Synthesis of Novel Bis[(5-cyanopyridin-6-yl)sulfanyl]butanes, Bis(2-*S*-alkylpyridines), and Bis(3-aminothieno[2,3-*b*]pyridines) Incorporating 2,6-Dibromophenoxy Moiety

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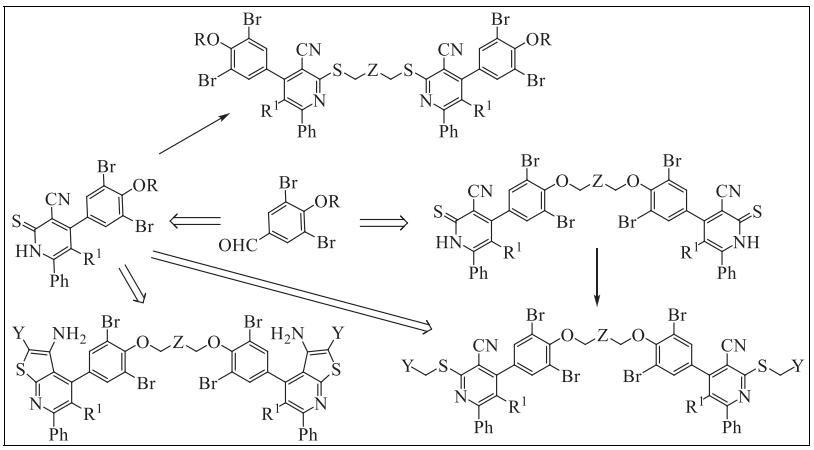
Received November 9, 2017
DOI 10.1002/jhet.3239
Published online 17 July 2018 in Wiley Online Library (wileyonlinelibrary.com).



The synthetic precursors pyridine-2(1*H*)-thiones **2a**,**b** and bis(pyridine-2(1*H*)-thione) derivative **4**, using aldehydes **1a**,**b** incorporating 2,6-dibromophenoxy moiety, were prepared and used to synthesize the novel target materials bis[(5-cyanopyridin-6-yl)sulfanyl]butanes **5a**,**b**, bis(2-*S*-alkylpyridines) **8a**,**b**, and bis(3-aminothieno[2,3-*b*]pyridines) **13a–c** through facile procedures. Characterization of the newly prepared compounds *via* elemental analyses and spectral data is established.

J. Heterocyclic Chem., **55**, 2046 (2018).

INTRODUCTION

Dihydropyridines show a wide spectrum of biological activities, such as antiarrhythmic, antihypertensive [1–4], and anticancer agents [5–7]. Moreover, pyridine-2(1*H*)-thiones show bioactivities such as antifungal and antibacterial [8].

On the other hand, 2-*S*-alkylpyridines show significant bioactivities as cardiovascular [9,10] and antioxidant [11]. Also, the thieno[2,3-*b*] pyridine derivatives show broad pharmacological activities such as antiviral [12], anti-inflammatory [13], antidiabetic [14,15], and anticancer [16–19].

This work plan was pointed to design efficient procedures for the synthesis of novel bis[(5-cyanopyridin-6-yl)sulfanyl] butanes **5a**,**b**, bis(2-*S*-alkylpyridines) **8a**,**b**, and bis(3-aminothieno[2,3-*b*]pyridines) **13a–c** incorporating 2,6-dibromophenoxy moiety of expected bioactivity using the pyridine-2(1*H*)-thione derivatives **2a**,**b** and bis(pyridine-2(1*H*)-thione) derivative **4** as synthetic precursors (Fig. 1).

RESULTS AND DISCUSSION

The first synthetic route which developed to prepare the bis(pyridine-2(1*H*)-thione) derivative **3**, incorporating 2,6-dibromophenoxy moiety, was failed. The failed route came from reacting a ternary mixture of 3,5-dibromobenzaldehyde (**1a**), 2-cyanoethanethioamide, and ethyl benzoylacetate in pyridine under reflux to prepare the corresponding ethyl 5-cyano-6-thioxo-1,6-dihydropyridine-3-carboxylate derivative **2a** whose ^{1}H-NMR spectrum revealed the signals of $\underline{CH_3}CH_2O$ (t, 3H, δ = 0.86 ppm), $CH_3\underline{CH_2}$ (q, 2H, δ = 3.98 ppm), aromatic protons in addition to NH (m, 8H, δ = 7.44–7.66 ppm), and OH (s, br, 1H, δ = 10.65 ppm). Compound **2a** was reacted with 1,4-dibromobutane in aqueous ethanolic potassium hydroxide solution under reflux to afford such a reaction product whose ^{1}H-NMR spectrum revealed the absence of NH group and the presence of two new signals at δ = 2.01 ppm (t, 4H) and δ = 2.87 ppm (t, 4H) corresponding to the introduction of $(CH_2)_4$ junction and the presence of two OH groups (s, 2H, δ = 10.52 ppm). Therefore, the product was formulated as the corresponding 1,4-bis[(5-cyano-3-ethoxycarbonylpyridin-6-yl)sulfanyl]butane derivative **5a** and not the starting material bis(pyridine-2(1*H*)-thione) derivative **4** (Scheme 1 and Experimental section). The formation of **5a** may be attributed to the higher nucleophilicity of *S*-atom at 6-position than *O*-atom at 4-(3,5-dibromo-4-hydroxyphenyl) moiety.

