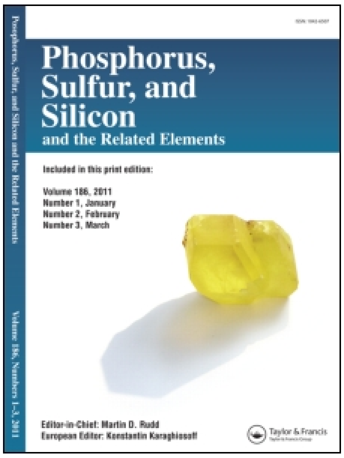

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1,3-Disubstitutedpyrazole-4-caboxaldehyde in Heterocyclic Synthesis: A Novel Synthesis of Pyridine-2(1*H*)-thione and Fused Nitrogen and/or Sulfur Heterocyclic Derivatives

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1,3-DISUBSTITUTEDPYRAZOLE-4-CABOXALDEHYDE IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHESIS OF PYRIDINE-2(1*H*)-THIONE AND FUSED NITROGEN AND/OR SULFUR HETEROCYCLIC DERIVATIVES

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Pyridine-2(1H)-thione 5 was synthesized from the reaction of 3-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-1-phenylpropenone (3) and cynothioacetamide (4). Compound 5 reacted with halogented compounds 6a–e to give 2-S-alkylpyridine derivatives 7a–e, which could be in turn cyclized into the corresponding thieno[2,3-b]-pyridine derivatives 8a–e. Compound 8a reacted with hydrazine hydrate to give 9. The latter compound reacted with acetic anhydride (10a), formic acid (10b), acetic acid, ethyl acetoacetate, and pentane-2,4-dione to give the corresponding pyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine 13a,b, pyrazolo[3′,4′:4,5]thieno[3,2-d]pyridine 14 and thieno[2,3-b]-pyridine derivatives 18 and 20, respectively. Alternatively, 8c reacted with 10a,b and nitrous acid to afford the corresponding pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine 24a,b and pyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine 26 derivatives, respectively. Finally compound 5 reacted with methyl iodide to give 2-methylthiopyridine derivative 27, which could be reacted with hydrazine hydrate to yield the corresponding pyrazolo[3,4-b]-pyridine derivative 29.

Keywords Pyrazolo[3′,4′:4,5]thieno[3,2-*d*]pyridine; pyridine-2(1*H*)-thione; pyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidine; pyrido[3′,2′:4,5]thieno[3,2-*d*]-[1,2,3]triazine; thieno[2,3-*b*]pyridine

INTRODUCTION

The pyrazole nucleus and its chemistry have found considerable attention due to outstanding biological activities such as anti-anxiety,[1] antibacterial, and antifungal properties.[2] These findings prompted this work to introduce several pharmacophores such as pyridine, pyrimidine, and thieno moieties into a pyrazole system hoping to obtain compounds with enhanced potency. For the last three decades, synthesis and characterization of heterocyclic derivatives of expected biological activities has gained considerable attention by this group of researchers.[3–13] A vast number of nitrogen heterocyclic derivatives have been synthesized from which compounds containing the pyridine nucleus and its azolo, azino, and thieno derivatives have constituted the main members. The reason is that these derivatives possess a wide range of biological activities and are commonly used in many pharmaceutical and medicinal preparations. The pyridine nucleus exhibits antitumor[14] and anti-amnsic[15]

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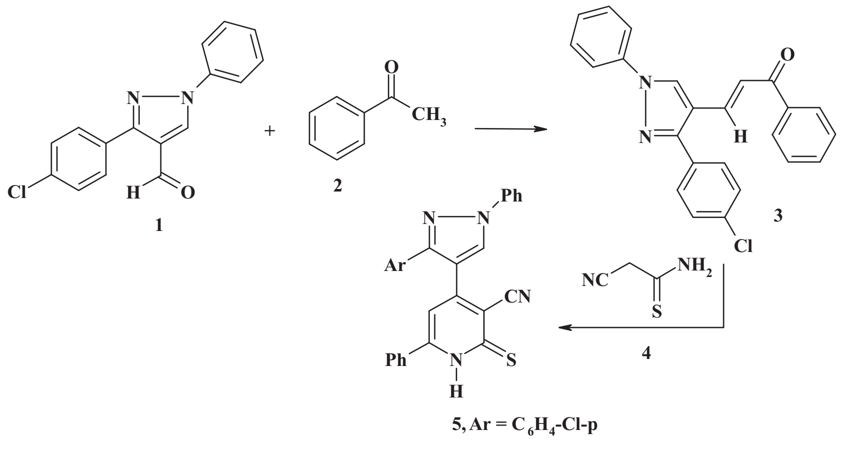
activities. On the other hand, the *S*-alkylpyridinethione derivatives have shown neurotropic[16] activity and are used as adenosine receptor ligands.[17,18] They also have also cardiovascular.[19] In addition, thieno[2,3-*b*]pyridine derivatives were reported to possess a broad range of biological activities such as antimicrobial,[20–24] anti-inflamatory,[25] neurotropic,[16] and ganadotropin-releasing hormone-antagonizing activities.[26]

Furthermore, the pyridothienopyrimidines are reported to possess antiallergic activity,[27] antiprotozoals active against phelasterides dicentrarchi,[28] antianaphylactic,[29] and antimicrobial[20,21] activities. In addition, these compounds possess antipyretic,[30] analgesic,[31] and hypo-holesterolenic[32] activities. Furthermore, the pyrazolo[3,4-*d*]pyridine derivatives have been used as antimicrobial[22,33,34] inhibitors of cyclindependent kinases[35,36] and inhibitors of phosphodiesterase.[37] Pyridine-2(1*H*)-thione was taken as the starting material for the present study.

