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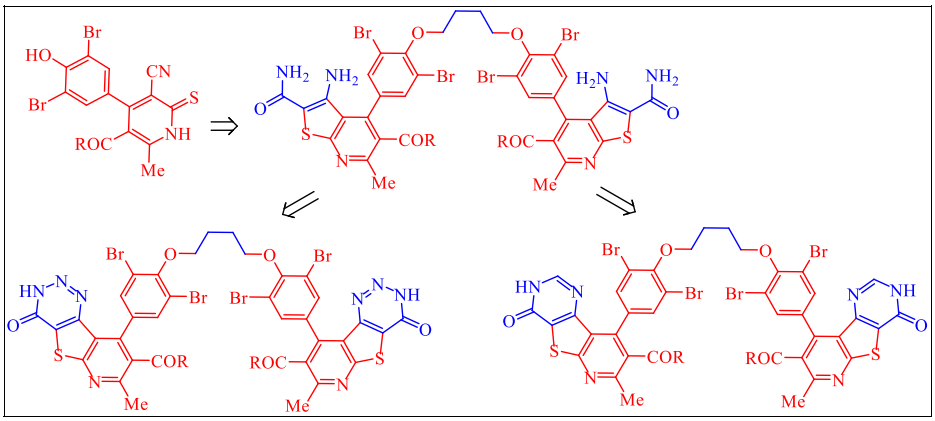

The starting materials pyridine-2(1*H*)-thiones are prepared and reacted with halogen-containing reagents in ethanolic sodium acetate solution to give the corresponding 2-*S*-alkylpyridines, which cyclized upon their boiling in methanolic sodium methoxide solution at reflux to give the corresponding thieno[2,3-*b*]pyridines in excellent yields. Bis (thieno[2,3-*b*]pyridine-2-carboxamides), incorporating 2,6-dibromophenoxy moiety, are prepared by the bis-*O*-alkylation of thieno[2,3-*b*]pyridine-2-carboxamide derivatives. Two synthetic routes are designed to prepare the target molecules pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones, pyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,3]triazin-4(3*H*)-ones, and their bis-analogues using thieno[2,3-*b*]pyridine-2-carboxamides and their bis-analogues. The structure of the target molecules is elucidated using elemental analyses as well as spectral data.

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INTRODUCTION

Many publications reported that dihydropyridines act as anticancer [1–5], antihypertensive, and antiarrhythmic [6–9] agents. Pyridine-2(1*H*)-thiones show antifungal and antibacterial activities [10]. 2-*S*-Alkylpyridines exhibit important bioactivities as antiradical [11], cardiovascular [12,13], and antioxidant [14]. Moreover, thieno[2,3-*b*]pyridines act as anticancer [15–17], antiviral [18], anti-inflammatory [19], antimicrobial [20], and antihypertensive [21]. Also, azines, incorporating fused thieno[2,3-*b*]pyridine, have interesting biological activities [22]. Pyrimidines act as antipyretic [22,23], antiallergic [24,25], antianaphylactic [26,27], antimicrobial [28], and antiprotozoals [29], agents while [1,2,3]triazines act as antifungal [30], antiprotozals [29], anticancer [31,32], and antimicrobial [33] agents. Construction of efficient synthetic routes for pyridines, pyridine-2(1*H*)-thiones, alkylthiopyridines, thieno[2,3-*b*]pyridines, pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines, and pyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,3]triazines of various bioactivities became the major goal of this research group, and several publications exhibited this effort [34–41]. This study was pointed to design facile methods for the preparation of novel hybrid molecules of pyrimidin-4(3*H*)-one or [1,2,3]triazin-4-(3*H*)-one on the skeleton of thieno[2,3-*b*]pyridine of potent bioactivity.

RESULTS AND DISCUSSION

2-Cyano-3-(3,5-dibromo-4-hydroxyphenyl)prop-2-enethioamide (**3**) was prepared by the reaction of 3,5-dibromo-4-hydroxybenzaldehyde (**1**) with 2-cyanoethanethioamide (**2**) in dioxane containing a few drops of triethylamine under stirring at room temperature in 96% yield. The starting material 5-acetyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**5a**) [41] was prepared, in 85% yield, by the reaction of cinnamonitrile derivative **3** with acetylacetone (**4a**) in boiling dioxane containing a few drops of triethylamine at reflux. Pyridine-2-(1*H*)-thione **5a** could also be prepared, in 82% yield, by the one-pot reaction of aldehyde **1**, 2-cyanoethanethioamide (**2**), and acetylacetone (**4a**) in boiling dioxane containing a few drops of triethylamine at reflux. In the same way,

the other starting material ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxylate (**5b**) [41] was prepared either by the reaction of cinnamonitrile derivative **3** with ethyl acetoacetate (**4b**) or by the one-pot reaction of **1**, **2**, and **4b** in boiling dioxane containing a few drops of triethylamine at reflux in 87% and 81% yield, respectively (Scheme 1 and Experimental section).

Pyridine-2(1*H*)-thiones **5a**,**b** reacted with each of chloroacetonitrile (**6a**), chloroacetamide (**6b**), ethyl chloroacetate (**6c**), 2-bromo-1-phenylethan-1-one (**6d**), and chloroacetone (**6e**) in ethanolic sodium acetate solution under stirring at room temperature to afford the corresponding 2-*S*-alkyl derivatives **8a–e** and **9a–e**, respectively, in excellent yields. The IR spectra of products **8** and **9** revealed the absence of C=S group and the presence of OH group. Moreover, their ^{1}H-NMR spectra revealed the absence of NH group and the presence of SCH_2 group in the region of δ = 4.00–4.92 ppm. Based on the above, the formation of *O*-alkyl compounds **7** was excluded (Scheme 2 and Experimental section).

