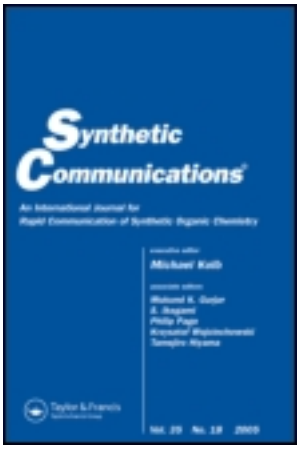

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EFFICIENT SYNTHESIS OF NEW FUNCTIONALIZED 2-(HETARYL)THIAZOLES

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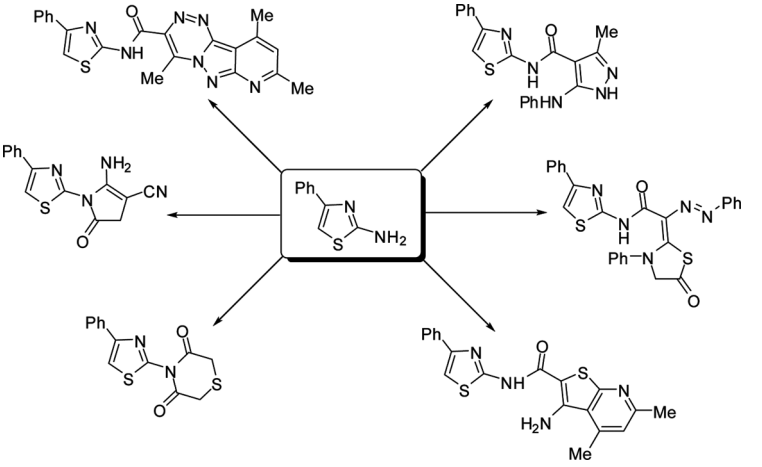
GRAPHICAL ABSTRACT



Abstract *An efficient synthesis of the hitherto unknown ring system, 2-heteroaryl-thiazoles, is described* via *the reaction of 3-oxo-N-(4-phenylthiazol-2-yl)butanamide (**1**) with diazotized heterocyclic amine, phenyl isothiocyanate, dimethylformamide–dimethylacetal, and hydrazine hydrate, and the reaction of 2-chloro-N-(4-phenylthiazol-2-yl)acetamide (**13**) with some sulfur nucleophiles and malononitrile. The structures of the compounds prepared were determined by analytical and spectral analyses.*

Keywords Japp–Klingmann; phenyl isothiocyanate; pyrazole; pyridine; thiazole

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INTRODUCTION

2-Aminothiazoles have received considerable attention because of their importance as versatile reagents.[1–5] The thiazole ring system is a common structural moiety found in numerous biologically active molecules.[6] This heterocyclic moiety has been employed in the preparation of different drugs required for the treatment of hypertension.[7] Some of the thiazole analogs are used as fungicides, inhibiting the in vivo growth of *Xanthomonas*, and as ingredients of herbicides or schistosomicidal and anthelmintic drugs.[8] They have been utilized for the treatment of pain,[9] as fibrinogen receptor antagonists with antithrombotic activity,[10] and as inhibitors of bacterial DNA gyrase B.[11] In the light of these facts and in continuation of our interest in the synthesis of heterocycles containing a thiazole moiety,[12–20] we report herein the results of our study of the reaction of 3-oxo-*N*-(4-phenylthiazol-2-yl)butanamide (**2**) and 2-chloro-*N*-(4-phenylthiazol-2-yl)acetamide (**13**) with some electrophilic and nucleophilic reagents. The aim of the present article is to present an efficient synthesis of novel 2-heteroaryl-thiazoles, which have not been reported.

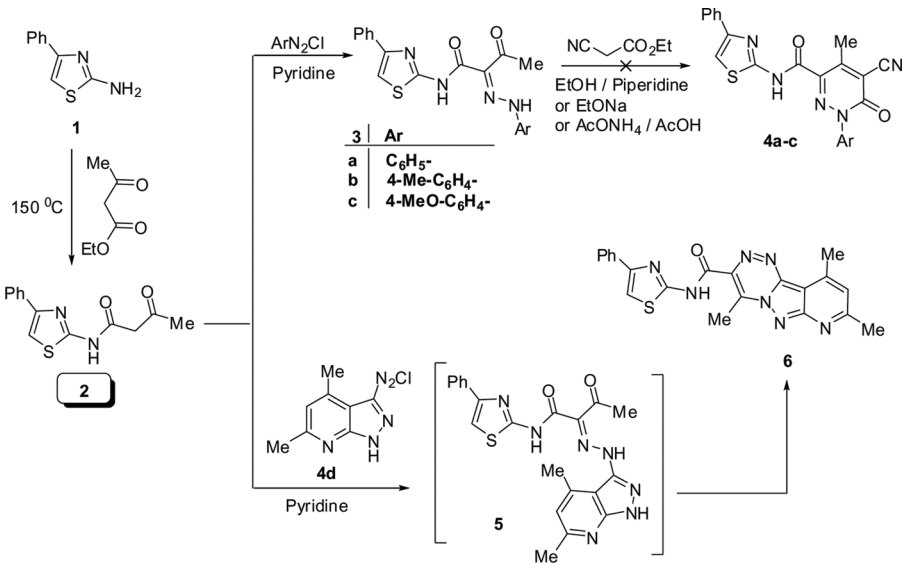
RESULTS AND DISCUSSION

The starting material, 3-oxo-*N*-(4-phenylthiazol-2-yl)butanamide (**2**), used in this study was prepared by the solvent-free reaction of 2-amino-4-phenylthiazole (**1**) with ethyl acetoacetate at 150 °C according to a literature procedure.[21] The chemical behavior of the versatile starting material **2** was tested toward many chemical reactions, for example, coupling reaction with aromatic and heterocyclic diazonium salts, phenyl isothiocyanate, and dimethylformamide–dimethylacetal (DMF-DMA).

