mixture was refluxed for 4 h and then left to cool at room temperature. The solid that formed was collected by filtration, dried, and recrystallized from ethanol.

Method (B): A mixture of the thiazolyl–pyrazole compound **10** (0.003 mol) and 4-formylpyrazole **12** (0.003 mol, 0.75 g) in 15-mL glacial acetic acid containing 1.0-g fused sodium acetate was refluxed for 2 h. The reaction mixture was allowed to cool at room temperature and then poured into ice water. The resulting precipitated solid was collected by filtration, dried, and recrystallized from ethanol.

3-Methyl-1-(4-methylthiazol-2-yl)-4-[(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-2-pyrazolin-5-one (14a). Yellowish brown crystals, yield 55%, mp 213–215°C; R_f value: 0.46 petroleum ether:ethyl acetate (5:1); IR ($\bar{\nu}$/cm^{-1}): 1671 (C=O), 1599 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 2.15 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 6.55 (s, 1H, HC=C), 6.95 (s, 1H, thiazole H-5), 7.15–7.80 (m, 11H, Ar—H and pyrazole H-5); MS (EI, 70 eV): *m/z* (%) = 425 (9.4), 374 (2.8), 257 (34.5), 177 (4.7), 134 (53.8), 118 (69.3), 102 (47.8), 93 (50.1), 77 (100), 64 (47.2). *Anal*. Calcd. for (425.13): C, 67.74; H, 4.50; N, 16.46. Found: C, 67.87; H, 4.58; N, 16.41.

3-Methyl-4-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-1-(4-phenylthiazol-2-yl)-2-pyrazolin-5-one (14b). Brown crystals, yield 63%, mp 261–263°C; R_f value: 0.41 petroleum ether: ethyl acetate (3:1); IR ($\bar{\nu}$/cm^{-1}): 1668 (C=O), 1603 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 2.35 (s, 3H, CH_3), 6.60 (s, 1H, HC=C), 7.10 (s, 1H, thiazole H-5), 7.20–7.85 (m, 16H, Ar—H and pyrazole H-5); MS (EI, 70 eV): *m/z* (%) = 487 (12.0), 456 (20.4), 307 (2.1), 257 (38.9), 203 (72.5), 176 (27.7), 148 (28.7), 134 (79.3), 102 (100), 91 (39.1), 77 (29.8). *Anal*. Calcd. for $C_{29}H_{21}N_5OS$ (487.15): C, 71.44; H, 4.34; N, 14.36. Found: C, 71.29; H, 4.24; N, 14.46.

Synthesis of 4-(oxo-thiazolidin-2-ylidene)-1-thiocarbamoyl-2-pyrazolin-5-one derivatives 18 and 19. To a cooled suspension of finely grounded potassium hydroxide (0.01 mol, 0.56 g) in 20-mL dimethylformamide, the pyrazolin-5-one compound **1** (0.01 mol, 1.57 g) was added and subsequently phenyl isothiocyanate (0.01 mol, 1.2 mL). The mixture was stirred at room temperature for 12 h, then treated with chloroacetyl chloride and/or ethyl bromoacetate (0.012 mol), and the stirring was continued for further 4 h. The reaction mixture was poured into ice-cooled water, and the resulting precipitated solid was collected by filtration, washed several times with water, and crystallized from ethanol to obtain **18** and **19**.

3-Methyl-4-(5-oxo-3-phenylthiazolidin-2-ylidene)-1-thiocarbamoyl-2-pyrazolin-5-one (18). Orange crystals, yield 78%, mp 185–187°C; R_f value: 0.66 petroleum ether:ethyl acetate (3:1); IR ($\bar{\nu}$ /cm^{-1}): 3239, 3208 (NH_2), 1753 (C=O thiazole ring), 1657 (C=O pyrazole ring), 1591 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 2.35 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 7.15–7.60 (m, 5H, Ar—H), 9.65 (s, 2H, NH_2); MS (EI, 70 eV): *m/z* (%) = 332 (60.1), 298 (21.1), 273 (27.11), 200 (55.2), 142 (17.2), 93 (86.1), 77 (100). *Anal*. Calcd. for $C_{14}H_{12}N_4O_2S_2$ (332.04): C, 50.59; H, 3.64; N, 16.86. Found: C, 50.72; H, 3.73; N, 16.77.

