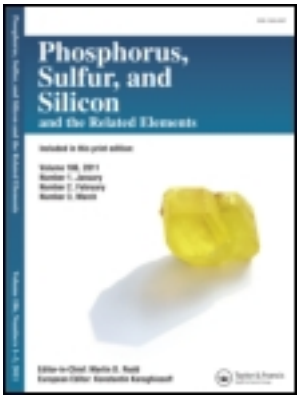

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis, Reactions, and Characterization of 6-Amino-4-(Benzo[b]Thiophen-2-YL)-2-Thioxo-1, 2-Dihydropyridine-3, 5-Dicarbonitrile

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SYNTHESIS, REACTIONS, AND CHARACTERIZATION OF 6-AMINO-4-(BENZO[b]THIOPHEN-2-YL)-2-THIOXO-1, 2-DIHYDROPYRIDINE-3, 5-DICARBONITRILE

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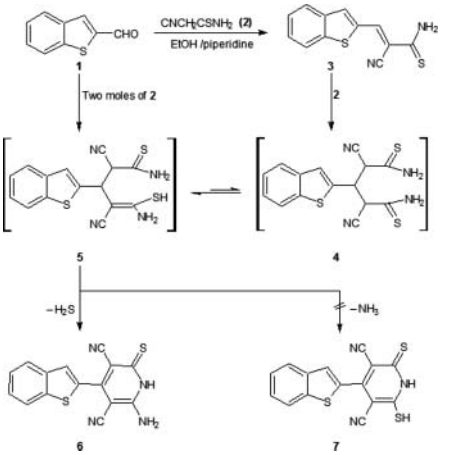
GRAPHICAL ABSTRACT



Abstract *Benzothiophene -2- carbaldehyde **1** reacted with 2-cyanoethanethioamide **2** in 1:2 molar ratios to give the corresponding 6-amino-4-(benzo[b]thiophen-2-yl)-2-thioxo-1, 2-dihydropyridine-3,5-dicarbonitrile **6**. The synthetic potentiality of compound **6** was investigated via its reaction with active halogen-containing reagents to afford the corresponding thieno[2,3-b]pyridine derivatives **11a,b**, **14**, **16**, and **19**. Also, compound **6** reacted with hydrazine hydrate to give the pyrazolo[3,4-b]pyridine derivative **21**. Compound **21** condensed with 4-(2-thienyl)benzaldehyde to afford pyrazolo[3,4-b]pyridine derivative **23.** Structural elucidation of all the newly synthesized heterocyclic compounds was based on elemental analyses, IR, ^{1}H NMR, and mass spectra.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords 3-(Benzo[b]thiophen-2-yl)-2-cyanoprop-2-enethioamide; 2-cyanoethanethioamide; thieno[2,3-b]pyridine and pyrazolo[3,4-b]pyridine

