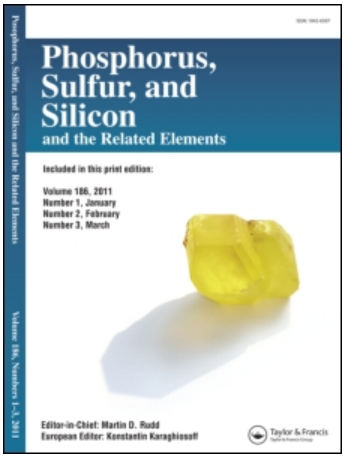

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis, Reactions, and Biological Activity of 4(1*H*-Indol-3-yl)-2-Thioxopyridine Derivatives

Fawzy A. Attaby[a]; Mostafa M. Ramla[b]; Eman M. Gouda[c]
[a] Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt [b] Chemistry of Natural and Microbial Prod. Dept., National Research Center, Dokki, Egypt [c] Biochemistry Department, Faculty of Veterinary Medicine, Cairo University, Giza, Egypt

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Synthesis, Reactions, and Biological Activity of 4(1*H*-Indol-3-yl)-2-Thioxopyridine Derivatives

Fawzy A. Attaby
Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

Mostafa M. Ramla
Chemistry of Natural and Microbial Prod. Dept., National Research Center, Dokki, Egypt

Eman M. Gouda
Biochemistry Department, Faculty of Veterinary Medicine, Cairo University, Giza, Egypt

*2-cyanoethanthioamide **1** reacted with 1H-indole-3-carbaldehyde **2** to give the corresponding 2-cyano-3-(1H-indol-3-yl)prop-2-enethioamide **3** in a very good yield, which in turn reacted with 2,4-pentanedione **4** to give 5-acetyl-1,2-dihydro-4(1H-indol-3-yl)-6-methyl-2-thioxopyridine-3-carbonitrile. The synthetic potential of **5** was examined through its reaction with several active halogen-containing reagents, e.g., 1-chloropropan-2-one, chloroacetonitrile, 2-chloroacetamide, ethyl chloroacetate, chloroacetic acid, ethyl chloroformate, methyl iodide, and 2-bromo-1-arylethanones **13a–c** to give the corresponding thieno[2,3-b]pyridine derivatives **15a–c**. The data of elemental analysis as well as the data of IR (cm^{-1}), ^1H NMR (δ ppm), and mass spectra elucidated structures of all newly synthesized heterocyclic compounds. All newly synthesized heterocyclic compounds were evaluated as antimicrobial and GST enzyme activity and at the GSH enzyme level.*

Keywords 2-cyanoethanthioamide; 1H-indole-3-carbaldehyde; prop-2-enethioamide; 2-thioxopyridine-3-carbonitrile; thieno[2,3-b]pyridine

INTRODUCTION

In continuation of our previous work,[1–18] the reported biological activity of 2-thioxopyridines,[19–21] thienopyridines,[22,23] as well as that of indole derivatives[24,25] stimulated our interest to synthesize several derivatives of these ring systems required for several chemical transformations and for medicinal chemistry programs.

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Address correspondence to Fawzy A. Attaby, Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt. E-mail: fattaby@hotmail.com

RESULTS AND DISCUSSION

Thus, it has been found that 2-cyanoethanethioamide **1** reacted with 1H-indole-3-carbaldehyde **2** in absolute ethanol containing a catalytic amount of triethyl amine to give the corresponding 2-cyano-3-(1H-indol-3-yl)prop-2-enethioamide **3** in a very good yield and pure state. Compound **3** reacted in turn with pentan-2,4-dione **4** in methanol containing a catalytic mixture of piperidine-pyridine (1:5) under reflux for 6–8 h.

The reaction product seemed to be formed via the addition of $-CH_2-$ in **4** on $-CH{=}C-$ in **3**, and this was followed by cyclization through elimination of one water molecule followed by auto-oxidation to afford **5**. The IR (cm^{-1}) of **5** showed bands of NH, CN, CO, and CS groups, and its ^1H NMR revealed signals of CH_3, $COCH_3$, NH, and indol-3-yl protons (cf. Experimental section). Moreover, its mass spectrum gave m/z = 307, which corresponded to the molecular weight of the molecular formula $C_{17}H_{13}N_3OS$ of the assigned structure (cf. Figure 1).