Compound **2** possesses two active sites (active methylene C-2 and thiazole C-5) for electrophilic substitution reaction by aromatic diazonium salts. The methylene group in compound **2** proved to be more reactive toward coupling reaction with diazonium salts than the thiazole C-5. Thus, compound **2** coupled smoothly with 1 mol of the diazonium salts of aniline, *p*-toulidine, and *p*-anisidine in pyridine to afford the corresponding arylhydrazone derivatives **3a–c** by reaction at the methylene site (Scheme 1). The structure of the arylhydrazone products **3a–c** were verified by elemental analyses and spectroscopic methods. For example, the infrared (IR) spectrum of **3c** revealed absorption bands at 3216, 3102, 1674, and 1656 cm^{-1} due to two (NH) and two carbonyl functions. Its ^1H NMR spectrum displayed, in addition to aromatic proton signals, four singlet signals at δ 2.40, 3.79, 13.36, and 13.70 ppm characteristic for the CH_3, OCH_3, hydrazone NH, and amidic NH protons, respectively.

It has been reported[22] that condensation of 2-arylhydrazonoketones with active methylene nitriles affords pyridazinones. In this context, compounds **3a–c** were allowed to react with ethyl cyanoacetate in refluxing ethanolic piperidine solution, sodium ethoxide, or glacial acetic acid containing ammonium acetate, in an attempt to get the pyridazinones **4a–c**. Unfortunately, the starting arylhydrazonoketones **3a–c** were recovered.

We turned our attention to study the reactivity of **2** toward diazotized heterocyclic amine, namely, 3-amino-4,6-dimethyl-pyrazolo[3,4-*b*]-pyridine (**4d**) as a possible synthetic route to attain a bridged head nitrogen heterocyclic system. Thus, coupling of **4d** with butanamide **2** in pyridine afforded the corresponding



Scheme 1. Synthetic route to pyrido[2′,3′:3,4]pyrazolo-[5,1-c][1,2,4]trazine-3-carboxamide (**6**).

pyrido[2′,3′:3,4]pyrazolo[5,1-*c*]triazine derivative **6** via the hetarylhydrazonoketone intermediate **5**. The mass spectrum of **6** clearly showed the molecular ion peak at m/z 415 (M^+) corresponding to the molecular weight of the molecular formula $C_{21}H_{17}N_7OS$.

The base-promoted nucleophilic addition of butanamide **2** to an equimolar amount of phenyl isothiocyanate in dimethylformamide containing potassium hydroxide afforded the corresponding thiocarbamoyl derivative **7** after neutralization with dilute HCl. The structure of **7** was confirmed on the basis of its elemental analysis and spectral data. The IR spectrum of **7** showed absorption bands at 3445, 3227, 1675, 1654, and 1288 cm^{-1}, indicating the presence of two (NH), two (C=O), and (C=S) groups, respectively. Moreover, its mass spectrum showed the molecular ion peak at m/z 369 (M^+), corresponding to the molecular formula $C_{18}H_{15}N_3O_2S_2$.

Treatment of thiocarbamoyl derivative **7** with hydrazine hydrate in refluxing ethanol afforded the isolable product (tested by thin-layer chromatography, TLC), identified as 3-methyl-5-(phenylamino)-N-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carboxamide (**8**). The IR spectrum of compound **8** showed absorption bands at 3365, 3278, 3150, and 1652 cm^{-1} due to three NH and amidic carbonyl functions. Its ^1H NMR revealed a singlet signal at δ 2.12 due to CH_3 protons, D_2O-exchangeable signals at 9.17, 11.37, and 13.12 due to three NH protons, and an aromatic multiplet and thiazole-H5 in the region δ 6.95–7.84 ppm.

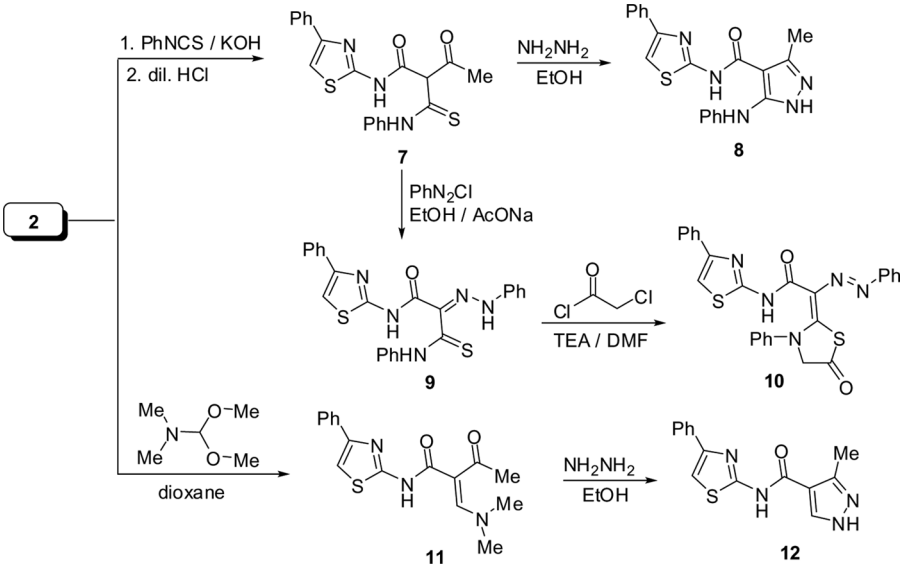
Treatment of **7** with the phenyl diazonium chloride in ethanol buffered with sodium acetate effected acetyl group cleavage (Japp–Klingmann reaction) with the formation of the corresponding phenylhydrazonothiocarbamoyl derivative **9**. The chemical structure of **9** was assigned on the basis of the spectral and elemental analyses. The IR spectrum showed absorption bands at 3412, 3234, 3154, 1658, and 1288 cm^{-1} due to three NH, amidic carbonyl and thiocarbonyl functions, respectively.