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INTRODUCTION

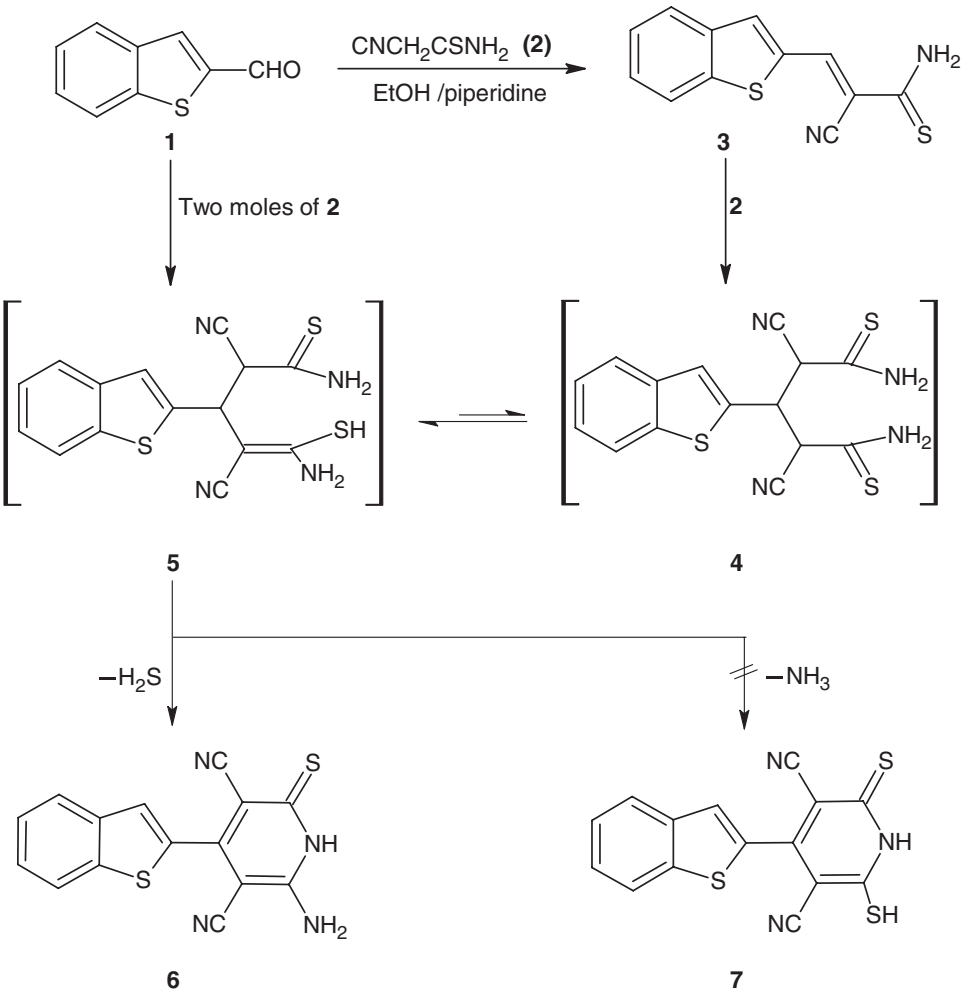
Pyridine-2(1H)-thiones containing two CN groups, NH, and C=S moieties are promising synthons in organic synthesis, in particular, for obtaining biologically active compounds. In conjunction with our previous work,[1–12] and the reported biological activity of each of 2-thioxopyridines,[13–15] thienopyridines,[16,17]and benzothiophene,[18] we were interested to synthesize several derivatives of these ring systems required for chemical transformations and a medicinal chemistry program.

RESULTS AND DISCUSSION

The present work reports a possible routes to the synthesis of 6-amino-4-(benzo[b]thiophen-2-yl)-2-thioxo-1, 2-dihydropyridine-3, 5-dicarbonitrile **6** as a starting material. It has been found that benzothiophene 2 carbaldehyde **1** reacted with 2-cyanoethanethioamide **2** to afford 3-(benzo[b]thiophen-2-yl)-2-cyanoprop-2-enethioamide **3** which in turn reacted with a second mole of **2** to give the reaction product **6** via the nonisolable structures **4** and **5**. The IR (cm^{-1}) of this reaction product showed the bands of NH_2, NH, and CN functions, and its ^1H NMR (δ ppm) revealed the signals of NH_2, NH, and aromatic protons. Moreover, its mass spectrum gave m/z = 308, which corresponded to the molecular formula $C_{15}H_8N_4S_2$ of the assigned structure (cf. Experimental section and Scheme 1). By considering the previously mentioned data in addition to the data of elemental analyses, compound **7** was rejected and we concluded that this reaction product underwent auto-oxidation under the experimental conditions to afford **6**, which was formulated as 6-amino-4-(benzo[b]thiophen-2-yl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile. (cf. Scheme 1 and Experimental section).To authenticate, compound **6** was also obtained by the reaction of both **1** and **2** in 1:2 molar ratio in a one pot reaction. It is remarkable to report here that compound **6** obtained through both pathways was identical in all physical and chemical properties.

The synthetic potential compound of **6** was investigated through its reaction with several active halogen containing compounds, e.g., 2-chloro-N-(4-bromophenyl) acetamide, chloroacetonitrile (**8a,b**). Thus, it has been found that compound **6** reacted with 2-chloro-N-(4-bromophenyl)acetamide (**8a**) in 1:1 ratio in methanolic sodium methoxide through dehydrochlorination to afford the corresponding 2-{[6-amino-4-(benzo[b]thiophen-2-yl)-3,5-dicyanopyridin-2-yl]sulfanyl}N-(4-bromophenyl)acetamide **9a**. The IR spectrum of **9a** showed the presence of absorption bands at 2224 and 1672 cm^{-1} due to CN and CO functions, respectively. The structure of compound **9a** was further elucidated via its cyclization in ethanolic potassium hydroxide solution to afford the corresponding thieno[2,3-b]pyridine derivative **11a** via the nonisolable intermediate **10a**.