The chemical structure and synthetic potential of **5** was investigated via its reactions with several active-halogen–containing reagents. Thus, it has been found that **5** reacted with 1-chloroprop-2-one **6a** in methanolic sodium methoxide solution to afford the corresponding thieno[2,3-b]pyridine derivative **9a** through the non-isolable intermediate **7a** and **8a**. The IR (cm^{-1}) of such reaction product showed no bands of CN function, and instead the newly formed NH_2 group was detected. Protons

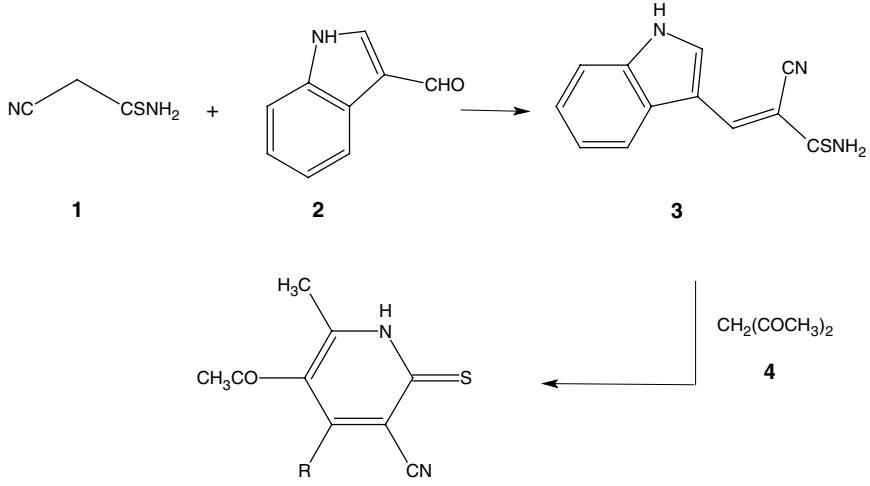
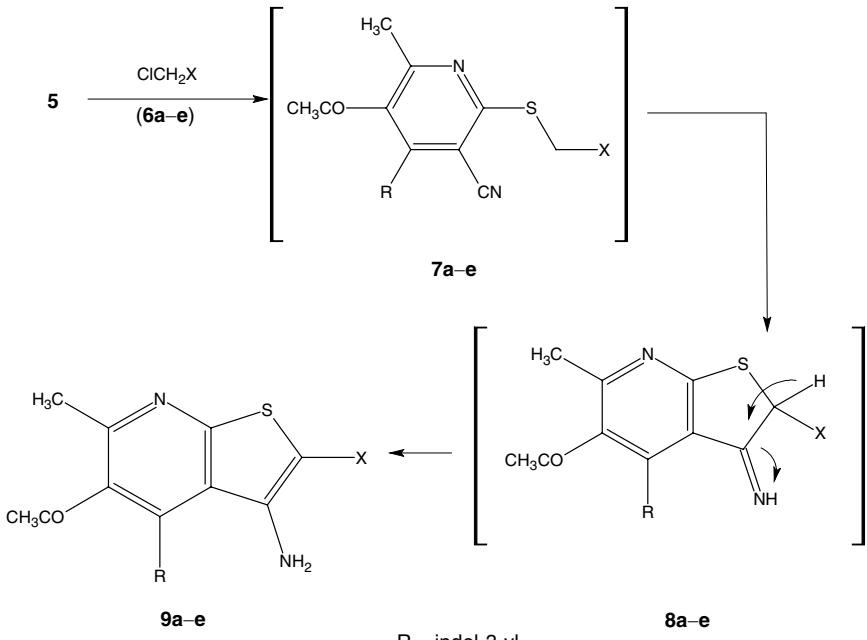


FIGURE 1

of NH_2 were also revealed by an ^1H NMR spectrum. By considering IR, ^1H NMR, and elemental analysis (cf. Experimental Section), structure **9a** was established and formulated as 1-[2-acetyl-3-amino-4-(1H-indol-3-yl)-6-methylthieno-[2,3-b]pyridin-5-yl] ethanone.