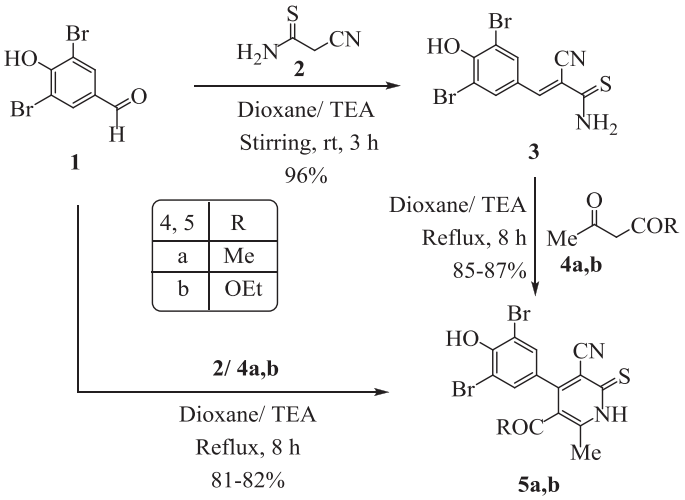
The intramolecular cyclization of **8a–e** and **9a–e** upon their boiling in methanolic sodium methoxide solution at reflux afforded the corresponding thieno[2,3-*b*]pyridine derivatives **10b–e** and **11b–e**, respectively, in excellent yields. It is a noteworthy that the cyclization of **8a** or **9a** afforded 2-carboxamide derivatives **10b** and **11b**, respectively, and not the expected 2-carbonitrile derivatives **10a** and **11a**, respectively. This could be explained by the basic hydrolysis of nitrile function to $CONH_2$ group.

Elemental analyses as well as the spectroscopic data of the obtained products **10** and **11** are in complete agreement with the proposed structures. The ^{1}H-NMR spectrum of **10b** as a representative example revealed the signals due to two NH_2 groups (2 s, 2H, δ = 5.82 and 7.26 ppm) (Scheme 2 and Experimental section).

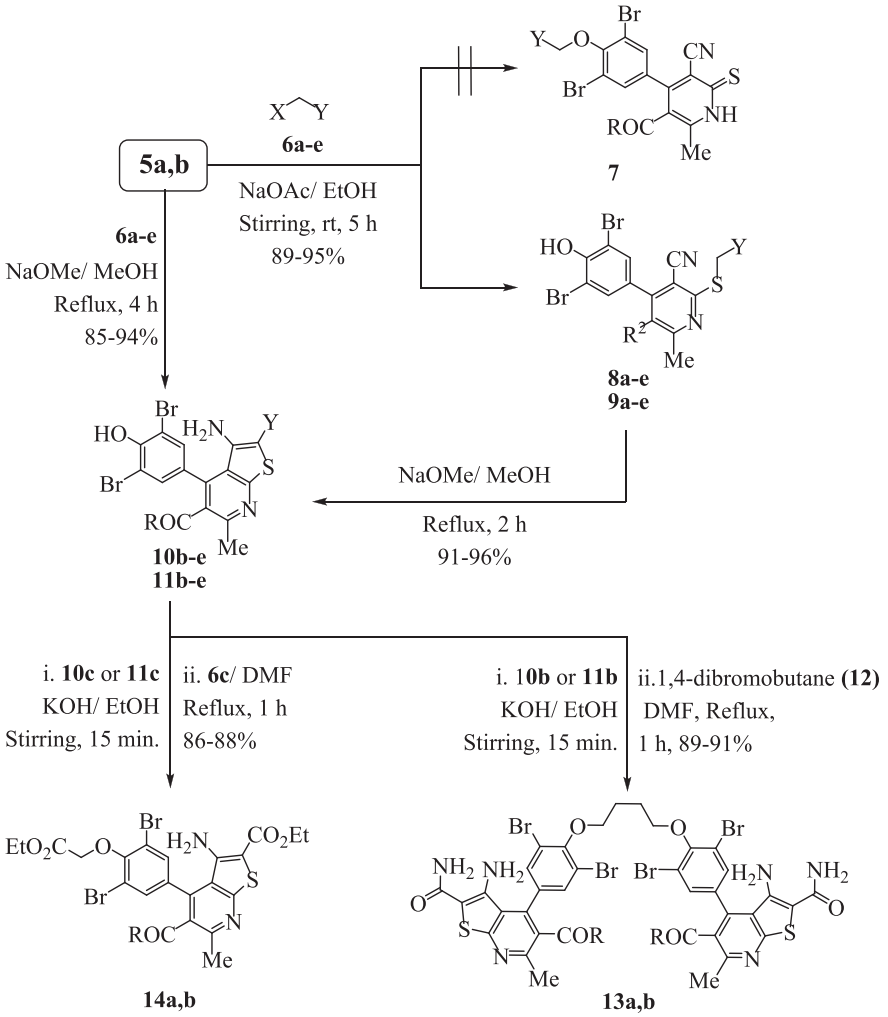
The *O*-alkylated thieno[2,3-*b*]pyridine derivatives could be prepared by reacting their potassium slats with halogen-containing reagents in boiling N, N-dimethylformamide (DMF) at reflux. Thus, both 4-(3,5-dibromo-4-hydroxyphenyl)thieno[2,3-*b*]pyridine-2-carboxamide derivatives **10b** and **11b** were bis-*O*-alkylated by the reaction of their potassium salts with 1,4-dibromobutane (**12**) in DMF to give bis(2-carboxamides) **13a**,**b**, respectively. In a similar manner, the reaction of potassium salts of ethyl 4-(3,5-dibromo-4-hydroxyphenyl) thieno[2,3-*b*]pyridine-2-carboxylate derivatives **10c** and **11c** with **6c** in DMF afforded the corresponding *O*-alkylated thieno[2,3-*b*]pyridine derivatives **14a**,**b** (Scheme 2 and Experimental section).