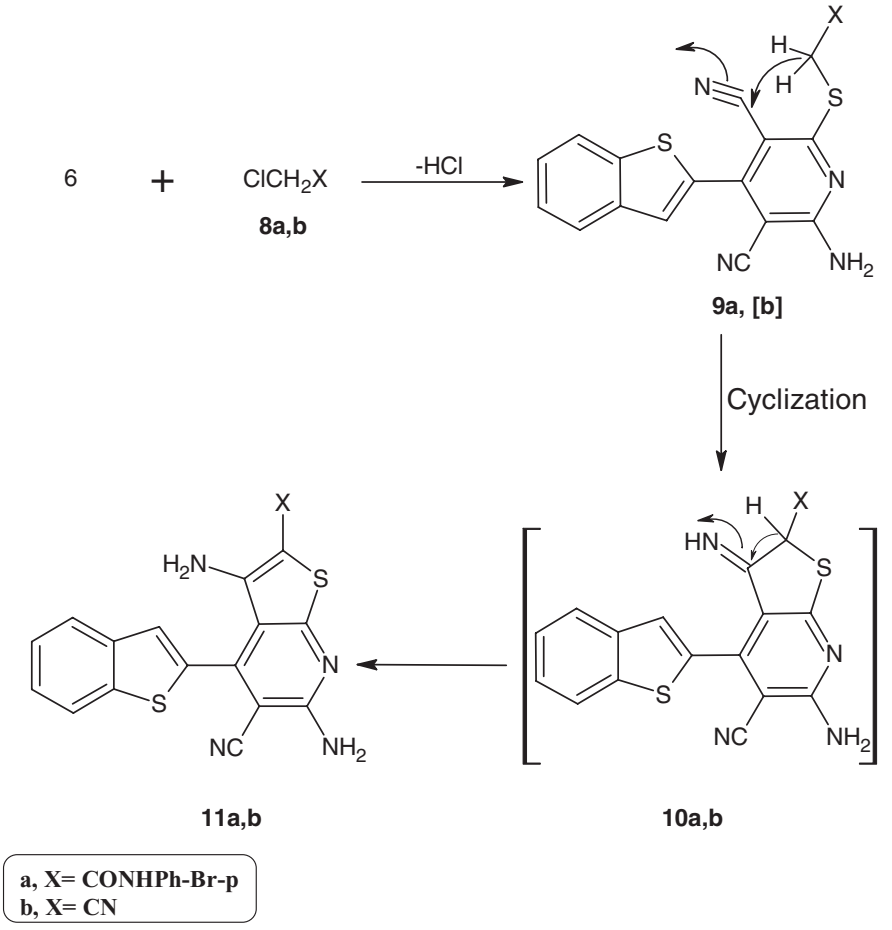
The ^1H NMR spectrum of compound **11a** revealed the signals at 6.10 and 9.40 ppm corresponded to $2NH_2$ and NH protons, respectively. Moreover, its mass spectrum gave the parent peak at m/z = 520, which corresponded to the molecular formula $C_{23}H_{14}BrN_5OS_2$ of the assigned structure, in addition to several peaks corresponding to fragments that confirm its structure (cf. Experimental section and Scheme 2). In a similar manner, compound **6** reacted with chloroacetonitrile (**8b**) under the same reaction conditions to afford directly the corresponding thieno[2,3-b]pyridine derivatives **11b**. The IR (cm^{-1}) of the reaction product showed bands corresponding to NH_2 and CN functions. On the other hand, its ^1H NMR spectrum revealed signals of NH_2 protons. Moreover, its mass spectrum gave the parent peak at m/z = 346, which corresponded to the molecular formula $C_{17}H_9N_5S_2$ of



Scheme 1

the assigned structure **11b**. The formation of compound **11b** proceeded via the nonisolable products **9b** and **10b**, respectively (cf. Scheme 2 and Experimental part).