Similarly, compound **5** reacted with each of chloroacetonitrile, ethyl chloroacetate, 2-chloroacetamide, and chloroacetic acid (**6b–e**) in methanolic sodium methoxide solution to give the corresponding thieno[2,3-b]pyridine derivatives **9b–e**, respectively, through the non-isolable intermediates **7b–e** and **8b–e** (cf. Figure 2). Moreover, structures **9a–e** were further elucidated based on the data of mass spectra, which gave m/z = 363, 346, 393, 364, and 365 respectively. These values of m/z corresponded to the molecular weights of the molecular for-



6–9a, X=$COCH_3$

b, X=CN

c, X=$COOC_2H_5$

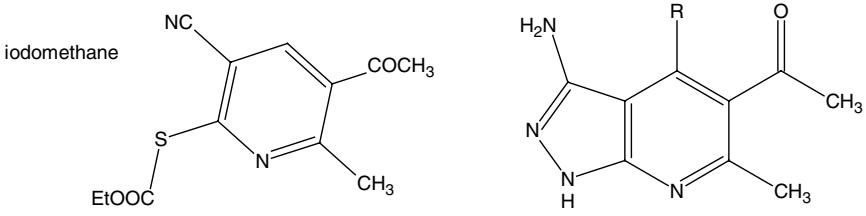
d, X=$CONH_2$

e, X=COOH

FIGURE 2

mulas $C_{20}H_{17}N_3O_2S$, $C_{19}H_{14}N_4OS$, $C_{21}H_{19}N_3O_3S$, $C_{19}H_{16}N_4O_2S$, and $C_{19}H_{15}N_3O_3S$ of the assigned structures **9a–e** (cf. Figure 2).

Further elucidation of each of structures **5** and **9a–e** was given through the reaction of **5** with ethyl chloroformate in methanolic sodium methoxide solution to afford the corresponding *S*-[5-acetyl-3-cyano-4-(1*H*-indol-3-yl)-6-methylpyridin-2-yl] *O*-ethyl thiocarbonate **10**. The reaction proceeded through dehydrochlorination only without cyclization, where no $-CH_2-$ was required for cyclization present. Compound **10** reacted with hydrazine hydrate to give the sulfur-free compound **11** (Scheme 1).



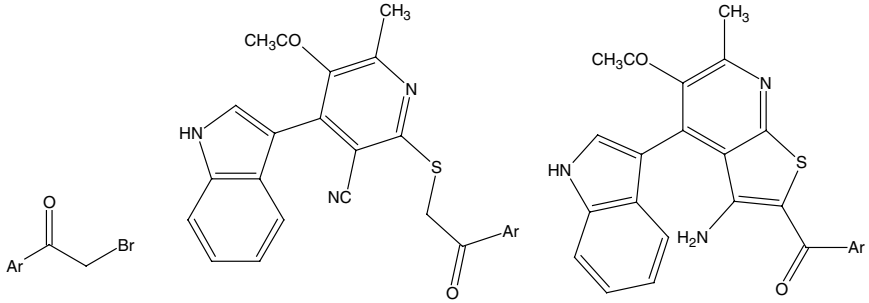
SCHEME 1

Compound **5** reacted with methyl iodide in methanolic sodium methoxide solution to give **12**. Compound **12**, in turn, reacted with hydrazine hydrate to give the sulfur-free compound **11**, which was prepared authentically via the reaction of **5** with hydrazine hydrate.

It is important to report here that the sulfur-free compound **11** obtained by the treatment of each of **5**, **10**, and **12** with hydrazine hydrate is identical in all physical and chemical properties. The IR, ^{1}H NMR, and elemental analysis were the basis on which the structures of **10**, **11**, and **12** were elucidated (cf. Experimental section). Moreover, the mass spectra of each of **10**, **11**, and **12** gave m/z = 379, 305, and 321, which corresponded to the molecular weights of the molecular formulas $C_{20}H_{17}N_3SO_3$, $C_{17}H_{15}N_5O$, and $C_{18}H_{15}N_3SO$ of the assigned structures **10–12**, respectively (cf. Figure 3).

