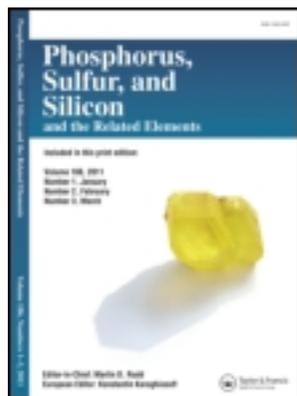


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Versatile Synthesis of N,S-Heterocycles Containing the Antipyrine Moiety

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Versatile Synthesis of N,S-Heterocycles Containing the Antipyrene Moiety

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A series of novel sulfide derivatives of expected biological activity were synthesized via the reaction of 4-(chloroacetyl)antipyrene (1) with several sulfur nucleophiles. The quantitatively available 2-aminothiazole derivatives 10 and 11 were coupled with pyrazolopyridinyl and aromatic diazonium salts to furnish a new series of the corresponding pyrazolopyridinylazo and arylazo-thiazole dyes 12 and 13. The reaction of 4-(cyanoacetyl)antipyrene (14) with phenyl isothiocyanate afforded the nonisolable adduct 15, which was used as a precursor for the synthesis of polyfunctionally substituted ketene N,S-acetal, dihydrothiazole, and thiazolidinone ring systems.

Keywords Antipyrene; sulfur nucleophiles; aminothiazole; ball-milling; azo coupling; phenyl isothiocyanate; ketene N,S-acetal; dihydrothiazole; thiazolidin-5-one

INTRODUCTION

Several classes of organic sulfur compounds are of widespread use in medicine^{1–3} and pharmacology (for example, antibacterial⁴ or antiinflammatory⁵ applications). Diverse pharmacological properties have been associated with antipyrene derivatives. These include antiinflammatory,⁶ analgesic,^{7,8} antidepressant,⁹ and antipyretic¹⁰ properties. It appeared interesting to prepare new sulfur compounds containing the antipyrene moiety with expected biological activity.

In continuation of our previous studies^{11,12} on the synthesis of a variety of thiazole derivatives from the readily obtainable and inexpensive starting materials for the dyeing of polyester fabrics, we report on the reactivity of 4-(chloroacetyl)-antipyrene (**1**)^{13,14} towards various sulfur and/or nitrogen nucleophiles, including different thiourea derivatives. The work also involved the addition of 4-(cyanoacetyl)-antipyrene (**14**)¹⁴ to phenyl isothiocyanate and has resulted in the formation of a variety

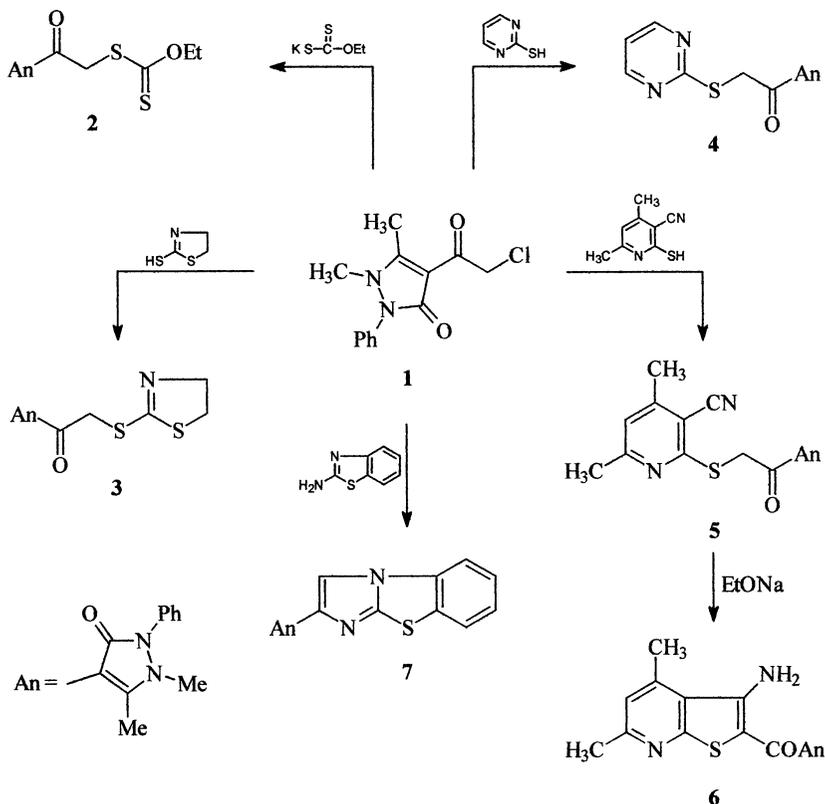
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of ketene N,S-acetal, dihydrothiazole, and thiazolidinone derivatives in which the antipyrine moiety is incorporated.

RESULTS AND DISCUSSION

Compound **1** was reacted with various sulfur nucleophile derivatives, e.g., *O*-ethyl xanthic acid potassium salt, 4,5-dihydrothiazole-2-thiol, and pyrimidine-2-thiol in acetone in the presence of anhydrous potassium carbonate as a catalyst to afford the corresponding sulfide derivatives **2**, **3**, and **4**, respectively. The structure of the latter products was confirmed on the basis of their correct elemental analysis and spectral data (Scheme 1).