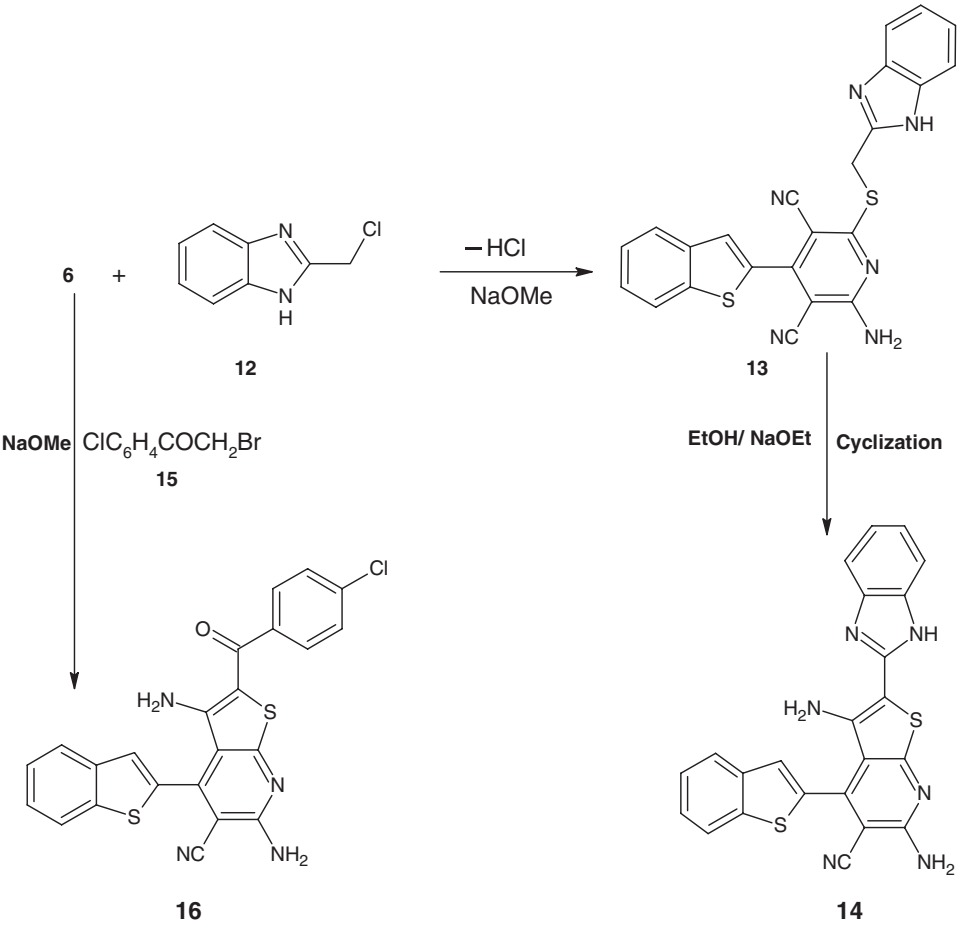
The chemical reactivity and synthetic potentiality of compound **6** were further investigated through its reaction with chloromethylbenzimidazole **12** to afford the reaction product **13** formed by dehydrochlorination. The IR of the reaction product **13** showed the bands of NH_2, NH, and CN functions and its ^1H NMR spectrum exhibited a singlet signal at $\delta = 4.15$ ppm assignable for SCH_2. Moreover, the mass spectrum of this reaction product gave the parent peak at m/z = 438, which corresponding to the molecular weight of the assigned structure, (cf. Scheme 3 and Experimental part). The structure of compound **13** was further elucidated via its cyclization to the corresponding thieno[2,3-b]pyridine **14** upon boiling in ethanol containing potassium hydroxide. Similarly, compound **6** reacted with *p*-chlorophenacyl bromide **(15)** under the same experimental conditions to afford directly the corresponding thieno[2,3-b] pyridine derivative **16**. The ^1H NMR spectrum of



Scheme 2

compound **16** exhibited the broad signal at $\delta = 7.03$ ppm assignable to $2NH_2$ and additional aromatic protons.