The ^{1}H NMR spectrum revealed the lack of acetyl signal and the presence of three singlet signals exchangeable with D_2O at δ 9.98, 12.46, and 13.26 ppm due to three NH protons, beside the expected multiplet signal for an aromatic protons and thiazole-H5 in the region 7.16–7.91 ppm.

The reaction of thiocarbamoyl derivatives with α-halocarbonyl compounds provides a facile one-pot synthesis of thiazole derivatives. Thus, treatment of thioacetanilide **9** with chloroacetyl chloride in dimethylformamide containing a catalytic amount of triethylamine at room temperature afforded the thiazolidin-5-one **10**. The structure of the latter product was established by the presence of a strong absorption band at 1735 cm^{-1} in the IR spectrum. This is considered to be a strong confirmation for the thiazolidinone nucleus formation. Another of evidence for the cyclization is the presence of a singlet signal, equivalent to two protons in the ^{1}H NMR spectrum at δ 4.24 ppm, which represents the C-4 protons of the thiazolidinone nucleus.

Enaminones are versatile intermediates for the synthesis of a variety of biologically important natural products, fine chemicals, and pharmacecuticals.[23] In this context, the reactivity of butanamide **2** toward DMF-DMA as a possible synthetic route to enaminone was investigated. Thus, when butanamide **2** was treated with DMF-DMA in boiling dioxane, it afforded the corresponding enaminone, namely 2-(*N,N*-dimethylaminomethylene)-3-oxo-*N*-(4-phenylthiazol-2-yl)butanamide (**11**). The IR spectrum of the latter product revealed absorption bands at 3172, 1682, and 1656 cm^{-1} due to NH and two carbonyl functions. Its ^{1}H NMR revealed signals at δ 2.47, 3.21, and 3.26 ppm due to acetyl CH_3 protons and *N,N*-dimethyl protons, in addition to the D_2O-exchangeable signal at δ 13.72 ppm due to the amidic NH proton, and an aromatic multiplet, thiazole H5, and olefinic proton in the region δ 7.26–8.35 ppm.

Compound **11** was treated with hydrazine hydrate, in refluxing ethanol, to afford the pyrazole derivative **12** (Scheme 2). The IR spectrum of pyrazole **12** revealed



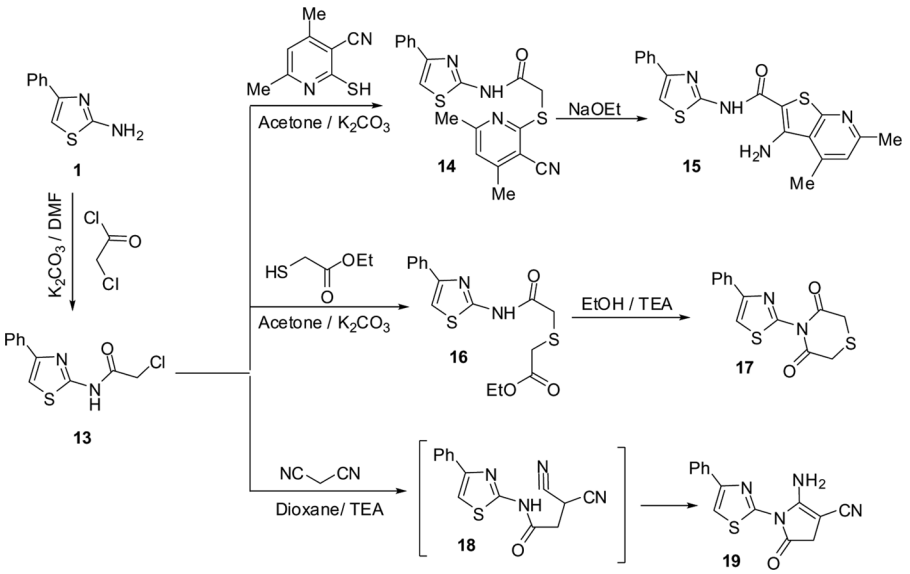
Scheme 2. Synthetic pathway to pyrazolo **8**, **12**, and thiazolidin-5-one **10** derivatives.

absorption bands at 3235, 3100, and 1661 cm^{-1} due to two NH and amidic carbonyl functions. Its ^1H NMR revealed two singlets at δ 2.14, and 8.98 ppm due to CH_3 protons and pyrazole-H5, beside two D_2O-exchangeable signals at δ 9.56 and 11.75 due to NH protons, and an aromatic multiplet in the region δ 6.68–7.85 ppm. Morever, its mass spectrum showed a molecular ion peak at m/z 284 (M^+) corresponding to the molecular weight of the molecular formula $C_{14}H_{12}N_4OS$.

In addition, α-chloroacetamides are highly reactive compounds.[24,25] They are extensively utilized as reactants or reaction intermediates because the imino and chloride functions of these compounds are suitably situated to enable reactions with common bidendate reagents to form a variety of heterocyclic compounds. Moreover, the active hydrogen at C-2 of these compounds can take part in a variety of condensation and substitution reactions. In this context, we synthesized 2-chloro-*N*-(4-phenylthiazol-2-yl)acetamide (**13**),[26] via treatment of 2-amino-4-phenylthiazole (**1**) with chloroacetyl chloride in DMF containing anhydrous potassium carbonate, to investigate its reactivity toward some sulfur nucleophiles and malononitrile.

