Synthesis, Reactions, and Spectral Characterization of New Fused Pyrazolothienopyridine and Pyrazolopyrrolopyridine Systems

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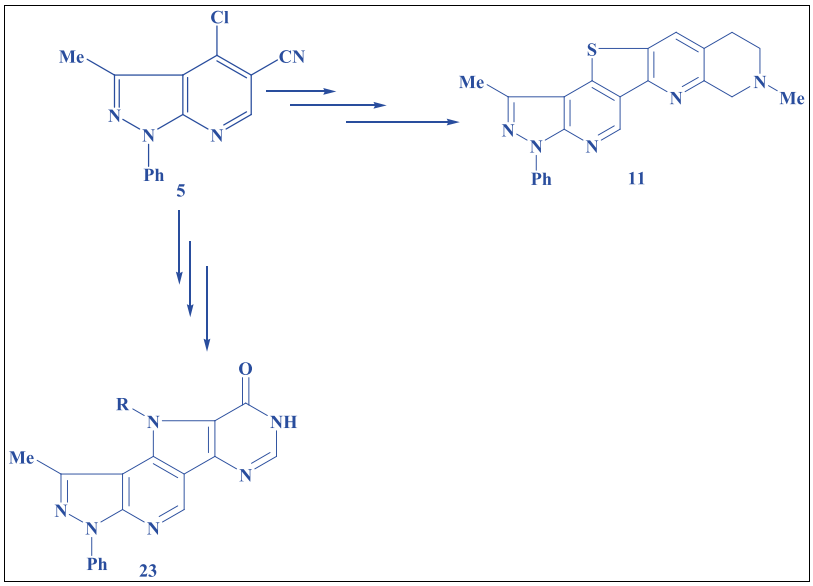


4-Oxo-1-phenyl-4,7-dihydropyrazolo[3,4-*b*]pyridine-5-carbonitrile compound (**4**) was prepared by the reaction of 5-amino-3-methyl-1-phenyl pyrazole (**1**) with ethyl 2-cyano-3-ethoxyacrylate followed by cyclization using diphenyl ether. The pyrazolopyridinone compound **4** was converted to the chloropyrazolopyridine **5** by the reaction with phosphorus oxychloride. Compound **5** was used as a starting material to synthesize 3-amino-4-substituted pyrazolothienopyridine derivatives **10a–f** and ethyl-3-aminopyrazolopyrrolopyridine-2-carboxylate **21**, which were used as a versatile precursors for synthesis of poly-fused heterocyclic compounds.

INTRODUCTION

Pyrazolo[3,4-*b*]pyridine compounds are a very interesting class of heterocyclic compounds and play an important role in medicinal chemistry [1,2] because they were used as an anxiolytic drug, which have similar effects to benzodiazepine drugs, but is structurally distinct and so is classed as a non-benzodiazepine anxiolytic drug [3,4]. The best examples of compounds from these categories are cartazolate, which acts as a $GABA_A$ receptor-positive allosteric modulator at the barbiturate binding site of the complex and has anxiolytic effects in animals. Tracazolate, which gave the same action as benzodiazepines, acts at the same receptor but has distinct chemical structures [5]. Etazolate is a selective inhibitor of type 4 phosphodiesterase (PDE4) [6] and acts as an adenosine antagonist of the A_1 and A_2 subtypes [7]. It also acts as a phosphodiesterase inhibitor selective for the PDE4 isoform and ICI-190,622 effective anxiolytic with significant advantages over benzodiazepines [8,9] (Fig. 1).

The pyrazolopyridine compounds exhibit a broad spectrum of biological activities such as antimalarial [10], antiproliferative [11], and cardiovascular activities [12–14] and are used as antiviral [15,16], antileishmanial [17], and anti-inflammatory agents [18].

Our target in this work aims to synthesize fused heterocyclic systems containing thienopyrazolopyridine nucleus. Earlier, we reported the synthesis of pyrazolo [3,4-*b*]pyridines and their sulfonamide derivatives as antibacterial agents [19], but recently, we have synthesized thieno[2,3-*c*]pyrazoles and we have tested them as antimicrobial, anti-inflammatory [20] and antioxidant against toxicity of 4-nonylphenol in *Clarias gariepinus* [21]. Also, some selenolo[2,3-*c*]pyrazole

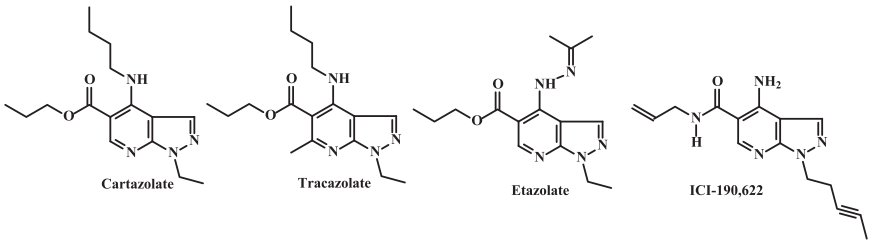


Figure 1. Non-benzodiazepine anxiolytic drugs containing pyrazolo[3,4-*b*]pyridine moiety.

compounds were synthesized and used as antimicrobial and anti-inflammatory agents [22].

RESULTS AND DISCUSSION

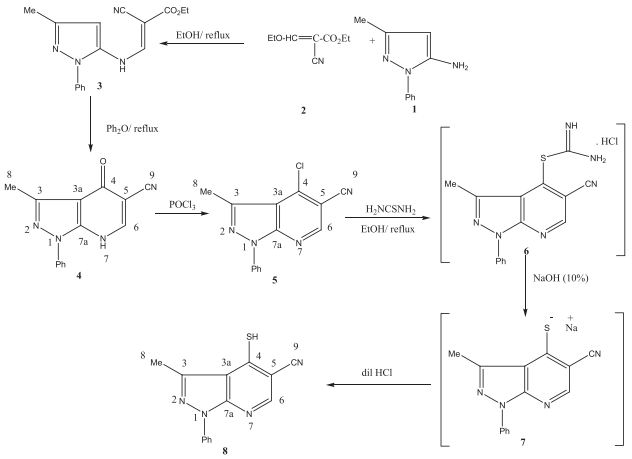
Condensation of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole (**1**) with ethyl 2-cyano-3-ethoxyacrylate (**2**) in refluxing ethanol afforded ethyl 2-cyano-3-(3-methyl-1-phenyl-1*H*-pyrazol-5-ylamino)acrylate (**3**), which was considered as a starting intermediate for building pyrazole[3,4-*b*]pyridine nucleus (**4**). The ethyl acrylate ester compound **3** was cyclized upon boiling in diphenyl ether through loss of ethanol molecule to give 3-methyl-4-oxo-1-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**4**). The structure of compounds **3** and **4** was established by their elemental and spectral analyses. IR spectrum of compound **3** showed an absorption band at 3130 cm^{-1} characteristic for NH group; 2973 and 2930 cm^{-1} for ethyl group; and 2118 and 1670 cm^{-1} for CN and CO groups, respectively. Upon cyclization of the pyrazolyl ester compound **3** to the oxopyrazolo[3,4-*b*] pyridine carbonitrile compound **4**, the band characteristic for NH group shifted to 3195 cm^{-1}, the band characteristic for CN group shifted to 2234 cm^{-1}, and the band characteristic for ethyl group disappeared. ^{1}H NMR of compound **3** in $CDCl_3$ showed triplet and quartet signals at δ 2.30 and 4.20 ppm characteristic for CH_3 and CH_2 ester group. The latter triplet and quartet signals disappeared by cyclization to compound **4**.