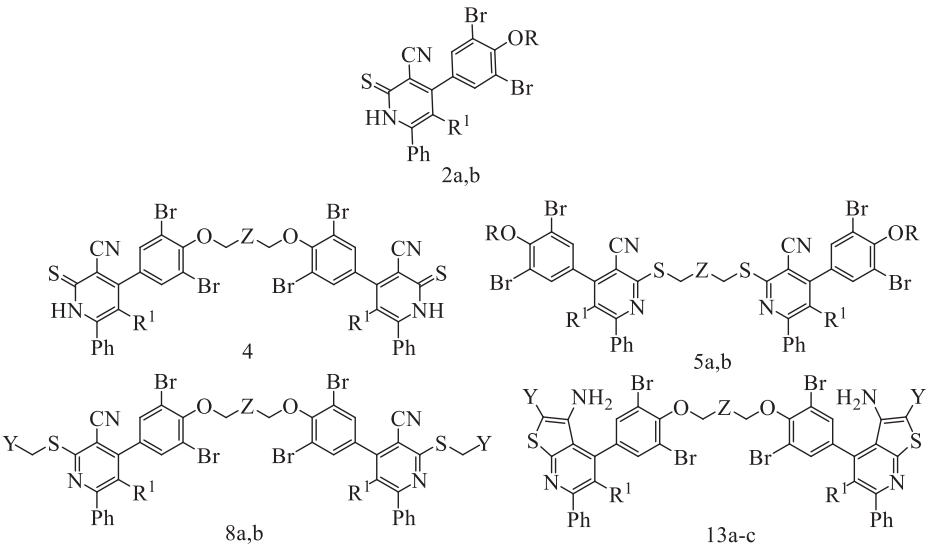
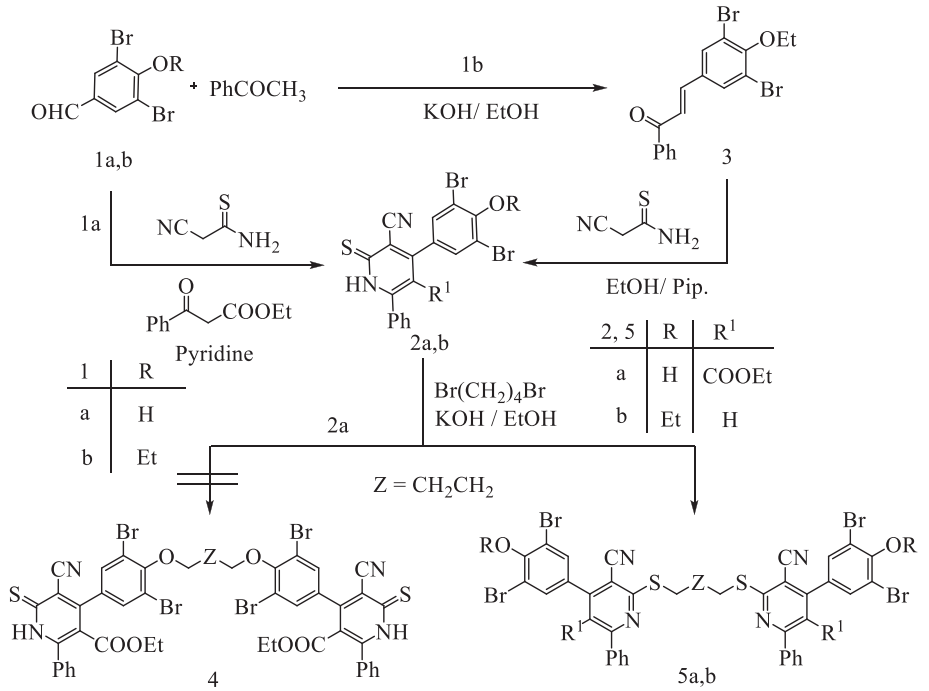


Figure 1. Structure of the synthetic precursors pyridine-2(1*H*)-thiones **2a**,**b** and bis(pyridine-2(1*H*)-thione) derivative **4** and the target materials bis[(5-cyanopyridin-6-yl)sulfanyl]butanes **5a**,**b**, bis(2-*S*-alkylpyridines) **8a**,**b**, and bis(3-aminothieno[2,3-*b*]pyridines) **13a–c.**

Scheme 1. Synthesis of 1,4-bis[(3-cyano-6-phenylpyridin-2-yl)sulfanyl]butanes **5a**,**b.**



On the other hand, α,β-unsaturated carbonyl derivative **3**, prepared *via* reacting 3,5-dibromo-4-ethoxybenzaldehyde (**1b**) with acetophenone in ethanolic potassium hydroxide solution with stirring, reacted with 2-cyanoethanethioamide in absolute ethanol containing a catalytic amount of piperidine under reflux to afford the corresponding pyridine-2(1*H*)-thione derivative **2b** whose ^{1}H-NMR spectrum revealed the signals of $\underline{CH_3}CH_2O$ (t, 3H, δ = 1.46 ppm), $CH_3\underline{CH_2}$ (q, 2H, δ = 4.15 ppm), and aromatic protons in addition to NH (m, 9H, δ = 7.42–8.14 ppm). Then, **2b** reacted with 1,4-dibromobutane to afford the corresponding 1,4-bis[(3-cyano-4-ethoxyphenylpyridin-2-yl)sulfanyl]butane derivative **5b** whose ^{1}H-NMR spectrum revealed the absence of NH

group and the presence of two $S\underline{CH_2}CH_2$ (t, 4H, δ = 1.95 ppm) and two $SCH_2\underline{CH_2}$— (t, 4H, δ = 2.87 ppm) (Scheme 1 and Experimental section).

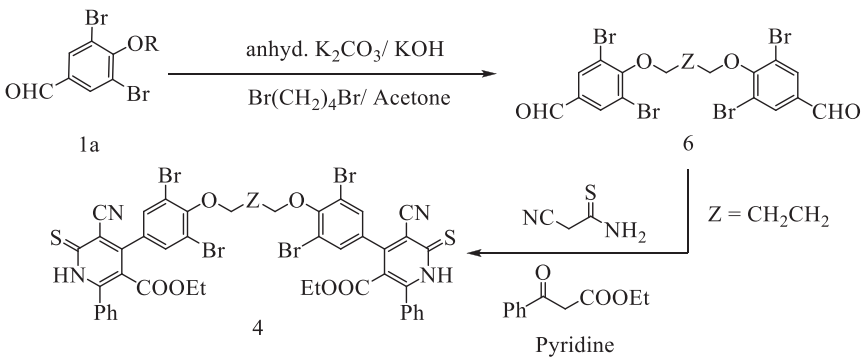
The failure of the first synthetic route to prepare bis(pyridine-2(1*H*)-thione) derivative **4** stimulate our interest to design another route *via* reacting **1a** with 1,4-dibromobutane in dry acetone containing anhydrous potassium carbonate and potassium hydroxide under reflux to afford the novel 1,4-bis(4-formylphenoxy) butane derivative **6** ^{1}H-NMR spectrum revealed the absence of OH signal and the presence of signals of $OCH_2\underline{CH_2}\underline{CH_2}CH_2O$ (m, 4H, δ = 2.10 ppm), $O\underline{CH_2}CH_2CH_2\underline{CH_2}O$ (t, 4H, δ = 4.16 ppm), and two $C\underline{H}O$ (s, 2H, δ = 9.90 ppm) (Scheme 2 and Experimental section). Then the bis(aldehyde) **6** reacted with 2-cyanoethanethioamide and ethyl benzoylacetate in pyridine under reflux to give the corresponding bis(pyridine-2(1*H*)-thione) derivative **4** whose IR spectrum (cm^{-1}) showed the absorption bands of NH at 3417, CN at 2213, CO at 1708, and CS at 1558. Its ^{1}H-NMR spectrum revealed the signals of two $\underline{CH_3}CH_2O$ (t, 6H, δ = 0.80 ppm), $OCH_2\underline{CH_2}\underline{CH_2}CH_2O$ (m, 4H, δ = 2.09 ppm), $O\underline{CH_2}CH_2CH_2\underline{CH_2}O$ and two $CH_3\underline{CH_2}O$ (m, 8H, δ = 4.14 ppm), and aromatic protons in addition to two NH groups (m, 16H, δ = 7.51–7.94 ppm) (Scheme 2 and Experimental section).

The synthetic potential of bis(pyridine-2(1*H*)-thione) derivative **4** was demonstrated *via* its reaction with iodomethane (**7a**) in refluxing methanolic sodium methoxide solution to give the corresponding bis(2-methylsulfanylpyridine) derivative **8a** in 44% yield. The IR (cm^{-1}) spectrum of **8a** showed the absence of the absorption band of CS group, and its ^{1}H-NMR spectrum revealed the absence of the signal of NH and the presence of two SCH_3 (s, 6H, δ = 2.71 ppm).