SCHEME 1

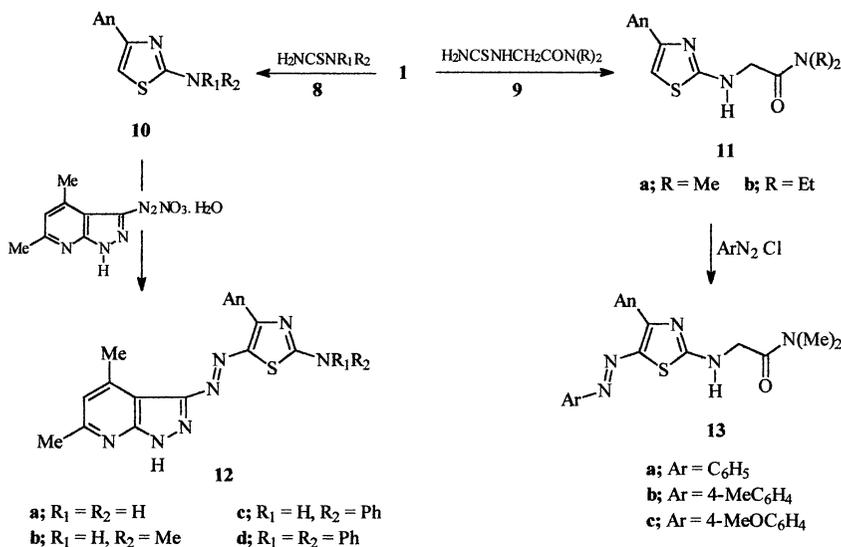
Similarly, compound **1** reacted with 4,6-dimethyl-2-mercaptopyrimidin-5(1H)-nitrile to yield the corresponding sulfide derivative **5** in good yield. The structure of compound **5** was assigned by means

of its elemental analysis and spectral properties. Also, compound **5** underwent cyclization on heating in a solution of ethanol containing sodium ethoxide to afford the corresponding thieno[2,3-*b*]pyridine derivative **6**. The structure of **6** was established on the basis of its elemental analysis and spectral data.

Compound **1** was allowed to react with 2-aminobenzothiazole in boiling ethanol to give the imidazo[2,1-*b*]benzothiazole derivative **7**. Compound **7** was assigned as the reaction product in accordance with its elemental analysis and spectral data.

2-Aminothiazoles are useful precursors for the synthesis of many important heterocyclic compounds, e.g., thiazole-pyrimidinones and –imidazoles as well as more involved polycondensed *N,S*-heterocycles. The chemistry (syntheses and reactions) of 2-aminothiazole derivatives was covered by our recent review.¹⁵

The syntheses of 2-amino-4-substituted-thiazoles are most easily accessible by various approaches, and even waste-free, solid-state reactions have been developed.^{16,17} The waste-free, solid-state reaction could be applied to 4-(chloroacetyl) antipyrine (**1**) and various thiourea derivatives **8** and **9**. The aminothiazole products **10** and **11** could be obtained with a 100% yield from stoichiometric reactions by ball-milling, followed by washings with Na_2CO_3 solutions (Scheme 2). This remarkable 3-cascade reaction of substitution, cyclization, and dehydration proceeds again¹⁶ in the solid state.

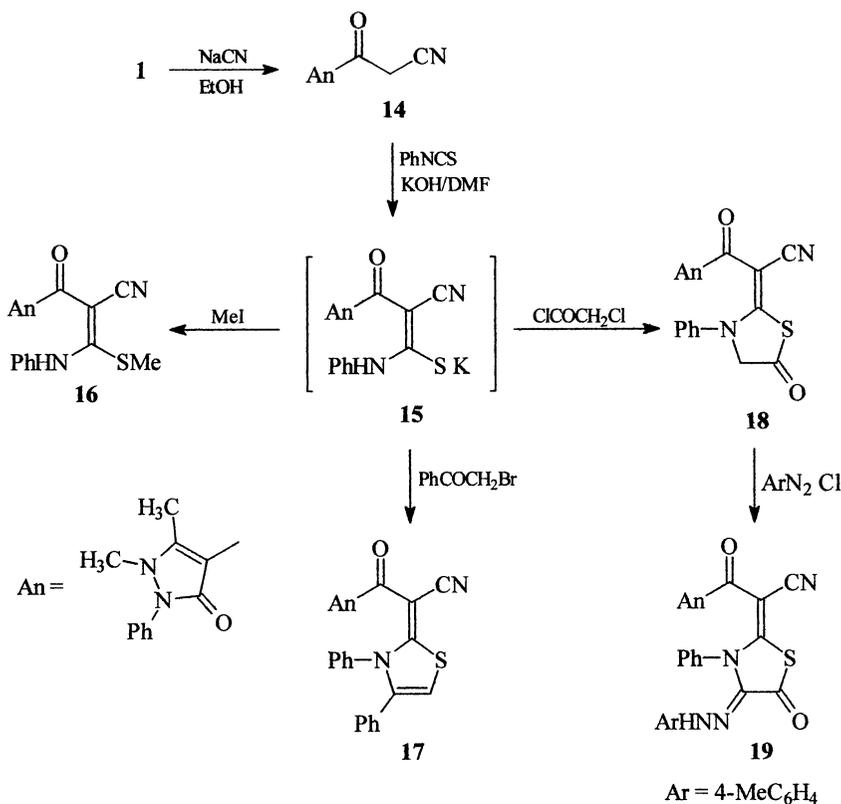


SCHEME 2

The reactivity of thiazolyl amine derivatives **10a-d** was tested towards a coupling reaction with 4,6-dimethylpyrazolo[3,4-*b*]pyridine-3-diazonium nitrate hydrate¹⁸ to afford the corresponding 5-(dimethylpyrazolo[3,4-*b*]pyridin-3-yl-azo)thiazole-2-yl amines **12a-d**.

Moreover, thiazol-2-yl amine **11a**, when coupled with a variety of aromatic diazonium salts in ethanol buffered with sodium acetate, yielded the corresponding 5-arylaazo-thiazol-2-yl amines **13a-c** in good yields. The molecular structures of **12a-d** and **13a-c** were secured by spectral data.

4-(Cyanoacetyl)antipyrine (**14**) was prepared previously by the treatment of **1** with sodium cyanide in ethanol as a polar solvent.¹⁴ The addition of **14** to an equimolar amount of phenyl isothiocyanate in DMF containing potassium hydroxide afforded the potassium sulfide salt **15** that was not isolated. Subsequent treatment of the salt **15** with methyl iodide afforded the corresponding ketene N,S-acetal **16** (Scheme 3).