Two synthetic routes were constructed for synthesis of the target molecules bis-azines **15** and **17** using thienopyridines **10** and **11** and their bis-analogues **13**. The bis (pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones) **15a**,**b** were prepared by the reaction of bis(2-carboxamides) **13a**,**b** in formic acid at reflux in good yields. Compounds **15a**,**b** could also be synthesized, in excellent yields, by the reaction of 2-carboxamide derivatives **10b** or **11b** in formic acid at reflux to give the corresponding pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **16a**,**b**, respectively. Then, the potassium salts of **16a**,**b** were bis-*O*-alkylated *via* their reaction with **12** in boiling DMF at reflux. On the same way, the bis (pyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,3]triazin-4(3*H*)-ones) **17a**,**b** were prepared by the direct diazotization of **13a**,**b** followed by their *in situ* self-coupling. Also,

Scheme 1. Synthesis of pyridine-2(1*H*)-thiones **5a**,**b**.



Scheme 2. Synthesis of thieno[2,3-*b*]pyridines **10b–e**, **11b–e**, **14a**,**b**, and their bis-analogues **13a**,**b** [Correction added on 13 May 2019, after first online publication: Scheme 2 was published twice in the original version of this article. The duplicate has been deleted.].



6	X	Y
a	Cl	CN
b	Cl	$CONH_2$
c	Cl	CO_2Et
d	Br	COPh
e	Cl	COMe

8,10	R	Y
a*	Me	CN
b	Me	$CONH_2$
c	Me	CO_2Et
d	Me	COPh
e	Me	COMe

9, 11	R	Y
a*	OEt	CN
b	OEt	$CONH_2$
c	OEt	CO_2Et
d	OEt	COPh
e	OEt	COMe

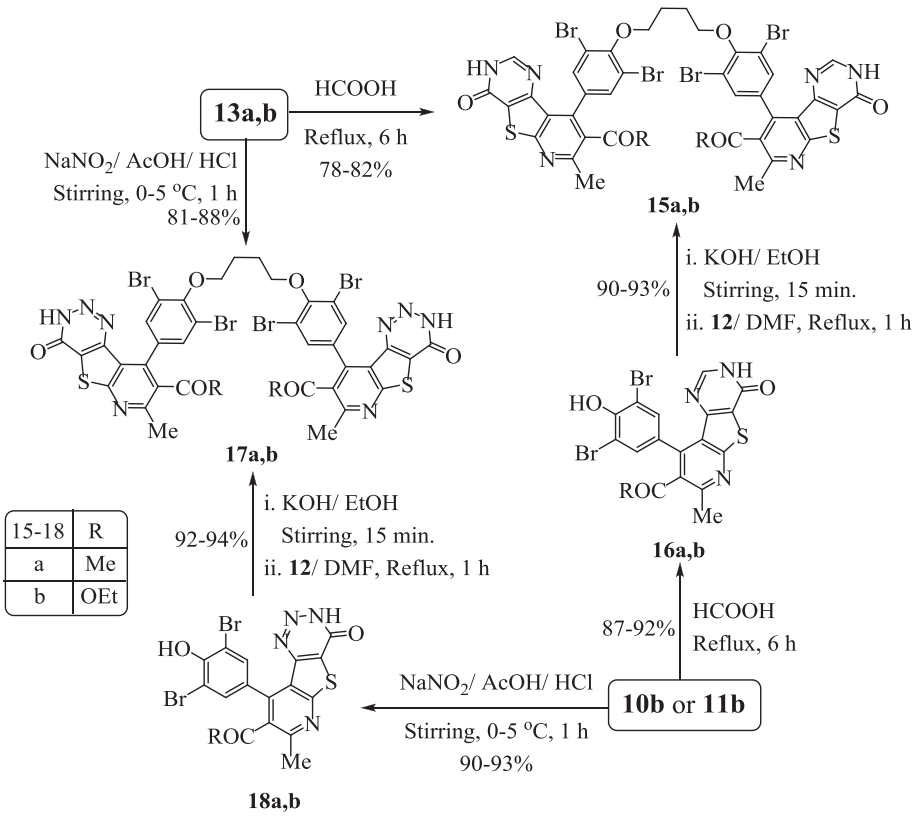
13, 14	R
a	Me
b	OEt

compounds **17a**,**b** could be by the reaction of **10b** or **11b** with nitrous acid to give [1,2,3]triazin-4(3*H*)-ones **18a**,**b**, respectively, followed by their bis-alkylation.