The 4-chloro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridine-5-carbonitrile compound (**5**) was prepared in quantitative yield according to literature procedure [23,24] by refluxing the pyrazolopyridine carbonitrile compound **4** with phosphorus oxychloride. The structure of chloropyridine **5** was established by its elemental and spectral analyses. IR spectrum revealed disappearance of absorption bands characteristic for NH and CO groups presented in the starting material **4**. ^{1}H NMR in $CDCl_3$ showed singlet signal at δ 8.67 ppm for CH pyridine. Compound **5** was converted to 4-mercapto-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**8**) by refluxing compound **5** with thiourea to afford the thiouronium salt **6**. Basic hydrolysis of the thiouronium salt **6** was carried out by reflux with sodium hydroxide solution (10%) to afford the corresponding sulfanyl sodium salt **7**, which upon acidification with conc. HCl solution afforded the mercapto pyrazolopyridine carbonitrile compound **8**. The chemical structure of compound **8** was elucidated by elemental and spectral analyses. Mass spectrum fragmentation pattern showed a base peak at 266 corresponding to the molecular ion peak (Scheme 1).

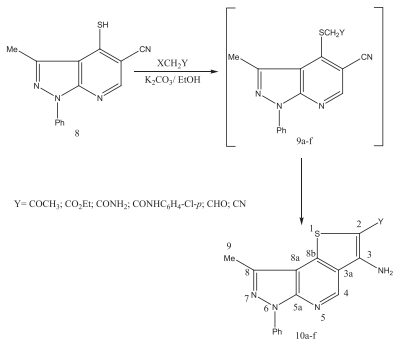
The thiole group in 4-mercapto-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile compound (**8**) was alkylated by the reaction with α-halogenated carbonyl compounds in refluxing ethanol in the presence of anhydrous sodium carbonate to afford the non-isolated *S*-alkylated pyrazolopyridine intermediates **9a–f**, which underwent Thorpe–Ziegler cyclization *in situ* to the 3-amino-2-substituted-pyrazolothieno-pyridines (**10a–f**) under the same reaction conditions. Formation of compounds **10a–e** was established on the basis of spectral analyses. IR spectra revealed appearance of absorption bands characteristic to NH_2 group. Also the ^{1}H NMR spectra showed appearance of singlet signals characteristic for NH_2 groups in compounds **10a–e** (Scheme 2).

Condensation of 3-amino-8-methyl-6-phenyl-6*H*-pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridine-2-carbaldehyde

Scheme 1. Synthesis of 4-mercapto-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**8**).



Scheme 2. Synthesis of 3-amino-2-substituted-8-methyl-6-phenyl-6*H*-pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridine (**10a–f**).

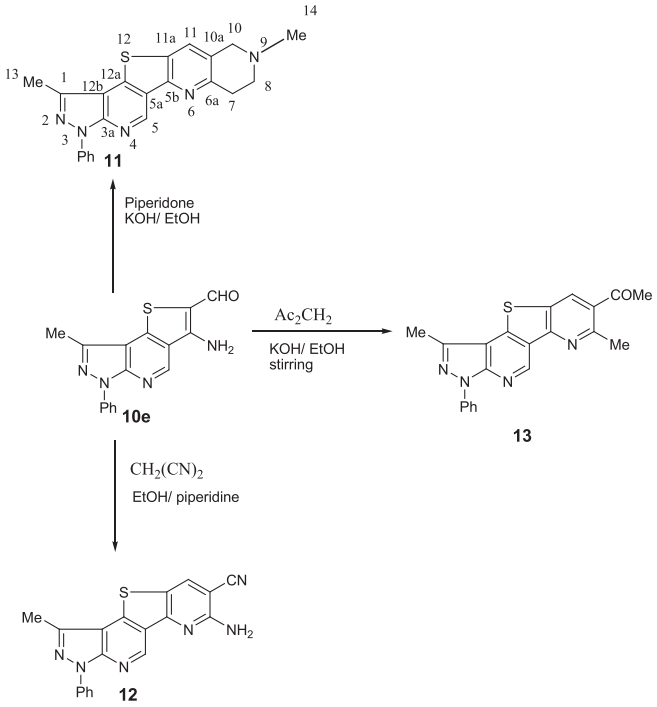


compound (**10e**) with *N*-methyl piperidone as a heterocyclic ketone in ethanol at room temperature in the presence of potassium hydroxide solution afforded the newly fused polyheterocyclic system, namely, 1,9-dimethyl-3-phenyl-7,8,9,10-tetrahydro-3*H*-pyrazolo [4″,3″:5′,6′]pyrido[3′,4′:4,5]thieno[3,2-*b*][1,6] naphthyridine (**11**).

When the amino pyrazolopyridine carbaldehyde compound **10e** was allowed to react with malononitrile in refluxing ethanol in the presence of piperidine as a basic catalyst, the amino pyridothienopyrazolopyridine carbonitrile compound **12** was obtained. The reaction proceeded via condensation of aldehydic group with active methylene in malononitrile followed by cycloaddition reaction of amino group on nitrile group to give the tetracyclic system **12**. Formation of compound **12** was confirmed by elemental and spectral data. Mass spectrum of compound **12** showed a peak at $m/z = 356$ corresponding to the molecular ion peak and the base peak. On the other hand, reaction of amino carboxyaldehyde compound **12** with acetyl acetone in ethanolic potassium hydroxide solution afforded 1-(1,7-dimethyl-3-phenylpyrido[2′,3′:4,5]thieno[2,3-*d*] pyrazolo[3,4-*b*]pyridin-8-yl)ethanone (**13**). The structure of compound **13** was elucidated by elemental and spectral analyses. IR spectrum revealed disappearance of absorption bands characteristic for NH_2 and CHO in the starting compound **10e** and appearance of absorption band at 1670 cm^{-1} for (C=O) of acetyl group. Mass spectrum showed peak at 372 as a molecular ion peak in addition to the base peak at 330 characteristic for molecular ion peak minus 43, which means the molecule losses of $COCH_3$ group (Scheme 3).

Condensation of the amino pyrazolothienopyridine carbonitrile compound **10f** with triethyl orthoformate in the presence of acetic anhydride afforded the ethyl fomimidate compound **14**. The imidate compound **14** was cyclized by the reaction with hydrazine hydrate through loss of ethanol molecule followed by cycloaddition reaction of NH group on CN group to afford the corresponding 8-amino-9-iminopyrazolopyridothieno-pyrimidine compound **15**. The structure of compound **15** was established by mp, thin-layer chromatography, IR, and mass spectra. Its IR spectrum showed absorption

Scheme 3. Reaction of amino carboxyaldehyde **10e** compound with active methylene compounds.