Thus, treatment of 2-chloroacetamide **13** with 4,6-dimethyl-2-mercaptonicotinonitrile in refluxing acetone containing sodium carbonate gave the corresponding sulfide derivative **14**, which underwent cyclization on heating in ethanolic sodium ethoxide solution to afford the corresponding thieno[2,3-*b*]pyridine derivative **15** (Scheme 3). The chemical structures of compounds **14** and **15** were established on the basis of their elemental analyses and spectral data.

The IR spectrum of **14** is characterized by the presence of a strong absorption bands at 3107, 2223, and 1689 cm^{-1} due to NH, nitrile, and carbonyl functions, respectively. Its ^1H NMR spectrum displayed two singlet signals at δ 2.35 and 2.40 due to the two methyl protons, a singlet signal at δ 4.28 due to the thiomethylene protons (SCH_2),



Scheme 3. Synthetic route to thieno[2,3-*b*]pyridine **15**, thiomorpholine-3,5-dione **17**, and pyrrole **19** derivatives.

a multiplet in the region δ 7.10–7.92 due to an aromatic and thiazole-H5 protons, and a singlet signal at δ 12.57 ppm exchangeable with D_2O due to a NH proton.

The IR spectrum of **15** clearly indicated the lack of a cyano absorption band and revealed the characteristics of NH_2 and NH absorption bands at 3509, 3403, and 3347 cm^{-1} in addition to the carbonyl absorption band at 1623 cm^{-1}. The strong decrease in the carbonyl absorption frequency is attributed to the highly chelated intramolecular H-bond structure. Its ^1H NMR spectrum confirmed the lack of the singlet signal that characterized the methylene protons and showed two singlet signals due to the two methyl protons at δ 2.40 and 2.80 in addition to a singlet signal at δ 7.00 for the pyridine-H5 proton and multiplet signal at δ 7.40–7.90 ppm for the aromatic and thiazole H5 protons. Also, its mass spectrum showed a molecular ion peak at m/z 490 (M^+) corresponding to the molecular weight of the molecular formula $C_{24}H_{22}N_6O_2S_2$.

The plausible mechanism for the formation of thieno[2,3-*b*]pyridine **15** is attributed to an initial alkylation of **13** with mercaptonicotinonitrile to form the isolable thioether **14**, which underwent intramolecular cyclization via nucleophilic addition of the active methylene group to the nitrile function and tautomerization according to the Thorpe–Ziegler reaction.[27]

In a similar manner, the reaction of **13** with ethyl thioglycolate in acetone containing anhydrous potassium carbonate afforded the corresponding sulfide **16**, which could be easily converted to thiomorpholine-3,5-dione **17** upon boiling in ethanolic triethylamine solution. The structures of isolated products **16** and **17** were verified by elemental analyses and spectroscopic data. For example, the IR spectrum of **17** revealed the lack of both an imino and carbonyl ester groups and the presence of absorption band at 1669 cm^{-1} due to an amidic carbonyl group. Its ^1H NMR spectrum displayed, in addition to the aromatic proton signals, a singlet signal at δ 5.24 ppm integrated for four protons due to the two methylene protons of thiomorpholine-3,5-dione ring.

Finally, the reaction of **13** with malononitrile in refluxing dioxane containing a catalytic amount of triethylamine furnished the functionalized pyrrole derivative **19**. The IR spectrum of the latter product showed the characteristic absorption bands of amino (NH_2), cyano (CN) and carbonyl (CO) groups at 3424, 3329, 2198, and 1692 cm^{-1}, respectively. Its ^1H NMR spectrum displayed a singlet signal at δ 4.10 due to the methylene protons (CH_2, ring), a broad singlet signal at δ 6.85 ppm exchangeable with D_2O due to the NH_2 protons, and thiazole H-5 proton, aromatic protons as multiplet signal in the region δ 7.40–7.60 ppm.

Compound **19** was thought to be formed via the initial displacement of the chloride ion by the active methylene group of malononitrile to form the nonisolable intermediate **18**, which in situ undergoes intramolecular cyclization via nucleophilic addition of the imino group to the nitrile function and tautomerization. Moreover, the formation of pyrrolidinone **19** is also in the line with previous report by Schaefer and Gewald.[28]

In conclusion, we have described an efficient synthesis of new pyrido[2′,3′:3,4]pyrazolo[5,1-*c*]triazine, pyrazole, thiazole, thieno[2,3-*b*]pyridine, thiomorpholine, and pyrrole derivatives containing thiazole template via the reaction of two versatile, and readily accessible starting materials, 3-oxo-*N*-(4-phenylthiazol-2-yl)butanamide and 2-chloro-*N*-(4-phenylthiazol-2-yl)acetamide with some chemical reagents.

EXPERIMENTAL

All melting points were measured on an electrothermal Gallenkamp melting-point apparatus. The IR spectra were recorded in potassium bromide disks on a Mattson 5000 FTIR spectrometer. The NMR spectra were recorded on a Brucker WP 300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.5 MHz in dimethylsulfoxide (DMSO-d_6) or $CDCl_3$ or CF_3COOD as solvent. Chemical shifts were related to that of the solvent. The mass spectrum were recorded on a Finnigan MAT 212 mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt, and the results were in a good agreement (±0.3%) with the calculated values. The starting materials 3-oxo-*N*-(4-phenylthiazol-2-yl)butanamide (**2**)[21] and 2-chloro-*N*-(4-phenylthiazol-2-yl)acetamide (**13**)[26] were prepared according to the literature.