Elemental analyses as well as the spectroscopic data of the obtained products **15** and **17** are in complete agreement with the proposed structures. The ^{1}H-NMR spectrum of **15a** as a representative example revealed the signals due to two pyrimidine CH-2 (s, 2H, δ = 8.14 ppm) and NH groups (s, 2H, δ = 12.93 ppm) (Scheme 3 and Experimental section).

Moreover, the target molecules pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **19a**,**b** and **21a**,**b** were prepared by the reaction of each of compounds **10b** and **11b** with carbon disulfide in pyridine at reflux or with acetic anhydride at reflux. It is a noteworthy that **10b** and **11b** reacted with one molecule of acetic anhydride to build up the pyrimidine ring fused with the thienopyridine skeleton (**20a**,**b**) followed by the acetylation of their phenolic group to give **21a**,**b**, respectively, as the final isolable product (Scheme 4 and Experimental section).

Scheme 3. Synthesis of the bis (pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones) **15a**,**b** and bis (pyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,3]triazin-4(3*H*)-ones) **17a**,**b**.



CONCLUSION

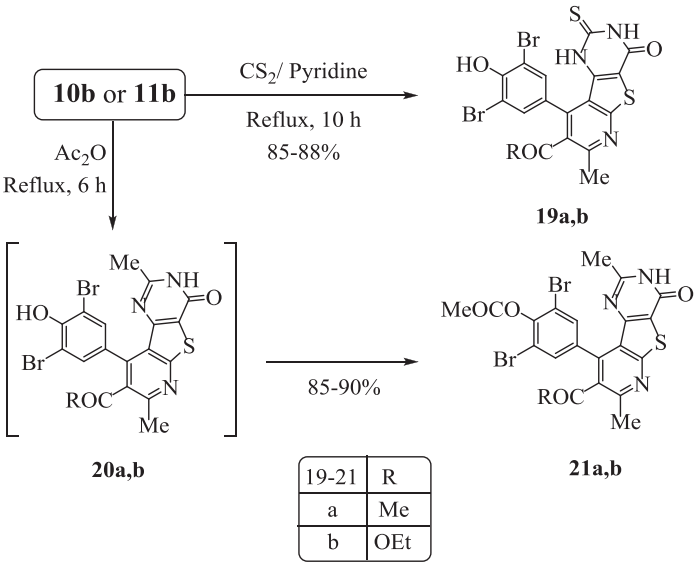
This study deals with the utility of pyridine-2(1*H*)-thiones in the synthesis of novel thieno[2,3-*b*]pyridines and their bis-analogues in excellent yields. Thieno[2,3-*b*] pyridine-2-carboxamides and their bis-analogues were designed to prepare the target molecules pyrido[3′,2′:4,5] thieno[3,2-*d*]pyrimidin-4(3*H*)-ones and pyrido[3′,2′:4,5] thieno[3,2-*d*][1,2,3]triazin-4(3*H*)-ones and their bis-analogues.

EXPERIMENTAL

Introduction. All organic solvents were acquired from commercial sources and used as received unless otherwise stated. All other chemicals were acquired from Merck (Merck KGaA, Darmstadt, Germany) or Aldrich (Sigma-Aldrich Corporation as a subsidiary of Merck KGaA, St. Louis, Missouri, USA). These chemicals were 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 manufactured by Thermo Fisher Scientific Inc., Fitchburg, Dane County, Wisconsin, USA. ^{1}H-NMR and ^{13} C-NMR spectra were recorded on Varian Mercury at 300 and 75 MHz respectively spectrophotometer using tetramethylsilane as an internal standard and DMSO-d_6 as solvent, and chemical shifts were expressed as δ ppm units. The instrument manufactured by Varian Inc., Palo Alto, California, USA. Elemental analyses were carried out on a EuroVector instrument C, H, N, S analyzer EA3000 series.

Procedure for synthesis of 2-cyano-3-(3,5-dibromo-4-hydroxyphenyl)prop-2-enethioamide (3). A solution of 3,5-dibromo-4-hydroxybenzaldehyde (**1**, 5 mmol) and 2-cyanoethanethioamide (**2**, 5 mmol) in 20 mL dioxane containing five drops of triethylamine was stirred at room temperature for 3 h, and then the reaction mixture was left to stand overnight. The solid that formed was collected by filtration, washed with cold ethanol, and recrystallized from dioxane/ethanol mixture to yield **3** as yellow crystals (96%); m.p. 260–262°C; IR (υ cm^{-1}): 3315, 3194 (NH_2), 2213 (CN), 1554 (CS); ^{1}H-NMR (DMSO-d_6): δ 7.05 (s, br, 2H, NH_2), 7.59 (s, 1H, CH=N), 7.79 (s, 2H, ArH's), 10.70 (s, br, 1H, OH); Ms m/z (%): 364 (66.4, M^++4), 362 (96.8, M^++2), 360 (36.0, M^+), 346 (32.2), 345 (29.1),

Scheme 4. Synthesis of the pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **19a**,**b** and **21a**,**b**.



338 (18.3), 301 (23.4), 276 (1.9), 264 (7.2); Anal. for $C_{10}H_6Br_2N_2OS$ (362.04): C, 33.18; H, 1.67; N, 7.74; S, 8.86; found: C, 33.45; H, 1.98; N, 7.45; S, 8.67%.