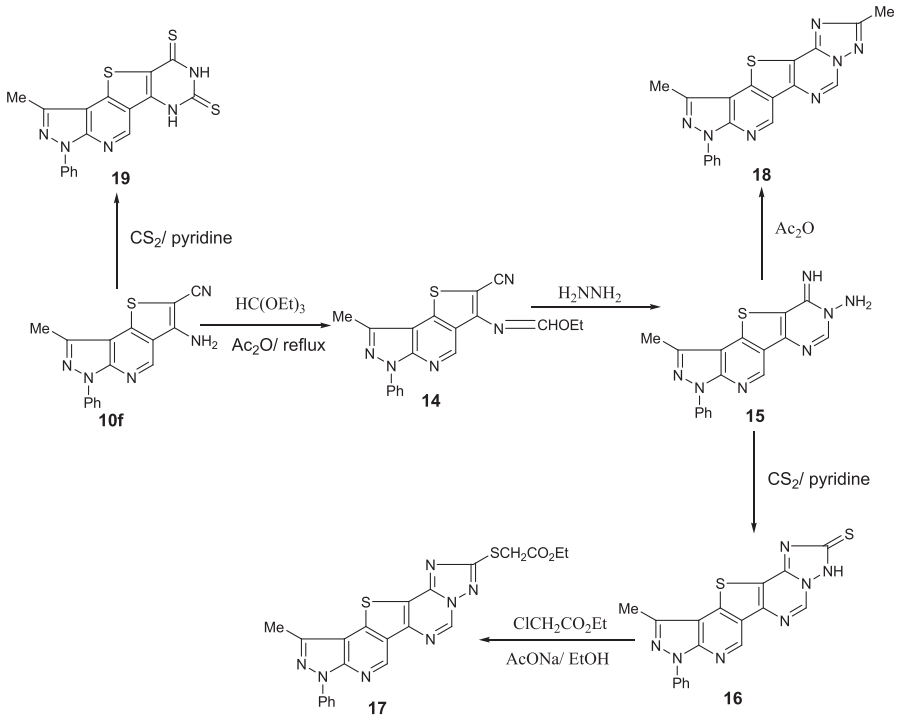
bands at 3420, 3270, and 3246 cm^{-1} characteristic for NH_2 and NH groups. Mass spectrum showed peak at 347 as a molecular ion peak and peak at 317 as a base peak.

The amino imino compound **15** was used as a versatile precursor for synthesis of other heterocyclic compounds **16–18**. Thus, reaction with carbon disulfide in pyridine on a steam bath afforded the triazolopyrazolopyridothienopyrimidine thione compound **16**, which was alkylated with ethyl chloroacetate in ethanol and fused sodium acetate to give the ethyl sulfanyl acetate derivative **17**. Also, reaction of the amino imino compound **15** with acetic anhydride afforded the dimethyl pyrazolopyridothieno-triazolopyrimidine compound **18**. The reaction proceeded with acetylation of amino group followed by tautomerism and cyclization by loss of water molecule to give the methyl pyrazolyl derivative **18**. The structure of compound **17** was established by elemental and spectral data. IR spectrum showed absorption bands at 1735 cm^{-1} for CO ester group. ^1H NMR spectrum in deuterated dimethyl sulfoxide (DMSO-d_6) showed triplet and quartet signals at δ 1.40 and 4.30 ppm for the ethyl ester group and singlet signal at δ 3.90 ppm for SCH_2 group. On the other hand, reaction of amino pyrazolothienopyridine carbonitrile compound **10f** with carbon disulfide in pyridine on a steam bath yielded the pyrazolopyridothienopyrimidine dithione compound **19** as tetracyclic system. IR spectrum of the dithione compound **19** showed absorption bands at 3421 and 1174 cm^{-1} characteristic for NH and C=S groups, respectively. Mass spectrum showed peak at *m*/*z* 380 characteristic for the molecular ion peak in addition to peak at *m*/*z* 300 as a base peak (Scheme 4).

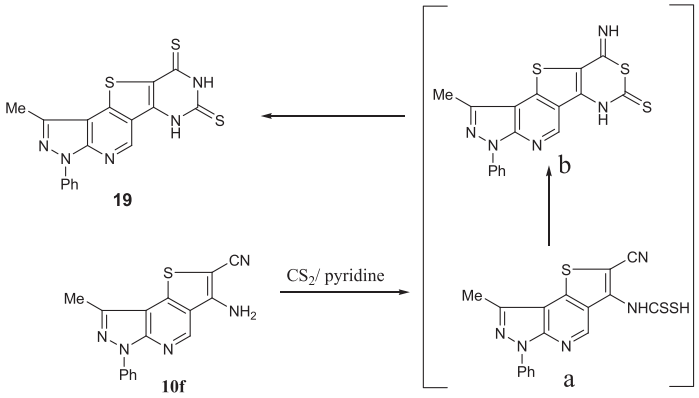
The mechanism for formation of pyrimidine dithione compound **19** was suggested to proceed through the addition of carbon disulfide on the amino group to give dithiocarbamic acid intermediate **a** followed by the addition of mercapto group on the cyano group to give the imino thiazine thione ring **b**. The latter intermediate **b** underwent Dimroth rearrangement between the imino group and sulfur atom in the thiazine ring, which yielded finally the pyrimidine dithione compound **19** as shown in Scheme 5.

The chlorine atom in chloropyrazolopyridine carbonitrile compound **5** underwent nucleophilic substitution reaction with ethyl glycinate in dimethylformamide and in the presence of potassium carbonate to afford ethyl pyrazolopyridinyl aminoacetate compound **20**, which underwent Thorpe–Ziegler cyclization upon heating with sodium ethoxide solution to afford ethyl-3-amino-1,6-dihydro-6*H*-phenylpyrazolo [3,4-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (**21**). Also, the ethyl aminoacetate compound **20** was cyclized to ethyl-3-amino-1-methyl-6*H*-phenylpyrazolo[3,4-*b*]pyrrolo [2,3-*d*]pyridine-2-carboxylate (**22**) upon heating in acetone in the presence of methyl iodide and anhydrous potassium carbonate.