The synthetic potentiality of **5** was further investigated through its reaction with 2-bromo-1-phenylethanone **13a** in methanolic sodium methoxide solution to give the corresponding 5-acetyl-4-(1*H*-indol-3-yl)-6-methyl-2-[(2-oxo-2-phenylethyl)thio]nicotinonitrile **14a**, its mass spectrum gave m/z = 425, which corresponded to the molecular weight of the molecular formula $C_{25}H_{19}N_3O_2S$ of the assigned structure **14a**.

Further confirmation of structure **14a** arose from its cyclization in 10% ethanolic KOH to give 1-[3-amino-2-benzoyl-4-(1*H*-indol-3-yl)-6-methylthieno[2,3-*b*]pyridin-5-yl]ethanone **15a**. The structures of **14a**



13a–c **14a, [b], [c]** **15a–c**

a, Ar = C_6H_5

b, Ar = C_6H_4-p-Cl

c, Ar = C-H_4-p-CH_3

SCHEME 2

and **15a** were elucidated based on the data of IR, ^{1}H NMR, and elemental analysis (cf. Experimental section). Opposite of the behavior of **13a** toward compound **5**, compounds **13b**,**c** reacted with **5** under the same experimental conditions to directly afford the corresponding **15b**,**c** via the non-isolable intermediates **14b**,**c**. All trials to isolate **14b**,**c** failed under varieties of experimental conditions (Scheme 2).

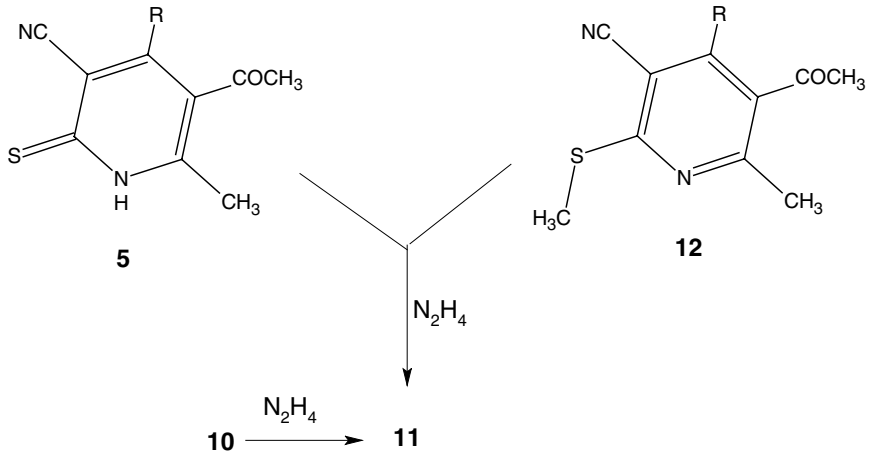


FIGURE 3

BIOLOGICAL EVALUATION

Materials and Methods

Fifteen male adult rats were allocated into 3 equal groups, each of 5 rats. The first group served as the control and received an IP injection of DMSO (vehicle). The second and third groups received a daily IP dose of 50 mg/kg of either compounds **15c** or **15b** for 3 successive days. Livers were taken after decapitation homogenized. The activity of glutathione-S-transferase (GST) and the level of glutathione (GSH) were determined according to Lee et al.[28] and Srivastava et al.,[26] respectively, and protein concentration was determined according to Bradford et al.[27] The antimicrobial effect of the newly synthesized heterocyclic compounds was evaluated on Top 10 *E. coli* strain at a level of 100 mg/mL of LB organ.

Results

Compounds **15b**,**c** showed that the highest antimicrobial effect reached to 90–70% inhibition of the bacterial growth. Compound **15c** induced a significant elevation (0.441 ± 0.018 μ/mg protein) for the GST enzyme, while compound **15b** had no effect on such enzyme (0.345 ± 0.182 μ/mg protein) compared to a normal value ($0.390 =$ or $- 0.016$ μ/mg protein). Whereas the level of GSH of **15c** (43.58 nμ/mg protein), but compound **15b** had no effect on it (48.63 ± 2.7 nμ/mg protein) compared to the control level (49.1 ± 2.5 nμ/mg protein).