SCHEME 3

Heterocyclization of **15** was achieved by the reaction with α -halogenated ketone, e.g., phenacyl bromide. The dihydrothiazole derivative **17** was obtained. The molecular structure of **17** was confirmed by analytical and spectral data.

On the other hand, the in situ cyclization of **15** with chloroacetyl chloride afforded the corresponding thiazolidin-5-one derivative **18**. The reactivity of the methylene group in compound **18** was tested toward the azo coupling reaction¹⁹ with diazonium salts. Thus, an equimolar amount of *p*-tolyl diazonium chloride at 0–5°C reacted with compound **18** to yield the corresponding monohydrazone derivative **19**.

EXPERIMENTAL

Melting points were determined with a Gallenkamp melting point apparatus (capillary method) and were uncorrected. Elemental analyses were carried out at the Microanalytical Unit of the Faculty of Science, Cairo University, and all compounds gave satisfactory elemental analyses. IR spectra (KBr) were recorded with a Mattson 5000 FTIR spectrometer (not all frequencies are reported). The ¹H NMR and ¹³C NMR spectra were acquired using a Bruker WP 300 spectrometer at 300 MHz (¹H) or 75.5 MHz (¹³C; in broad-band mode). Mass spectra were obtained with a Finnigan MAT 212 instrument by an electron impact at 70 eV.

General Procedure for the Synthesis of Sulfide Derivatives (2–5)

A mixture of **1** (1.32 g, 5.0 mmol), the corresponding thiol derivative (5.0 mmol) (namely *O*-ethyl xanthic acid potassium salt, 4,5-dihydrothiazole-2-thiol, pyrimidine-2-thiol, and 4,6-dimethyl-2-mercaptopyridine-4-thione), and anhydrous potassium carbonate (0.35 g, 2.5 mmol) in acetone (30 mL) was refluxed for 4 h. The excess acetone was evaporated under reduced pressure. The residue was washed with water and recrystallized from the appropriate solvent.

Dithiocarbonic Acid *S*-(2-antipyrinyl-2-oxo-ethyl) *O*-Ethyl Ester (**2**)

Yellow crystals, yield 72%, m.p. 95–96°C (EtOH). IR (cm⁻¹): 3050, 2980, 2924, 1679, 1640, 1593, 1524, 1486, 1455, 1408, 1376, 1313, 1235, 1117, 1082, 1044, 763, 717. ¹H NMR (CDCl₃) δ /ppm: 1.40 (t, *J* = 7.15 Hz, 3H, CH₃), 2.65 (s, 3H, CH₃), 3.35 (s, 3H, CH₃), 4.65 (q, *J* = 7.15

Hz, 2H, CH₂), 4.70 (s, 2H, CH₂), 7.35–7.55 (m, 5H, Ar-H). ¹³C NMR (CDCl₃) δ/ppm: 12.36, 13.64, 33.40, 44.98, 69.99, 104.84, 126.75 (2C), 128.83, 129.58 (2C), 133.39, 155.34, 163.61, 187.84, 213.95. Anal. calcd. for C₁₆H₁₈N₂O₃S₂ (350.46): C, 54.83; H, 5.18; N, 7.99. Found: C, 54.92; H, 5.22; N, 7.94.

4-[2-(4,5-Dihydrothiazol-2-ylsulfanyl)acetyl]antipyrene (3)

Yellow crystals, yield 70%, m.p. 184–185°C (EtOH). IR (cm⁻¹): 3042, 2917, 1652, 1635, 1568, 1490, 1455, 1410, 1374, 1339, 1306, 1264, 1156, 1087, 969, 920, 766, 720. ¹H NMR (CDCl₃) δ/ppm: 2.65 (s, 3H, CH₃), 3.35 (s, 3H, CH₃), 3.40 (t, J = 8.20 Hz, 2H, CH₂), 4.20 (t, J = 8.20 Hz, 2H, CH₂), 4.65 (s, 2H, CH₂), 7.2–7.50 (m, 5H, Ar-H). ¹³C NMR (CDCl₃) δ/ppm: 12.39, 33.42, 35.68, 42.19, 64.34, 104.67, 126.66 (2C), 128.72, 129.54 (2C), 133.46, 155.57, 163.59, 164.74, 188.61. Anal. calcd. for C₁₆H₁₇N₃O₂S₂ (347.46): C, 55.31; H, 4.93; N, 12.09. Found: C, 55.21; H, 4.86; N, 12.03.

4-[2-(Pyrimidin-2-ylsulfanyl)acetyl]antipyrene (4)

White crystals, yield 82%, m.p. 235–236°C (EtOH-DMF mixture, 2:1). IR (cm⁻¹): 3059, 2908, 1656, 1641, 1593, 1562, 1547, 1525, 1489, 1455, 1416, 1377, 1329, 1318, 1239, 1213, 1189, 1143, 1087, 997, 890, 823, 768, 749, 721. ¹H NMR (CDCl₃/CF₃COOD) δ/ppm: 2.65 (s, 3H, CH₃), 3.40 (s, 3H, CH₃), 4.75 (s, 2H, CH₂), 7.05 (t, 1H, Ar-H), 7.30–7.55 (m, 5H, Ar-H), 8.55 (d, 2H, Ar-H). ¹³C NMR (CDCl₃/CF₃COOD) δ/ppm: 12.24, 32.92, 40.71, 104.68, 116.70, 128.35 (2C), 130.00 (2C), 130.54, 131.78, 153.10, 157.01 (2C), 163.08, 170.80, 188.59. MS *m/z* (%): 340 (M⁺, 94), 307 (18), 244 (9), 215 (100), 189 (38), 125 (14), 106 (22), 56 (61). Anal. calcd. for C₁₇H₁₆N₄O₂S (340.40): C, 59.98; H, 4.74; N, 16.46. Found: C, 59.85; H, 4.79; N, 16.40.