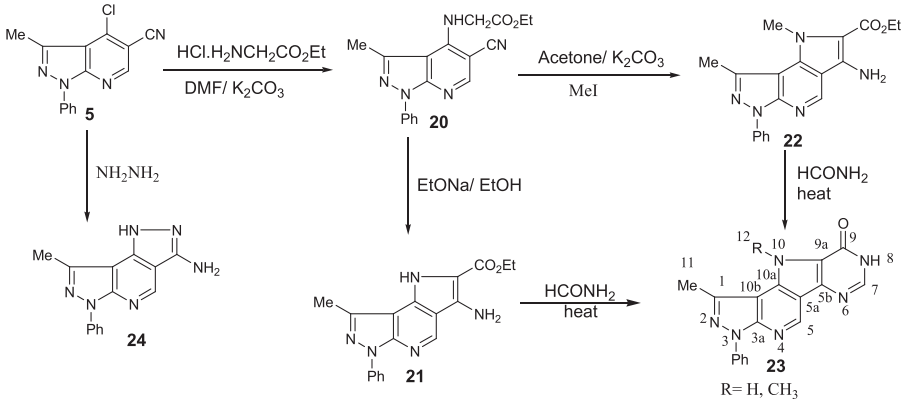
Scheme 4. Synthesis and reactions of 8-amino-9-imino-1-methyl-3-phenyl-3,9-dihydro-8*H*-pyrazolo[4″,3″:5′,6′]pyrido[3′,4′:4,5]thieno[3,2-*d*]pyrimidine (**15**).



Scheme 5. The suggested mechanism for formation pyrazolopyridothienopyrimidine dithione.



Scheme 6. Synthesis and reactions of ethyl pyrazolopyrrolopyridine carboxylate compounds **21** and **22**.



Both compounds **21** and **22** reacted with formamide to give the tetracyclic pyrazolopyridopyrrolopyrimidine compounds (**23a**, **b**). The structure of compound **23a** was confirmed by its IR, ^{1}H NMR, and ^{13}C NMR analyses. IR spectrum showed two absorption bands at 3446 and 3350 cm^{-1} characteristic for 2NH groups and at 1654 cm^{-1} for CO amidic group. ^{1}H NMR spectrum in DMSO-d_6 showed two singlet signals at δ 8.13 and 9.16 ppm characteristic for CH and NH groups, respectively. ^{13}C NMR showed signal at δ 163.38 ppm characteristic for CO pyrimidine.

The chloro pyrazolo[3,4-*b*]pyridine carbonitrile compound **5** reacted with hydrazine hydrate in refluxed ethanol to give 8-methyl-6-phenyl-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3-yl amine (**24**). The reaction proceeded through nucleophilic displacement of chlorine with hydrazino group followed by cycloaddition reaction of amino group to cyano group to give compound **24**. Formation of compound **24** was established by the elemental and spectral analyses. IR spectrum revealed disappearance of absorption bands at 2234 cm^{-1} characteristic for (CN), which presented in compound **5** and appearance of absorption bands at 3432, 3279, and 3152 cm^{-1} for NH and NH_2 groups. Mass spectrum of compound **24** showed a peak at $m/z = 264$ corresponding to its molecular ion peak and as a base peak (Scheme 6).

CONCLUSION

The aim of this work was to synthesize new 3-amino-2-substituted-8-methyl-6-phenyl-6*H*-pyrazolo[3,4-*b*]thieno [2,3-*d*]pyridine derivatives (**10a–f**), which were used as a versatile precursor for synthesis of new heterocyclic rings fused to pyrazolothienopyridine system, namely: pyridine, naphthyridine, pyrimidine, and triazolopymidine.

EXPERIMENTAL

All melting points are corrected and measured on a Gallenkamp apparatus (LABEQUIP LTD., Ontario, Canada). The IR spectra were recorded using on a Shimadzu 470 IR-spectrophotometer (LABEQUIP LTD., Ontario, Canada) using KBr wafer technique. ^{1}H NMR

and ^{13}C NMR spectra were measured on 400 MHz Jeol and 400 MHz Bruker spectrometers in deuterated chloroform ($CDCl_3$) or DMSO-d_6 with trimethylsilyl as internal standard and chemical shifts are expressed as ppm. Mass spectrometric analysis was recorded on a Jeol JMS-600 mass spectrometer. Elemental analyses were determined on an Elemental Analyses System GmbH VARIOEL $V_{2,3}$ CHNS Mode in the central lab of Assiut University, and all results were found to be in an acceptable range (±0.25). Compounds **1** and **3** were prepared according to literature procedure [23,24] with mp 114–117 and 180°C, respectively.

Ethyl 2-cyano-3-((3-methyl-1-phenyl-1*H*-pyrazol-5-yl) amino)acrylate (3). A mixture of ethyl 2-cyano-3-ethoxyacrylate (**2**) (10.4 g, 0.06 mol) and 5-amino-3-methyl-1-phenyl pyrazole (**1**) (10.6 g, 0.06 mol) in absolute ethanol (100 mL) was refluxed for 1 h and then cooled. The solid product that formed upon cooling was filtered off and recrystallized from ethanol to give **3** as white crystals in 78% yield; mp: 198–200°C; ir: NH 3183, CH aliphatic 2973, CN 2218, C=O 1670 cm^{-1}; ^1H nmr: δ ($CDCl_3$) 1.28 (t, 3H, CH_3 ester), 2.32 (s, 3H, CH_3), 4.20 (q, 2H, CH_2 ester), 7.39–756 (m, 5H, ArH), 7.61 (d, 1, H, –CH=C), and 10.83 ppm (s, 1H, NH); ms *m/z* 296 (M^+) as molecular ion peak and at *m/z* =250 as base peak. *Anal*. Calcd for $C_{16}H_{16}N_4O_2$ (296.33): C, 64.85%; H, 5.44%; N, 18.91%. Found: C, 64.51%; H, 5.22%; N, 18.73%.

3-Methyl-4-oxo-1-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*] pyridine-5-carbonitrile (4). The acrylate **3** (3 g, 0.01 mol) was added to boiling biphenyl ether (20 mL) and heated under reflux for 30 min until the crystals were precipitated and then allowed to cool. The solid product was collected, washed with petroleum ether, and recrystallized from ethanol to give **4** as orange crystals in 60% yield; mp: 297–298°C; ir: NH 3195, CH aromatic 3059, CN 2234, CO 1670 cm^{-1}; ^1H nmr: δ ($CDCl_3$) 2.49 (s, 3H, CH_3), 7.36–7.71 (m, 5H, Ar-H), 8.35 (s, 1H, CH pyridine), and 10.72 ppm (s, 1H, NH). *Anal*. Calcd for $C_{14}H_{10}N_4O$ (250.26): C, 67.19%; H, 4.03%; N, 22.39%. Found: C, 67.02%; H, 4.01%; N, 22.15%.

4-Chloro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (5). A mixture of **4** (3.5 g, 0.01 mol) in phosphorous oxychloride (20 mL) was refluxed for 4 h, allowed to cool, poured into ice–water mixture, and then neutralized with Na_2CO_3. The solid product was collected by filtration and recrystallized from pure ethanol to afford **5** as yellow crystals in 91% yield; mp: 164–165°C; ir: CN 2234 cm^{-1}; ^1H nmr: δ ($CDCl_3$) 2.83 (s, 3H, CH_3), 7.2–7.54 (m, 5H, Ar-H), and 8.64 ppm (s, 1H, CH pyridine); ^{13}C nmr: δ 9.88 (C8: CH_3 pyrazole), 109.89 (C3a), 110.07 (C5), 116.63 (C9: CN), 124.44, 122.31, 116.68 (C11–C15 aromatic), 133.34 (C10: aromatic), 137.76 (C4), 138.99 (C3), 146.15 (C6), 146.79 (C7a). *Anal*. Calcd for $C_{14}H_9ClN_4$ (268.70): C, 62.58%; H, 3.38%; Cl, 13.19%; N, 20.85%. Found: C, 62.41%; H, 3.22%; Cl, 13.01%; N, 20.45%.