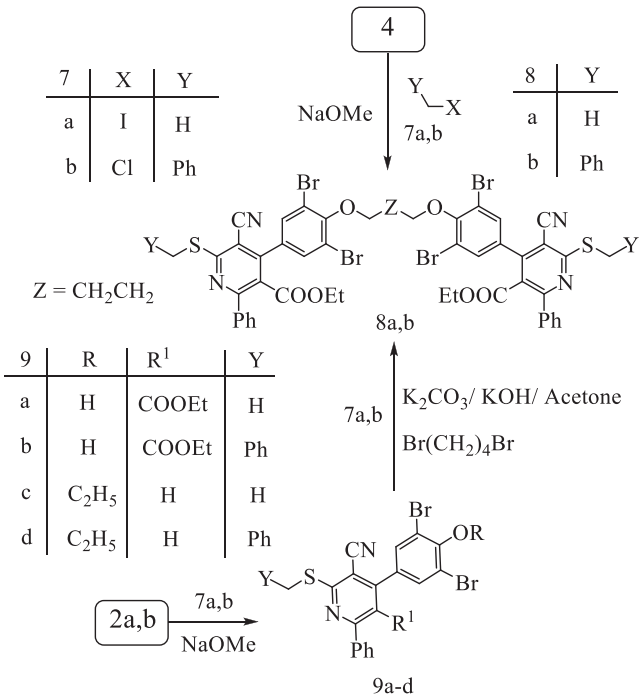
Another synthetic route was designed for the preparation of **8a** in more pure form and a higher yield%, *via* reacting pyridine-2(1*H*)-thione derivative **2a** with iodomethane (**7a**) in boiling methanolic sodium methoxide solution under reflux to give 6-methylsulfanyl-2-phenylnicotinate derivative **9a**, whose ^{1}H-NMR spectrum revealed the signal of SCH_3 (s, 3H, 2.76 δ ppm), whose potassium salt reacted with 1,4-dibromobutane in dry acetone under reflux to afford such a reaction product, in 76% yield (Scheme 3 and Experimental section). In a similar manner, bis(2-benzylsulfanylpyridine) derivative **8b** could be prepared either by the direct reaction of bis(pyridine-2(1*H*)-thione) derivative **4** with benzyl chloride (**7b**) or by the reaction of **2a** with **7b** to give 2-benzylsulfanyl-2-phenylnicotinate derivative **9b** followed by reacting its potassium salt with 1,4-dibromobutane to afford an identical reaction product in 40% and 72% yield, respectively (Scheme 3 and Experimental section). Moreover, pyridine-2(1*H*)-thione derivative **2b** reacted with each of **7a**,**b** to afford the corresponding 2-methylsulfanylpyridine derivative **9c** and 2-benzylsulfanylpyridine derivative **9d** respectively in excellent yields (Scheme 3 and Experimental section).

Unfortunately, our trails to prepare bis(thieno[2,3-*b*] pyridine) derivatives **13a–c** by the direct reaction of bis(pyridine-2(1*H*)-thione) derivative **4** with **10a–c** under various reaction conditions were failed. Therefore, another synthetic route was developed to achieve the synthesis of bis(thieno[2,3-*b*]pyridine) derivatives **13a–c** by performing the reaction of halo-containing compounds **10a–c** with pyridine-2(1*H*)-thione derivative 2**a** to afford the corresponding thieno[2,3-*b*] pyridine derivatives **12a–e** incorporating hydroxy group which then used as synthetic precursors to synthesize bis(thieno[2,3-*b*]pyridine) **13a–c** (Scheme 4). Thus, compound **2a** reacted with ethyl chloroacetate (**10a**) in ethanolic sodium acetate solution under reflux to give the corresponding ethyl 5-cyano-6-(ethoxycarbonylmethylsulfanyl) nicotinate derivative **11a** whose IR (υ cm^{-1}) showed the absorption bands corresponding to OH group at 3380, CN group at 2224 in addition to CO groups at 1726 and 1704 and whose ^{1}H-NMR revealed the signals due to two $OCH_2\underline{CH_3}$ groups (t, 6H, δ = 0.85 ppm), two $O\underline{CH_2}CH_3$ groups (q, 4H, δ = 3.93 and 4.04 ppm), and $\underline{SCH_2}$ (s, 3H, δ = 4.21 ppm) (Experimental section). Compound **11a**

Scheme 2. Synthesis of bis(pyridine-6(1*H*)-thione) derivative **4.**



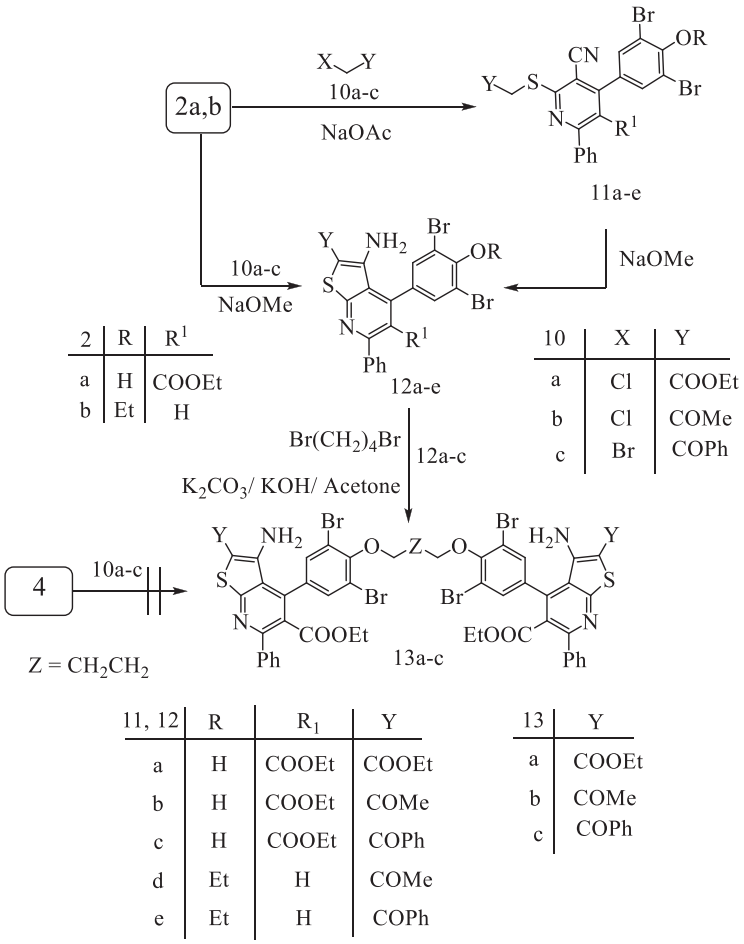
Scheme 3. Synthesis of bis(2-methyl- and 2-benzylsulfanylpyridine) derivatives **8a**,**b.**