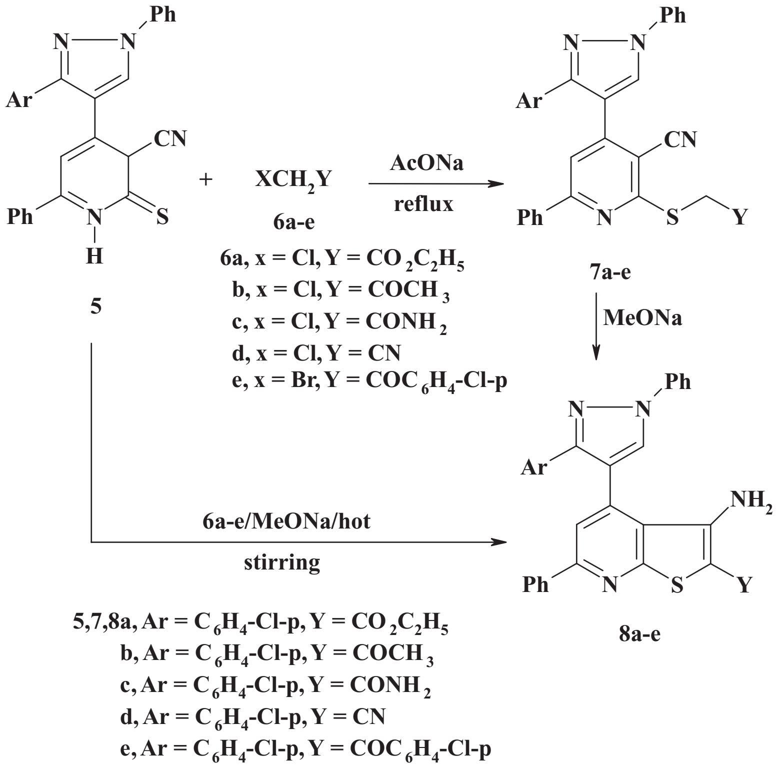
RESULTS AND DISCUSSION

The starting material 4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**5**) was prepared in good yield via the reaction of 3-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-phenylpropenone (**3**) with cyanothioacetamide (**4**) in absolute ethanol in the presence of a catalytic amount of piperidine. Thus, the IR spectrum of **5** showed the presence of the bands of the NH group (3280 cm^{-1}) and the nitrile function at (2219 cm^{-1}). The ^1H NMR spectrum of **5** revealed signals of the ring NH at $\delta = 7.0$ ppm and 5H-pyrazole at $\delta = 9.1$ ppm, in addition to the aromatic protons (m, 15H, 7.42–7.99 δ ppm) (see Scheme 1 and the Experimental section).



Scheme 1

The synthetic potential of **5** was demonstrated via its reaction with a variety of halogenated active methylene reagents **6a–e**. Thus, it has been found that **5** reacted with ethyl chloroacetate (**6a**) in boiling ethanol in the presence of sodium acetate to give a reaction product resulting from equimolecular addition of **6a** to **5** and the loss of one molecule of hydrogen chloride. The IR spectrum of this reaction product showed among its absorption bands those corresponding to the presence of CN group (2215 cm^{-1}) and C=O (1743 cm^{-1}). Its ^1H NMR spectrum revealed signals of $CH_2\underline{CH_3}$ (t, 3H at $\delta = 1.32$–1.37 ppm), $\underline{CH_2}CH_3$ (q, 2H at $\delta = 4.32$–4.34 δppm), $S\underline{CH_2}CO$ (s, 4.27 ppm). Based on the above data, in addition to correct elemental analysis, this compound was formulated as ethyl 2-[(3-cyano-6-phenyl-pyridin-2-yl)thio]acetate derivative **7a** (see the Experimental section). In a similar manner, compound **5** reacted with each of chloroacetone (**6b**), chloroacetamide (**6c**), chloroacetonitrile (**6d**), and 1-(4-chlorophenyl)-2-bromoethanone (**6e**) to give the corresponding 2-*S*-alkylpyridine derivatives **7b–e**, respectively. The structures of **7b–e** were established based on the correct data of elemental analyses and spectra (see the Experimental section and Scheme 2).

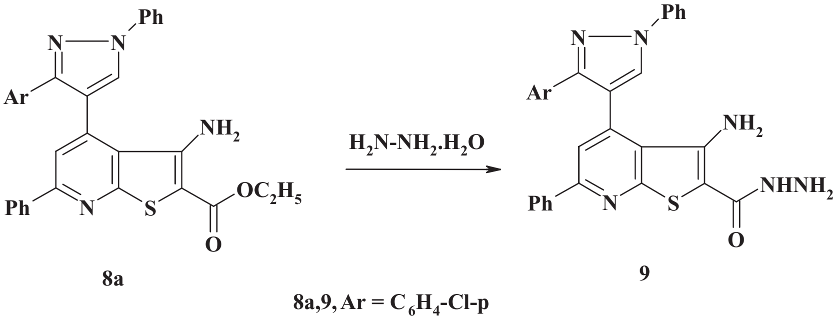


Scheme 2

A further proof for the structures of **7a**–**e** came from their cyclization by boiling in sodium methoxide solution to give the corresponding thieno[2,3-*b*]pyridine derivatives **8a–e**, respectively. The IR spectra of **8a–e** were found to be free from the absorption bands of the nitrile function, and instead new bands of the NH_2 function were detected. Analytical data of **8a–e** were found almost identical to that of **7a–e**, respectively, proving that the nitrile function is involved in the cyclization step via addition of the active methylene group at position-2 of the pyridine ring to the nitrile function at position-3 of **7a–e**. The ^1H NMR spectra of **8a**–**e** were also found to be free from the signals of the active methylene group, proving also its involvement in the cyclization step leading to the formation of **8a**–**e**.

Another piece of solid evidence for the structures of **8a**–**e** came from their independent synthesis by performing the reaction between **5** and **6a**–**e**, respectively, in a hot methanolic/sodium methoxide solution for 2 h. Compounds **8a–e** prepared via this route were found to be completely identical in all aspects (analyses, IR and ^{1}H NMR spectra) with **8a–e** prepared via the first route (see the Experimental section).

An unequivocal support for the structure of compound **8** came from the series of reactions concerning which compound contains the ester group at position-2 of the thienyl moiety. Thus, it has been found that **8a** reacted with hydrazine hydrate to give **9**. The IR spectrum of this product showed the presence of the absorption bands of NH_2, NH, and C=O groups. Its ^{1}H NMR spectrum revealed signals of two NH_2 and NH groups in addition to the aromatic protons and 5H-pyrazole. Based on the above data, this reaction product could then be formulated as the 3-amino-4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-6-phenylthieno[2,3-*b*]pyridine-2-carbohydrazide (**9**) (see the Experimental section and Scheme 3).