4-Mercapto-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (8). A mixture of chloro compound **5** (4 g, 0.01 mol) and thiourea (1.1 g, 0.01 mol) in dry ethanol (20 mL) was heated under reflux for 2 h. The obtained solid product of thiouronium salt was filtered off, dissolved in sodium hydroxide solution (10%, 50 mL), and refluxed for 30 min. The sodium salt solution was allowed to cool and then was acidified with dilute HCl to just neutral; solid mercapto compound was filtered off, washed with water, and recrystallized from ethanol to afford orange crystals of **8** in 75% yield; mp: 243–245°C; ir: NH 3446 cm^{-1}, CN 2225 cm^{-1}; ^1H nmr: δ ($CDCl_3$) 2.69 (s, 3H, CH_3), 7.36–7.71 (m, 5H, Ar-H), 8.40 (s, 1H, CH pyridine), and 8.74 ppm (s, 1H, NH); ms: *m/z* = 266.12 (M^+) and base peak. *Anal*. Calcd for $C_{14}H_{10}N_4S$ (266.32): C, 63.14%; H, 3.78%; N, 21.04%; S, 12.04%. Found: C, 63.04%; H, 3.45%; N, 21.01%; S, 12.03%.

Reaction of (8) with different halo compounds such as α-halo ketones, α-halo ester, α-halo amide, α-halo anilides, and α-halo nitrites: formation of 10a–f. ***General procedure.*** A mixture of compound **8** (0.01 mol), α-halogenated carbonyl compounds (0.01 mol), and anhydrous potassium carbonate (2 g, 0.015 mol) in ethanol (20 mL) was refluxed for 1 h, and then the mixture was allowed to cool. The solid product was collected, washed with water several times, dried, and recrystallized from the proper solvent.

2-Acetyl-3-amino-8-methyl-6-phenyl-6H-pyrazolo[3,4-b] thieno[2,3-d]pyridine (10a). Produced according to the aforementioned general procedure as yellow crystals from ethanol in 71% yield; mp: 320–321°C; ir: NH_2 3431, 3328 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 2.10, 2.63 (2s, 6H, $2CH_3$), 7.27 (s, 2H, NH_2), 7.19–7.49 (m, 5H, Ar-H), 8.12 (s, 1H, CH pyridine), and 8.79 ppm (s, 2H, NH_2); ^{13}C nmr: δ 13.91 (C9: CH_3 pyrazole), 29.17 (C11: CH_3 acetyl), 105.27 (C3a), 110.75 (C8b), 121.28, 123.34, 126.24 (C13–C17: 5CH aromatic carbons), 129.32 (C8a), 139.43 (C2), 141.50 (C12: C–N of aromatic), 142.15 (C8), 146.21 (C4), 149.39 (C5a), 150.96 (C3), 190.47 (C10: CO); ms *m/z* = 322 (M^+) and base peak. *Anal*. Calcd for $C_{17}H_{14}N_4OS$ (322.39): C, 63.34%; H, 4.38%; N, 17.38%; S, 9.94%. Found: C, 63.12%; H, 4.34%; N, 17.50%, S, 9.80%.

Ethyl-3-amino-8-methyl-6-phenyl-6H-pyrazolo[3,4-b]thieno [2,3-d]pyridine-2-carboxylate (10b). Produced according to the previous general procedure as brown crystals from acetic acid in 72% yield; mp: 238–240°C; ir: NH_2 3436, 3328, CH aliphatic 2976, CO 1670 cm^{-1}; ^1H nmr: δ ($CDCl_3$) 1.45 (t, 3H, CH_3 ester), 2.8 (s, 3H, CH_3 pyrazole), 4.42 (q, 2H, CH_2 ester), 7.28 (s, 2H, NH_2), 7.3–7.55 (m, 5H, Ar H), and 8.20 ppm (s, 1H, CH pyridine); ^{13}C nmr: 13.92 (C9: CH_3 pyrazole), 14.87 (C13: CH_3 ester), 60.20 (C12: CH_2 ester), 121.24, 123.50, 126.16 (C15–C19: 5 aromatic carbons), 129.30 (C3a), 139.30 (C8a), 141.66 (C3), 142.10 (C14: –C–N of

aromatic), 145.55 (C8), 149.23 (C4), 150.75 (C5a), 164.40 (C10: CO ester); ms $m/z = 351$ (M^+) and base peak. *Anal*. Calcd for $C_{18}H_{16}N_4O_2S$ (352.41): C, 61.35%; H, 4.58%; N, 15.90%; S, 9.10%. Found: C, 61.25%; H, 4.40%; N, 15.78%; S, 9.08%.

3-Amino-8-methyl-6-phenyl-6H-pyrazolo[3,4-b]thieno[2,3-d] pyridine-2-carboxamide (10c). Produced according to the previous general procedure as yellow crystals from ethanol in 85% yield; mp: 250–251°C; ir: $2NH_2$ 3443, 3333, 3185, CO 1675 cm^{-1}; ^1H nmr: (DMSO-d_6) δ 2.67 (s, 3H, CH_3), 7.27 (s, 2H, NH_2), 7.36–7.71 (m, 5H, Ar-H), 8.21 (s, 1H, CH pyridine), and 9.20 ppm (s, 2H, NH_2); ^{13}C nmr: δ 13.5 (C9: CH_3), 97.01 (C8a), 110.42 (C3a), 120.83, 123.91, 125.97, 129.15 (C12–C16: 5C aromatic), 139.03 (C11: C–N aromatic), 139.15 (C8b: C4 in pyridine), 141.53 (C2), 144.82 (C8), 144.82 (C4), 148.31 (C3), 148.59 (C5a), 166.49 (C10: CO amide); ms $m/z = 322.78$ as base beak and molecular ion peak. *Anal*. Calcd for $C_{16}H_{13}N_5OS$ (323.37): C, 59.43%; H, 4.05%; N, 21.66%; S, 9.91%. Found: C, 59.41%; H, 4.01%; N, 21.53%; S, 9.88%.