underwent a Thrope-Ziegler reaction *via* its boiling in methanolic sodium methoxide solution to give the corresponding diethyl 3-aminothieno[2,3-*b*]pyridine-2,5-dicarboxylate derivative **12a** whose IR (υ cm^{-1}) showed the absorption bands corresponding to OH group at 3477, NH_2 group at 3347 and 3189 in addition to CO group at 1723 and 1680 and whose ^{1}H-NMR revealed the absence of SCH_2 signal and the presence of signals due to two $OCH_2\underline{CH_3}$ groups (t, 6H, δ = 0.71 and 0.83 ppm) and two $O\underline{CH_2}CH_3$ groups (q, 4H, δ = 3.78 and 3.90 ppm) (Scheme 4 and Experimental section). The structure of **12a** was more confirmed by its independent synthesis *via* another route by reacting **2a** with **10a** in boiling methanolic sodium methoxide solution under reflux to give such a reaction product which was found completely identical in all aspects with **12a** prepared *via* the first route (Scheme 4 and Experimental section). In a similar manner, thieno[2,3-*b*] pyridine derivatives **12b–e** were prepared either by the direct reaction of **2a,b** with each of chloroacetone (**10b**) and 2-bromo-1-phenylethanone (**10c**) respectively in boiling methanolic sodium methoxide solution under reflux or by the two steps synthesis *via* reacting **2a,b** with each of **10b** and **10c** respectively in ethanolic sodium acetate solution under reflux to afford the corresponding 2-*S*-alkylpyridine derivative **11c–e** respectively followed by their Thrope-Ziegler cyclization, *via* boiling in methanolic sodium methoxide solution, to afford identical reaction products. Ethyl 2-acetyl-3-aminothieno[2,3-*b*]pyridine-5-carboxylate derivative **12b** was prepared directly by the reaction of **2a** with chloroacetone (**10b**) in ethanolic sodium acetate solution under reflux without the isolation of 2-(2-oxopropylsulfanyl) nicotinonitrile [**11b**] (Scheme 4 and Experimental section).

The isolation of ethyl 3-aminothieno[2,3-*b*]pyridine-5-carboxylate derivatives **12a–c** with 3,5-dibromo-4-hydroxyphenyl moiety at 4-position facilities the reaction of their potassium salts with 1,4-dibromobutane in dry acetone to afford the corresponding bis(thieno[2,3-*b*] pyridine) derivatives **13a–c** (Scheme 4). Thus, diethyl 3-aminothieno[2,3-*b*]pyridine-2,5-dicarboxylate derivative **12a** reacted with 1,4-dibromobutane in dry acetone containing a catalytic amount of anhydrous potassium carbonate and potassium hydroxide under reflux to afford the corresponding 1,4-bis(4-[3-amino-2,5-diethoxycarbonylthieno[2,3-b]pyridin-4-yl]phenoxy) butane derivative **13a** whose ^{1}H-NMR revealed the absence of the signal corresponding to OH group and the presence of the signals due to $OCH_2\underline{CH_2}\underline{CH_2}CH_2O$ (m, 4H, δ = 2.14 ppm) and $O\underline{CH_2}CH_2CH_2\underline{CH_2}O$ (m, 4H, δ = 4.19 ppm) (Scheme 4 and Experimental section). In a similar manner, the potassium salts of thieno[2,3-*b*] pyridine derivatives **12b**,**c** were reacted with 1,4-dibromobutane to afford the corresponding bis(thieno[2,3-*b*]pyridine) derivatives **13b**,**c**, respectively (Scheme 4 and Experimental section).

Scheme 4. Synthesis of bis(thieno[2,3-*b*]pyridine) derivatives **13a–c.**



EXPERIMENTAL

Introduction. All organic solvents were acquired from commercial sources and used as received unless otherwise stated. All other chemicals were acquired from Merck, Aldrich, or Acros and used without further purification. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile Attenuated Total Reflectance sampling accessory on the Nicolet iS10 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on Varian Mercury at 300 MHz spectrophotometer using TMS as an internal standard and DMSO-d_6 as solvent and chemical shifts were expressed as δ ppm units. Elemental analyses were carried out on a EuroVector instrument C, H, N, S analyzer EA3000 Series.

General procedures and spectral data.

General procedure for compounds 2a and 4. A ternary mixture of each of **1a** (10 mmol) or **6** (5 mmol), 2-cyanoethanethioamide (10 mmol) and ethyl benzoylacetate (10 mmol) in pyridine (20 mL) was heated under reflux for 5 h. The reaction mixture was heated to evaporate half its volume, cooled, poured onto ice-cold water, and then neutralized (pH = 7) with drops of glacial acetic acid. The products so formed were collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent to yield **2a** and **4**, respectively.

Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-2-phenyl-6-thioxo-1,6-dihydro-pyridine-3-carboxylate (2a). Yellow crystals recrystallized from dioxane/ethanol mixture (62%); m.p. 216–218°C; IR (υ cm^{-1}): 3427 (OH), 3218 (NH), 2230 (CN), 1697 (CO), and 1572 (CS); ^{1}H-NMR (DMSO-d_6): δ 0.86 (t, 3H, $\underline{CH_3}CH_2$), 3.98 (q, 2H, $CH_3\underline{CH_2}$), 7.44–7.66 (m, 8H, 7 ArH's and NH) and 10.65 (s, br, 1H, OH); *Anal*. Calcd for $C_{21}H_{14}Br_2N_2O_3S$ (534.22): C, 47.21; H, 2.64; N, 5.24; S, 6.00; found: C, 47.35; H, 2.58; N, 5.05; S, 6.11%.

1,4-Bis(2,6-dibromo-4-[5-cyano-3-ethoxycarbonyl-2-phenyl-6-thioxo-1,6-dihydropyridin-4-yl]phenoxy) butane (4). Yellow crystals recrystallized from dioxane/ethanol mixture (41%); m.p. 158–160°C; IR (υ cm^{-1}): 3417 (NH), 2213 (CN), 1708 (CO), and 1558 (CS); ^{1}H-NMR (DMSO-d_6): δ 0.80 (t, 6H, 2 $\underline{CH_3}CH_2O$), 2.09 (m, 4H,

$OCH_2\underline{CH_2}\underline{CH_2}CH_2O$), 4.14 (m, 8H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}O$ and 2 $CH_3\underline{CH_2}$), and 7.51–7.94 (m, 16H, 14 ArH's and 2 NH); *Anal*. Calcd for $C_{46}H_{34}Br_4N_4O_6S_2$ (1122.53): C, 49.22; H, 3.05; N, 4.99; S, 5.71; found: C, 49.40; H, 3.23; N, 4.74; S, 5.99%.

Procedure for 4-(3,5-dibromo-4-ethoxyphenyl)-6-phenyl-2-thioxo-1,2-dihydro-pyridine-3-carbonitrile (2b). A mixture of **3** (10 mmol) and 2-cyanoethanethioamide (10 mmol) in 30 mL of ethanol containing three drops of piperidine was heated under reflux for 5 h. The solid product so formed was collected by filtration, washed with cold ethanol, and then recrystallized from ethanol/dioxane mixture as yellow crystals (70%); m.p. 226–228°C; IR (υ cm^{-1}): 3159 (NH), 2219 (CN), and 1560 (CS); ^{1}H-NMR (DMSO-d_6): δ 1.46 (t, 3H, $\underline{CH_3}CH_2$), 4.15 (q, 2H, $CH_3\underline{CH_2}$), and 7.42–8.14 (m, 9H, 8 ArH's and NH); *Anal*. Calcd for $C_{20}H_{14}Br_2N_2OS$ (490.21): C, 49.00; H, 2.88; N, 5.71; S, 6.54; found: C, 49.13; H, 2.65; N, 5.84; S, 6.32%.