2-[2-Antipyrinyl-2-oxo-ethylsulfanyl]-4,6-dimethylnicotinonitrile (5)

Yellow crystals, yield 78%, m.p. 187–188°C (EtOH). IR (cm⁻¹): 3063, 2894, 2218, 1666, 1641, 1578, 1510, 1493, 1409, 1367, 1264, 1087, 988, 872, 770, 723, 616. ¹H NMR (CDCl₃) δ/ppm: 2.40 (s, 6H, 2CH₃), 2.65 (s, 3H, CH₃), 3.35 (s, 3H, CH₃), 4.80 (s, 2H, CH₂), 6.75 (s, 1H, pyridine H-5), 7.30–7.55 (m, 5H, Ar-H). ¹³C NMR (CDCl₃) δ/ppm: 12.41, 20.00, 24.53, 33.49, 39.64, 104.72, 105.31, 115.19, 119.78, 126.68 (2C), 128.75, 129.60 (2C), 133.63, 151.61, 155.64, 161.06, 161.53, 163.83, 189.38. MS *m/z* (%): 392 (M⁺, 8), 271 (22), 215 (100), 189 (11), 106 (14), 77 (21), 56

(51). Anal. calcd. for $C_{21}H_{20}N_4O_2S$ (392.47): C, 64.27; H, 5.14; N, 14.28. Found: C, 64.18; H, 5.07; N, 14.21.

Synthesis of 3-Amino-2-(antipyrinylcarbonyl)-4,6-dimethylthieno [2,3-*b*] pyridine (6)

The nicotinonitrile derivative **5** (1.96 g, 10.0 mmol) was added to a solution of sodium ethoxide (from 0.23 g Na, 10.0 mmol) in absolute ethanol (30 mL). The solution was refluxed for 2 h, left to cool, and diluted with cooled water (50 mL). The solid obtained was filtered and recrystallized from ethanol.

Yellow crystals, yield 66%, m.p. 254–255°C (EtOH). IR (cm^{-1}): 3406, 3327, 2975, 1641, 1620, 1588, 1555, 1471, 1445, 1376, 1354, 1302, 1267, 1244, 1110, 1017, 966, 849. 1H NMR ($CDCl_3/CF_3COOD$) δ/ppm : 2.40 (s, 6H, 2CH₃), 2.65 (s, 3H, CH₃), 3.35 (s, 3H, CH₃), 6.90 (s, 1H, pyridine H-5), 7.40–7.60 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3/CF_3COOD$) δ/ppm : 12.48, 20.20, 23.28, 33.66, 95.72, 107.43, 121.98, 122.33, 127.21 (2C), 129.43, 129.79 (2C), 132.84, 144.66, 149.30, 154.58, 160.34, 160.87, 163.83, 186.47. Anal. calcd. for $C_{21}H_{20}N_4O_2S$ (392.47): C, 64.27; H, 5.14; N, 14.28. Found: C, 64.36; H, 5.21; N, 14.18.

Synthesis of 2-Antipyrinyl-imidazo[2,1-*b*]benzothiazole (7)

A mixture of **1** (1.32 g, 5.0 mmol) and 2-aminobenzothiazole (0.75 g, 5.0 mmol) was refluxed in absolute ethanol (30 mL) for 8 h. The precipitate upon cooling was collected by filtration and recrystallized from ethanol.

White crystals, yield 74%, m.p. 216–217°C (EtOH). IR (cm^{-1}): 3041, 2939, 1644, 1591, 1595, 1457, 1311, 1268, 1213, 1134, 755, 719. 1H NMR (DMSO-*d*₆) δ/ppm : 2.70 (s, 3H, CH₃), 3.30 (s, 3H, CH₃), 7.30–7.55 (m, 10H, 9Ar-H and olefin C=CH). ^{13}C NMR (DMSO) δ/ppm : 12.35, 33.29, 104.72, 123.87 (2C), 124.79, 126.89 (2C), 127.31, 129.05, 129.67 (2C), 133.21, 135.46, 141.22, 144.71, 152.73, 155.21, 157.52, 163.37. MS *m/z* (%): 360 (M⁺, 100), 215 (48), 174 (22), 150 (82), 119 (56), 93 (60), 77 (90), 56 (78). Anal. calcd. for $C_{20}H_{16}N_4OS$ (360.43): C, 66.65; H, 4.47; N, 15.54. Found: C, 66.54; H, 4.41; N, 15.47.

Synthesis of Aminothiazole Derivatives (10) and (11)

A mixture of **1** (2.0 mmol) and thiourea derivative **8** or **9** (2.0 mmol) was ball-milled at 70°C for 60 min. After drying at 0.01 bar at 80°C, quantitative yields of **10.HCl** or **11.HCl** were obtained. The free bases **10** and **11** were obtained by washing the fine powder of the hydrochloride

with 5% Na₂CO₃ solution, followed by water and drying at 80°C in a vacuum.

2-Amino-4-antipyrinylthiazole (10a)

White crystals, yield 100%, m.p. 235–236°C; lit.^{17,20} m.p. 235°C. IR (cm⁻¹): 3327, 3151, 2956, 1636, 1593. ¹H NMR (DMSO-*d*₆) δ/ppm: 2.70 (s, 3H, CH₃), 3.15 (s, 3H, CH₃), 6.55 (s, 2H, NH₂), 7.15 (s, 1H, thiazole H-5), 7.25–7.50 (m, 5H, Ar-H). ¹³C NMR (DMSO) δ/ppm: 10.80, 33.86, 100.44, 102.71, 122.46 (2C), 124.80, 127.31 (2C), 133.58, 141.00, 150.58, 162.26, 165.62. Anal. calcd. for C₁₄H₁₄N₄OS (286.35): C, 58.72; H, 4.93; N, 19.57. Found: C, 58.83; H, 4.99; N, 19.64.