3-Amino-8-methyl-6-phenyl-6H-pyrazolo[3,4-b]thieno[2,3-d] pyridine-2-N-(4-chloro phenyl)carboxamide (10d). Produced according to the previous general procedure as pale brown crystals from acetic acid in 67% yield; mp: 290–292°C; ir: NH_2 3440, 3330 cm^{-1}; ^1H nmr (DMSO-d_6) 2.71 (s, 3H, CH_3), 7.37 (s, 2H, NH_2), 7.31–7.36, 7.49–7.58 (2m, 5H, Ar-H), 7.76, 8.23 (2d, 4H, CH-Ar), 8.23 (s, 1H, CH pyridine), 9.26 (s, 1H, NH). ^{13}C nmr: 13.99 (C9: CH_3 pyrazole), 89.44 (C8a), 110.73 (C4), 121.26, 121.30, 122.82, 123.96 (C19–C23: 5C aromatic), 128.72, 129.57, 139.44, 139.94 (C13, C14, C16, C17, *p*-Cl-phenyl), 142.00 (C15: C–Cl), 143.74 (C18, C–N phenyl), 145.35 (C15, C–N *p*-Cl phenyl), 149.14 (C8b), 150.25 (C2), 152.81 (C8), 150.25 (C4), 155.62 (C3), 163.92 (C5a), 163.58 (C10, CO). *Anal*. Calcd for $C_{22}H_{16}ClN_5OS$ (433.91): C, 60.90%; H, 3.72%; Cl, 8.17%; N, 16.14%; S, 7.39%. Found: C, 60.88%; H, 3.66%; Cl, 8.14%; N, 16.03%; S, 7.34%.

3-Amino-8-methyl-6-phenyl-6H-pyrazolo[3,4-b]thieno[2,3-d] pyridine-2-carbaldehyde (10e). Produced according previous general procedure as pale yellow from ethanol in 58% yield; mp: 250–252°C; ir: NH_2 3299, 3189, CO 1617; ^1H nmr: (DMSO-d_6) δ 2.63 (s, 3H, CH_3), 7.27 (s, 2H, NH_2), 7.38–7.72 (m, 5H, Ar-H), 8.09 (s, 1H, CH pyridine), 8.39 (s, 2H, NH_2), and 8.99 ppm (s, 1H, CHO). *Anal*. Calcd for $C_{16}H_{12}N_4OS$ (308.36): C, 62.32%; H, 3.92%; N, 18.17%; S, 10.40%. Found: C, 62.21%; H, 3.90%; N, 18.13%; S, 10.22%.

3-Amino-8-methyl-6-phenyl-6H-pyrazolo[3,4-b]thieno[2,3-d] pyridine-2-carbonitrile (10f). Produced according to the previous general procedure as pale yellow from ethanol in 75% yield; mp: 289–290°C; ir: NH_2 3432, 3338, CN 2197 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.63 (s, 3H, CH_3), 7.27 (s, 2H, NH_2), 7.33–7.57 (m, 5H, Ar-H), 8.19 (s, 1H, CH pyridine), 9.2 (s, 2H, NH_2); ^{13}C nmr (DMSO-d_6) δ: 13.84 (C9: CH_3 pyrazole), 110.66 (C10, CN), 116.11, 121.37, 122.04 (C12–C16: 5C aromatic), 126.59 (C2), 129.59 (C11), 139.25 (C3a), 141.62 (C4), 142.13 (C8b), 145.27 (C8a), 149.12 (C5a) 153.34 (C3: C–NH_2). *Anal*. Calcd for $C_{16}H_{11}N_5S$ (305.36): C, 62.93%; H, 3.63%; N, 22.94%; S, 10.50%. Found: C, 62.90%; H, 3.58%; N, 22.88%; S, 10.34%.

1,9-Dimethyl-3-phenyl-7,8,9,10-tetrahydro-3*H*-pyrazolo [4″,3″:5′,6′]pyrido[3′,4′:4,5] thieno[3,2-*b*][1, 6]naphthyridine (11). A mixture of **10e** (1.54 g, 0.001 mol) and *N*-methyl-4-piperidone (0.56 mL, 0.005 mol) in ethanolic KOH (20 mL, 10%) was stirred at room temperature for 1 h. The solid product that separated from the hot mixture was filtered off and recrystallized from the acetic acid into yellow crystals of compound **11** in 67% yield; mp: 235–237°C; ir: CH aromatic 3075, CH aliphatic 2938, 2838, C=N 1592 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.59, 2.85 (2s, 6H, $2CH_3$), 2.97–2.98 (t, 2H, CH_2), 3.83 (t, 2H, CH_2), 3.35 (s, 2H, CH_2), 7.28–7.59 (m, 5H, Ar-H), and 8.26, 8.29 ppm (2s, 2H, 2CH pyridine). ^{13}C nmr δ ($CDCl_3$):13.89 (C13: CH_3 pyrazole), 32.52 (C10: CH_2 piperidine), 45.79 (C14, CH_3–N piperidine), 52.97 (C9: CH_2 piperidine), 57.56 (C7: CH_2 piperidine), 121.65–124.97 (C15–C20, 6C aromatic), 126.16 (C10a), 128.27 (C12a), 129.14 (C6a), 139.41 (C1), 141.78 (C5b), 144.45 (C6a), 149.77 (C3a). *Anal*. Calcd for $C_{22}H_{19}N_5S$ (385.49): C, 68.55%; H, 4.97%; N, 18.17%; S, 8.32%. Found: C, 68.23%; H, 4.80%; N, 18.09%; S, 8.28%.

7-Amino-1-methyl-3-phenylpyrido[4,5]thieno[2,3-*d*]pyrazolo [3,4-*b*]pyridine-8-carbonitrile (12). A mixture of **10e** (1.54 g, 5 mmol), malononitrile (0.33 g, 1 mmol), and a few drops of piperidine in ethanol (20 mL) was refluxed for 2 h. The solid product that separated from the hot mixture was filtered off, washed with ethanol, and recrystallized from dioxane into orange crystals of **12** in 60% yield; mp: >300°C; ir: NH_2 3387, 3346, CN 2219 cm^{-1}; ^1H nmr: (DMSO-d_6) δ 2.60 (s, 3H, CH_3), 7.16 (s, 2H, NH_2), 7.36–7.57 (m, 5H, Ar-H), and 8.14, 8.45 ppm (2s, 2H, 2CH pyridine); ms: $m/z = 356$ as a molecular ion peak and base peak. *Anal*. Calcd for $C_{19}H_{12}N_6S$ (356.41): C, 64.03%; H, 3.39%; N, 23.58%; S, 9.00%. Found: C, 64.00%; H, 3.28%; N, 23.51%; S, 8.93%.

1-(1,7-Dimethyl-3-phenylpyrido[4,5]thieno[2,3-*d*]pyrazolo [3,4-*b*]pyridin-8-yl)ethan-1-one (13). A mixture of **10e** (1.54 g, 1 mmol) and acetylacetone (0.5 mL, 5 mmol) in ethanolic KOH (20 mL, 10%) was stirred for 2 h. The solid product that separated from the hot mixture was filtered off and recrystallized from dioxane to afford orange crystals of 13 in 46% yield; mp: 230–232°C; ir: CH aromatic; CH aliphatic 3040, 2923, α,β-unsat CO 1670, C=N 1628 cm^{-1}; ms: (*m/z*) 372 (M^+), 330 (M^+–CH_3CO) as the base peak. *Anal*. Calcd for $C_{21}H_{16}N_4OS$ (372.45): C, 67.72%; H, 4.33%; N, 15.04%; O, 4.30%; S, 8.61. Found: C, 67.66%; H, 4.23%; N, 15.00%; O, 4.18%; S, 8.43%.