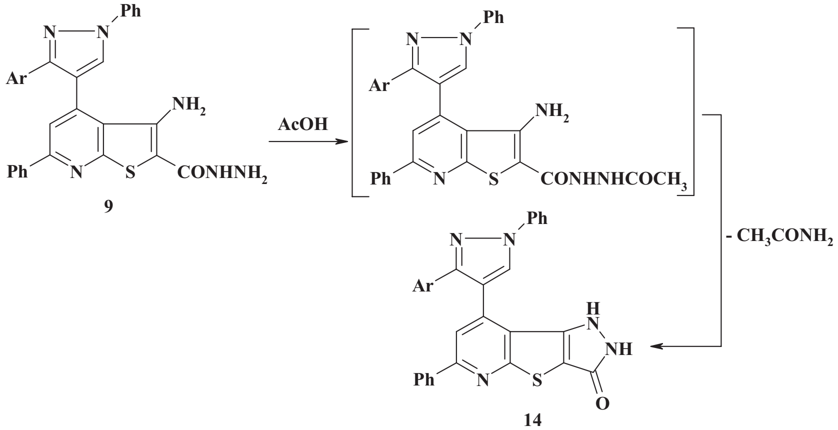
8a,9, Ar = C_6H_4-Cl-p

Scheme 3

The isolation of compound **9** with its adjacent NH_2 and $CONHNH_2$ functions stimulated the insertion to utilize them as versatile starting material for the synthesis of several, otherwise difficult to obtain heterocyclic derivatives through its reactions with a variety of activated reagents. Thus, it has been found that **9** reacted with acetic anhydride (**10a**) to give a reaction product with molecular formula $C_{31}H_{21}ClN_6OS$ corresponding to acetylation of the NH_2 group at the thiophene ring followed by cyclization via loss of one molecule of water **13a**. The structure of **13a** was established based on the correct data of elemental analyses and spectra. The IR spectrum of this reaction product showed the presence of absorption bands of NH_2 (3494, 3362 cm^{-1}) and the ring —CO group (1673 cm^{-1}). The ^{1}H NMR spectrum of this reaction product revealed signals of NH_2 and methyl at pyrimidine ring (see the Experimental section and Scheme 4).

Moreover, compound **9** reacted with formic acid (**10b**), giving rise to the 3-aminopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidinone derivative **13b**. The structure of **13b** was elucidated on the basis of elemental analysis and spectral data. The IR spectra of **13b** showed the presence of one NH_2 and one CO. The ^{1}H NMR spectrum of **13b** revealed also signals of NH_2 group (s, 2H, at $\delta = 6.02$ ppm) in addition to the multiplet of aromatic protons (at $\delta = 7.27$–8.30 ppm) (see the Experimental section). The formation of **13b** in this reaction is assumed to proceed via initial formylation of the NH_2 group at position-3 of the thienyl moiety of **9** followed by enolization, subsequent loss of the elements of water, to yield the final isolable **13b** (Scheme 4).

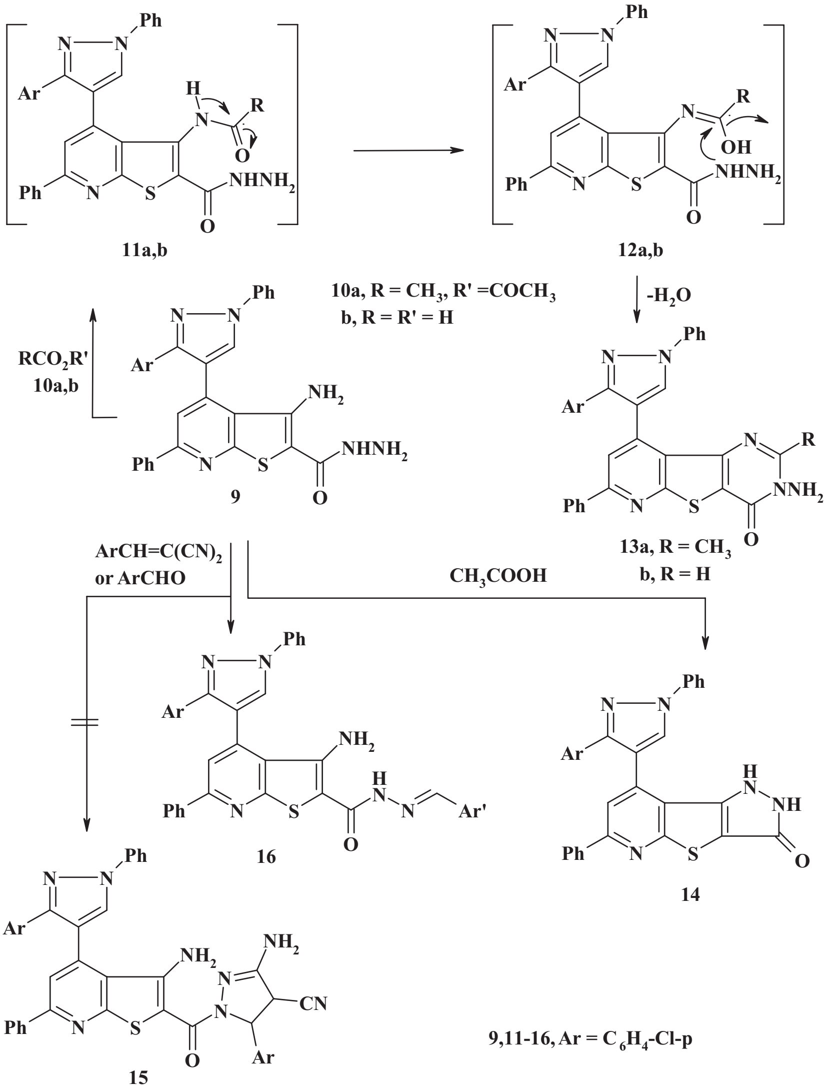
On the other hand, compound **9** was boiled in glacial acetic acid to afford the corresponding pyrazolo[3′,4′:4,5]thieno[3,2-*d*]pyridine derivative **14**. The structure of **14** could be confirmed based on the correct elemental analysis and spectral data backgrounds (see the Experimental section and Scheme 4). Compound **14** was formed according to the following mechanism[38,39]:



Compound **9** reacted also, with 3-(4-chlorophenyl)-2-cyanopropenonitrile with the aim of obtaining the expected pyrazole derivative **15**.

Unexpectedly, the ^{1}H NMR spectrum of this reaction product did not agree with the expected value of **15**. Instead, and surprisingly, the ^{1}H NMR spectrum of this product was found to be in agreement with compound **16**. This conclusion could be explained by the fact that compound **9**, instead of reacting of 3-(4-chloro-phenyl)-2-cyanopropenonitrile to give the expected **15**, underwent ylidene exchange with the liberation of the molecule of malononitrile to give the final isolable **16**. The structure of compound **16** could be elucidated via its preparation via another route by reacting compound **9** with 4-chlorobenzaldehyde to afford **16**. Compound **16** prepared via this route was found to be completely identical with **16** prepared before in all aspects (mp = 320–322°C, mixed mp = 320–322°C, IR and ^{1}H NMR data), (see the Experimental section and Scheme 4).