3-Methyl-4-(4-oxo-3-phenylthiazolidin-2-ylidene)-1-thiocarbamoyl-2-pyrazolin-5-one (19). Orange powder, yield 65%, mp 253–255°C; R_f value: 0.54 petroleum ether:ethyl acetate (3:1); IR ($\bar{\nu}$ /cm^{-1}): 3247, 3190 (NH_2), 1743 (C=O, thiazole ring), 1655 (C=O, pyrazole ring), 1595 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 2.35 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 7.10–7.55 (m, 5H, Ar—H), 9.55 (s, 2H, NH_2); MS (EI, 70 eV): *m/z* (%) = 332 (3.5), 289 (8.1), 200 (100.0), 170 (6.3), 142 (7.2), 93 (10.4), 77 (21.8). *Anal*. Calcd. for $C_{14}H_{12}N_4O_2S_2$ (332.04): C, 50.59; H, 3.64; N, 16.86. Found: C, 50.43; H, 3.70; N, 16.92.

Synthesis of 3-methyl-1-(4-substituted-thiazol-2-yl)-4-(4-oxo-3-phenyl-thiazolidin-2-yl)-2-pyrazolin-5-one derivatives 20a and 20b. A mixture of the 1-thiocarbamoyl-2-pyrazolin-5-one derivative **19** (0.002 mol, 0.66 g), the appropriate α-halogenated reagents, bromoacetone and/or phenacyl bromide (0.005 mol), and 0.5-mL triethylamine was refluxed in 20-mL ethanol for 4 h. The reaction mixture was poured into cooled water, and the resulting precipitated solid was collected by filtration, washed several times with water, and crystallized from EtOH to give **20a** and **20b**, respectively.

3-Methyl-1-(4-methyl-thiazol-2-yl)-4-(4-oxo-3-phenylthiazolidin-2-ylidene)-2-pyrazolin-5-one (20a). Orange powder, yield 58%, mp 181–182°C; R_f value: 0.36 petroleum ether:ethyl acetate (2:1); IR ($\bar{\nu}$/cm^{-1}): 1718 (C=O, thiazole ring), 1661 (C=O, pyrazole ring), 1601 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 2.15 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 6.65 (s, 1H, thiazole H-5), 7.15–7.60 (m, 5H, Ar—H); MS (EI, 70 eV): *m/z* (%) = 370(11.8), 344 (16.2), 257 (16.6), 236 (16.1), 149 (32.2), 129 (39.4), 102 (70.8), 91 (75.6), 77 (100), 64 (76.1). *Anal*. Calcd. for $C_{17}H_{14}N_4O_2S_2$ (370.06): C, 55.12; H, 3.81; N, 15.12. Found: C, 55.21; H, 3.77; N, 15.18.

3-Methyl-1-(4-phenyl-thiazol-2-yl)-4-(4-oxo-3-phenylthiazolidin-2-ylidene)-2-pyrazolin-5-one (20b). Orange powder, yield 64%, mp 195–197°C; R_f value: 0.51 petroleum ether:ethyl acetate (2:1); IR ($\bar{\nu}$/cm^{-1}): 1722 (C=O, thiazole), 1658 (C=O, pyrazole), 1595 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 2.15 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 6.60 (s, 1H, thiazole H-5), 7.14–7.71 (m, 10H, Ar—H); MS (EI, 70 eV): *m/z* (%) = 432 (16.8), 419 (8.2), 380 (15.6), 330 (27.2), 257 (34.2), 243 (18.4), 195 (17.8), 177 (21.6), 134 (35.6), 102 (47.5), 91 (25.3), 77 (100), 64 (47.7). *Anal*. Calcd. for $C_{22}H_{16}N_4O_2S_2$ (432.07): C, 61.09; H, 3.73; N, 12.95. Found: C, 61.26; H, 3.65; N, 12.84.