Ethyl *N*-(2-cyano-8-methyl-6-phenyl-6*H*-pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridin-3-yl) formimidate (14). A mixture of aminocarbonitrile compound **10f** (3 g, 0.01 mol) and triethyl orthoformate (10 mL) in acetic anhydride (10 mL) was refluxed for 2 h and then cooled. The solid product was filtered off and recrystallized from ethanol into buff crystals of **14** in 57% yield; mp: 210–211°C. ir: CH aliphatic CN 2988, 2206 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 1.23 (t, 3H, CH_3 ester), 2.69 (s, 3H, CH_3 pyrazole), 4.16 (q, 2H, CH_2 ester), 7.26–7.29, 7.45–7.48 (2m, 5H, Ar-H), 8.11 (s, 1H, CH pyridine), 8.7 (s, 1H, N–CH–O); ms: *m/z* = 361 as a molecular ion peak and base peak. *Anal.* Calcd for $C_{19}H_{15}N_5OS$ (361.42): C, 63.14%; H, 4.18%; N, 19.38%; S, 8.87%. Found: C, 63.11%; H, 4.09%; N, 19.26%; S, 8.76%.

8-Amino-9-imino-1-methyl-3-phenyl-3,9-dihydro-8*H*-pyrazolo[4″,3″:5′,6′]pyrido[3′,4′:4,5]thieno[3,2-*d*]pyrimidine (15). A solution of **14** (4 g, 0.01 mol) in cold dioxane (10 mL) was stirred at room temperature, then hydrazine hydrate (98%, 2 mL) was added to the solution with stirring for 1 h. The solid product that formed was collected and recrystallized from ethanol-dioxane as white crystals of **15** in 68% yield; mp: 265–266°C; ir: 3420, 3270, 3246 cm^{-1} (NH_2, NH), 1635 cm^{-1} (C=N). ms: *m/z* 347 as a molecular ion peak and base peak at *m/z* = 317. *Anal.* Calcd for $C_{17}H_{13}N_7S$ (347.40): C, 58.78%; H, 3.77%; N, 28.22%; S, 9.23%. Found: C, 58.48%; H, 3.63%; N, 28.19%; S, 9.19%.

11-Methyl-9-phenyl-3*H*-pyrazolo[4″,3″:5′,6′]pyrido[3′,4′:4,5]thieno[2,3-*e*][1, 2, 4]-triazolo[1,5-*c*]pyrimidine-2(9*H*)-thione (16). A mixture of compound **15** (0.4 g, 1 mmol) and carbon disulfide (1.5 mL) in pyridine (5 mL) was refluxed on a steam bath for 4 h. The solid precipitate that formed upon heating was recrystallized from ethanol to afford orange crystals of **16** in 45% yield; ir: NH 3430 and C=N 1590 cm^{-1}; mp: 298–300°C; ^1H nmr: (DMSO-d_6) δ 2.51 (s, 3H, CH_3 pyrazole), 7.38–7.41, 7.57–7.62 (m, 5H, Ar-H), 8.58 (s, 1H, CH pyridine), and 8.10 ppm (s, 1H, NH). *Anal.* Calcd for $C_{18}H_{11}N_7S_2$ (389.45): C, 55.51%; H, 2.85%; N, 25.18%; S, 16.46%. Found: C, 55.42%; H, 2.76%; N, 25.09%; S, 16.35%.

Ethyl 2-((11-methyl-9-phenyl-9*H*-pyrazolo[4″,3″:5′,6′]pyrido[3′,4′:4,5]thieno[2,3-*e*][1,2,4]-triazolo[1,5-*c*]pyrimidin-2-yl)thio)acetate (17). A mixture of the triazolothione **15** (0.2 g, 0.4 mmol) and ethyl chloroacetate (0.06 mL, 0.4 mmol) in ethanol (30 mL) in the presence of anhydrous sodium acetate (2 g) was refluxed for 2 h and then cooled. The solid product was filtered off, washed several times with water, and recrystallized from ethanol into yellow crystals of **17**; mp: >300°C, yield 65%; ir: CH aromatic 3030, CH aliphatic 2920, 2850, CO ester 1735; ^1H nmr: (DMSO-d_6) δ 1.40 (t, 3H, CH_3), 2.75 (s, 3H, CH_3), 3.90 (s, 2H, SCH_2), 4.30 (q, 2H, CH_2), 7.25–7.80 (m, 5H, ArH), and 10.80 ppm (s, 1H, NH). *Anal.* Calcd for $C_{22}H_{17}N_7O_2S_2$ (475.54): C, 55.57%; H, 3.60%; N, 20.62%; S, 13.48%. Found: C, 55.48%; H, 3.52%; N, 20.54%; S, 13.32%.

2,11-Dimethyl-9-phenyl-9*H*-pyrazolo[4″,3″:5′,6′]pyrido[3′,4′:4,5]thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (18). Compound **15** (0.2 g, 0.5 mmol) and acetic anhydride (3 mL) were gently refluxed for 3 h. The solid product obtained after cooling was filtered off and recrystallized from acetic acid to give white crystals of **18** in 40% yield; mp: >300°C; ir: CH aromatic 3061, CH aliphatic 2994, C=N 1625 cm^{-1}; ms: *m/z* 371 as a molecular ion peak and base peak. *Anal.* Calcd for $C_{19}H_{13}N_7S$ (371.42): C, 61.44%; H, 3.53%; N, 26.40%; S, 8.63%. Found: C, 61.35%; H, 3.48%; N, 26.32%; S, 8.53%.

1-Methyl-3-phenyl-3*H*-pyrazolo[4″,3″:5′,6′]pyrido[3′,4′:4,5]thieno[3,2-*d*]-pyrimidine-7,9(6*H*,8*H*)-dithione (19). A mixture of amino carbonitrile compound **10f** (2 g, 5 mmol) and carbon disulfide (1.5 mL) in pyridine (5 mL) was refluxed on steam bath for 4 h. The solid precipitate that formed upon heating was recrystallized from ethanol to afford orange crystals in 45% yield; mp: >300°C; ir: NH 3421, C=N 1589, C=S 1174 cm^{-1}; ms: *m/z* 380 as a molecular ion peak and at *m/z* = 300 as base peak. *Anal.* Calcd for $C_{17}H_{11}N_5S_3$ (381.49): C, 53.52%; H, 2.91%; N, 18.36%; S, 25.21. Found: C, 53.49%; H, 2.85%; N, 18.31%; S, 25.18%.