General procedure for synthesis of compounds 5a,**b**. A mixture of **3** (5 mmol) and each of 1,3-dicarbonyl derivatives **4a**,**b** (5 mmol) or a ternary mixture of **1** (5 mmol), **2** (5 mmol), and **4a**,**b** (5 mmol) in 20 mL dioxane containing five drops of triethylamine was boiled at reflux for 8 h, and then the reaction mixture was left to stand 2 h. The products so formed were collected by filtration, washed with cold ethanol, and recrystallized from dioxane to yield **5a**,**b**, respectively.

5-Acetyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (5a). Yellow crystals (85% from **3** or 82% from ternary mixture); m.p. 284–286°C; IR (υ cm^{-1}): 3410 (OH), 3207 (NH), 2228 (CN), 1681 (CO), 1570 (CS); ^{1}H-NMR (DMSO-d_6): δ 1.91 (s, 3H, $COCH_3$), 2.35 (s, 3H, CH_3), 7.62 (s, 2H, ArH's), 10.70 (s, br, 1H, OH), 14.28 (s, br, 1H, NH); Anal. for $C_{15}H_{10}Br_2N_2O_2S$ (442.13): C, 40.75; H, 2.28; N, 6.34; S, 7.25; found: C, 40.50; H, 1.95; N, 6.61; S, 7.01%.

Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxylate (5b). Yellow crystals (87% from **3** or 81% from ternary mixture); m.p. 270–272°C; IR (υ cm^{-1}): 3427 (OH), 3217 (NH), 2230 (CN), 1697 (CO), 1577 (CS); ^{1}H-NMR (DMSO-d_6): δ 0.86 (t, 3H, J = 7.2 Hz, $C\underline{H}_3CH_2$), 2.46 (s, 3H, CH_3), 3.97 (q, 2H, J = 7.2 Hz, $CH_3C\underline{H}_2$), 7.58 (s, 2H, ArH's), 10.56 (s, br, 1H, OH), 14.40 (s, br, 1H, NH); Anal. for $C_{16}H_{12}Br_2N_2O_3S$ (472.15): C, 40.70; H, 2.56; N, 5.93; S, 6.79; found: C, 40.48; H, 2.96; N, 6.30; S, 6.36%.

General procedure for synthesis of compounds 8a–e and 9a–e. A mixture of each of **5a**,**b** (5 mmol) and each of **6a–e** (5 mmol) in absolute ethanol (30 mL) containing anhydrous sodium acetate (5 mmol) was stirred at room temperature for 5 h. The products so formed were filtrated, washed with water, and then recrystallized from ethanol to give the final products **8a–e** and **9a–e**, respectively.

5-Acetyl-2-cyanomethylsulfanyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylnicotinonitrile (8a). Colorless crystals (94%); m.p. 98–100°C; IR (υ cm^{-1}): 3419 (OH), 2230, 2222 (CN), 1687 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.09 (s, 3H, $COCH_3$), 2.54 (s, 3H, CH_3), 4.42 (s, 2H, SCH_2), 7.66 (s, 2H, ArH's), 10.65 (s, br, 1H, OH); Anal. for $C_{17}H_{11}Br_2N_3O_2S$ (481.16): C, 42.44; H, 2.30; N, 8.73; S, 6.66; found: C, 44.20; H, 2.59; N, 8.65; S, 6.85%.

2-{[5-Acetyl-3-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylpyridin-2-yl]sulfanyl}acetamide (8b). Colorless crystals (92%); m.p. 126–128°C; IR (υ cm^{-1}): 3357 (OH), 3291, 3229 (NH_2), 2221 (CN), 1688, 1665 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.07 (s, 3H, $COCH_3$), 2.46 (s, 3H, CH_3), 4.00 (s, 2H, SCH_2), 7.19 (s, br, 2H, NH_2), 7.63 (s, 2H, ArH's), 10.65 (s, br, 1H, OH); Anal. for $C_{17}H_{13}Br_2N_3O_3S$ (499.18): C, 40.90; H, 2.62; N, 8.42; S, 6.42; found: C, 41.11; H, 2.49; N, 8.28; S, 6.30%.

Ethyl {[5-acetyl-3-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylpyridin-2-yl]sulfanyl}acetate (8c). Colorless crystals (91%); m.p. 182–184°C; IR (υ cm^{-1}): 3356 (OH), 2223 (CN), 1729, 1687 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.21 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 2.06 (s, 3H, $COCH_3$), 2.43 (s, 3H, CH_3), 4.14 (m, 4H, $OC\underline{H}_2CH_3$ and SCH_2), 7.64 (s, 2H, ArH's), 10.62 (s, br, 1H, OH); Anal.

for $C_{19}H_{16}Br_2N_2O_4S$ (528.22): C, 43.20; H, 3.05; N, 5.30; S, 6.07; found: C, 43.02; H, 2.88; N, 5.45; S, 6.22%.

5-Acetyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-2-[2-oxo-2-phenyl-ethylsulfanyl]nicotinonitrile (8d). Colorless crystals (95%); m.p. 180–182°C; IR (υ cm^{-1}): 3462 (OH), 2220 (CN), 1689 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.02 (s, 3H, $COCH_3$), 2.13 (s, 3H, CH_3), 4.90 (s, 2H, SCH_2), 7.54–8.11 (s, 7H, ArH's), 10.66 (s, 1H, OH); Anal. for $C_{23}H_{16}Br_2N_2O_3S$ (560.26): C, 49.31; H, 2.88; N, 5.00; S, 5.72; found: C, 49.15; H, 2.99; N, 5.12; S, 5.58%.