4-Antipyrinyl-2-(methylamino)thiazole (10b)

White crystals, yield 100%, m.p. 182–183°C. IR (cm⁻¹): 3268, 2890, 1636, 1563, 1494, 1455, 1397, 1329, 1245, 1152, 1066, 907, 831, 788. ¹H NMR (CDCl₃) δ/ppm: 2.70 (s, 3H, CH₃), 3.00 (s, 3H, CH₃), 3.15 (s, 3H, CH₃), 5.25 (s, 1H, NH), 7.30–7.55 (m, 6H, Ar-H and thiazole H-5). ¹³C NMR (CDCl₃) δ/ppm: 12.53, 31.98, 35.61, 103.22, 105.46, 124.19 (2C), 126.54, 129.04 (2C), 135.25, 143.04, 152.26, 164.44, 169.29. MS *m/z* (%): 300 (M⁺, 100), 285 (10), 226 (10), 208 (22), 167 (14), 150 (15), 77 (10), 56 (25). HR-MS calcd. for C₁₅H₁₆N₄OS: 300.1044, found 300.1044. Anal. calcd. for C₁₅H₁₆N₄OS (300.38): C, 59.98; H, 5.37; N, 18.65. Found: C, 59.93; H, 5.33; N, 18.69.

4-Antipyrinyl-2-(phenylamino)thiazole (10c)

White crystals, yield 100%, m.p. 252°C; lit.²¹ m.p. 247–248 °C. IR (cm⁻¹): 3261, 3040, 1618, 1532, 1495, 1446, 1411, 1312, 1251, 844, 749, 696. ¹H NMR (DMSO-*d*₆) δ/ppm: 2.75 (s, 3H, CH₃), 3.15 (s, 3H, CH₃), 6.90–7.70 (m, 11H, Ar-H and thiazole H-5), 10.15 (s, 1H, NH). ¹³C NMR (DMSO) δ/ppm: 12.17, 35.18, 102.27, 103.06, 116.76 (2C), 121.02, 124.25 (2C), 126.53, 128.87 (2C), 129.01 (2C), 135.01, 141.23, 142.89, 152.09, 162.32, 163.38. Anal. calcd. for C₂₀H₁₈N₄OS (362.45): C, 66.28; H, 5.01; N, 15.46. Found: C, 66.35; H, 5.06; N, 15.42.

4-Antipyrinyl-2-(diphenylamino)thiazole (10d)

White crystals, yield 100%, m.p. 205–206°C. IR (cm⁻¹): 3146, 3061, 1651, 1593, 1505, 1451, 1408, 1333, 1303, 1233, 1151, 1066, 813, 768. ¹H NMR (CF₃COOD) δ/ppm: 2.50 (s, 3H, CH₃), 3.45 (s, 3H, CH₃), 7.25–7.70 (m, 16H, Ar-H and thiazole H-5). ¹³C NMR (CF₃COOD) δ/ppm: 10.75,

32.99, 95.26, 126.04 (4C), 129.12 (2C), 129.94, 130.38, 130.92, 131.28 (2C), 131.37 (2C), 131.90 (4C), 133.42 (2C), 141.44, 147.69, 158.71, 170.92. MS m/z (%): 438 (M^+ , 100), 346 (8), 289 (10), 219 (20), 77 (12), 56 (15). HR-MS calcd. for $C_{26}H_{22}N_4OS$: 438.1514, found 438.1508. Anal. calcd. for $C_{26}H_{22}N_4OS$ (438.54): C, 71.21; H, 5.06; N, 12.78. Found: C, 71.32; H, 5.13; N, 12.72.

2-(4-Antipyrinyl-thiazol-2-ylamino)-*N,N*-dimethylacetamide (11a)

White crystals, yield 100%, m.p. 212–213°C. IR (cm^{-1}): 3326, 3134, 2936, 1661, 1640, 1594, 1540, 1476, 1408, 1371, 1332, 1255, 1147, 1104, 1067, 1036, 790, 745, 697, 635, 587. 1H NMR ($CDCl_3$) δ/ppm : 2.70 (s, 3H, CH_3), 3.00 (s, 6H, 2 CH_3), 3.10 (s, 3H, CH_3), 4.15 (s, 2H, CH_2), 6.20 (s, 1H, NH), 7.20–7.45 (m, 6H, Ar-H and thiazole H-5). ^{13}C NMR ($CDCl_3$) δ/ppm : 12.52, 35.59 (2C), 35.78, 46.01, 103.47, 105.29, 124.16 (2C), 126.53, 129.02 (2C), 135.19, 142.70, 152.18, 164.32, 166.70, 167.88. MS m/z (%): 371 (M^+ , 21), 299 (100), 271 (4), 213 (5), 151 (5), 72 (20), 56 (22). HR-MS calcd. for $C_{18}H_{21}N_5O_2S$: 371.1416, found 371.1417. Anal. calcd. for $C_{18}H_{21}N_5O_2S$ (371.46): C, 58.20; H, 5.70; N, 18.85. Found: C, 58.06; H, 5.78; N, 18.80.

2-(4-Antipyrinyl-thiazol-2-ylamino)-*N,N*-diethylacetamide (11b)

White crystals, yield 100%, m.p. 165–166°C. IR (cm^{-1}): 3259, 3120, 3040, 2990, 2936, 1661, 1641, 1593, 1548, 1530, 1489, 1460, 1404, 1349, 1318, 1288, 1245, 1152, 1098, 1066, 790, 750, 698, 647, 592. 1H NMR ($CDCl_3$) δ/ppm : 1.15 (t, $J = 7.00$ Hz, 3H, CH_3), 1.20 (t, $J = 7.00$ Hz, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 3.30 (q, $J = 7.00$ Hz, 2H, CH_2), 3.40 (q, $J = 7.00$ Hz, 2H, CH_2), 4.15 (s, 2H, CH_2), 6.20 (s, 1H, NH), 7.20–7.50 (m, 6H, Ar-H and thiazole H-5). ^{13}C NMR ($CDCl_3$) δ/ppm : 12.54, 12.90, 14.00, 35.58, 40.49, 40.93, 45.94, 103.50, 105.32, 124.18 (2C), 126.55, 129.03 (2C), 135.17, 142.61, 152.16, 164.33, 166.86, 166.96. MS m/z (%): 399 (M^+ , 72), 372 (56), 299 (100), 271 (10), 213 (11), 151(6), 77 (16), 56 (64). Anal. calcd. for $C_{20}H_{25}N_5O_2S$ (399.51): C, 60.13; H, 6.31; N, 17.53. Found: C, 60.08; H, 6.28; N, 17.55.