As a further continuation of exploring the synthetic potential of **9**, it was thus of value to investigate its reaction with a variety of active methylene esters and ketones. Thus, it has been found that a reaction product of molecular formula $C_{33}H_{23}ClN_6O_2S$ was obtained upon reacting **9** with ethyl acetoacetate in boiling glacial acetic acid. This formula corresponded to an equimolecular addition of **9** to the ester and the loss of one molecule of water and one molecule of ethanol. The IR spectrum of this reaction product showed the presence of absorption bands of one NH_2 group (3430, 3390 cm^{-1}) and CO group (1670 cm^{-1}). Its ^{1}H NMR spectrum revealed the presence of signals of one CH_3 (s, 3H, at $\delta = 2.29$ ppm) and NH_2 (s, 2H, at $\delta = 5.99$ ppm) (see the Experimental section). No proton signals corresponding to the ethyl ester group were detected. This means that the ester group was consumed in the reaction to give the final isolable product, which was formulated as 3-amino-2-[(3-methylpyrazol-5-on-1-yl)carbonyl]-6-phenyl-4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]thieno[2,3-*b*]pyridine (**18**). The formation of **18** in this reaction is assumed to proceed via initial condensation between the carbonyl group of ethyl acetoacetate and the amino group of hydrazonyl with the loss of molecule

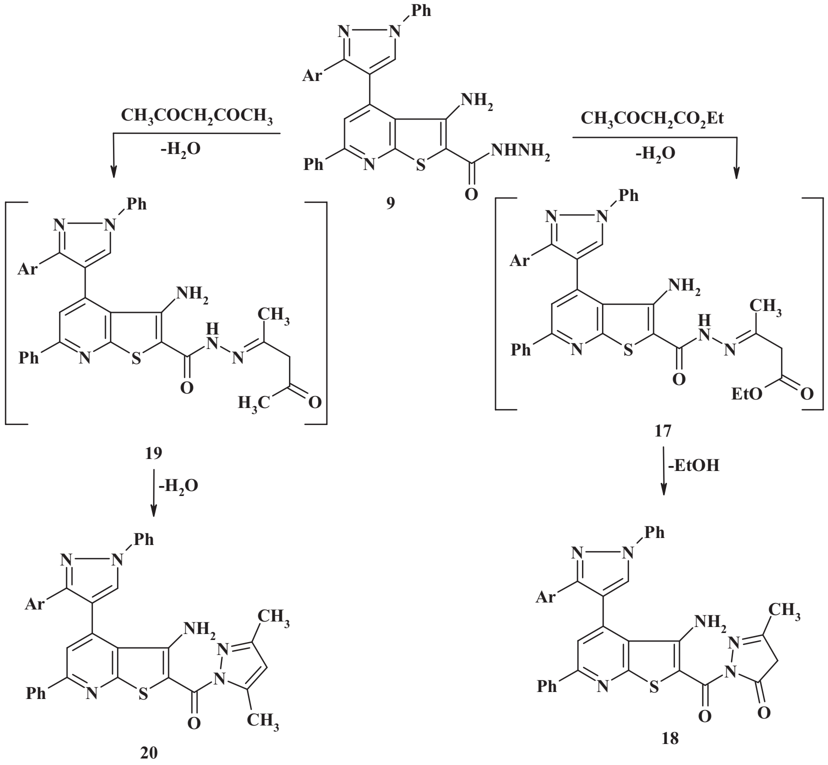


Scheme 4

of water and cyclization via loss of one molecule of ethanol to yield the final isolable **18** through the intermediate **17**.

The reaction between **9** and pentane-2,4-dione was also investigated. Thus, a reaction product of molecular formula $C_{34}H_{25}ClN_6OS$ was obtained upon reacting **9** with pentane-2,4-dione (see Scheme 5).

This formula corresponded to equimolecular addition followed by the loss of two molecules of water to give compound **20**. Only the bands of NH_2 group (3430, 3380 cm^{-1}) and one CO group (1680 cm^{-1}) were detected in the IR spectrum of this reaction product. Also signals of one NH_2 group (s, 2H, at $\delta = 6.22$ ppm) and two CH_3 groups (2.28 and 2.53 δ ppm) were detected in the ^1H NMR spectrum of this reaction product. By



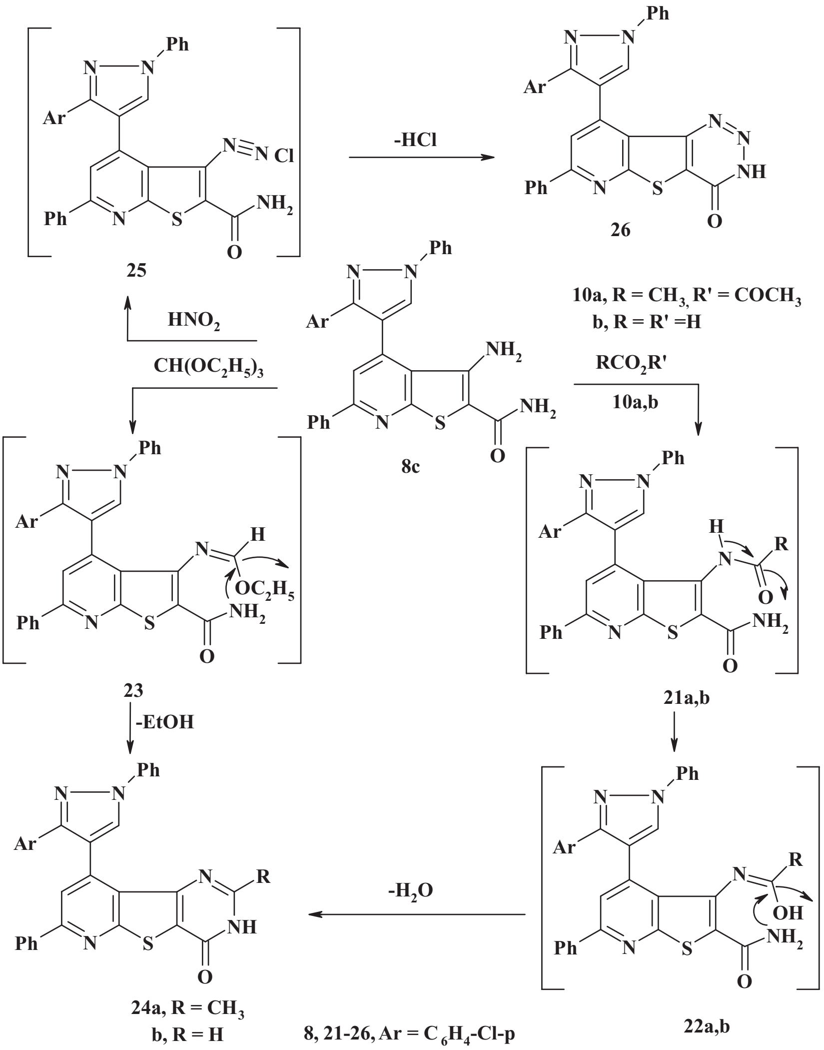
9,17-20, Ar = C_6H_4-Cl-p

Scheme 5

collecting the above data in addition to correct elemental analysis, this reaction product could be formulated as 3-amino-2-[(3,5-dimethylpyrazol-5-on-1-yl)carbonyl]-4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-6-phenylthieno[2,3-*b*]pyridine (**20**) (see the Experimental section and Scheme 5).