5-Acetyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-2-[2-oxopropyl-sulfanyl]nicotinonitrile (8e). Colorless crystals (92%); m.p. 116–118°C; IR (υ cm^{-1}): 3380 (OH), 2219 (CN), 1700 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.06 (s, 3H, $COCH_3$), 2.31 (s, 3H, CH_2COCH_3), 2.43 (s, 3H, CH_3), 4.24 (s, 2H, SCH_2), 7.63 (s, 2H, ArH's), 10.62 (s, br, 1H, OH); Anal. for $C_{18}H_{14}Br_2N_2O_3S$ (498.19): C, 43.40; H, 2.83; N, 5.62; S, 6.44; found: C, 43.66; H, 2.98; N, 5.44; S, 6.25%.

Ethyl 5-cyano-6-cyanomethylsulfanyl-4-(3,5-dibromo-4-hydroxyphenyl)-2-methylnicotinate (9a). Colorless crystals (90%); m.p. 176–178°C; IR (υ cm^{-1}): 3419 (OH), 2229, 2221 (CN), 1720 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.98 (t, J = 7.2 Hz, 3H, CH_3CH_2), 2.61 (s, 3H, CH_3), 4.12 (q, J = 7.2 Hz, 2H, CH_3CH_2), 4.43 (s, 2H, SCH_2), 7.68 (s, 2H, ArH's), 10.61 (s, 1H, OH); Anal. for $C_{18}H_{13}Br_2N_3O_3S$ (511.19): C, 42.29; H, 2.56; N, 8.22; S, 6.27; found: C, 42.05; H, 2.70; N, 8.41; S, 6.08%.

Ethyl 6-carbamoylmethylsulfanyl-5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-2-methylnicotinate (9b). Colorless crystals (89%); m.p. 204–206°C; IR (υ cm^{-1}): 3365 (OH, NH_2), 2220 (CN), 1719, 1665 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.96 (t, J = 7.2 Hz, 3H, CH_3CH_2), 2.54 (s, 3H, CH_3), 4.06–4.13 (3, 4H, SCH_2 and CH_3CH_2), 7.25 (s, br, 2H, NH_2), 7.63 (s, 2H, ArH's), 10.60 (s, br, 1H, OH); Anal. for $C_{18}H_{15}Br_2N_3O_4S$ (529.20): C, 40.85; H, 2.86; N, 7.94; S, 6.06; found: C, 41.02; H, 3.01; N, 7.78; S, 5.89%.

Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-6-ethoxycarbonylmethylsulfanyl-2-methylnicotinate (9c). Pale yellow crystals (91%); m.p. 88–90°C; IR (υ cm^{-1}): 3380 (OH), 2224 (CN), 1726, 1714 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.96 (t, J = 6.8 Hz, 3H, OCH_2CH_3), 1.21 (t, J = 7.0 Hz, 3H, $CH_2CO_2CH_2CH_3$), 2.47 (s, 3H, CH_3), 4.06–4.18 (m, 6H, 2 OCH_2CH_3 and SCH_2), 7.65 (s, 2H, ArH's), 10.58 (s, br, 1H, OH); Anal. for $C_{20}H_{18}Br_2N_2O_5S$ (558.24): C, 43.03; H, 3.25; N, 5.02; S, 5.74; found: C, 43.21; H, 3.05; N, 5.20; S, 5.51%.

Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-2-methyl-6-(2-oxo-2-phenylethylsulfanyl)nicotinate (9d). Pale yellow crystals (95%); m.p. 200–202°C; IR (υ cm^{-1}): 3462 (OH), 2220 (CN), 1718 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.95 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.57 (s, 3H, CH_3), 4.07 (q, J = 7.2 Hz, 2H, CH_3CH_2), 4.92 (s, 2H, SCH_2), 7.54–8.11 (s, 7H, ArH's), 10.52 (s, br, 1H, OH); Anal. for $C_{24}H_{18}Br_2N_2O_4S$ (590.29): C, 48.83; H, 3.07; N, 4.75; S, 5.43; found: C, 48.70; H, 3.20; N, 4.60; S, 5.29%.

Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-2-methyl-6-((2-oxopropyl)thio)nicotinate (9e). Colorless crystals (92%); m.p. 106–108°C; IR (υ cm^{-1}): 3385 (OH), 1719, 1700 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.95 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.32 (s, 3H, $COCH_3$), 2.62 (s, 3H, CH_3), 4.06–4.16 (m, 4H, OCH_2CH_3 and SCH_2), 7.58 (s, 2H, ArH's), 10.63 (s, 1H, OH); Anal. for $C_{19}H_{16}Br_2N_2O_4S$ (528.22): C, 43.20; H, 3.05; N, 5.30; S, 6.07; found: C, 43.56; H, 2.87; N, 5.69; S, 5.77%.

General procedure for synthesis of compounds 10b–e and 11b–e. ***Method "A" for synthesis of compounds 10b–e and 11b–e.*** A mixture of each of **8a–e** or **9a–e** (5 mmol) in methanolic sodium methoxide solution (prepared from 10 mmol of sodium metal in 15 mL of methanol) was boiled at reflux for 2 h. Then the reaction mixture was cooled, poured onto 100 g of crushed ice, and neutralized by diluted HCl. The products that formed were filtrated, washed with ethanol, and then recrystallized from the proper solvent to give the final products **10b–e** and **11b–e**, respectively. The cyclization of **8a** and **9a** gave **10b** and **11b**, respectively.