General Procedure for the Synthesis of Arylhydrazone Derivatives (3a–c)

The appropriate diazonium salt of aromatic amines (2 mmol) was added to a cold solution of butanamide **2** (0.52 g, 2 mmol) in 30 ml pyridine. The addition was carried out portionwise with stirring at 0–5 °C over a period of 30 min. After complete addition, the reaction mixture was stirred for a further 2 h and then diluted with water. The precipitated solid was collected by filtration, washed with water, dried, and finally recrystallized from a mixture of EtOH-DMF (2:1) to afford the arylhydrazones **3a–c**.

2-(Phenylhydrazono)-3-oxo-*N*-(4-phenylthiazol-2-yl)butanamide (3a). Yellow crystals, yield 55%, mp 220–221 °C. IR ($\bar{\nu}$/cm^{-1}): 3208 (NH), 3097 (NH), 1670 (C=O), 1652 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 7.18–7.95 (m, 11H, Ar-H and thiazole-H_5), 13.52 (bs, 1H, NH), 13.75 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 26.5, 108.6, 114.8, 118.2, 125.3, 127.8, 128.3, 128.6, 134.1, 140.1, 145.2, 148.3, 158.1, 160.2, 192.5. MS (EI, 70 eV): m/z (%) = 364 (M^+, 19.2), 321 (25.0), 256 (14.3), 203 (6.4), 176 (49.8), 149 (30.1), 134 (18.02), 111 (35.1), 97 (69.4), 85 (47.5), 73 (74.0), 55 (94.7). Anal. calcd. for $C_{19}H_{16}N_4O_2S$ (364.42): C, 62.62; H, 4.43; N, 15.37. Found: C, 62.48; H, 4.49; N, 15.26.

2-(4-Methylphenylhydrazono)-3-oxo-*N*-(4-phenylthiazol-2-yl)butanamide (3b). Reddish brown crystals, yield 62%, mp 200–201 °C. IR ($\bar{\nu}$/cm^{-1}): 3225 (NH), 3105 (NH), 1672 (C=O), 1621 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 7.14–7.91 (m, 10H, Ar-H and thiazole-H_5), 13.43 (bs, 1H, NH), 13.71 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 21.3, 26.4, 108.8, 117.0, 127.2, 128.1, 129.8, 133.9, 136.8, 142.2, 148.2, 158.3, 160.4, 192.1. MS (EI, 70 eV): m/z (%) = 378 (M^+, 36.7), 335 (28.9), 239 (9.1), 203 (36.5), 176 (88.0), 134 (29.6), 97 (59.1), 83 (63.7), 77 (29.2), 57 (100). Anal. calcd. for $C_{20}H_{18}N_4O_2S$ (378.45): C, 63.47; H, 4.79; N, 14.80. Found: C, 63.63; H, 4.67; N, 14.86.

2-(4-Methoxyphenylhydrazono)-3-oxo-*N*-(4-phenylthiazol-2-yl) butanamide (3c). Red crystals, yield 70%, mp 210–211 °C. IR ($\bar{\nu}$/cm^{-1}): 3216 (NH), 3102 (NH), 1674 (C=O), 1656 (C=O).^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 7.00–8.05 (m, 10H, Ar-H and thiazole-H_5), 13.36 (s,

1H, NH), 13.7 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 26.3, 56.1, 108.9, 114.8, 119.4, 124.7, 127.3, 128.2, 133.7, 139.4, 141.0, 148.7, 158.6, 161.3, 192.4. Anal. calcd. for $C_{20}H_{18}N_4O_3S$ (394.45): C, 60.90; H, 4.60; N, 14.20. Found: C, 60.98; H, 4.52; N, 14.12.

Synthesis of 4,8,10-Trimethyl-*N*-(4-phenylthiazol-2-yl)pyrido[2′,3′:3,4]pyrazolo-[5,1-*c*][[1,2,4]triazine-3-carboxamide (6)

The diazonium salt of 3-amino-4,6-dimethylpyrazolo[3,4-*b*]pyridine **4d** (2 mmol) [prepared by addition of a cold solution of sodium nitrite (0.138 g, 2 mmol) dissolved in 3 ml water to a stirred ice-cold solution of 3-amino-4,6-dimethylpyrazolo[3,4-*b*]pyridine (0.324 g, 2 mmol), dissolved in 3 ml concentrated HCl and 2 ml water] was added to a cold solution of butanamide **2** (0.52 g, 2 mmol) in 30 ml pyridine. The addition was carried out portionwise with stirring at 0–5 °C over a period of 30 min. After complete addition, the reaction mixture was stirred for a further 4 h, then kept in an ice chest for 24 h, and finally diluted with water. The precipitated solid was collected by filtration, washed with water, dried, and finally recrystallized from ethanol to afford compound **6**.

Yellow crystals, yield 42%, mp > 300 °C. IR ($\bar{\nu}$/cm^{-1}): 3349 (NH), 1686 (C=O). ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.16–8.16 (m, 7H, Ar-H, pyridine-H_3 and thiazole-H_5), 13.84 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 10.2, 20.1, 21.6, 96.1, 108.5, 115.3, 117.4, 124.7, 127.2, 128.1, 131.8, 133.5, 133.8, 140.5, 157.9, 159.2, 161.0, 161.9, 164.8. MS (EI, 70 eV): m/z (%) = 415 (M^+, 55.9), 382 (24.8), 240 (38.2), 175 (37.3), 168 (40.1), 154 (29.8), 134 (100), 104 (47.6), 91 (19.3), 76 (57.5), 66 (62.9). Anal. calcd. for $C_{21}H_{17}N_7OS$ (415.47): C, 60.71; H, 4.12; N, 23.60. Found: C, 60.80; H, 4.15; N, 23.57.