Procedure for 3-(3,5-dibromo-4-ethoxyphenyl)-1-phenylprop-2-en-1-one (3). A solution of potassium hydroxide (prepared from 10 mmol of KOH in 2 mL of water) was added to a solution of acetophenone (10 mmol) in 10 mL ethanol. Then a solution of **1b** (10 mmol) in 20 mL ethanol was added portion-wisely to the reaction mixture with stirring at room temperature. After complete addition, the stirring was continued for 2 h, and the solid that formed was collected by filtration, washed with cold ethanol, and recrystallized from ethanol as colorless crystals (84%); m. p. 108–110°C; IR (υ cm^{-1}): 1674 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.42 (t, J = 6.9 Hz, 3H, $\underline{CH_3}CH_2$), 4.07 (q, J = 6.9 Hz, 2H, $CH_3\underline{CH_2}$), and 7.55–8.28 (m, 9H, 7 ArH's and $\underline{CH}$═$\underline{CH}$COPh); *Anal*. Calcd for $C_{17}H_{14}Br_2O_2$ (410.10): C, 49.79; H, 3.44; found: C, 49.62; H, 3.55%.

General procedure for compounds 5a,b. A mixture of each of **4a,b** (10 mmol), potassium hydroxide (20 mmol for **2a** or 10 mmol for **2b**), and 1,4-dibromobutane (5 mmol) in aqueous ethanol (50 mL, prepared from 25 mL of water and 25 mL of ethanol) was heated under reflux for 4 h. The products so formed (after cooling, pouring onto a beaker containing 100-g ice and neutralization by diluted HCl for **8a** or after cooling only for **8b**) were collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent to yield **5a,b**, respectively.

1,4-Bis[(5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-3-ethoxycarbonyl-2-phenyl-pyridin-6-yl)sulfanyl]butane (5a). Colorless crystals recrystallized from ethanol (55%); m.p. 98–100°C; IR (υ cm^{-1}): 3424 (OH), 2230 (CN), and 1695 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.80 (t, 6H, 2 $\underline{CH_3}CH_2O$), 2.01 (t, 4H, $S\underline{CH_2}CH_2CH_2\underline{CH_2}S$), 2.87 (t, 4H, $SCH_2\underline{CH_2}\underline{CH_2}CH_2S$), 3.96 (m, 4H, 2 $CH_3\underline{CH_2}$), 7.41–7.84 (m, 14H, ArH's), and 10.52 (s, 2H, 2 OH); *Anal*. Calcd for $C_{46}H_{34}Br_4N_4O_6S_2$ (1122.53): C, 49.22; H, 3.05; N, 4.99; S, 5.71; found: C, 49.13; H, 3.42; N, 4.83; S, 5.92%.

1,4-Bis[(3-cyano-4-(3,5-dibromo-4-ethoxyphenyl)-6-phenylpyridin-2-yl)sulfanyl]-butane (5b). Colorless crystals recrystallized from ethanol (61%); m.p. 108–110°C; IR (υ cm^{-1}): 2222 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.08 (t, 6H, 2 $\underline{CH_3}CH_2O$), 1.95 (t, 4H, $S\underline{CH_2}CH_2CH_2\underline{CH_2}S$), 2.87 (t, 4H, $SCH_2\underline{CH_2}\underline{CH_2}CH_2S$), 4.05 (q, 4H, 2 $CH_3\underline{CH_2}$), and 7.01–8.20 (m, 16H, ArH's); *Anal*. Calcd for $C_{44}H_{34}Br_4N_2O_2S_2$ (1034.51): C, 51.08; H, 3.31; N, 5.42; S, 6.20; found: C, 51.23; H, 3.47; N, 5.35; S, 6.932%.

General procedure for compounds 6, 8a,b, and 13a–c. A mixture of 1,4-dibromobutane (5 mmol) and each of the appropriate aromatic hydroxy compounds **1a, 9a,b**, and **12a–c** (10 mmol), potassium hydroxide (2 mmol), anhydrous potassium carbonate (20 mmol) in dry acetone (50 mL) was heated under reflux for 12 h. The reaction mixture was cooled to room temperature and filtered off, and the filtered cake was washed with 10 mL of dry acetone, and the filterate was added to the above mother liquor, and then the resulting solution was concentrated to its half volume, cooled, and poured into a beaker containing 100-g ice. The products were collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent to yield **6**, **8a**,**b**, and **13a–c**, respectively.

1,4-Bis(2,6-dibromo-4-formylphenoxy) butane (6). Colorless crystals recrystallized from dioxane/ethanol mixture (85%); m.p. 188–190°C; IR (υ cm^{-1}): 2848, 2750 (ald. H stretch), and 1689 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.10 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2O$), 4.16 (t, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}O$), 8.18 (s, 4H, ArH's), and 9.90 (s, 2H, 2 CHO); *Anal*. Calcd for $C_{18}H_{14}Br_4O_4$ (613.92): C, 35.22; H, 2.30; found: C, 35.10; H, 2.39%.

1,4-Bis(2,6-dibromo-4-[6-methylsulfanyl-5-cyano-3-ethoxycarbonyl-2-phenyl-pyridin-4-yl]phenoxy) butane (8a). Colorless crystals recrystallized from ethanol (44% from **4** or 76% from **9a**); m.p. 116–118°C; IR (υ cm^{-1}): 2214 (CN) and 1705 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.82 (t, 6H, 2 $\underline{CH_3}CH_2O$), 2.12 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2O$), 2.71 (s, 6H, 2 SCH_3), 3.91 (m, 4H, 2 $CH_3\underline{CH_2}O$), 4.12 (m, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}O$), and 7.54–8.24 (m, 14H, ArH's); *Anal*. Calcd for $C_{48}H_{38}Br_4N_4O_6S_2$ (1150.58): C, 50.11; H, 3.33; N, 4.87; S, 5.57; found: C, 50.19; H, 3.49; N, 4.69; S, 5.61%.

1,4-Bis(2,6-dibromo-4-[6-benzylsulfanyl-5-cyano-3-ethoxycarbonyl-2-phenyl-pyridin-4-yl]phenoxy) butane (8b). Colorless crystals recrystallized from ethanol (40% from **4** or 72% from **9b**); m.p. 138–140°C; IR (υ cm^{-1}): 2214 (CN) and 1705 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.82 (t, 6H, 2 $\underline{CH_3}CH_2O$), 2.12 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2O$), 3.91 (m, 4H, 2 $CH_3\underline{CH_2}O$), 4.12 (m, 8H, 2 SCH_2 and $O\underline{CH_2}CH_2CH_2\underline{CH_2}O$), and 7.48–7.85 (m, 24H, ArH's); *Anal*. Calcd for $C_{60}H_{46}Br_4N_4O_6S_2$ (1302.78): C, 55.32; H, 3.56; N, 4.30; S, 4.92; found: C, 55.48; H, 3.41; N, 4.60; S, 4.61%.