Discussion

Lipid peroxidation, an oxidative deterioration of poly unsaturated components of membrane lipids, is considered a biomarker for the cytotoxic effects of many compounds. GST and GSH play an important role in providing a chemoprotective state against toxic, neoplastic, and mutagenic effects mediated by many compounds and drug metabolism.[27]

Conclusion

Compound **15c** has a cytotoxic effect due to elevation in GST and reduction in GSH, whereas compound **15b** has no effect.

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 Varian Mercury 300 MHz and Varian Gemini 200 MHz. Spectrometers used TMS as the internal standard, and $CDCl_3$, DMSO-d_6, and $(CD_3)_2CO$ as solvents and chemical shifts are expressed as δ ppm units. Mass spectra were recorded on Shimadzu GCMS-QP1000EX using inlet type at 70 eV. The Microanalytical Center of Cairo University, Giza, Egypt, performed microanalyses.

Synthesis of 5-Acetyl-1,2-dihydro-4(1H-indol-3-yl)-6-methyl-2-thioxopyridine-3-carbonitrile (5)

A solution of **1** (3 g, 0.03 mole) and **2** (4.35 g, 0.03 mole) in absolute ethanol (50 mL) containing a catalytic amount of piperidine (0.4 mL) was stirred at r.t. for 15–25 min. The product that formed was filtered off and dried well. The isolated product **3** (2.27 g, 0.01 mole) reacted with pentan-2,4-dione **4** (1 g, 0.01 mole) in methanol (50 mL) containing a catalytic mixture of piperidine-pyridine (0.5:1.5 mL) under reflux for 5 h. The reaction mixture was then poured onto ice-cold water. The product that formed was collected by filtration, washed with cold ethanol, and then crystallized from ethanol as brick-red crystals, m.p. 165°C; IR (cm^{-1}): 3350 (NH), 3065 (CH-aromatic), 2890–2930 (CH-aliphatic), 2220 (CN), 1724 (C=O) and 1550 (C=S); ^{1}H NMR (δ ppm): 2.0 (s, 3H, CH_3), 2.7 (s, 3H, $\underline{CH_3}CO$), 7.0–8.2 (m, 7H, pyridine-NH, indole-NH and indole protons): Anal. calcd./found for $C_{17}H_{13}N_3OS$ (307.36) (%): C, 66.43/66.6; H, 4.26/4.2; N, 13.67/13.8; S, 10.43/10.2.

Synthesis of 9a–e (General Procedure)

A solution of 5 (1.56 g, 0.005 mole) and each of **6a–e** (0.46 g, 0.37 g, 0.66 g, 0.47 g, and 0.48 g, respectively; 0.005 mole of each) in methanol containing sodium methoxide (prepared by 0.11 g sodium in 50 mL methanol) was heated under reflux for 3–5 h. The products that formed were collected by filtration, washed with cold ethanol, and then crystallized from ethanol to give **9a–e**, respectively.

1,1′-[3-amino-4-(1*H*-indol-2-yl)-6-methylthieno[2,3-*b*]pyridine-2,5-diyl]diethanone (9a)

As green crystals, m.p. 201–205°C; IR (cm^{-1}): 3430, 3395, 3330, 3342 (NH2 and NH), 3079 (CH-aromatic), 2898–2926 (CH-aliphatic) and 1715 (C=O); ^{1}H NMR (δ ppm): 1.1 (s, 3H, CH_3), 2.7 (s, 6H, two $CO\underline{CH_3}$), 5.1 (s, br., 2H, NH_2), 7.2–8.5 (m, 6H, indole-NH and indole protons). Anal. calcd./found for $C_{20}H_{17}N_3O_2S$ (363.43) (%): C, 66.10/65.8; H, 4.71/4.7; N, 11.56/11.8; S, 8.80/9.0.