Synthesis of 3-Oxo-2-(phenylthiocarbamoyl)-*N*-(4-phenylthiazol-2-yl)butanamide (7)

Butanamide **2** (0.52 g, 2 mmol) was added to a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in 20 ml dimethylformamide. After the mixture had been stirred for 30 min, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the mixture. Stirring was continued for 24 h, and then the mixture was poured over crushed ice containing hydrochloric acid. The solid product formed was filtered off, washed with water, dried, and finally recrystallized from ethanol to afford compound **7**.

Yellow crystals, yield 87%, mp 127–128 °C. IR ($\bar{\nu}$/cm^{-1}): 3445 (NH), 3327 (NH), 1675 (C=O), 1654 (C=O), 1288 (C=S). ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 4.47 (s, 1H, CH), 7.25–7.96 (m, 11H, Ar-H and thiazole-H_5), 11.76 (s, 1H, NH), 12.96 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 29.8, 72.7, 108.4, 122.6, 124.7, 127.2, 127.8, 128.1, 128.3, 133.6, 140.7, 156.3, 160.7, 162.5, 167.5, 198.8. MS (EI, 70 eV): m/z (%) = 395 (M^+, 24.6), 352 (36.1), 303 (15.5), 259 (46.2), 235 (12.3), 175 (100), 160 (41.7), 92 (30.2), 77 (57.5), 43 (69.6). Anal. calcd. for $C_{20}H_{17}N_3O_2S_2$ (395.50): C, 60.74; H, 4.33; N, 10.62. Found: C, 60.81; H, 4.27; N, 10.58.

Synthesis of 3-Methyl-5-(phenylamino)-*N*-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carboxamide (8)

Hydrazine hydrate (80%, 0.1 ml, 1 mmol) was added to a solution of the compound **7** (0.395 g, 1 mmol) in 20 ml ethanol. The reaction mixture was heated under reflux for 6 h and then left to cool. The solid product was filtered off, washed with ethanol, dried, and recrystallized from ethanol to afford compound **8**.

Yellow crystals, yield 78%, mp 192–193 °C. IR ($\bar{\nu}$/cm^{-1}): 3365 (NH), 3278 (NH), 3150 (NH), 1652 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H, CH_3), 6.95–7.84 (m, 11H, Ar-H and thiazole-H_5), 9.17 (s, 1H, pyrazole NH), 11.37 (s, 1H, NH), 13.12 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 12.8, 93.8, 108.7, 116.4, 120.1, 124.7, 127.2, 128.1, 129.2, 133.8, 139.6, 141.1, 143.3, 148.9, 157.8, 159.6, 160.2. Anal. calcd. for $C_{20}H_{17}N_5OS$ (375.45): C, 63.98; H, 4.56; N, 18.65. Found: C, 63.98; H, 4.56; N, 18.65.

Synthesis of 3-(Phenylamino)-2-(phenylhydrazono)-*N*-(4-phenylthiazol-2-yl)-3-thioxopropanamide (9)

The diazonium salt of aniline (2 mmol) was added to a cold solution of compound **8** (0.75 g, 2 mmol) in 50 ml ethanol buffered with sodium acetate trihydrate (3 g). The addition was carried out portionwise with stirring at 0–5 °C over a period of 30 min. After complete addition, the reaction mixture was stirred for a further 2 h, then kept in an ice chest for 6 h, and finally diluted with water. The precipitated solid was collected by filtration, washed with water, dried, and finally recrystallized ethanol to afford compound **9**.

Orange crystals, yield 76%, mp 170–171 °C. IR ($\bar{\nu}$/cm^{-1}): 3412 (NH), 3234 (NH), 3154 (NH), 1658 (C=O), 1288 (C=S). ^{1}H NMR ($CDCl_3$): δ 7.16–7.91 (m, 16H, Ar-H and thiazole-H_5), 9.98 (s, 1H, NH), 12.46 (s, 1H, NH), 13.26 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 109.2, 115.5, 122.4, 124.7, 127.2, 128.1, 128.6, 128.8, 129.2, 133.7, 139.2, 145.8, 149.7, 155.7, 156.4, 159.4, 160.4. MS (EI, 70 eV): m/z (%) = 457 (M^+, 11. 6), 297 (13.5), 282 (100), 254 (15.6), 175 (45.6), 160 (36.8), 135 (59.3), 92 (46.2), 77 (42.8). Anal. calcd. for $C_{24}H_{19}N_5OS_2$ (457.57): C, 63.00; H, 4.19; N, 15.31. Found: C, 63.08; H, 4.12; N, 15.39.

Synthesis of 2-(5-Oxo-3-phenylthiazolidin-2-ylidene)-2-(phenylazo)-*N*-(4-phenylthiazol-2-yl)acetamide (10)

Chloroacetyl chloride (0.224 g, 2 mmol) was added dropwise with stirring to a solution of compound **9** (0.814 g, 2 mmol) in 25 ml dimethylformamide containing 0.5 ml of triethylamine at room temperature. Stirring was continued for a further 4 h, and then the reaction mixture was poured into ice-cooled water. The precipitated solid was collected by filtration, washed with water, dried, and finally recrystallized from ethanol to afford compound **10**.