Also, compound **8c** reacted with acetic anhydride (**10a**) to give 2-methyl-9-[3-(4-chloropheyl)-1-phenyl-1*H*-pyrazol-4-yl)]-7-phenylpyrido-[3′,2′:4,5]thieno[3,2-*d*] pyrimidin-4(3*H*)-one (**24a**), whose structure was established based on correct elemental analysis and spectral data studies. The formation of **24a** in this reaction is assumed to proceed first via acetylation of the NH_2 group at position-3 of the thiophene moiety in **8c**, followed by enolization and subsequent loss of the elements of water to give the final isolable product **24a** (see Scheme 6).

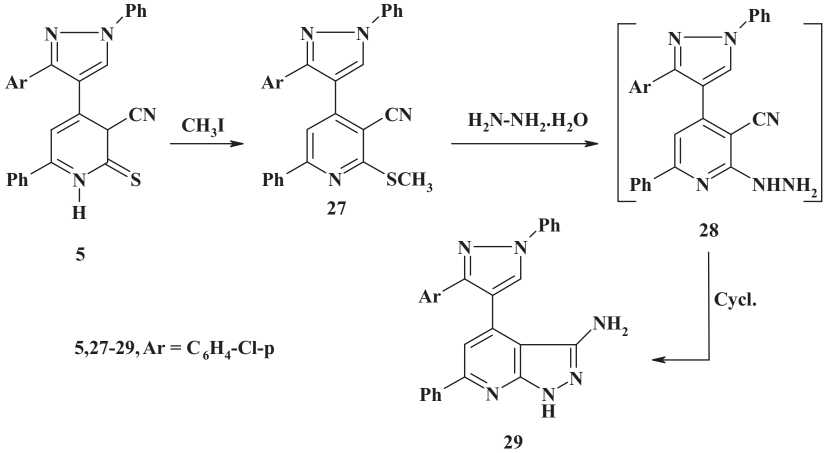
Moreover, compound **8c** also reacted with formic acid (**10b**) to give **24b**. The IR spectrum of the reaction product showed the disappearance of the absorption bands of the two NH_2 groups and instead showed the presence of only one NH, a fact which was confirmed by the ^{1}H NMR data. Compound **24b** is assumed to be formed via initial formylation of the amino group followed by enolization and subsequent loss of the elements of water to yield the final isolable product (see the Experimental section and Scheme 6). Compound **24b** could be prepared via another route by reacting **8c** with triethylortoformate to give **24b**. Compound **24b** prepared via this route was found to be identical in all backgrounds as **24b** previously prepared.



Scheme 6

On the other hand, compound **8c** reacted with nitrous acid to give **26**. The IR spectrum of this reaction product showed the absorption band that corresponded to NH and CO groups. Moreover, its ^{1}H NMR spectrum revealed a signal corresponding to NH. Based on the above data, compound **26** could be formulated as 9-[(3-(4-chloropheyl)-1-phenyl-1H-pyrazol-4-yl)]-7-phenyl pyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazin-4(3*H*)-one **(26)** (see the Experimental section and Scheme 6).

Finally, compound **5** reacted with methyl iodide in sodium methoxide to afford a reaction product corresponding to equimolecular addition of **5** to the reagent followed by the loss of one molecule of hydrogen iodide to give **27**. The IR spectrum of this reaction product showed the band of the nitrile function at (2221 cm^{-1}). The ^{1}H NMR of **27** revealed the signal of methyl (s, 3H, 2.76). Based on the above data, this reaction product could be formulated as the 2-methylthionicotinonitrile derivative **27** (see Scheme 7 and the Experimental section).



Scheme 7

The 2-methylthionicotinonitrile derivative **27** reacted with hydrazine hydrate to give a sulfur-free reaction product of molecular formula $C_{27}H_{19}ClN_6$. This formula corresponded to equimolecular addition of the reactant and reagent and the loss of one molecule of methyl mercaptan. The band of the nitrile function was entirely absent in the IR spectrum of the reaction product, and instead a band of new amino group was detected (3418, 3383 cm^{-1}) and NH (3317 cm^{-1}) in this spectrum. The ^{1}H NMR spectrum revealed one NH$_2$ (s, 2H, at $\delta = 4.59$ ppm) and one NH (s, 1H, at $\delta = 12.29$ ppm). Based on the above data, the reaction product could be formulated as the 3-aminopyrazolo[3,4-*b*]pyridine derivative **29**, most likely formed via the intermediary of the non-isolable 2-hydrazinopyridine derivative **28** (see the Experimental section and Scheme 7).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded as KBr discs on a Shimadzu FTIR-8201PC spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz and Varian Gemini 200 MHz. Spectrometers using TMS as an internal standard and DMSO-d$_6$ as solvents and chemical shifts are expressed as δ ppm units. The Microanalytical Center of Cairo University performed microanalyses. Compounds **1**[40] and **3**[41] were prepared according to procedures in the literature.

Synthesis of 4-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (5)

A mixture of each of **3** (0.01 mol) and **4** (0.01 mol) in absolute ethanol (30 mL) containing a catalytic amount of piperidine (0.4 mL) was heated under reflux for 4 h. The product formed was collected by filtration, washed with cold ethanol, and then crystallized from ethanol to give **5** as yellow crystals (72%); mp 240–242°C; IR(υ cm^{-1}): NH (3280), CN (2219), ^{1}H NMR (δ ppm): 7.00 (br, 1H, NH) and 7.42–7.99 (m, 15H, ArH's), 9.10 (s, 1H, 5H-pyrazole), Anal. for $C_{27}H_{17}ClN_4S$ (464.97): calcd./found(%): C (69.74/69.77), H (3.69/3.71), Cl (7.62/7.65) N (12.05/12.03), S (6.90/6.92).

Synthesis of 7a–e

A mixture of **5** (0.01 mol), each of **6a–e** (0.01 mol), and sodium acetate (0.015 mol, 2.04 g) in ethanol (20 mL) was heated under reflux for 2 h. The products thus formed were collected by filtration, washed with cold ethanol, and then crystallized from the proper solvent to give **7a–e**, respectively.