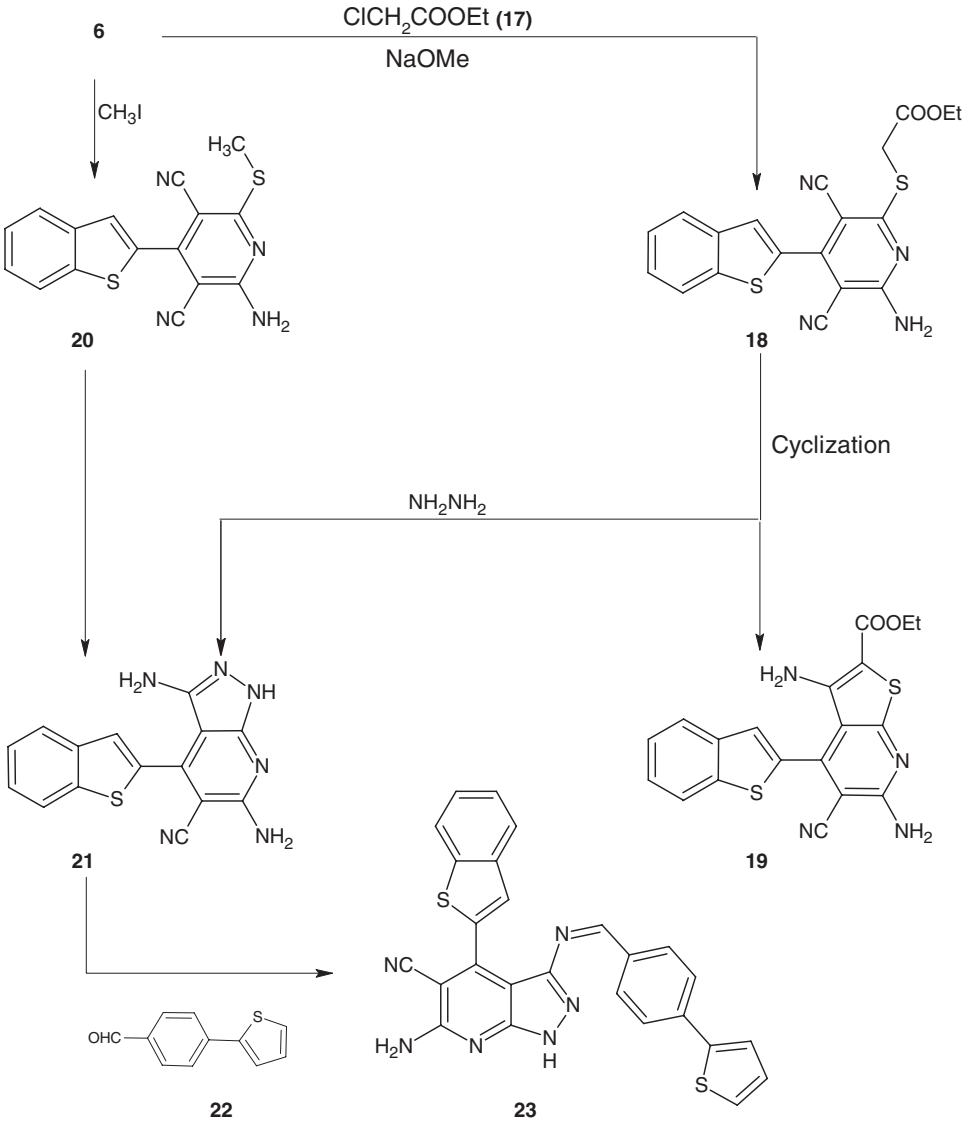
In further investigation, compound **6** reacted with ethylchloroacetate **17** in sodium methoxide solution to afford the reaction product **18** which was formed via dehydrochlorination. The IR of compound **18** showed the absorption bands corresponding to NH_2, CN, and ester CO; its ^{1}H NMR spectrum revealed the signals of the $COOCH_2CH_3$ protons. Also, ^{13}C NMR Of compound **18** was found in good agreement with the assigned structure. Considering the previously mentioned data and the data of elemental analyses, such reaction product could be formulated as {**[6-**amino-4-(benzo[b]thiophen-2-yl)-3,5-dicyanopyridin-2-yl]sulfanyl}acetate **18**. The structure of compound **18** was further elucidated via its cyclization to the corresponding ethyl 3, 6-diamino-4-(benzo[b]thiophen-2-yl)-5-cyanothieno[2,3-*b*]pyridine-2-carboxylate **19** upon boiling in ethanolic potassium hydroxide solution. Finally, it was found that compound **6** reacted with methyl iodide to afford the corresponding 2-amino-4-(benzo[b]thiophen-2-yl)-6-(methylsulfanyl) pyridine-3, 5-dicarbonitrile (**20**). Compound **20** reacted with hydrazine hydrate to give



Scheme 3

the corresponding 3, 6-diamino-4-(benzo[b]thiophen-2-yl)-1*H*- pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**21**). The ^{1}H NMR Spectrum of compound **21** showed the newly formed NH_2 and NH groups at δ = 4.59 and 11.79 ppm. Moreover, its mass spectrum gave the parent peak at m/z = 306, which corresponds to the molecular weight of the assigned structure **21**.

An authentic sample of compound **21** was obtained via the reaction of compound **18** with hydrazine hydrate and the reaction product was found to be identical in all physical and chemical properties with that given from the reaction of compound **20** with hydrazine hydrate. A chemical identification of compound **21** arose from its condensation with 4(2-thienyl) benzaldehyde (**22**) in pyridine to afford 6-amino-4-(benzo[b]thiophen-2-yl)-3-({-[4-(thiophen-2-yl)phenyl]methylidene}amino) 1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**23**).The ^{1}H NMR spectrum of this reaction product revealed signals at (δ ppm) 4.59 (br, 2H, NH_2), 7.18–7.94 (m, 12H, Ar-H's), 8.74 (s, 1H, N=CH) and 11.90 (br, 1H, NH). Its mass spectrum gave m/z = 476, which corresponds to the molecular weight of compound **23**.