1,4-Bis(2,6-dibromo-4-[3-amino-2,5-diethoxycarbonyl-6-phenylthieno[2,3-b]-pyridin-4-yl]phenoxy) butane (13a). Yellow crystals recrystallized from ethanol (58%); m.p. 110–112°C; IR (υ cm^{-1}): 3347, 3189 (NH_2), 1723, and 1680 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.81 (m, 12H, 4 $OCH_2\underline{CH_3}$), 2.14 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2O$), 3.88 (m, 8H, 4 $O\underline{CH_2}CH_3$), 4.19 (m, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}O$), 5.80 (s, br, 4H, 2 NH_2), and 7.50–7.82 (m, 14H, ArH's); *Anal*. Calcd for $C_{54}H_{46}Br_4N_4O_{10}S_2$ (1294.71): C, 50.09; H, 3.58; N, 4.33; S, 4.95; found: C, 50.20; H, 3.38; N, 4.40; S, 4.80%.

1,4-Bis(2,6-dibromo-4-[2-acetyl-3-amino-5-ethoxycarbonyl-6-phenylthieno[2,3-b]-pyridin-4-yl]phenoxy) butane (13b). Yellow crystals recrystallized from dioxane/ethanol mixture (63%); m.p. 240–242°C; IR (υ cm^{-1}): 3365, 3272 (NH_2), 1724 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.83 (t, J = 7.2 Hz, 6H, 2 $\underline{CH_3}CH_2$), 2.15 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2O$), 2.40 (s, 6H, 2 $CO\underline{CH_3}$), 3.89 (q, J = 7.2 Hz, 4H, 2 $CH_3\underline{CH_2}O$), 4.19 (m, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}O$), 6.51 (s, br, 4H, 2 NH_2), and 7.49–7.80 (m, 14H, ArH's); *Anal*. Calcd for $C_{52}H_{42}Br_4N_6O_8S_2$ (1234.66): C, 50.59; H, 3.43; N, 4.54; S, 5.19; found: C, 50.43; H, 3.25; N, 4.72; S, 5.43%.

1,4-Bis(2,6-dibromo-4-[3-amino-2-benzoyl-5-ethoxycarbonyl-6-phenylthieno[2,3-b]pyridin-4-yl]phenoxy) butane (13c). Yellow crystals recrystallized from dioxane/ethanol mixture (59%); m.p. 108–110°C; IR (υ cm^{-1}): 3355, 3274 (NH_2), and 1720 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.83 (t, J = 7.2 Hz, 6H, 2 $\underline{CH_3}CH_2$), 2.15 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2O$), 3.89 (q, J = 7.2 Hz, 4H, 2 $CH_3\underline{CH_2}O$), 4.19 (m, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}O$), 6.92 (s, br, 4H, 2 NH_2), and 7.52–7.89 (m, 24H, ArH's); *Anal*. Calcd for $C_{62}H_{46}Br_4N_4O_8S_2$ (1358.80): C, 54.80; H, 3.41; N, 4.12; S, 4.72; found: C, 54.96; H, 3.52; N, 3.94; S, 4.60%.

General procedure for compounds 8a, 9a, and 9c. A mixture of each of **4** or **2a**,**b** (10 mmol) and iodomethane (**7a**, 20 mmol for **4** or 10 mmol for **2a**,**b**) in methanolic sodium methoxide solution (20 mmol of sodium metal for **2a** and **4** or 10 mmol of sodium metal for **2b** in 20 mL of methanol) was heated under reflux for 2 h. The products so formed were collected by filtration, washed with cold ethanol, and then recrystallized from the proper solvent to yield **8a**, **9a**, and **9c**, respectively.

Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylsulfanyl-2-phenyl-nicotinate (9a). Colorless crystals recrystallized from ethanol (88%); m.p. 242–244°C; IR (υ cm^{-1}): 3427 (OH), 2222 (CN), and 1693 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.85 (t, J = 7.2 Hz, 3H, $\underline{CH_3}CH_2O$), 2.76 (s, 3H, SCH_3), 3.95 (q, J = 7.2 Hz, 2H, $CH_3\underline{CH_2}O$), 7.53–7.70 (m, 7H, ArH's), and 10.53 (s, br, 1H, OH); *Anal*. Calcd for $C_{22}H_{16}Br_2N_2O_3S$ (548.25): C, 48.20; H, 2.94; N, 5.11; S, 5.85; found: C, 48.35; H, 2.78; N, 5.00; S, 5.70%.

4-(3,5-Dibromo-4-ethoxyphenyl)-2-methylsulfanyl-6-phenylnicotinonitrile (9c). Colorless crystals recrystallized from dioxane/ethanol (90%); m.p. 164–166°C; IR (υ cm^{-1}): 2219 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.45 (t, J = 6.9 Hz, 3H, $\underline{CH_3}CH_2$), 2.76 (s, 3H, SCH_3), 4.11 (q, J = 6.9 Hz, 2H, $CH_3\underline{CH_2}$), and 7.55–8.32 (m, 8H, ArH's); *Anal*. Calcd for $C_{21}H_{16}Br_2N_2OS$ (504.24): C, 50.02; H, 3.20; N, 5.56; S, 6.36; found: C, 50.24; H, 3.04; N, 5.70; S, 6.45%.

General procedure for compounds 8b, 9b, and 9d. A mixture of each of **4** or **2a**,**b** (10 mmol) and benzyl chloride (**7b**, 20 mmol for **4** or 10 mmol for **2a**,**b**) in methanolic sodium methoxide solution (20 mmol of sodium metal for **2a** and **4** or 10 mmol of sodium metal for **2b** in 20 mL of methanol) was heated under reflux for 2 h. The products so formed were collected by filtration, washed with cold ethanol, and then recrystallized from the proper solvent to yield **8b**, **9b**, and **9d**, respectively.

Ethyl 6-benzylsulfanyl-5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-2-phenyl-nicotinate (9b). Colorless crystals recrystallized from ethanol (81%); m.p. 234–236°C; IR (υ cm^{-1}): 3425 (OH), 2221 (CN), and 1690 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.85 (t, J = 7.2 Hz, 3H, $\underline{CH_3}CH_2O$), 3.90 (q, J = 7.2 Hz, 2H, $CH_3\underline{CH_2}O$), 4.12 (s, 2H, SCH_2), 7.52–7.66 (m, 12H, ArH's), and 10.53 (s, br, 1H, OH); *Anal*. Calcd for $C_{28}H_{20}Br_2N_2O_3S$ (624.34): C, 53.86; H, 3.23; N, 4.49; S, 5.14; found: C, 53.97; H, 3.08; N, 4.23; S, 5.32%.