Method "B" for synthesis of compounds 10b–e and 11b–e. A mixture of each of **5a**,**b** (5 mmol) and each of **6a–e** (5 mmol) and in methanolic sodium methoxide solution (prepared from 15 mmol of sodium metal in 15 mL of methanol) was boiled at reflux for 4 h. Then the reaction mixture was cooled, poured onto 100 g of crushed ice, and neutralized by diluted HCl. The products that formed were filtrated, washed with ethanol, and then recrystallized from the proper solvent to give the final products **10b–e** and **11b–e**, respectively. The reaction of **5a** and **5b** with **6a** gave **10b** and **11b**, respectively.

5-Acetyl-3-amino-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylthieno[2,3-b]pyridine-2-carboxamide (10b). Yellow crystals (dioxane/ethanol mixture, 92% from **8a**, 94% from **8b**, or 87% from **5a/6b**); m.p. 330–332°C; IR (υ cm^{-1}): 3478, 3321, 3129 (OH, NH_2), 1681, 1654 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.04 (s, 3H, $COCH_3$), 2.46 (s, 3H, CH_3), 5.82 (s, 2H, NH_2), 7.26 (s, 2H, $CONH_2$), 7.59 (s, 2H, ArH's), 10.60 (s, br, 1H, OH); Ms m/z (%): 501 (34.4, M^++4), 499 (64.7, M^++2), 497 (33.1, M^+), 454 (62.7), 443 (15.5), 437 (71.1), 410 (57.6), 396 (49.1); Anal. for $C_{17}H_{13}Br_2N_3O_3S$ (499.18): C, 40.90; H, 2.62; N, 8.42; S, 6.42; found: C, 41.15; H, 2.77; N, 8.62; S, 6.32%.

Ethyl 5-acetyl-3-amino-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylthieno[2,3-b]pyridine-2-carboxylate (10c). Yellow crystals (dioxane, 93% from **8c** or 90% from **5a/6c**); m.p. 320–322°C; IR (υ cm^{-1}): 3477 (OH), 3346, 3188 (NH_2), 1676 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.20 (t, J = 7.2 Hz, 3H, CH_3CH_2), 2.06 (s, 3H, $COCH_3$), 2.51 (s, 3H, CH_3),

4.15 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2$), 5.82 (s, 2H, NH_2), 7.63 (s, 2H, ArH's), 10.58 (s, br, 1H, OH); Ms m/z (%): 530 (32.1, M^++4), 528 (65.5, M^++2), 526 (33.5, M^+), 514 (6.4), 511 (23.2), 497 (17.1), 485 (13.4), 457 (15.5), 410 (17.1); Anal. for $C_{19}H_{16}Br_2N_2O_4S$ (528.22): C, 43.20; H, 3.05; N, 5.30; S, 6.07; found: C, 43.36; H, 3.28; N, 5.08; S, 5.94%.

5-Acetyl-3-amino-2-benzoyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylthieno[2,3-b]pyridine (10d). Yellow crystals (dioxane, 95% from **8d** or 88% from **5a/6d**); m.p. 282–284°C; IR (υ cm^{-1}): 3462, 3280 (OH, NH_2), 1690 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.01 (s, 3H, $COCH_3$), 2.15 (s, 3H, CH_3), 5.80 (s, 2H, NH_2), 7.52–8.13 (s, 2H, ArH's), 10.48 (s, 1H, OH); Ms m/z (%): 562 (5.3, M^++4), 560 (12.5, M^++2), 558 (5.9, M^+), 519 (5.7), 512 (4.3), 502 (3.4), 483 (5.2), 455 (4.3), 439 (3.9); Anal. for $C_{23}H_{16}Br_2N_2O_3S$ (560.26): C, 49.31; H, 2.88; N, 5.00; S, 5.72; found: C, 49.44; H, 2.98; N, 4.87; S, 5.61%.

3-Amino-2,5-diacetyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylthieno[2,3-b]pyridine (10e). Yellow crystals (dioxane, 92% from **8e** or 87% from **5a/6e**); m.p. 316–318°C; IR (υ cm^{-1}): 3450, 3313 (OH, NH_2), 1693 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.06 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$), 2.46 (s, 3H, CH_3), 5.78 (s, 2H, NH_2), 7.60 (s, 2H, ArH's), 10.52 (s, 1H, OH); Ms m/z (%): 500 (35.6, M^++4), 498 (63.9, M^++2), 498 (33.5, M^+), 496 (73.2, M^+), 481 (66.2), 426 (76.7), 409 (82.5), 381 (69.7), 396 (49.1); Anal. for $C_{18}H_{14}Br_2N_2O_3S$ (498.19): C, 43.40; H, 2.83; N, 5.62; S, 6.44; found: C, 43.63; H, 2.69; N, 5.47; S, 6.66%.