Ethyl 2-({4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-3-cyano-6-phenylpyridin-2-yl}thio)acetate (7a). Crystallized from ethanol as yellow crystals (73%); mp 180–182°C; IR (υ cm^{-1}): CN (2215), C=O (1743); ^1H NMR (δ ppm): 1.32–1.37 (t, 3H, $CH_2\underline{CH_3}$), 4.27 (s, 2H, $-S\underline{CH_2}$), 4.32–4.34 (q, 2H, $-O\underline{CH_2}CH_3$), 7.40–7.89 (m, 15H, ArH's), 9.10 (s, 1H, 5H-pyrazole), Anal. for $C_{31}H_{23}ClN_4O_2S$ (551.059): calcd./found(%): C (67.57/67.55), H (4.21/4.23), Cl (6.43/6.45), N (10.17/10.15), S (5.82/5.85).

4-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]6-phenyl-2-[(2-oxo-propyl) thio]nicotinonitrile (7b). Crystallized from dioxane as buff crystals (67%); mp 226–228°C; IR (υ cm^{-1}): CN (2220), C=O (1715), ^1H NMR (δ ppm): 2.30 (s, 3H, $SCH_2CO\underline{CH_3}$), 4.36 (s, 2H, $S\underline{CH_2}COCH_3$), 7.49–7.97 (m, 15H, ArH's), 9.08 (s, 1H, 5H-pyrazole), Anal. for $C_{30}H_{21}ClN_4OS$ (521.003) calc./found C (69.16/69.19), H (4.06/4.03), Cl (6.80/6.83), N (10.75/10.72), S (6.15/6.17).

2-({4-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-3-cyano-6-phenyl-pyridin-2-yl}thio)acetamide (7c). Crystallized from dioxane as white crystals (70%); mp 267–269°C; IR (υ cm^{-1}): NH_2 (3450,3410), CN (2215), C=O (1682), ^1H NMR (δ ppm): 4.08 (s, 2H, $S\underline{CH_2}CONH_2$), 7.23 (s, 2H, $SCH_2CO\underline{NH_2}$), 7.42–8.18 (m, 15H, ArH's), 9.07 (s, 1H, 5H-pyrazole), Anal. for $C_{29}H_{20}ClN_5OS$ (522.02): calcd./found(%): C (66.72/66.75), H (3.86/3.84), Cl (6.79/6.82), N (13.42/13.44), S (6.14/6.12).

4-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2-[(cyanomethyl)thio]-6-phenylnicotinonitrile (7d). Crystallized from dioxane/ethanol as gray crystals (68%); mp 23–25°C; IR (υ cm^{-1}): CN (2221), $CH_2\underline{CN}$ (2232), ^1H NMR (δ ppm): 4.51 (s, 2H, $S\underline{CH_2}CN$), 7.40–8.25 (m, 15H, ArH's), 9.11 (s, 1H, 5H-pyrazole), Anal. for $C_{29}H_{18}ClN_5S$ (504.006): calcd./found(%): C (69.11/69.13), H (3.60/3.63), Cl (7.03/7.00),N (13.90/13.92), S (6.36/6.34).

4-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2-[2-(4-chlorophenyl)oxo-ethyl]thio]-6-phenylnicotinonitrile (7e). Crystallized from ethanol as yellow crystals (71%); mp 135–137°C; IR (υ cm^{-1}): CN (2222), C=O (1697), ^1H NMR (δ ppm): 5.02 (s, 2H, $S\underline{CH_2}CO$), 7.41–8.13 (m, 19H, ArH's), 9.11 (s, 1H, 5H-pyrazole), Anal. for $C_{35}H_{22}Cl_2N_4OS$ (617.547): calcd./found(%): C (68.07/68.05), H (3.59/3.61), Cl (11.48/11.51), N (9.07/9.05), S (5.19/5.21).

Synthesis of Thieno[2,3-*b*]pyridine Derivatives 8a–e

Method A. A mixture of each of **5** (0.01 mol) and sodium methoxide (0.01 mol, 0.23 g of sodium in 20 mL of CH_3OH) was heated before boiling for 2 min, then each of **6a–e** (0.01 mol) was added and stirred for 2 h at room temperature. The products formed were collected by filtration, washed with cold ethanol, and then crystallized from the proper solvent to give the final products **8a–e**, respectively.

Method B. A mixture of each of **7a–e** (0.01 mol) in methanolic sodium methoxide was heated under reflux for 2 h. The products formed were collected by filtration, washed with cold ethanol, and then crystallized from the proper solvent to give **8a–e**, respectively.

Ethyl 3-amino-4-[(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)]-6-phenylthieno[2,3-*b*]pyridine-2-carboxylate (8a). Crystallized from dioxane as yellow crystals (67%); mp 267–269°C; IR (υ cm^{-1}): NH_2 (3492, 3380), C=O (1674), ^{1}H NMR (δ ppm):1.28–1.33 (t, 3H, $COCH_2\underline{CH_3}$), 4.22–4.25 (s, 2H, $CO\underline{CH_2}CH_3$), 6.17 (s, 2H, NH_2), 7.37–8.18 (m, 15H, ArH's), 8.96 (s, 1H, 5H-pyrazole), Anal. for $C_{31}H_{23}ClN_4O_2S$ (551.059): calcd./found(%): C (67.57/67.55), H (4.21/4.23), Cl (6.43/6.44), N (10.17/10.19), S (5.82/5.85).

3-Acetyl-3-amino-4-[(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-phenylthieno[2,3-*b*]pyridine (8b). Crystallized from acetic acid as pale yellow crystals (67%); mp 254–256°C; IR (υ cm^{-1}): NH_2 (3449, 3278), C=O (1681), ^{1}H NMR (δ ppm): 2.37 (s, 3H, $CO\underline{CH_3}$), 6.20 (s, 2H, NH_2), 6.98–8.03 (m, 15H, ArH's), 8.76 (s, 1H, 5H-pyrazole), Anal. for $C_{30}H_{21}N_4OSCl$ (521.033): calcd./found(%): C (69.16/69.18), H (4.06/4.04), Cl (6.80/6.83), N (10.75/10.72), S (6.15/16.12).

3-Amino-4-[(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)]-6-phenylthieno[2,3-*b*]pyridine-2-carboxamide (8c). Crystallized from dioxane as yellow crystals (67%); mp 267–269°C; IR (υ cm^{-1}): NH_2 (3458, 3318), C=O (1658), ^{1}H NMR (δ ppm): 6.19 (s, 2H, NH_2), 7.22 (s, 2H, $CONH_2$), 7.37–8.14 (m, 15H, ArH's), 8.96 (s, 1H, 5H-pyrazole), Anal. for $C_{29}H_{20}ClN_5OS$ (522.02): calcd./found(%): C (66.72/66.75), H (3.86/3.83), Cl (6.79/7.01), N (13.42/10.44) and S (6.14/16.12).