2-Benzylsulfanyl-4-(3,5-dibromo-4-ethoxyphenyl)-6-phenyl-nicotinonitrile (9d). Colorless crystals recrystallized from dioxane/ethanol (84%); m.p. 138–140°C; IR (υ cm^{-1}): 2222 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.45 (t, J = 6.9 Hz, 3H, $\underline{CH_3}CH_2$), 4.12 (q, J = 6.9 Hz, 2H, $CH_3\underline{CH_2}$), 4.72 (s, 2H, $S\underline{CH_2}$), and 7.26–8.32 (m, 13H, ArH's); *Anal*. Calcd for $C_{27}H_{20}Br_2N_2OS$ (580.33): C, 55.88; H, 3.47; N, 4.83; S, 5.53; found: C, 56.01; H, 3.31; N, 5.09; S, 5.71%.

General procedure for compounds 11a–e. A mixture of **2a**,**b** (5 mmol) and each of **10a–c** (5 mmol) in ethanol (20 mL) containing anhydrous sodium acetate (5 mmol) was heated under reflux for 2 h. The products so formed were collected by filtration, washed with cold ethanol, dried, and then recrystallized from the proper solvent to give the final products **11a** and **11c–e**, respectively. Reaction of **2a** with **10b** gave **12b** and not **11b**.

Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-6-(ethoxycarbonylmethylsulfanyl)-2-phenylnicotinate (11a). Pale yellow crystals recrystallized from ethanol (72%); m.p. 108–110°C; IR (υ cm^{-1}): 3380 (OH), 2224 (CN), 1726, and 1704 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.85 (t, 6H, 2 $OCH_2\underline{CH_3}$), 3.93 (q, 2H, $O\underline{CH_2}CH_3$), 4.04 (q, 2H, $O\underline{CH_2}CH_3$), 4.21 (s, 2H, SCH_2), 7.53–7.71 (m, 7H, ArH's), and 10.54 (s, br, 1H, OH); *Anal*. Calcd for $C_{25}H_{20}Br_2N_2O_5S$ (620.31): C, 48.41; H, 3.25; N, 4.52; S, 5.17; found: C, 48.60; H, 3.39; N, 4.70; S, 5.05%.

Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-6-(2-oxo-2-phenylethylsulfanyl)-2-phenylnicotinate (11c). Pale yellow crystals recrystallized from ethanol (81%); m.p. 188–190°C; IR (υ cm^{-1}): 3462 (OH), 2220 (CN), and 1718 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.82 (t, *J* = 6.3 Hz, 3H, $OCH_2\underline{CH_3}$), 3.90 (q, *J* = 6.3 Hz, 2H, $CH_3\underline{CH_2}$), 5.02 (s, 2H, SCH_2), 7.19–8.09 (m, 12H, ArH's), and 10.53 (s, br, 1H, OH); *Anal*. Calcd for $C_{29}H_{20}Br_2N_2O_4S$ (652.35): C, 53.39; H, 3.09; N, 4.29; S; 4.92; found: C, 53.59; H, 3.27; N, 4.17; S, 4.60%.

4-(3,5-Dibromo-4-ethoxyphenyl)-2-(2-oxopropylsulfanyl)-6-phenyl-nicotinonitrile (11d). Yellow crystals recrystallized from ethanol (81%); m.p. 170–172°C; IR (υ cm^{-1}): 2207 (CN) and 1711 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.44 (t, *J* = 6.9 Hz, 3H, $\underline{CH_3}CH_2O$), 2.30 (s, 3H, $COCH_3$), 4.10 (q, *J* = 6.9 Hz, 2H, $CH_3\underline{CH_2}O$), 4.37 (s, 2H, SCH_2), and 7.53–8.21 (m, 8H, ArH's); *Anal*. Calcd for $C_{23}H_{18}Br_2N_2O_2S$ (546.27): C, 50.57; H, 3.32; N, 5.13; S, 5.87; found: C, 50.81; H, 3.20; N, 4.95; S, 6.05%.

4-(3,5-Dibromo-4-ethoxyphenyl)-2-(2-oxo-2-phenylethylsulfanyl)-6-phenylnicotino-nitrile (11e). Colorless crystals recrystallized from ethanol/dioxane (90%); m.p. 196–198°C; IR (υ cm^{-1}): 2212 (CN) and 1680 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.45 (t, *J* = 7.2 Hz, 3H, $\underline{CH_3}CH_2O$), 4.12 (q, *J* = 7.2 Hz, 2H, $CH_3\underline{CH_2}O$), 5.06 (s, 2H, SCH_2), 7.17–8.15 (m, 13H, ArH's); *Anal*. Calcd for $C_{28}H_{20}Br_2N_2O_2S$ (608.34): C, 55.28; H, 3.31; N, 4.60; S, 5.27; found: C, 55.01; H, 3.48; N, 4.83; S, 5.41%.

General procedure "A" for compounds 12a,c–e. A mixture of each of **11a**,**c–e** (10 mmol) in methanolic sodium methoxide solution (prepared from 20 mmol of sodium metal in 20 mL of methanol) was heated under reflux for 2 h. The products so formed (by cooling, pouring onto 100 g of crushed ice, and adding dil. HCl for **12a**,**c** or by cooling only for **12d**,**e**) were collected by filtration, washed with cold ethanol, dried, and then recrystallized from the proper solvent to give the **12a**,**c–e**, respectively.

General procedure "B" for compounds 12a,c–e. A mixture of **2a**,**b** (10 mmol) and each of **10a–c** (10 mmol) in methanolic sodium methoxide solution (prepared from 30 mmol of sodium metal in 20 mL of methanol) was heated under reflux for 4 h. The products so formed (by cooling, pouring onto 100 g of crushed ice, and adding dil. HCl for **12a**,**c** or by cooling only for **12d**,**e**) were collected by filtration, washed with cold ethanol, dried, and then recrystallized from the proper solvent to give the **12a–e**, respectively.

Diethyl 3-amino-4-(3,5-dibromo-4-hydroxyphenyl)-6-phenylthieno[2,3-b]pyridine-2,5-dicarboxylate (12a). Yellow crystals recrystallized from ethanol/dioxane mixture (77% from **2a** or 84% from **11a**); m.p. 228–230°C; IR (υ cm^{-1}): 3477 (OH), 3347, 3189 (NH_2), 1723, and 1680 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.71 (t, 3H, $OCH_2\underline{CH_3}$), 0.83 (t, 3H, $OCH_2\underline{CH_3}$), 3.78 (q, 2H, $O\underline{CH_2}CH_3$), 3.90 (q, 2H, $O\underline{CH_2}CH_3$), 7.46–7.69 (m, 9H, 7 ArH's and NH_2), and 10.57 (s, br, 1H, OH); *Anal*. Calcd for $C_{25}H_{20}Br_2N_2O_5S$ (620.31): C, 48.41; H, 3.25; N, 4.52; S, 5.17; found: C, 48.54; H, 3.40; N, 4.68; S, 5.01%.