Synthesis of 4,6-Dimethylpyrazolo[3,4-*b*]pyridin-3-ylazo thiazoles(12a–d)

A solution of 4,6-dimethylpyrazolo[3,4-*b*]pyridine-3-diazonium nitrate hydrate (5.0 mmol, 1.27 g in 10 mL H_2O) was added with continuous

stirring to a cold (0–5°C) solution of the aminothiazole derivatives **10** (5.0 mmol) in pyridine (30 mL). The reaction mixture was allowed to rest at (0–5°C) for 2 h, was diluted with water, and then the solid was collected by filtration. The pyrazolopyridinylazo-thiazoles **12a–d** thus obtained were dried and recrystallized from ethanol-DMF mixture (3:1).

2-Amino-4-antipyrinyl-5-(4,6-dimethylpyrazolo[3,4-*b*]pyridin-3-ylazo)thiazole (12a)

Red crystals, yield 75%, m.p. 241–241°C. IR (cm⁻¹): 3281, 3180, 3094, 1612, 1592, 1496, 1416, 1305, 1268, 1198, 1142, 830, 750, 695. ¹H NMR (CDCl₃/CF₃COOD) δ/ppm: 2.80 (s, 3H, CH₃), 3.00 (s, 3H, CH₃), 3.15 (s, 3H, CH₃), 3.60 (s, 3H, CH₃), 7.35–7.75 (m, 6H, Ar-H and pyridine-H). ¹³C NMR (CDCl₃/CF₃COOD) δ/ppm: 13.31, 19.87, 20.22, 33.71, 95.41, 114.72, 120.01, 122.07, 128.88 (2C), 129.90, 131.24 (2C), 133.06, 136.14, 139.45, 143.92, 149.97, 151.41, 157.23, 160.52, 170.09. MS *m/z* (%): 459 (M⁺, 10), 342 (18), 310 (20), 272 (20), 228 (45), 198 (25), 184 (52), 162 (100), 155 (15), 70 (40). Anal. calcd. for C₂₂H₂₁N₉OS (459.53): C, 57.50; H, 4.61; N, 27.43. Found: C, 57.66; H, 4.70; N, 27.40.

4-Antipyrinyl-2-(methylamino)-5-(4,6-dimethylpyrazolo[3,4-*b*]pyridin-3-ylazo)-thiazole (12b)

Red crystals, yield 72%, m.p. 270–271°C. IR (cm⁻¹): 3174, 2938, 1646, 1590, 1498, 1456, 1392, 1283, 1192, 1151, 1081, 1036, 826, 744. ¹H NMR (CDCl₃/CF₃COOD) δ/ppm: 2.75 (s, 3H, CH₃), 2.95 (s, 3H, CH₃), 3.10 (s, 3H, CH₃), 3.30 (s, 3H, CH₃), 3.50 (s, 3H, CH₃), 7.30–7.75 (m, 6H, Ar-H and pyridine-H). ¹³C NMR (CDCl₃/CF₃COOD) δ/ppm: 12.99, 19.93, 20.05, 33.40, 33.59, 95.05, 114.14, 120.26, 121.60, 128.62 (2C), 129.58, 130.86 (2C), 132.66, 134.98, 140.85, 143.55, 149.76, 151.06, 156.75, 162.42, 170.05. MS *m/z* (%): 473 (M⁺, 82), 343 (100), 300 (32), 210 (36), 162 (65), 93 (35), 56 (42). Anal. calcd. for C₂₃H₂₃N₉OS (473.55): C, 58.33; H, 4.90; N, 26.62. Found: C, 58.41; H, 4.94; N, 26.68.

4-Antipyrinyl-2-(phenylamino)-5-(4,6-dimethylpyrazolo[3,4-*b*]pyridin-3-ylazo)-thiazole (12c)

Violet crystals, yield 83%, m.p. 291–292°C. IR (cm⁻¹): 3256, 3077, 1651, 1569, 1489, 1450, 1301, 1260, 1239, 1148, 833, 751. ¹H NMR (CDCl₃/CF₃COOD) δ/ppm: 2.80 (s, 3H, CH₃), 2.90 (s, 3H, CH₃), 3.05 (s, 3H, CH₃), 3.60 (s, 3H, CH₃), 7.40–7.80 (m, 11H, Ar-H and pyridine-H). ¹³C NMR (CDCl₃/CF₃COOD) δ/ppm: 13.28, 20.14, 20.36, 33.63, 95.49,

114.40, 121.61, 123.32 (2C), 128.75 (2C), 129.66, 130.38, 131.04 (4C), 132.89, 135.02, 135.30, 141.64, 143.41, 149.90, 151.71, 156.34, 159.79, 160.18, 168.66. MS m/z (%): 535 (M^+ , 10), 507 (20), 475 (17), 362 (22), 343 (100), 310 (25), 272 (22), 228 (52), 184 (65), 155 (25), 70 (60). Anal. calcd. for $C_{28}H_{25}N_9OS$ (535.62): C, 62.79; H, 4.70; N, 23.54. Found: C, 62.86; H, 4.76; N, 23.50.