5-acetyl-3-amino-4-(1*H*-indol-2-yl)-6-methylthieno[2,3-*b*]pyridine-2-carbonitrile (9b)

As dark green crystals, m.p. 180–183°C; IR (cm^{-1}): 3455, 3400, 3365, 3330 (NH_2 and NH), 3082 (CH-aromatic), 2889–2955 (CH-aliphatic), 2218 (CN) and 1718 (C=O); ^1H NMR (δ ppm): 1.0 (s, 3H, CH_3), 2.6 (s, 3H, CO$\underline{CH_3}$), 5.4 (s, br., 2H, NH_2), 7.1–8.2 (m, 6H, indole-NH and indole protons). Anal. calcd./found for $C_{19}H_{14}N_4OS$ (346.40) (%): C, 65.99/66.1; H, 4.40/4.4; N,13.81/13.8; S, 9.03/9.1.

Ethyl 5-Acetyl-3-amino-4-(1*H*-indol-2-yl)-6-methylthieno[2,3-*b*]pyrid-ine-2-carboxylate 9c

As yellowish-white crystals, m.p. 216°C; IR (cm^{-1}): 3458, 3420, 3350, 3339 (NH_2 and NH), 3089 (CH-aromatic), 2886–2942 (CH-aliphatic) 1732 (ester CO) and 1710 (acetyl C=O); ^1H NMR (δ ppm): 1.0 (s, 3H, CH_3), 1.3 (t, 3H, $\underline{CH_3}CH_2$–), 2.4 (s, 3H, CO$\underline{CH_3}$), 4.3 (q, 2H, $CH_3\underline{CH_2}$–), 5.6 (s, br., 2H, NH_2), 7.3–8.4 (m, 6H, indole-NH and indole protons). Anal. calcd./found for $C_{21}H_{19}N_3O_3S$ (393.45) (%): C, 64.10/64.3; H, 4.87/4.7; N, 10.68/10.8; S, 8.15/8.1.

5-Acetyl-3-amino-4-(1*H*-indol-2-yl)-6-methylthieno[2,3-*b*]pyridine-2-carboxamide 9d

As yellowish-white crystals, m.p. 280–283°C; IR (cm^{-1}): 3478, 3432, 3358, 3344 (NH_2 and NH), 3078 (CH-aromatic), 2877–2921 (CH-aliphatic) 1714 (acetyl CO) and 1685 (amide C=O); ^1H NMR (δ ppm): 1.1 (s, 3H, CH_3), 2.6 (s, 3H, CO$\underline{CH_3}$), 5.3 (s, br., 2H, NH_2), 6.3 (s, br., 2H, CO$\underline{NH_2}$) and 7.1–8.3 (m, 6H, indole-NH and indole protons). Anal. calcd./found for $C_{19}H_{16}N_4O_2S$ (364.42) (%): C, 62.62/63.0; H, 4.43/4.2; N, 15.37/15.4; S,8.80/9.0.

5-Acetyl-3-amino-4-(1*H*-indol-2-yl)-6-methylthieno[2,3-*b*]-pyridine-2-carboxylic Acid 9e

As dark brown crystals, m.p. 206–209°C; IR (cm^{-1}): 3250–3455 (br., OH acidic), 3079 (CH-aromatic), 2853–2930 (CH-aliphatic) 1715 (carboxylic CO) and 1705 (acetyl C=O); ^1H NMR (δ ppm): 1.2 (s, 3H, CH_3), 2.5 (s, 3H, CO$\underline{CH_3}$), 5.1 (s, br., 2H, NH_2), 7.1–8.3 (m, 6H, indole-NH and indole protons) and 12.3 (s, 1H, COO$\underline{H}$). Anal. calcd./found for $C_{19}H_{15}N_3O_3S$ (365.40) (%): C, 62.45/62.6; H, 4.14/4.2; N, 11.50/11.4 ; S, 8.78/8.6.