Synthesis of 3-methyl-4-phenylthiocarbamoyl-2-pyrazolin-5-one derivatives 21 and 22. To a cold suspension of finely divided KOH (0.01 mol, 0.56 g) in DMF (20-mL) were added the pyrazolin-5-one derivatives **10** and/or **3** (0.01 mol) followed by phenyl isothiocyanate (0.01 mol, 1.20-mL). The mixture was stirred at room temperature overnight, poured into ice-cold water, and then neutralized with dilute HCl. The resultant solid product was collected by filtration, washed with water, dried, and recrystallized from ethanol to afford the corresponding thiocarbamoyl derivatives **21** and/or **22**, respectively.

3-Methyl-1-(4-methyl-thiazol-2-yl)-4-phenylthiocarbamoyl-2-pyrazolin-5-one (21a). Yellow crystals, yield 64%, mp 178–179°C; R_f value: 0.32 petroleum ether:ethyl acetate (3:1); IR ($\bar{\nu}$ /cm^{-1}): 3123 (NH), 1656 (C=O), 1598 (C=N); ^{1}H NMR ($CDCl_3$/CF_3COOD): δ/ppm = 2.15 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 6.65 (s, 1H, thiazole H-5), 6.90–7.45 (m, 5H, Ar—H); MS (EI, 70 eV): *m/z* (%) = 330 (16.8), 311 (16.2), 300 (23.6), 260 (19.2), 246 (47.2), 243 (18.4), 172 (20.8), 177 (21.6), 133 (19.9), 107 (31.5), 91 (100), 77 (31.4), 65 (42.7). *Anal*. Calcd. for $C_{15}H_{14}N_4OS_2$ (330.06): C, 54.52; H, 4.27; N, 16.96. Found: C, 54.66; H, 4.19; N, 16.89.

3-Methyl-1-(4-phenyl-thiazol-2-yl)-4-phenylthiocarbamoyl-2-pyrazolin-5-one (21b). Yellow crystals, yield 80%, mp 190–192°C; R_f value: 0.49 petroleum ether:ethyl acetate (3:1); IR ($\bar{\nu}$ /cm^{-1}): 3106 (NH), 1649 (C=O), 1591 (C=N); ^{1}H NMR ($CDCl_3$/CF_3COOD): δ/ppm = 2.15 (s, 3H, CH_3), 6.65 (s, 1H, thiazole H-5), 6.90–7.65 (m, 10H, Ar—H); MS (EI, 70 eV): *m/z* (%) = 392 (7.6), 359 (20.7), 300 (10.4), 257 (79.1), 174 (15.5), 134 (39.5), 102 (27.6), 93 (100), 76 (55.4). *Anal*. Calcd. for $C_{20}H_{16}N_4OS_2$ (392.08): C, 61.20; H, 4.11; N, 14.27. Found: C, 60.32; H, 4.18; N, 14.18.

3-Methyl-4-phenylthiocarbamoyl-1-thiocarbamoyl-2-pyrazolin-5-one (22). White crystals, yield 75%, mp 110–111°C; R_f value: 0.38 petroleum ether:ethyl acetate (3:1); IR ($\bar{\nu}$/cm^{-1}): 3338, 3241, 3185 (NH_2 and NH), 1662 (C=O), 1630 (C=N); ^{1}H NMR ($CDCl_3$/CF_3COOD): δ/ppm = 2.15 (s, 3H, CH_3), 7.10–7.55 (m, 5H, Ar—H); MS (EI, 70 eV): *m/z* (%) = 292 (11.8), 265 (7.8), 217 (8.1), 199 (56.2), 182 (19.7), 143 (58.4), 134 (23.4), 115 (32.9), 84 (46.6), 80 (50.5), 77 (50.8), 64 (100), 55 (43.7). *Anal*. Calcd. for $C_{12}H_{12}N_4OS_2$ (292.05): C, 49.29; H, 4.14; N, 19.16. Found: C, 49.41; H, 4.07; N, 19.11.