Ethyl 2-acetyl-3-amino-4-(3,5-dibromo-4-hydroxyphenyl)-6-phenylthieno-[2,3-b]-pyridine-5-carboxylate (12b). Yellow crystals recrystallized from ethanol/dioxane mixture (82%); m.p. 270–272°C; IR (υ cm^{-1}): 3448 (OH), 3365, 3272 (NH_2), and 1724 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.83 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 2.40 (s, 3H, CH_3), 3.88 (q, *J* = 7.2 Hz, 2H, $O\underline{CH_2}CH_3$), 6.50 (s, br, 2H, NH_2), 7.50–7.67 (m, 7H, ArH's), and 10.46 (s, 1H, OH); *Anal*. Calcd for $C_{24}H_{18}Br_2N_2O_4S$ (590.28): C, 48.83; H, 3.07; N, 4.75; S, 5.43; found: C, 48.95; H, 3.16; N, 4.52; S, 5.35%.

Ethyl 3-amino-2-benzoyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-phenyl-thieno[2,3-b]-pyridine-5-carboxylate (12c). Yellow crystals recrystallized from ethanol/dioxane mixture (80% from **2a** or 90% from **11c**); m.p. 258–260°C; IR (υ cm^{-1}): 3458 (OH), 3355, 3274 (NH_2), and 1720 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.85 (t, *J* = 6.9 Hz, 3H, $OCH_2\underline{CH_3}$), 3.92 (q, *J* = 6.9 Hz, 2H, $CH_3\underline{CH_2}$), 6.92 (s, br, 2H, NH_2), 7.50–7.79 (m, 12H, ArH's), and 10.48 (s, br, 1H, OH); *Anal*. Calcd for $C_{29}H_{20}Br_2N_2O_4S$ (652.35): C, 53.39; H, 3.09; N, 4.29; S, 4.92; found: C, 53.20; H, 3.00; N, 4.40; S, 5.06%.

2-Acetyl-3-amino-4-(3,5-dibromo-4-ethoxyphenyl)-6-phenylthieno[2,3-b]-pyridine (12d). Orange crystals recrystallized from dioxane (74% from **2b** or 85% from **11d**); m.p. 198–200°C; IR (υ cm^{-1}): 3464 and 3285 (NH_2); ^{1}H-NMR (DMSO-d_6): δ 1.47 (t, *J* = 6.9 Hz, 3H, $\underline{CH_3}CH_2O$), 2.40 (s, 3H, $CO\underline{CH_3}$), 4.15 (s, *J* = 6.9 Hz, 2H, $CH_3\underline{CH_2}O$), 6.78 (s, br, 2H, NH_2), and 7.52–8.26 (m, 8H, ArH's); *Anal*. Calcd for $C_{23}H_{18}Br_2N_2O_2S$ (546.27): C, 50.57; H, 3.32; N, 5.13; S, 5.87; found: C, 50.71; H, 3.19; N, 5.04; S, 5.95%.

3-Amino-2-benzoyl-4-(3,5-dibromo-4-ethoxyphenyl)-6-phenylthieno[2,3-b] pyridine (12e). Yellow crystals recrystallized from DMF (81% from **2b** or 86% from **11e**); m.p. 238–240°C; IR (υ cm^{-1}): 3468, 3318 (NH_2); ^{1}H-NMR (DMSO-d_6): δ 1.48 (t, *J* = 7.2 Hz, 3H, $\underline{CH_3}CH_2O$), 4.17 (s, *J* = 7.2 Hz, 2H, $CH_3\underline{CH_2}O$), 7.21 (s, br, 2H, NH_2), and 7.51–8.26 (m, 13H, ArH's); *Anal*. Calcd for $C_{28}H_{20}Br_2N_2O_2S$ (608.34): C, 55.28; H, 3.31; N, 4.60; S, 5.27; found: C, 55.12; H, 3.47; N, 4.44; S, 5.09%.

REFERENCES AND NOTES

[1] Saini, A.; Kumar, S.; Sandhu, J. S. J Sci Ind Res 2008, 67, 95.
[2] Desai, B.; Sureja, D.; Naliapara, Y.; Shah, A.; Saxena, A. K. Bioorg Med Chem 2001, 9, 1993.
[3] Nakayama, H.; Kasoaka, Y. Heterocycles 1996, 42, 901.
[4] Boer, R.; Gekeler, V. Drugs Fut 1995, 20, 499.
[5] Abdel-Fattah, M. A.; El-Naggar, M. A. M.; Rashied, R. M. H.; Gary, B. D.; Piazza, G. A.; Abadi, A. H. Med Chem 2012, 8, 392.

[6] Bashandy, M. S.; Al-Said, M. S.; Al-Qasoumi, S. I.; Ghorab, M. M. Arzneimittelforschung 2011, 61, 521.

[7] Al-Said, M. S.; Bashandy, M. S.; Al-Qasoumi, S. I.; Ghorab, M. M. Eur J Med Chem 2011, 46, 137.

[8] Salem, M. A.; Thabet, H. K.; Ismail, M. A.; Ammar, Y. A. Chem Sci J 2011, 36, 1.

[9] Krauze, A.; Vitolina, R. O.; Romanova, M. R.; Dubur, G. Y. Pharm Chem J 1991, 22, 366.

[10] Krauze, A.; Baumane, L.; Sile, L.; Cherniva, L.; Vilums, M.; Vitolona, R.; Dubur, G. Y.; Stradins, J. Chem Heterocycl Compd 2004, 40, 876.

[11] Kirule, E.; Krauze, A. A.; Velena, A. H.; Antipova, D. J.; Arnicane, G. J.; Vucina, I. A. Pharm Chem J 1992, 26, 411.

[12] Shuck-Lee, D.; Chen, F. F.; Willard, R.; Raman, S.; Ptak, R. Antimicrob Agents Chemother 2008, 52, 3169.

[13] Liu, H.; Li, Y.; Wang, X. Y.; Wang, B.; He, H. Y.; Liu, J. Y.; Xiang, M. L.; He, J.; Wu, X. H.; Yang, L. Bioorg Med Chem Lett 2013, 23, 2349.

[14] Bahekar, R. H.; Jain, M. R.; Jadav, P. A.; Prajapati, V. M.; Patel, D. N.; Gupta, A.; Sharma, A.; Tom, R.; Bandyopadhya, D.; Modi, H.; Patel, P. R. Bioorg Med Chem 2007, 15, 6782.

[15] Kamata, M.; Yamashita, T.; Kina, A.; Funata, M.; Mizukami, A.; Sasaki, M.; Tani, A.; Funami, M.; Amano, N.; Fukatsu, K. Bioorg Med Chem Lett 2012, 22, 3643.

[16] Willemann, C.; Grunert, R.; Bednarski, P. J.; Troschutz, R. Bioorg Med Chem 2009, 17, 4406.

[17] Zeng, X. X.; Zheng, R. L.; Zhou, T.; He, H. Y.; Liu, J. Y.; Zheng, Y.; Tong, A. P.; Xiang, M. L.; Song, X. R.; Yang, S. Y.; Yu, L. T.; Wei, Y. Q.; Zhao, Y. L.; Yang, L. Bioorg Med Chem Lett 2010, 20, 6282.

[18] Pevet, I.; Brule, C.; Tizot, A.; Gohier, A.; Cruzalegui, F.; Boutin, J. A.; Goldstein, S. Bioorg Med Chem 2011, 19, 2517.

[19] Feng, L.; Reynisdóttir, I.; Reynisson, J. Eur J Med Chem 2012, 54, 463.