4-Antipyrinyl-2-(diphenylamino)-5-(4,6-dimethylpyrazolo[3,4-*b*] pyridin-3-ylazo)-thiazole (12d)

Red crystals, yield 81%, m.p. 264–265°C. IR (cm^{-1}): 3089, 2919, 1657, 1591, 1479, 1447, 1411, 1305, 1150, 1024, 828, 756, 694. 1H NMR ($CDCl_3/CF_3COOD$) δ/ppm : 2.55 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 7.00–7.55 (m, 16H, Ar-H and pyridine-H). ^{13}C NMR ($CDCl_3/CF_3COOD$) δ/ppm : 13.50, 20.05, 20.32, 33.60, 96.03, 114.42, 121.46 (2C), 125.76 (4C), 128.89 (2C), 129.40, 131.06 (2C), 131.50 (4C), 133.08 (2C), 136.54, 143.18, 143.79, 150.01, 152.11, 155.91, 159.66, 160.27, 162.33, 162.75, 169.85. MS m/z (%): 611 (M^+ , 15), 453 (44), 449 (50), 343 (52), 283 (20), 210 (20), 194 (28), 169 (100), 77 (36). Anal. calcd. for $C_{34}H_{29}N_9OS$ (611.72): C, 66.76; H, 4.78; N, 20.61. Found: C, 66.62; H, 4.69; N, 20.66.

Synthesis of 2-(4-antipyrinyl-5-arylazo-thiazol-2-ylamino)-*N,N*-dimethylacetamides (13a–c)

A solution of sodium nitrite (0.70 g in 10 mL water) was gradually added to a well-cooled (0–5°C) solution of the aromatic amine (10.0 mmol) in concentrated HCl (3.0 mL). The diazonium salt solution was added with continuous stirring to a cold (0–5°C) solution of the aminothiazole derivative **11a** (10.0 mmol) in ethanol (50.0 mL) and sodium acetate (4.0 g). The reaction mixture was allowed to stir at (0–5°C) for 2 h, and then the solid was collected by filtration. The arylazothiazoles **13a–c** thus obtained, were dried and recrystallized from ethanol.

2-(4-Antipyrinyl-5-phenylazo-thiazol-2-ylamino)-*N,N*-dimethylacetamide (13a)

Red crystals, yield 86%, m.p. 233–234°C. IR (cm^{-1}): 3294, 2955, 1672, 1650, 1613, 1594, 1536, 1492, 1426, 1402, 1343, 1315, 1267, 1200, 1188, 1087, 752, 692, 641, 608. 1H NMR ($CDCl_3$) δ/ppm : 2.35 (s, 3H, CH_3), 3.00 (s, 6H, 2 CH_3), 3.15 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 6.90 (s, 1H, NH), 7.20–7.50 (m, 8H, Ar-H), 7.70 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$) δ/ppm : 12.94,

35.40, 35.65, 35.84, 45.38, 105.10, 121.95 (2C), 124.73 (2C), 126.81, 128.88 (2C), 129.08 (2C), 135.01, 141.47, 148.91, 152.84, 154.95, 160.12, 163.17, 167.06, 168.04. MS m/z (%): 475 (M^+ , 92), 403 (100), 375 (14), 327 (13), 299 (51), 283 (8), 214 (8), 105 (16), 93 (42), 77 (62), 56 (77). Anal. calcd. for $C_{24}H_{25}N_7O_2S$ (475.57): C, 60.61; H, 5.30; N, 20.62. Found: C, 60.52; H, 5.34; N, 20.55.

2-(4-Antipyrinyl-5-(*p*-tolylazo)thiazol-2-ylamino)-*N,N*-dimethylacetamide (13b)

Red crystals, yield 88%, m.p. 260–261°C. IR (cm^{-1}): 3289, 2939, 1674, 1651, 1619, 1596, 1537, 1494, 1456, 1424, 1405, 1335, 1314, 1264, 1210, 1090, 828, 748, 696, 639, 599. 1H NMR ($CDCl_3/CF_3COOD$) δ/ppm : 2.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.90 (s, 6H, 2 CH_3), 3.30 (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 7.15–7.50 (m, 9H, Ar-H). ^{13}C NMR ($CDCl_3/CF_3COOD$) δ/ppm : 13.06, 21.31, 33.98, 35.62, 35.82, 46.92, 96.42, 122.29 (2C), 127.46 (2C), 129.68 (2C), 129.96 (2C), 132.22, 141.99, 144.78, 148.90, 150.73, 155.76, 161.48, 164.67, 168.14 (2C). MS m/z (%): 489 (M^+ , 100), 444 (21), 417 (94), 371 (18), 324 (8), 299 (63), 283 (7), 214 (6), 119 (6), 106 (14), 91 (57), 56 (72). Anal. calcd. for $C_{25}H_{27}N_7O_2S$ (489.59): C, 61.33; H, 5.56; N, 20.03. Found: C, 61.21; H, 5.47; N, 20.11.

2-(4-Antipyrinyl-5-(*p*-methoxy-phenylazo)thiazol-2-ylamino)-*N,N*-dimethylacetamide (13c)

Red crystals, yield 77%, m.p. 252–253°C. IR (cm^{-1}): 3302, 3056, 2935, 1677, 1646, 1619, 1601, 1579, 1531, 1494, 1468, 1421, 1407, 1340, 1315, 1253, 1203, 1146, 1088, 1033, 839, 751, 696, 638, 592. 1H NMR ($CDCl_3$) δ/ppm : 2.30 (s, 3H, CH_3), 2.90 (s, 6H, 2 CH_3), 3.15 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 6.75 (s, 1H, NH), 6.80 (d, 2H, Ar-H), 7.15–7.40 (m, 5H, Ar-H), 7.60 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$) δ/ppm : 12.92, 35.46, 35.63, 35.83, 45.35, 55.43, 105.26, 114.15 (2C), 123.56 (2C), 124.62 (2C), 126.71, 129.06 (2C), 135.08, 141.68, 146.80, 147.16, 154.97, 160.59, 163.26, 167.15, 167.27. Anal. calcd. for $C_{25}H_{27}N_7O_3S$ (505.59): C, 59.39; H, 5.38; N, 19.39. Found: C, 59.51; H, 5.44; N, 19.33.