Synthesis of 4-(3-phenyl-4-substitutedthiazol-2-ylidene)-1-thiocarbamoyl-2-pyrazolin-5-one derivatives 23. A mixture of **22** (0.003 mol, 0.87 g) and the appropriate α-bromoketone (namely, bromoacetone and phenacyl bromide) (0.003 mol) in 20-mL ethanol containing 0.5 mL of triethylamine was refluxed for 4–6 h (monitored by TLC, petroleum ether:ethyl acetate (2:1)). The separated solid on cooling was collected by filtration, washed several times with ethanol, and crystallized from EtOH: DMF mixture (5:1).

4-(4-Methyl-3-phenylthiazol-2-ylidene)-3-methyl-1-thiocarbamoyl-2-pyrazolin-5-one (23a). Yellowish white crystals, yield 70%, mp 198–199°C; R_f value: 0.46 petroleum ether:ethyl acetate (3:1); IR ($\overline{\nu}$/cm^{-1}): 3122, 3167 (NH_2), 1641 (C=O), 1589 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 2.09 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 5.21 (s, 1H, thiazole H-5), 7.02–7.35 (m, 5H, Ar—H), 9.45 (s, 2H, NH_2); MS (EI, 70 eV): *m/z* (%) = 330 (10.1), 319 (11,3), 303 (11.2), 271 (31.1), 214 (17.4), 200 (85.2), 170 (7.1), 142 (17.6), 118 (34.7), 93 (29.4), 77 (100). *Anal*. Calcd. for $C_{15}H_{14}N_4OS_2$ (330.06): C, 54.52; H, 4.27; N, 16.96. Found: C, C, 54.71; H, 4.20; N, 17.07.

4-(3,4-Diphenylthiazol-2-ylidene)-3-methyl-1-thiocarbamoyl-2-pyrazolin-5-one (23b). Yellow powder, yield 75%, mp 301–305°C; R_f value: 0.28 petroleum ether:ethyl acetate (3:1); IR ($\overline{\nu}$/cm^{-1}): 3125, 3104 (NH_2), 1655 (C=O), 1599 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 2.15 (s, 3H, CH_3), 5.20 (s, 1H, thiazole H-5), 7.20–7.70 (m, 10H, Ar—H), 9.55 (s, 2H, NH_2); MS (EI, 70 eV): *m/z* (%) = 392 (12.4), 355 (18.9), 304 (23.4), 259 (55.3), 177 (31.2), 134 (44.2), 108 (29.2), 91 (100), 77 (62.4). *Anal*. Calcd. for $C_{20}H_{16}N_4OS_2$ (392.08): C, 61.20; H, 4.11; N, 14.27. Found: C, 61.13; H, 4.16; N, 14.34.

Synthesis of 3-methyl-4-(4-substituted-3-phenylthiazol-2-ylidene)-1-(4-substituted-thiazol-2-yl)-2-pyrazolin-5-one derivatives 24a–c. To a mixture of **23** (0.002 mol) and the appropriate α-bromoketone (0.002 mmol), e.g. bromoacetone and phenacyl bromide in 20-mL ethanol, few drops of triethylamine were added as a catalyst and allowed to reflux for 4 h. The resulting solid that formed during heating was filtered, dried, and recrystallized from DMF:H_2O mixture (3:1).