Synthesis of *S*-[5-acetyl-3-cyano-4-(1*H*-indol-3-yl)-6-methylpyridin-2-yl] *O*-ethyl thiocarbonate 10

A solution of **5** (1.56 g, 0.005 mole) and ethyl chloroformate (0.54 g, 0.005 mole) in methanol containing sodium methoxide (prepared by 0.11 g of sodium in 50 mL methanol) was heated under reflux for 3–5 h. The product that formed was collected by filtration, washed with cold ethanol, and then crystallized from ethanol to give **10** as red crystals, m.p. 136–138°C; IR (cm^{-1}): 3345 (NH), 3087 (CH-aromatic), 2888–2932 (CH-aliphatic) and 1728 (ester C=O), 1712 (C=O acetyl); ^1H NMR (δ ppm): 1.0 (s, 3H, CH_3), 1.5 (t, 3H, $\underline{CH_3}CH_2$—), 2.6 (s, 3H, $CO\underline{CH_3}$), 4.3 (q, 2H, $CH_3\underline{CH_2}$—), 7.0–8.2 (m, 6H, indole-NH and indole protons). Anal. calcd./found for $C_{20}H_{17}N_3O_3S$ (379.43) (%): C, 63.31/63.1; H, 4.52/4.7; N, 11.07/11.2; S, 8.45/8.5.

1-[3-amino-4-(1*H*-indol-3-yl)-6-methyl-1*H*-pyrazolo[3,4-*b*]-pyridin-5-yl]ethanone Hydrazone 11 (General Procedure)

A solution of **5**, **10**, or **12** (0.01 of each) and hydrazine hydrate (15 mL) in ethanol was heated under reflux for 11–15 h until the odor of H_2S, CH_3SH or EtOCOSH ceased. The reaction mixture evaporated to one third of its volume. The product that formed was collected by filtration, washed with cold ethanol, and then crystallized from ethanol to give **10** as yellow crystals, m.p. 133–136°C; IR (cm^{-1}): 3458, 3423, 3345 (NH_2 and NH), 3089 (CH-aromatic), 2878–2912 (CH-aliphatic) and 1705 (acetyl CO); ^1H NMR (δ ppm): 1.0 (s, 3H, CH_3–), 2.3 (s, 3H, $CO\underline{CH_3}$), 5.3 (s, br., 2H, NH_2), 7.1–8.4 (m, 7H, indole-NH, pyrazole-NH and indole protons) Anal. calcd./found for $C_{17}H_{15}N_5O$ (305.33) (%): C, 66.87/67.0; H, 4.95/5.0; N, 22.95/23.1.

5-Acetyl-4-(1*H*-indol-3-yl)-6-methyl-2-(methylthio)-nicotinonitrile 12

A solution of **5** (1.56 g, 0.005 mole) and methyl iodide (1.42 g, 0.01 mole) and potassium carbonate in a ratio of 1:2:1 in acetone (40 mL) were stirred for 7–9 hr. at r.t. The reaction mixture was filtrated and then evaporated to half of its volume, and the obtained product was collected by filtration, washed with cold water, and then crystallized from ethanol to give **12** as yellow crystals, m.p. 100–103°C; IR (cm^{-1}): 3323 (NH-indole), 3087 (CH-aromatic), 2878–2923 (CH-aliphatic), 2218 (CN) and 1713 (CO acetyl); ^1H NMR (δ ppm): 1.0 (s, 3H, CH_3–), 1.5 (s, 3H, $S\underline{CH_3}$), 2.3(s, 3H, $CO\underline{CH_3}$) and 7.0-8.2 (m, 6H, indole-NH and indole

protons). Anal. calcd./found for $C_{18}H_{15}N_3OS$ (321.39) (%): C, 67.27/67.1; H, 4.70/4.7; N, 13.07/31.1; S, 9.98/10.1.

Synthesis of 14a and 15b,c (General Procedure)

A solution of **5** (1.56 g, 0.005 mole) and each of 2-bromo-1-phenylethanone, 2-bromo-1-(4-chlorophenyl)ethanone, and 2-bromo-1-(4-methylphenyl)ethanone **13a–c** (0.99 g, 1.17 g, and 1.06 g, respectively; 0.005 mole of each) in methanol containing sodium methoxide (prepared by 0.005 atom of sodium in 50 mL methanol) was heated under reflux for 3–5 h. The products that formed were collected by filtration, washed with cold ethanol, and then crystallized from ethanol to give **14a** and **15b,c**, respectively.