Synthesis of Compounds 16, 17, and 18

To a cold suspension of finely divided KOH (0.56 g, 10.0 mmol) in DMF (30 mL) were added the cyanoacetyl-antipyrine **14** (2.55 g, 10.0 mmol) followed by phenyl isothiocyanate (1.20 mL, 0.01 mol). The mixture

was stirred at room temperature overnight, and then was treated with the appropriate halogenated compound (10.0 mmol). The stirring was continued at room temperature for 8 h. The reaction mixture was poured into ice-cold water. The resultant solid product was collected by filtration, washed with water, dried, and recrystallized from the proper solvent.

2-Antipyrinyl-3-methylsulfanyl-3-phenylaminoacrylonitrile (16)

Yellow crystals, yield 44%, m.p. 173–174°C (EtOH). IR (cm^{-1}): 3173, 2964, 2106, 1644, 1599, 1556, 1443, 1337, 1266, 1130, 887, 732. ^1H NMR (CDCl_3) δ/ppm : 2.55 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 7.10–7.70 (m, 10H, Ar-H), 10.75 (s, 1H, NH). ^{13}C NMR (CDCl_3) δ/ppm : 12.30, 18.78, 33.32, 103.56, 110.23, 114.21, 127.11 (2C), 128.49 (2C), 129.00 (3C), 129.60 (3C), 132.84, 135.11, 154.58, 161.39, 163.31, 179.81. Anal. calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_2\text{S}$ (404.48): C, 65.33; H, 4.98; N, 13.85. Found: C, 65.43; H, 5.04; N, 13.93.

3-Antipyrinyl-2-(3,4-diphenyl-3H-thiazol-2-ylidene)-3-oxopropionitrile (17)

Yellow crystals, yield 66%, m.p. 192–193°C (EtOH). IR (cm^{-1}): 3060, 2843, 2197, 1631, 1606, 1547, 1474, 1449, 1412, 1363, 1320, 1256, 1240, 1221, 1156, 1120, 1051, 971, 895, 866, 768, 703, 590. ^1H NMR ($\text{CDCl}_3/\text{CF}_3\text{COOD}$) δ/ppm : 2.80 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 7.10–7.85 (m, 15H, Ar-H), 8.15 (s, 1H, $\text{C}=\text{CH}$), 8.35 (d, 2H, Ar-H). ^{13}C NMR ($\text{CDCl}_3/\text{CF}_3\text{COOD}$) δ/ppm : 11.25, 34.01, 86.57, 102.81, 123.98, 125.88, 126.29, 126.59, 128.05 (2C), 129.31 (2C), 129.61 (2C), 130.40 (2C), 131.62 (2C), 131.73 (2C), 132.46, 134.96, 135.15, 135.83, 149.02, 152.88, 153.42, 163.07, 170.95. MS m/z (%): 490 (M^+ , 100), 387 (19), 356 (12), 105 (62), 77 (20). HR-MS calcd. for $\text{C}_{29}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$: 490.1463, found 490.1455. Anal. calcd. for $\text{C}_{29}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$ (490.58): C, 71.00; H, 4.52; N, 11.42. Found: C, 71.11; H, 4.61; N, 11.37.

3-Antipyrinyl-3-oxo-2-(5-oxo-3-phenylthiazolidin-2-ylidene)propionitrile (18)

Yellow crystals, yield 52%, m.p. 244–245°C (EtOH- CHCl_3 mixture, 3:1). IR (cm^{-1}): 2965, 2209, 1739, 1662, 1614, 1525, 1485, 1414, 1363, 1318, 1227, 1200, 1170, 1132, 1067, 979, 720, 694. ^1H NMR ($\text{DMSO}-d_6$) δ/ppm : 2.30 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 3.85 (s, 2H, CH_2), 7.10–7.40 (m, 10H, Ar-H). ^{13}C NMR ($\text{DMSO}-d_6$) δ/ppm : 9.88, 29.77, 32.35, 86.61, 104.78,

111.76, 124.53 (2C), 126.15, 127.43 (6C), 128.34, 132.62, 133.37, 153.11, 159.78, 167.81, 171.33, 181.96. MS m/z (%): 430 (M^+ , 15), 388 (4), 356 (5), 311 (7), 215 (100), 188 (25), 143 (10), 106 (10), 77 (27). Anal. calcd. for $C_{23}H_{18}N_4O_3S$ (430.48): C, 64.17; H, 4.21; N, 13.01. Found: C, 64.31; H, 4.28; N, 13.06.

Synthesis of 3-Antipyrinyl-3-oxo-2-[5-oxo-3-phenyl-4-(*p*-tolylhydrazono)-thiazolidin-2-ylidene]-propionitrile (19)

A freshly cooled solution of *p*-tolylidiazonium chloride (prepared by adding cold sodium nitrite solution [0.35 g in 10 mL H_2O] to a cold suspension of *p*-toluidine (0.53 g, 5.0 mmol) in 1.5 mL concentrated HCl) was added with continuous stirring to a cold (0–5°C) solution of the thiazolidinone derivative **18** (2.15 g, 5.0 mmol) in pyridine (25 mL). The reaction mixture was allowed to stir at (0–5°C) for 2 h, and then the solid was collected by filtration. The *p*-tolylazo derivative **19** thus obtained was dried and recrystallized from ethanol.

Red crystals, yield 64%, m.p. 210–211°C. IR (cm^{-1}): 3203, 3040, 2942, 2207, 1728, 1664, 1614, 1538, 1489, 1412, 1362, 1208, 1146, 1084, 984, 866. 1H NMR ($CDCl_3$) δ /ppm: 2.25 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 7.00–7.60 (m, 14H, Ar-H), 10.30 (s, 1H, NH). Anal. calcd. for $C_{30}H_{24}N_6O_3S$ (548.61): C, 65.68; H, 4.41; N, 15.32. Found: C, 65.60; H, 4.47; N, 15.29.

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