3-Methyl-4-(4-methyl-3-phenylthiazol-2-ylidene)-1-(4-methylthiazol-2-yl)-2-pyrazolin-5-one (24a). Brown powder, yield 67%, mp 215–217°C; R_f value: 0.43 petroleum ether:ethyl acetate (2:1); IR ($\overline{\nu}$/cm^{-1}): 1641 (broad, C=O), 1598 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 1.95 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 5.35 (s, 1H, thiazoline H-5), 6.75 (s, 1H, thiazole H-5), 7.05–7.40 (m, 5H, Ar—H); MS (EI, 70 eV): *m/z* (%) = 368 (18.2), 350 (38.5), 320 (11.2), 272 (14.2), 217 (22.5), 190 (73.3), 177 (100), 145 (91.0), 117 (32). *Anal*. Calcd. for $C_{18}H_{16}N_4OS_2$ (368.08): C, 58.67; H, 4.38; N, 15.21. Found: C, 58.86; H, 4.46; N, 15.14.

3-Methyl-4-(4-methyl-3-phenylthiazol-2-ylidene)-1-(4-phenylthiazol-2-yl)-2-pyrazolin-5-one (24b). Brown powder, yield 56%, mp 230–232°C; R_f value: 0.38 petroleum ether:ethyl acetate (2:1); IR ($\overline{\nu}$/cm^{-1}): 1651 (broad, C=O), 1595 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 1.95 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 5.40 (s, 1H, thiazoline H-5), 7.25 (s, 1H, thiazole H-5), 7.05–7.75 (m, 10H, Ar—H); MS (EI, 70 eV): *m/z* (%) = 430 (15.2), 415 (14.9), 404 (19.4), 379 (34.3), 353 (22.7) 338 (41.2), 299 (33.5), 254 (53.6), 215 (56.4), 174 (100), 148 (34.4), 134 (25.3), 102 (17.2), 91 (29.8), 77 (21.4). *Anal*. Calcd. for $C_{23}H_{18}N_4OS_2$ (430.09): C, 64.16; H, 4.21; N, 13.01. Found: C, 64.23; H, 4.19; N, 13.08.

3-Methyl-4-(3,4-diphenylthiazol-2-ylidene)-1-(4-phenylthiazol-2-yl)-2-pyrazolin-5-one (24c). Yellow powder, yield 70%, mp 295–297°C.; R_f value: 0.53 petroleum ether:ethyl acetate (2:1); IR ($\overline{\nu}$/cm^{-1}): 1667 (C=O), 1616 (C=N); ^{1}H NMR (DMSO-d_6): δ/ppm = 2.15 (s, 3H, CH_3), 5.20 (s, 1H, thiazoline H-5), 6.75 (s, 1H, thiazole H-5), 7.20–7.86 (m, 15H, Ar—H); MS (EI, 70 eV): *m/z* (%) = 492 (35.9) 407 (35.9), 308 (35.4), 267 (41.0), 234 (36.8), 214 (37.3), 158 (39.1), 98 (40.5), 80 (100.0). *Anal*. Calcd. for $C_{28}H_{20}N_4OS_2$ (492.11): C, 68.27; H, 4.09; N, 11.37. Found: C, 68.16; H, 4.01; N, 11.44.

Antioxidant activity screening assay by the ABTS method. This assay employs the radical cation derived from 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) as stable free radical. The advantage of ABTS-derived free radical method over other methods is that the produced color remains stable for more than 1 h, and the reaction is stoichiometric [18,19]. Thus, our reported compounds in this work were screened for antioxidant activity by the latter method. For each of the investigated compounds, 2 mL of ABTS solution (60 μM) was added to 3 mL MnO_2 suspension (25 mg/mL), all prepared in 5 mL aqueous phosphate buffer solution (pH 7, 0.1 M). The mixture was shaken, centrifuged, and filtered, and the absorbance of the resulting green blue solution (ABTS radical solution) at 734 nm was adjusted to approx. ca. 0.5. Then, 50 μL of (2 mM) solution of the tested compound in spectroscopic grade MeOH/phosphate buffer (1:1) was added. The absorbance was measured and the reduction in color intensity was expressed as inhibition percentage. L-Ascorbic acid was used as standard antioxidant (Positive control). Blank sample was run without ABTS and using MeOH/phosphate buffer (1:1) instead of tested compounds. Negative control was run with ABTS and MeOH/phosphate buffer (1:1) only [21,22].

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