Scheme 4

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra from KBr discs were recorded on a Bruker Vector 22 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined in DMSO-d_6 and $CDCl_3$ at 300 MHz on a Varian Mercury VX spectrometer using TMS as an internal standared. Chemical shifts are expressed as δ or ppm. Mass spectra were recorded on a GCMS-QP 1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

Synthesis of Compound 6 (General Procedures)

Method A. An equimolar amount of arylidine **3** (0.24 g, 1.0 mmol), cyanoethanethioamide (**2**) (0.10 g, 1.0 mmol) and piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 5 h. The excess of ethanol was evaporated under vacuum. The solid obtained was collected by filtration and crystallized from ethanol to give compound **6**.

Method B. A mixture of benzothiophene-2-carbaldehyde (0.16g, 1.0 mmol), cyanoethane-thioamide (**2**) (0.20 g, 2.0 mmol), and piperdine (0.5 mL) in ethanol (30 mL) was heated under reflux for 5 h. The excess of ethanol was evaporated under vacuum. The solid obtained was collected by filtration and crystallized from ethanol to give compound **6**.

6-Amino-4-(benzo[b]thiophen-2-yl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile 6: Yellow crystals, mp 270 °C; **IR** (ν cm^{-1}): 3447, 3347, 3227, 3141 (NH_2 and NH), 2202 (CN at C-3), 2178 (CN at C-5), and 1538 (C=S); **MS** (m/z): 308 (M^+, 100% corresponding to the molecular formula $C_{15}H_8N_4S_2$ of the assigned structure), 307 (M^+- H, 73.6%), 290 (M^+ -NH_2, 2H, 8.8%), 264(M^+ -CN, NH_2, 2H, 16.5%); **^{1}H NMR** (δ ppm): 6.80 (br, 2H, NH_2), 7.41–8.08 (m, 5H, aromatic H's), and 8.60 (br, 1H, NH). Anal. for $C_{15}H_8N_4S_2$ (308), Calcd./Found (%): C (58.42/58.32) H (2.61/2.50) N (18.17/17.92) S (20.80/20.60).

Synthesis of compounds 9a, 11b, 13, 16, 18, and 20: A solution of **6** (0.5 mmol, 0.15 g) and the appropriate reagent **8a** (0.5 mmol, 0.124 g), **8b** (0.5mmol, 0.04g), **12** (0.5 mmol, 0.83 g), **15** (0.5 mmol, 0.12 g), **17** (1 mmol, 0.124g), and methyl iodide (2 mmol, 0.284 g) in methanol containing sodium methoxide (prepared by 0.6 g of sodium in 40 mL methanol) was stirred for 5 h. The product that formed was collected by filtration, washed with cold ethanol, and then recrystallized from ethanol to give **9a**, **11b**, **13**, **16**, **18**, **and 20**, respectively.

2-{[6-Amino-4-(benzo[b]thiophen-2-yl)-3, 5-dicyanopyridin-2-yl]sulfanyl}-*N*-(4-bromophenyl)acetamide 9a: Yellow crystals, mp 270 °C; **IR** (ν cm^{-1}): 3447, 3347, 3227, 3141 (NH_2 and NH), 2202 (CN) and 1670 (amidic CO); **^{1}H NMR** (δ ppm): 4.73 (s, 2H, SCH_2); 6.10 (br, 2H, NH_2); 7.34–8.13 (m, 9H, aromatic H's) and 9.20 (br, 1H, NH); Anal. for $C_{23}H_{14}BrN_5OS_2$ (520), Calcd./Found (%): C (53.08/53.20) H (2.71/2.50) Br (15.35/15.25) N (13.46/13.30) S (12.32/12.20).

3,6-Diamino-4-(benzo[b]thiophen-2-yl)thieno[2,3-*b*]pyridine-2,5-dicarbonitriles 11b: Yellow crystals, mp 170 °C; **IR** (ν cm^{-1}): 3450, 3336, 3221 (NH_2), and 2216, 2191 (2CN); **MS** (m/z): 346 (M^+-1, 0.2% corresponding to the molecular formula $C_{17}H_9N_5S_2$); **^{1}H NMR** (δ ppm): 6.10 (br, 4H, $2NH_2$) and 7.51–8.23 (m, 5H, aromatic H's). Anal. for $C_{17}H_9N_5S_2$ (347), Calcd./Found (%): C (58.78/58.60) H (2.59/2.50) N (20.17/19.80) S (18.44/18.30).