Ethyl(5-cyano-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)glycinate (20). A mixture of chloropyrazolo[3,4-*b*]pyridine carbonitrile compound **5** (3 g, 0.01 mol), ethyl glycinate hydrochloride (3 g, 0.02 mol), and anhydrous potassium carbonate (3.4 g, 2.5 mmol) in dimethylformamide (35 mL) was heated on steam bath at 70–80°C for 8 h. After cooling, the reaction mixture was poured into ice–water mixture slowly with stirring. The solid product was filtered off and recrystallized from ethanol to give white crystals of **20** in 83% yield; mp: 199–200°C; ir NH 3398, CH aliphatic 2988, CN 2216 and CO 1731 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 1.39 (t, 3H, CH_3), 2.85 (s, 3H, CH_3), 4.38 (q, 2H, CH_2), 4.65 (d, 2H, CH_2), 7.31–7.41, 7.49–7.57 (m, 5H, Ar-H), 8.13 (s, 1H, CH pyrimidine), and 8.41 ppm (s, 1H, NH). *Anal.* Calcd for $C_{18}H_{17}N_5O_2$ (353.37): C, 64.47%; H, 5.11%; N, 20.88%. Found: C, 64.42%; H, 5.07%; N, 20.83%.

Ethyl-3-amino-8-methyl-6-phenyl-1,6-dihydropyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (21). To a solution of the ethyl glycinate derivative **20** (3.5 g, 0.01 mol) in absolute ethanol (20 mL), a few drops of ethanolic sodium ethoxide were added. The mixture was heated under reflux for 30 min. The solid product was filtered off and recrystallized from ethanol as pale brown crystals of compound **21** in 91% yield; mp: 263–265°C; ir: NH_2, NH 3487, 3301, CO 1656 cm^{-1}; ^1H nmr: (DMSO-d_6) δ 1.27 (t, 3H, CH_3), 2.75 (s, 3H,

CH_3), 4.33 (q, 2H, CH_2), 7.41–7.68 (m, 5H, Ar-H), 8.17 (s, 1H, CH pyridine), 7.19 (s, 2H, NH_2), and 10.62 ppm (s, 1H, NH); ms: *m/z* 335 as molecular ion peak and base peak. *Anal*. Calcd for $C_{18}H_{17}N_5O_2$ (335.37): C, 64.47%; H, 5.11%; N, 20.88%. Found: C, 64.45%; H, 5.07%; N, 20.80%.

Ethyl-3-amino-1,8-dimethyl-6-phenyl-1,6-dihydropyrazolo [3,4-*b*]pyrrolo[2,3-*d*]pyridine-2-carboxylate (22). A mixture of the ethyl pyrazolopyridinyl glycinate compound **20** (1.7 g, 5 mmol), methyl iodide (0.75 mL, 5 mmol), and anhydrous potassium carbonate (3 g, 0.022 mol) in acetone was refluxed with stirring for 24 h; after that, the mixture was allowed to cool. The solid product was filtered off and recrystallized from ethanol to give yellow crystals of compound **22** in 76% yield; mp: 238–240°C; ir: NH_2 3446, CH aliphatic 3350, 2976, CO 1654 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 1.47 (t, 3H, CH_3), 2.95 (s, 3H, CH_3 pyrazole), 4.27 (s, 3H, CH_3 pyrrole), 4.45 (q, 2H, CH_2), 7.28 (s, 2H, NH_2), 7.33–7.37, 7.52–7.56 (m, 5H, Ar-H), and 8.15 ppm (s, 1H, CH pyridine). *Anal*. Calcd for $C_{19}H_{19}N_5O_2$ (349.39): C, 65.32%; H, 5.48%; N, 20.04%. Found: C, 65.29%; H, 5.44%; N, 20.01%.

General procedure for synthesis of pyrazolopyridopyrrolopyrimidine (23a, b). A suspension of the amino ester compounds **21** or **22** (1 g) in formamide(10 mL) was refluxed for 3 h. The solid product that separated from the hot mixture was filtered off, washed several times with ethanol, and recrystallized from dioxaneto give the pyrimidine derivatives **23a** and **23b**.

1-Methyl-3-phenyl-3,10-dihydropyrazolo[4",3":5',6']pyrido[3',4 ':4,5]pyrrolo[3,2-d]pyrimidin-9(8H)-one (23a). Produced according to the previous general procedure as gray crystals in 75% yield; mp: >300°C; ir: 2NH 3446, 3350, CH aliphatic 2976, CO 1654 cm^{-1}; ^1H nmr: (DMSO-d_6) δ 2.86 (s, 3H, CH_3), 7.31–7.35, 7.53–7.57 (2m, 5H, Ar-H), 8.13 (s, 1H, CH pyrimidine), 8.28 (s, 1H, NH pyrrole), and 9.16 ppm (s, 1H, NH pyrimidine); ^{13}C nmr: (DMSO-d_6) δ 14.91 (C11: CH_3 pyrazole), 121.45 (C15 phenyl), 122.30 (C13, C17 phenyl), 126.15 (C14, C16 phenyl), 129.45 (C12: C–N phenyl), 136.44 (C10b), 139.82 (C5b), 140.22 (C1), 141.74 (C5), 144.13 (C5a), 144.23 (C10a), 150.37 (C7), 154.40 (C3a), 163.38 (C9: C=O pyrimidine). *Anal*. Calcd for $C_{17}H_{12}N_6O$ (316.32): C, 64.55%; H, 3.82%; N, 26.57%. Found: C, 64.51%; H, 3.79%; N, 26.52%.

1,10-Dimethyl-3-phenyl-3H-pyrazolo[4",3":5',6']pyrido[3',4' :4,5]pyrrolo[3,2-d] pyrimidin-9(8H)-one (23b). Produced according previous general procedure as pale yellow crystals in 68% yield; mp: >300°C; ir: NH pyrimidine 3340, CH aromatic 3050, CH aliphatic 2940, 2824, CO amide 1667, C=N 1608 cm^{-1}; ^1H nmr: (DMSO-d_6) δ 2.90 (s, 3H, CH_3), 4.15 (s, 3H, CH_3 pyrrole), 7.40–7.85 (m, 5H, Ar-H), 8.13 (s, 1H, CH pyrimidine), and 9.85 ppm (s, 1H, NH pyrimidine). *Anal*. Calcd for $C_{18}H_{14}N_6O$ (330.35): C, 65.44%; H, 4.27%; N, 25.44%. Found: C, 65.40%; H, 4.23%; N, 25.41%.

3-Amino-8-methyl-6-phenyl-1,6-dihydrodipyrazolo[3,4-*b*: 3′,4′-*d*]pyridine (24). A mixture of chloro compound **5** (1.4 g, 5 mmol) and hydrazine hydrate (99%, 1 mL, 0.02 mol) in ethanol (40 mL) was refluxed for 3 h and then left to cool. The precipitated solid was collected and recrystallized from ethanol to give **24** as brown crystals; mp: 268–270°C; yield 85%; ir: NH, NH 3432, 3279, 3152, C=N 1644 cm^{-1}; ^1H nmr: (DMSO-d_6) δ 2.67 (s, 3H, CH_3), 6.00 (s, 2H, NH_2), 7.28–7.30, 7.49–7.53 (m, 5H, Ar-H), 8.25 (s, 1H, CH pyridine), and 8.91 ppm (s, 1H, NH); ms: *m/z* = 246 as molecular ion peak and base peak. *Anal*. Calcd for $C_{14}H_{12}N_6$ (264.29): C, 63.62%; H, 4.58%; N, 31.80%. Found: C, 63.59%; H, 4.55%; N, 31.77%.

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