3-Amino-4-[(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)]-6-phenylthieno[2,3-*b*]pyridine-2-carbonitrile (8d). Crystallized from acetic acid as yellow crystals (69%); mp 292–294°C; IR (υ cm^{-1}): NH_2 (3462, 3345), CN (2194), ^{1}H NMR (δ ppm): 6.00 (s, 2H, NH_2), 7.38–8.19 (m, 15H, ArH's), 8.96 (s, 1H, 5H-pyrazole), Anal. for $C_{29}H_{18}ClN_5S$ (504.006): calcd./found(%): C (69.11/69.13), H (3.60/3.63), Cl (7.03/7.05), N (13.90/13.93), S (6.36/6.32).

3-Amino-2-(4-chlorobenzoyl)-4-[(3-(4-chloropheyl)-1-phenyl-1*H*-pyrazol-4-yl]-6-phenylthieno[2,3-*b*]pyridine (8e). Crystallized from acetic acid as yellow crystals (67%); mp 243–245°C; IR (υ cm^{-1}): NH_2 (3475, 3305), C=O (1678), Anal. for $C_{35}H_{22}Cl_2N_4OS$ (617.547): calcd./found(%): C (68.07/68.05), H (3.59/3.61), Cl (11.48/11.50), N (9.07/9.10), S (5.19/5.22).

Synthesis of 3-Amino-4-[(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-phenylthieno[2,3-*b*]pyridine-2-carbohydrazide (9)

A solution of **8a** (0.01 mol) in hydrazine hydrate (10 mL) and pyridine (30 mL) was heated under reflux for 10 h. The reaction mixture was evaporated to one-third of its volume and allowed to cool, then was treated with ethanol. The solid product was collected by filtration and crystallized from dioxane to give **9** as yellow crystals (72%); mp 198–199°C; IR (υ cm^{-1}): $NHNH_2$ (3494, 3362, 3318), C=O (1669), ^{1}H NMR (δ ppm): 3.6 (s, 2H, $CONH\underline{NH_2}$), 6.15 (s, 2H, NH_2 at thiophene ring), 7.35–8.16 (m, 16H, ArH's and $CO\underline{NH}NH_2$), 8.90 (s, 1H, 5H-pyrazole), Anal. for $C_{29}H_{21}ClN_6OS$ (537.05): calcd./found(%): C (64.86/64.89), H (3.94/3.96), Cl (6.60/6.63), N (15.65/15.67), S (5.97/6.00).

Synthesis of (13a,b)

A solution of **9** (0.01 mol) and each of acetic anhydride **(10a)** and formic acid **(10b)** (20 mL of each) was heated under reflux for 5 h. Excess solvent was evaporated in vacuo and cooled. The solid formed was collected by filtration, washed with ethanol, and crystallized from acetic acid to give **13a**,**b**, respectively.

3-Amino-9-[(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)]-2-methyl-7-phenylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (13a). Crystallized from acetic acid as buff crystals (69%); mp 286–288°C; IR (υ cm^{-1}): NH_2 (3494, 3362), C=O (1673), ^{1}H NMR (δ ppm): 2.21 (s, 3H, CH_3 at pyrimidine ring), 7.29–8.22 (m, 17H, ArH's and NNH_2), 8.97 (s, 1H, 5H-pyrazole), Anal. for $C_{31}H_{21}ClN_6OS$ (561.057): calcd./found(%): C (66.36/66.33), H (3.77/3.75), Cl (6.32/6.35), N (14.98/14.96), S (5.72/5.74).

3-Amino-9-[(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)]-7-phenylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (13b). Crystallized from acetic acid as yellow crystals (73%); mp 350–352°C; IR (υ cm^{-1}): NH_2 (3450, 3330), C=O (1673), ^{1}H NMR (δ ppm): 6.02 (s, 2H, NNH_2), 7.27–8.30 (m, 16H, ArH's and 2H-pyrimidine), 8.98 (s, 1H, 5H-pyrazole), Anal. for $C_{30}H_{19}ClN_6OS$ (547.03): calcd./found(%): C (65.87/65.85), H (3.50/3.52), Cl (6.48/6.51), N (5.36/5.34), S (5.86/5.90).

Synthesis of 8-[(3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-phenyl-1,2-dihydropyrazolo[3′,4′:4,5]thieno[3,2-*d*]pyridin-3-one (14)

A solution of **9** (0.01 mol) in glacial acetic acid (30 mL) was heated under reflux for 5 h. The excess solvent was evaporated in vacuo and cooled. The solid product was collected by filtration, washed with ethanol, and crystallized from acetic acid to give **14** as brown crystals (67%); mp 307–309°C, IR (υ cm^{-1}): two NH (3435, 3380), C=O (1675), ^{1}H NMR (δ ppm): 3.89 (s, 1H, NH), 5.96 (s, 1H, NH), 7.26–8.25 (m, 15H, ArH's), 8.99 (s, 1H, 5H-pyrazole), Anal. for $C_{29}H_{18}ClN_5OS$ (520.005): calcd./found(%): C (66.98/67.01), H (3.49/3.47), Cl (6.82/6.85), N (13.47/3.50), S (6.17/6.15).

Synthesis of 3-amino-*N*-(4-chlorophenylmethylene)4-[(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)]-6-phenylthieno[2,3-*b*]pyridine-2-carbohyrazide (16). A solution of each of **9** (0.01 mol) and 4-chlorobenzaldehyde or (4-chlorobenzylidene)malononitrile (0.01 mol) in pyridine (30 mL) was heated under reflux for 5 h. The excess solvent was evaporated in vacuo and cooled. The solid product was collected by filtration, washed with ethanol, and crystallized from dioxane/ethanol to give **16** as yellow crystals (71%); mp 320–322°C; IR (υ cm^{-1}): NH_2 (3455, 3342), NH (3320), C=O (1670), ^{1}H NMR (δ ppm): 6.77 (s, 2H, NH_2 at thiophene ring), 7.37–8.20 (m, 19H, ArH's), 8.96 (s, 1H, 5H-pyrazole), 11.56 (s, 1H, $\mathrm{CO\underline{NH}{-}N{=}}$), Anal. for $C_{36}H_{24}ClN_6OS$ (659.587): calcd./found(%): C (65.55/65.58), H (3.67/3.65), Cl (10.75/10.73), N (12.74/2.77), S (4.86/4.85).