Yellow crystals, yield 75%, mp 154–155 °C IR ($\bar{\nu}$/cm^{-1}): 3175 (NH), 1735 (C=O, ring), 1656 (C=O), 1585 (N=N). ^{1}H NMR ($CDCl_3$): δ 4.24 (s, 2H, CH_2 ring), 7.26–7.96 (m, 16H, Ar-H and thiazole-H_5), 13.15 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 49.5, 108.8, 114.4, 120.2, 123.0, 124.8, 127.5, 127.8, 128.2, 128.3, 129.0, 133.6, 138.5, 150.1, 153.1, 159.3, 161.1, 163.5, 170.1, 198.2. MS (EI, 70 eV): m/z (%) = 497 (M^+,

12.8), 392 (27.1), 337 (24.9), 322 (32.8), 294 (65.2), 176 (100), 160 (76.9), 105 (57.5), 77 (81.2). Anal. calcd. for $C_{24}H_{19}N_5OS_2$ (497.59): C, 62.76; H, 3.85; N, 14.07. Found: C, 62.68; H, 3.78; N, 14.16.

Synthesis of 2-(*N,N*-Dimethylaminomethylene)-3-oxo-*N*-(4-phenylthiazol-2-yl)butanamide (11)

A mixture of butanamide **2** (1.3 g, 5 mmol) and DMF-DMA (0.53 ml, 5 mmol) in 25 ml dioxane was refluxed for 3 h and then left to cool. The yellow precipitated product was filtered off, washed with light petroleum ether, dried, and recrystallized from a mixture of ethanol–dioxane (1:1) to afford the enaminone **11**.

Yellow crystals, yield 64%, mp 230–231 °C IR ($\bar{\nu}$/cm^{-1}): 3172 (NH), 1682 (C=O), 1656 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 3.21 (s, 3H, NCH_3), 3.26 (s, 3H, NCH_3), 7.26–8.35 (m, 7H, Ar-H, thiazole-H_5 and olefinic CH=), 13.72 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 29.4, 45.3, 108.3, 115.2, 124.7, 127.5, 128.1, 133.8, 154.2, 156.1, 158.7, 162.3, 193.7. Anal. calcd. for $C_{16}H_{17}N_3O_2S$ (315.39): C, 60.93; H, 5.43; N, 13.32. Found: C, 60.87; H, 5.38; N, 13.40.

Synthesis of 3-Methyl-*N*-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carboxamide (12)

A mixture of enaminone **11** (0.63 g, 2 mmol) and hydrazine hydrate (0.2 ml, 4 mmol) in 25 ml absolute ethanol was refluxed for 2 h. The solid product, which separated during heating, was collected by filtration, washed with ethanol, dried, and finally recrystallized from ethanol to afford compound **12**.

Dark brown crystals, yield 68%, mp 242–243 °C. IR ($\bar{\nu}$/cm^{-1}): 3235 (NH), 3100 (NH), 1661 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H, CH_3), 7.12–7.96 (m, 6H, Ar-H and thiazole-H5), 8.98 (s, 1H, pyrazole-H_5), 9.26 (s, 1H, pyrazole NH), 13.21 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 92.2, 108.4, 116.4, 120.2, 124.7, 127.6, 128.2, 129.3, 131.2, 133.9, 140.1, 143.8, 154.3, 157.8, 160.3. MS (EI, 70 eV): m/z (%) = 284 (M^+, 5.5), 264 (13.8), 236 (24.3), 176 (31.9), 161 (10.9), 134 (32.9), 111 (46.6), 98 (67.3), 77 (24.7), 71 (79.9), 57 (100), 55 (93.7). Anal. calcd. for $C_{14}H_{12}N_4OS$ (284.34): C, 59.14; H, 4.25; N, 19.70. Found: C, 59.02; H, 4.14; N, 19.86.

Synthesis of 2-(3-Cyano-4,6-dimethylpyridin-2-ylthio)-*N*-(4-phenylthiazol-2-yl)acetamide (14)

A mixture of 2-chloro-*N*-(4-phenylthiazol-2-yl)acetamide (**13**) (0.504 g, 2 mmol), 4,6-dimethyl-2-mercaptonicotinonitrile (0.328 g, 2 mmol), and anhydrous potassium carbonate (0.35 g, 2.5 mmol) in 30 ml acetone was refluxed for 4 h. The excess acetone was evaporated under reduced pressure. The residue was collected by filtration, washed with water, dried, and finally recrystallized from ethanol to afford compound **14.**

Yellow crystals, yield 75%, mp 178–179 °C. IR (ν/cm^{-1}): 3107 (NH), 2223 (CN), 1689 (C=O).^{1}HNMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.28 (s, 2H, SCH_2), 6.75 (s, 1H, pyridine-H_5), 7.1–7.92 (m, 6H, Ar-H and thiazole-H_5), 12.57 (s, 1H, NH).^{13}C NMR (DMSO-d_6): δ 20.4, 24.3, 38.5, 105.2, 108.6, 115.5, 124.8, 125.6, 127.2, 128.1, 133.8, 143.3, 154.7, 157.6, 159.9, 162.3,

165.2. Anal. calcd. for $C_{19}H_{16}N_4OS_2$ (380.49): C, 59.98; H, 4.24; N, 14.73. Found: C, 60.28; H, 4.29; N, 14.84.

Synthesis of 3-Amino-4,6-dimethyl-*N*-(4-phenylthiazol-2-yl)thieno[2,3-*b*]pyridine-2-carboxamide (15)

The nicotinonitrile derivative **14** (1.9 g, 5 mmol) was added to solution of an equimolar amount of sodium ethoxide (prepared from dissolving 0.125 g sodium in 30 ml absolute ethanol). The solution was refluxed for 2 h, left to cool, and diluted with 50 ml cooled water containing a few drops of dilute HCl. The solid obtained was filtered off, washed with ethanol, dried, and finally recrystallized from a mixture of EtOH-DMF (1:2) mixture to afford compound **15**.