2-Amino-6-[(1*H*-benzimidazol-2-ylmethyl)sulfanyl]-4-(benzo[b]thiophen-2-yl)pyridine-3,5-dicarbonitrile 13: White crystals, mp 300 °C; **IR** (ν cm^{-1}): 3327, 3164 (NH_2 and NH), and 2208 (CN); **MS** (m/z): 438 (M^+, 100% corresponding to the molecular formula $C_{23}H_{14}N_6S_2$ of the assigned structure), 437 (M^+- H, 81.1%), and 319 (M^+- benzimidazolyl ring, 2H, 73.6%). **^{1}H NMR** (δ ppm): 4.15 (s, 2H, SCH_2), 4.73 (s, 2H, NH_2), and 7.15–8.13 (m, 10H, aromatic H's, and NH). Anal. for $C_{23}H_{14}N_6S_2$(438), Calcd./Found (%): C (62.99/62.90) H (3.22/3.12) N (19.16/18.90) S (14.62/14.50).

3,6-Diamino-4-(benzo[b]thiophen-2-yl)-2-[(4-chlorobenzoyl)]thieno[2,3-*b*]pyridine-5-carbonitrile 16: Red crystals, mp >300 °C; **IR** (ν cm^{-1}): 3454, 3343 (NH_2) and 2215 (CN); **^{1}H NMR** (δ ppm): 7.03 (br, 4H, $2NH_2$) and 7.51–8.18 (m, 9H,

aromatic H's). Anal. For $C_{23}H_{13}ClN_6OS_2$ (460), Calcd./Found (%): C (59.93/59.90) H (2.84/2.7) Cl (7.69/7.5) N (12.15/12.0) S (13.91/13.60).

{**[6-Amino-4-(benzo[b]thiophen-2-yl)-3,5-dicyanopyridin-2-yl]sulfanyl**} **acetate 18:** Yellow crystals, mp 220 °C; **IR** (ν cm^{-1}): 3422, 3326, 3225 (NH_2), 2209 (CN), and 1724 (ester CO); **^{1}H NMR** (δ ppm): 1.23 (t, 3H, –$CH_2\underline{CH_3}$, J = 7.2Hz); 4.13 (q, 2H, –$\underline{CH_2}CH_3$, J = 7.2 Hz); 4.22 (s, 2H, SCH_2); and 7.48–8.12 (m, 7 H, aromatic H's, and NH_2); **^{13}C NMR** (DMSO-d_6) (δ ppm): 13.8, 31.9, 44.9, 61.2, 86.6, 93.5, 114.5, 120.7, 124.6, 125.9, 127.4, 132.9, 138.5, 140.1, 150.8, 159.3, 165.7, 167.7, and 184.3. Anal. for $C_{19}H_{14}N_4O_2S_2$(394), Calcd./Found (%): C (57.85/57.62) H (3.58/3.40) N (14.20/14.10) S (16.26/16.30).

2-Amino-4-(benzo[b]thiophen-2-yl)-6-(methylsulfanyl)-pyridine-3,5-dicarbonitrile 20: Pale yellow crystals mp 250 °C; **IR** (ν cm^{-1}): 3415, 3326, 3226 (NH_2), 2210 (CN); **^{1}H NMR** (δ ppm):2.43 (s, 3H, CH_3); 6.80 (br, 2H, NH_2); 7.41–8.07 (m, 5H, aromatic H's). Anal. for $C_{16}H_{10}N_4S_2$ (322), Calcd./Found (%): C (63.35/63.30) H (3.11/3.10) N (17.39/17.20) S (19.87/19.60).

Synthesis of compounds 11a, 14, and 19: A solution of the compounds **9a**, **13**, or **18** (0.5 mmol, 0.26 g for **9a**, 0.22 g for **13** and 0.20 g for **18**) in ethanol (30 mL) and potassium hydroxide was heated under reflux for 4 h. The mixture was cooled, poured onto ice-cold water, and acidified with hydrochloric acid. The solid products were collected by filtration, washed with water, and crystallized from ethanol to give compounds **11a**, **14**, and **19**, respectively.