Synthesis of 3-Amino-4-[(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)]-2-(3-methyl-1*H*-pyrazol-5-on-1-yl)carbonyl]-6-phenylthieno[2,3-*b*]pyridine (18)

A solution of **9** (0.01 mol) and ethyl acetoacetate (0.01 mol) in acetic acid (30 mL) was heated under reflux for 4 h. The excess solvent was evaporated in vacuo and cooled.

The solid product was collected by filtration, washed with ethanol, and crystallized from acetic acid to give **18** as yellow crystals (67%); mp above 360°C; IR (υ cm^{-1}): NH_2 (3430, 3390), CO (1670), ^1H NMR (δ ppm): 2.10 (s, 2H, $CO\underline{CH_2}C(CH_3) = N$), 2.29 (s, 3H, CH_3 at pyrazolone), 5.99 (s, 2H, NH_2), 7.31–8.09 (m, 15H, ArH's), 9.09 (s, 1H, 5H-pyrazole), Anal. for $C_{33}H_{23}ClN_6O_2S$ (603.094): calcd./found(%): C (65.72/65.74), H (3.84/3.81), Cl (5.88/5.91), N (13.93/13.95), S (5.32/5.35).

Synthesis of 3-Amino-4-[(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)] 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]-6-phenylthieno[2,3-*b*]pyridine (20)

A solution of **9** (0.01 mol) and pentane-2,4-dione (30 mL) was heated under reflux for 5 h. The excess solvent was evaporated in vacuo and cooled. The solid product was collected by filtration, washed with ethanol, and crystallized from dioxane to give **20** as yellow crystals (73%); mp 260–262°C; IR (υ cm^{-1}): NH_2 (3430, 3380), C=O (1680), ^1H NMR (δ ppm): 2.28 (s, 3H, CH_3 at pyrazolone-5), 2.53 (s, 3H, CH_3 at pyrazolone-3), 6.22 (s, 2H, NH_2), 7.37–8.19 (m, 16H, ArH's), 8.98 (s, 1H, 5H-pyrazole), Anal. for $C_{34}H_{25}ClN_6OS$ (601.121): calcd./found(%): C (67.93/67.95), H (4.19/4.16), Cl (5.90/5.93), N (13.98/14.01), S (5.33/5.35).

Synthesis of 2-Methyl-9-[(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)]-7-phenylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (24a)

A mixture of **8c** (0.01 mol) and acetic anhydride **(10a)** (20 mL) was heated under reflux for 5 h. The excess solvent was evaporated in vacuo and allowed to cool. The solid product was formed collected by filtration and crystallized from acetic acid to give **24a** as brown crystals (69%); mp 357–359°C; IR (υ cm^{-1}): NH (3420), C=O (1673), ^1H NMR (δ ppm): 2.12 (s, 3H, CH_3 at pyrimidine-2), 7.25–8.19 (m, 15H, ArH's), 8.96 (s, 1H, 5H-pyrazole), 12.60 (s, 1H, NH), Anal. for $C_{31}H_{20}ClN_5OS$ (546.041): calcd./found (%): C (68.19/68.22), H (3.69/3.66), Cl (6.49/6.51), N (12.83/12.85), S (5.87/5.85).

Synthesis of 9-[(3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-7-phenyl-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (24b)

A solution of **8c** (0.01 mol) and formic acid **(10b)** (20 mL) was heated under reflux for 3 h. The excess solvent was evaporated in vacuo and allowed to cool. The solid product formed was collected by filtration and crystallized from acetic acid to give **24b** as yellow crystals (66%); mp 364–366°C; IR (υ cm^{-1}): NH (3455), ^1H NMR (δ ppm): 7.25–8.21 (m, 16H, ArH's and CH at pyrimidine-2), 8.95 (s, 1H, 5H-pyrazole), 12.75 (s, 1H, NH), Anal. for $C_{30}H_{18}ClN_5OS_2$ (532.016): calcd./found (%): C (67.73/67.71), H (3.41/3.44), Cl (6.66/6.67), N (13.16/13.13), S (6.03/6.05).

Synthesis of 9-[(3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-7-phenyl-pyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,3]triazin-4(3*H*)-one (26)

A stirred cold solution (0–5°C) of the **8c** (0.01 mol) in acetic acid (5 mL) and concentrated hydrochloric acid (2 mL) was treated with a cold solution of sodium nitrite (0.01 mol, 0.23 g in 5 mL of H_2O) dropwise with stirring. Stirring was continued for 1 h. The reaction mixture was then allowed to stand at room temperature for 15 min. The solid obtained was collected by filtration and crystallized from dioxane as to give **26** as pale yellow crystals (68%); mp 264–266°C; IR (υ cm^{-1}): NH (3203), C=O (1686), ^{1}H NMR (δ ppm): 7.25–8.30 (m, 15H, ArH's) 9.05 (s, 1H, 5H-pyrazole), 15.47 (s, 1H, NH), Anal. for $C_{29}H_{17}ClN_6OS$ (533.004): calcd./found(%): C (65.35/65.38), H (3.21/3.23), Cl (6.65/6.63), N (15.77/5.80), S (6.02/6.05).

Synthesis of 4-[(3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)]-6-phenyl-2-methylthionicotinonitrile (27)

A mixture of **5** (0.01 mol) and iodomethane (0.015 mol) in methanolic sodium methoxide was heated under reflux for 2 h then cooled. The solid formed was collected by filtration and washed with water, then crystallized from acetic acid to give **27** as buff crystals (73%); mp 267–269°C; IR(υ cm^{-1}): CN (2221), ^{1}H NMR (δ ppm): 2.76 (s, 3H, CH_3 at pyridine), 7.42–8.18 (m, 15H, ArH's) and 9.08 (s, 1H, 5H-pyrazole), Anal. for $C_{28}H_{19}ClN_4S$ (478.996): calcd./found(%): C (70.21/70.24), H (4.00/4.03), Cl (7.40/7.42), N (11.70/.73), S (6.69/6.72).

Synthesis of 4-[(3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)]-6-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-3-amine (29)

A solution of **27** (0.01 mol), hydrazine hydrate (5 mL), and pyridine (30 mL) was heated under reflux for 1 week. The excess solvent was evaporated in vacuo and cooled. The solid formed was collected by filtration, dried, and crystallized from ethanol to give **29** as yellow crystals (67%); mp 180–182°C; IR (υ cm^{-1}): NH_2 (3418, 3383), NH (3317); ^{1}H NMR (δ ppm): 4.59 (s, 2H, NH_2), 7.27–8.13 (m, 15H, ArH's), 8.96 (s, 1H, 5H-pyrazole), 12.29 (s, 1H, NH) $C_{27}H_{19}ClN_6$ (462.933): calcd./found(%): C (70.05/70.03), H (4.14/4.16), Cl (7.66/7.68), N (18.15/18.12).

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