Yellow crystals, yield 77%, mp 270–271 °C. IR ($\bar{\nu}$/cm^{-1}): 3509 (NH), 3403, 3347 (NH_2), 1623 (C=O). ^{1}H NMR ($CDCl_3$/CF_3COOD): δ 2.40 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 7.00 (s, 1H, pyridine-H_5), 7.40–7.90 (m, 6H, Ar-H and thiazole-H_5). ^{13}C NMR ($CDCl_3$/CF_3COOD): δ 19.2, 24.3, 106.0, 108.7, 123.5, 124.6, 124.9, 127.3, 128.2, 133.9, 145.9, 146.5, 147.0, 153.5, 155.7, 160.1, 163.5. Anal. calcd. for $C_{19}H_{16}N_4OS_2$ (380.49): C, 59.98; H, 4.24; N, 14.73. Found: C, 60.21; H, 4.09; N, 14.88.

Synthesis of Ethyl 2-(2-Oxo-2-(4-phenylthiazol-2-ylamino)ethylthio)acetate (16)

A mixture of 2-chloro-*N*-(4-phenylthiazol-2-yl)acetamide (**13**) (0.504 g, 2 mmol), ethyl thioglycolate (0.24 g, 2 mmol), and anhydrous potassium carbonate (0.35 g, 2.5 mmol) in 30 ml acetone was refluxed for 4 h. The excess acetone was evaporated under reduced pressure. The residue was collected by filtration, washed with water, dried, and finally recrystallized from ethanol to afford compound **16**.

Yellow crystals, yield 75%, mp 112–113 °C. IR ($\bar{\nu}$/cm^{-1}): 3362 (NH), 1724 (C=O, ester), 1677 (C=O, amide). ^{1}H NMR ($CDCl_3$): δ 1.40 (t, $J = 7.2$ Hz, 3H, CH_3), 4.29 (s, 2H, SCH_2), 4.65 (q, $J = 7.2$ Hz, 2H, OCH_2), 4.78 (s, 2H, SCH_2), 7.35–7.86 (m, 6H, Ar-H and thiazole-H_5), 12.76 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.1, 33.4, 37.9, 62.0, 108.6, 124.7, 127.2, 128.3, 133.6, 154.6, 159.6, 165.1, 172.3. Anal. calcd. for $C_{15}H_{16}N_2O_3S_2$ (336.43): C, 53.55; H, 4.79; N, 8.33. Found: C, 53.44; H, 4.85; N, 8.41.

Synthesis of 4-(4-Phenylthiazol-2-yl)thiomorpholine-3,5-dione (17)

A few drops of triethylamine were added to a solution of sulfide **16** (0.672 g, 2 mmol) in 25 ml ethanol. The reaction mixture was heated under reflux for 8 h and then left to cool. The solid product was filtered off, washed with ethanol, dried, and finally recrystallized from ethanol to afford compound **17**.

Yellow crystals, yield 85%, mp 132–133 °C. IR ($\bar{\nu}$/cm^{-1}): 1669 (C=O, amide). ^{1}H NMR ($CDCl_3$): δ 5.24 (s, 4H, $2CH_2$ ring), 7.18–7.92 (m, 6H, Ar-H and thiazole-H_5). ^{13}C NMR ($CDCl_3$): δ 30.5, 109.2, 125.8, 128.2, 128.8, 133.8, 159.1, 162.6, 170.0. MS (EI, 70 eV): m/z (%) = 290 (M^+, 29.5), 262 (13.9), 248 (18.6), 174 (75.9), 160 (100), 130 (50.2), 77 (55.6). Anal. calcd. for $C_{13}H_{10}N_2O_2S_2$ (290.36): C, 53.77; H, 3.47; N, 9.65. Found: C, 53.68; H, 3.41; N, 9.59.

Synthesis of 2-Amino-5-oxo-1-(4-phenylthiazol-2-yl)-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (19)

Triethylamine 0.5 ml was added to a mixture of 2-chloro-*N*-(4-phenylthiazol-2-yl)acetamide (**13**) (0.504 g, 2 mmol) and malononitrile (0.132 g, 2 mmol) in 25 ml dioxane. The reaction mixture was heated under reflux for 6 h, left to cool, and then poured into ice-cold water. The solid product that formed was filtered off, washed with dilute ethanol, dried, and recrystallized from dioxane to afford compound **19**.

Yellow crystals, yield 76%, mp 276–277 °C. IR ($\bar{\nu}$/cm^{-1}): 3424, 3329 (NH_2), 2198 (CN), 1692 (C=O, pyrrole ring).^{1}H NMR (DMSO-d_6): δ 4.10 (s, 2H, CH_2), 6.85 (s, 2H, NH_2), 7.40–7.60 (m, 6H, Ar-H and thiazole-H_5). ^{13}C NMR (DMSO-d_6): δ 39.4, 83.2, 105.6, 115.9, 125.9, 127.6, 128.4, 128.8, 137.3, 160.1, 161.6, 164.7, 168.2 MS (EI, 70 eV): m/z (%) = 282 (M^+, 15.7), 254 (35.6), 216 (63.3), 176 (100), 108 (32.8), 122 (28.0), 77 (69.1), 66 (55.4). Anal. calcd. for $C_{14}H_{10}N_4OS$ (282.32): C, 59.56; H, 3.57; N, 19.85. Found: C, 59.68; H, 3.43; N, 19.67.

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