3,6-Diamino-4-(benzo[b]thiophen-2-yl)-*N*-(4-bromophenyl)-5-cyanothieno-[2,3-*b*]pyridine-2-carboxamide 11a: Yellow crystals, mp 310 °C; **IR** (ν cm^{-1}): 3464, 3324, 3215 (NH_2 and NH) and 2228 (CN); **MS** (m/z): 522 (M^++2, 5.4%), 521 (M^++1, 8.9%), 520 (M^+, 21.4% corresponding to the molecular formula $C_{23}H_{14}BrN_5OS_2$ of the assigned structure), 519 (M^+- H, 12.7%), 349 (M^+-NHPh-Br, 100%) and 321 (M^+-CONHPh-Br, 17.3%); **^{1}H NMR** (δ ppm): 6.10 (br, 4H, $2NH_2$); 7.43–8.16 (m, 9H, aromatic H's) and 9.40 (br, 1H, NH); Anal. for $C_{23}H_{14}BrN_5OS_2$ (520), Calcd./Found (%): C (53.08/53.10) H (2.71/2.60) Br (15.35/15.15) N (13.46/13.20) S (12.32/12.20).

3,6-Diamino-2-(1*H*-benzimidazol-2-yl)-4-(benzo[b]thiophen-2-yl)thieno[2,3-*b*]pyridine-5-carbonitrile 14: Red crystals, mp 160 °C; **IR** (ν cm^{-1}): 3339, 3213 (NH_2 and NH), 3056 (aromatic CH) and 2214 (CN). **^{1}H NMR** (**δ ppm**): 6.80 (br, 4H, $2NH_2$) and 7.15–8.13 (m, 10H, aromatic H's and NH). Anal. for $C_{23}H_{14}N_6S_2$ (438); Calcd./Found (%): C (62.99/62.80) H (3.22/3.20) N (19.16/18.80) S (14.62/14.40).

Ethyl 3, 6-diamino-4-(benzo[b]thiophen-2-yl)-5-cyanothieno[2,3-*b*]pyridine-2-carboxylate 19: Yellow crystals, mp 240 °C**; IR** (ν cm^{-1}): 3419, 3324, 3225 (NH_2), 2209 (CN) and 1690 (ester CO with H-bonding); **^{1}H NMR** (δ ppm): 1.32 (t, 3H, –$CH_2\underline{CH_3}$, J = 6.9 Hz); 4.32 (q, 2H, –$\underline{CH_2}CH_3$, J = 6.9Hz); 6.11 (br, 4H, $2NH_2$) and 7.52–8.26 (m, 5 H, aromatic H's); Anal. for $C_{19}H_{14}N_4O_2S_2$ (394), Calcd./Found (%): C (57.85/57.70) H (3.58/3.40) N (14.20/14.10) S (16.26/16.10).

Synthesis of compound 21: A solution of compound **18** (0.39 g, 1 mmol) or **20** (0.322 g, 1 mmol) in hydrazine hydrate (15 mL) and ethanol (20 mL) was heated under reflux for 5 h; the excess solvents were evaporated and cooled. The solid was collected by filtration, dried, and crystallized from ethanol to give **21**.

3,6-Diamino-4-(benzo[b]thiophen-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 21: Yellow crystals, mp 300 °C; **IR** (ν cm^{-1}): 3370, 3317, 3194 (NH_2 and NH) and 2214 (CN); **MS** (m/z): 306 (M^+, 80%), 305 (M^+ -1, 50%); **^{1}H NMR** (δ ppm): 4.59 (s, 2H, NH_2)*; 6.86(s, 2H, NH_2)*, 7.47–8.13 (m, 5H, aromatic H's), and 11.79 (br, 1H,

NH)*. Anal. for $C_{15}H_{10}N_6S$ (306), Calcd./Found (%): C (58.81/58.50) H (3.29/3.10) N (27.43/27.20) S (10.47/10.30).

Synthesis of compound 23: A solution of **21** (0.306 g, 1 mmol) and **22** (0.188 g, 1 mmol) in pyridine (15 mL) and ethanol (20 mL) was heated under reflux for 5h; the excess solvents were evaporated and cooled. The solid was collected by filtration, dried, and crystallized from ethanol to give **23**.

6-Amino-4-(benzo[b]thiophen-2-yl)-3-({-[4-(thiophen-2-yl)phenyl]methyl-idene}amino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 23: Yellow crystals, mp256 °C; **IR** (ν cm^{-1}): 3370, 3317, 3194 (NH_2 and NH), and 2214 (CN); **MS** (m/z): 476(M^+, 7.4%); **^{1}H NMR** (δ ppm): 4.59 (s, 2H, NH_2)*; 7.18–7.94 (m, 12H, aromatic H's), 8.74 (s, 1H, N=CH); and 11.90 (br,1H, NH)*. Anal. for $C_{26}H_{16}N_6S_2$ (476), Calcd./Found (%): C (65.55/65.50) H (3.36/3.20) N (17.65/17.40) S (13.45/13.30).

*Lost after D_2O exchange.

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