Synthesis of 5-Acetyl-4-(1*H*-indol-3-yl)-6-methyl-2-[(2-oxo-2-phenyl-ethyl)thio]nicotinonitrile 14a

As yellow crystals, m.p. 226–228°C; IR (cm^{-1}): 3345 (NH-indole), 3089 (CH-aromatic), 2889–2933 (CH-aliphatic), 2220 (CN) and 1712 (ketonic C=O); ^1H NMR (δ ppm): 1.1 (t, 3H, CH_3—), 2.4 (s, 3H, CO$\underline{CH_3}$), 3.3 (s, 2H, —CH_2—), 7.2–8.4 (m, 11H, indole-NH, indole and aromatic protons). Anal. calcd./found for $C_{25}H_{19}N_3O_2S$ (425.50) (%): C, 70.57/70.6; H, 4.50/4.4; N, 9.88/9.9; S, 7.54/7.6.

1-[3-Amino-2-(4-chlorobenzoyl)-4-(1*H*-indol-3-yl)-6-methylthieno[2,3-*b*]pyridin-5-yl]ethanone 15b

As brown crystals, m.p. 190–193°C; IR (cm^{-1}): 3456, 3364, 3335 (NH_2 and NH), 3093 (CH-aromatic), 2878–2921 (CH-aliphatic) and 1715 (ketonic C=O); ^1H NMR (δ ppm): 1.2 (s, 3H, CH_3—), 2.6 (s, 3H, CO$\underline{CH_3}$), 5.3 (s, 2H, NH_2), 7.1–8.3 (m, 10H, indole-NH, indole and aromatic protons). Anal. calcd./found for $C_{25}H_{18}ClN_3O_2S$ (459.94) (%): C, 65.28/65.3; H, 3.94/4.0; N, 9.14/9.2; S, 6.97/7.0; Cl, 7.71/7.8.

1-[3-Amino-2-(4-methylbenzoyl)-4-(1*H*-indol-3-yl)-6-methylthieno-[2,3-*b*]pyridin-5-yl]ethanone 15c

As red crystals, m.p. 322–325°C; IR (cm^{-1}): 3466, 3353, 3332 (NH_2 and NH), 3090 (CH-aromatic), 2879–2928 (CH-aliphatic) and 1712 (ketonic C=O); ^1H NMR (δ ppm): 1.2 (s, 6H, two CH_3—), 2.3 (s, 3H, CO$\underline{CH_3}$), 5.1 (s, 2H, NH_2), 7.0–8.4 (m, 10H, indole-NH, indole and aromatic protons). Anal. calcd./found for $C_{26}H_{21}N_3O_2S$ (439.52) (%): C, 71.05/71.1; H, 4.82/4.9; N, 9.56/9.6; S, 7.30/7.4.

Synthesis of 1-[3-Amino-2-benzoyl-4-(1*H*-indol-3-yl)-6-methylthieno-[2,3-*b*]pyridin-5-yl]ethanone 15a

A solution of **14a** in ethanol (50 mL) containing 10 mL 10% potassium hydroxide was heated under reflux for 5–7 h. The reaction mixture was then poured onto ice-cold water, and the product that formed was collected by filtration, washed with water, and then crystallized from ethanol to give **15a** as yellow crystals, m.p. 243–245°C; IR (cm^{-1}): 3453, 3342, 3328 (NH_2 and NH), 3099 (CH-aromatic), 2869–2932 (CH-aliphatic) and 1715 (ketonic C=O); ^1H NMR (δ ppm): 1.0 (s, 3H, CH_3—), 2.5 (s, 3H, $CO\underline{CH_3}$), 5.3 (s, 2H, NH_2), 7.1–8.3 (m, 11H, indole-NH, indole and aromatic protons). Anal. calcd./found for $C_{25}H_{19}N_3O_2S$ (425.50) (%): C, 70.57/70.6; H, 4.50/4.5; N, 9.88/9.9; S, 7.54/7.4.

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