Ethyl 3-amino-2-carbamoyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylthieno[2,3-b]pyridine-5-carboxylate (11b). Yellow crystals (dioxane, 94% from **9a**, 96% from **9b**, or 90% from **5b/6b**); m.p. 326–328°C; IR (υ cm^{-1}): 3477 (OH), 3444, 3320 (NH_2), 1723, 1653 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.96 (t, J = 7.2 Hz, 3H, $C\underline{H}_3CH_2$), 2.55 (s, 3H, CH_3), 4.06 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2$), 5.84 (s, 2H, NH_2), 7.27 (s, 2H, $CONH_2$), 7.55 (s, 2H, ArH's), 10.45 (s, br, 1H, OH); Ms m/z (%): 531 (3.8, M^++4), 529 (7.0, M^++2), 527 (3.3, M^+), 514 (6.4), 513 (5.0), 470 (4.8), 467 (7.3), 441 (4.8); Anal. for $C_{18}H_{15}Br_2N_3O_4S$ (529.20): C, 40.85; H, 2.86; N, 7.94; S, 6.06; found: C, 41.05; H, 3.02; N, 7.81; S, 6.12%.

Diethyl 3-amino-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylthieno[2,3-b]pyridine-2,5-dicarboxylate (11c). Yellow crystals (dioxane, 91% from **9c** or 85% from **5b/6c**); m.p. 286–288°C; IR (υ cm^{-1}): 3477 (OH), 3347, 3189 (NH_2), 1723, 1680 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.96 (t, J = 7.2 Hz, 3H, $C\underline{H}_3CH_2$), 1.20 (t, J = 7.2 Hz, 3H, $C\underline{H}_3CH_2$), 2.56 (s, 3H, CH_3), 4.07 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2$), 5.78 (s, 2H, NH_2), 7.60 (s, 2H, ArH's), 10.45 (s, br, 1H, OH); Ms m/z (%): 560 (25.3, M^++4), 558 (52.7, M^++2), 556 (23.3, M^+), 529 (30.2), 513 (27.5), 483 (38.2), 468 (28.8), 452 (23.1), 410 (39.5); Anal. for $C_{20}H_{18}Br_2N_2O_5S$ (558.24): C, 43.03; H, 3.25; N, 5.02; S, 5.74; found: C, 42.88; H, 3.33; N, 5.14; S, 5.63%.

Ethyl 3-amino-2-benzoyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylthieno[2,3-b]pyridine-5-carboxylate (11d). Yellow crystals (dioxane, 95% from **9d** or 90% from **5b/6d**); m.p. 248–250°C; IR (υ cm^{-1}): 3458 (OH), 3355, 3274 (NH_2), 1720 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.96 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 2.55 (s, 3H, CH_3), 4.10 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2$), 5.95 (s, 2H, NH_2), 7.55–8.13 (s, 7H, ArH's), 10.50 (s, br, 1H, OH); Ms m/z (%): 592 (44.5, M^++4), 590 (85.8, M^++2), 588 (41.2, M^+), 559 (19.4), 543 (5.9), 515 (1.1), 511 (4.6), 483 (3.4), 77 (100.0); Anal. for $C_{24}H_{18}Br_2N_2O_4S$ (590.29): C, 48.83; H, 3.07; N, 4.75; S, 5.43; found: C, 48.99; H, 3.21; N, 4.54; S, 5.26%.

Ethyl 2-acetyl-3-amino-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylthieno[2,3-b]pyridine-5-carboxylate (11e). Yellow crystals (dioxane/ethanol mixture, 89% from **5b/6e** at stirring or 94% from **5b/6e** at reflux); m.p. 290–292°C; IR (υ cm^{-1}): 3448 (OH), 3365, 3272 (NH_2), 1724 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.95 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 2.12 (s, 3H, $COCH_3$), 2.62 (s, 3H, CH_3), 4.10 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2$), 5.75 (s, 2H, NH_2), 7.59 (s, 2H, ArH's), 10.55 (s, 1H, OH); Ms m/z (%): 530 (56.0, M^++4), 528 (100.0, M^++2), 526 (49.9, M^+), 513 (35.7), 512 (20.9), 499 (26.2), 483 (16.1), 481 (5.3), 455 (2.6); Anal. for $C_{19}H_{16}Br_2N_2O_4S$ (528.22): C, 43.20; H, 3.05; N, 5.30; S, 6.07; found: C, 43.02; H, 3.14; N, 5.08; S, 6.26%.

General procedure for synthesis of the potassium salts of 10b,c, 11b,c, 16a,b, and 18a,b. A mixture of the appropriate hydroxy containing compounds **10b**,**c**, **11b**,**c**, **16a**,**b**, and **18a**,**b** (10 mmol) in ethanolic potassium hydroxide solution (10 mmol/30 mL ethanol) was stirred at room temperature for 15 min. The solvent was then removed *in vacuo*, and the solid was triturated with dry ether, collected by filtration, dried, and used in the next reaction without further purification.

General procedure for synthesis of compounds 13a,b, 14a,b, 15a,b, and 17a,b. A mixture of 1,4-dibromobutane (**12**) (5 mmol) and each of the appropriate potassium salt of **10b**, **11b**, **16a**,**b**, and **18a**,**b** (10 mmol) or a mixture of **6c** and each of the appropriate potassium salt of **10c** and **11c** in DMF (15 mL) was heated at reflux for 1 h. After cooling, the mixture was poured into a beaker containing 200 g ice. The products were filtrated, washed with cold ethanol, and recrystallized from the proper solvent to yield **13a**,**b**, **14a**,**b**, **15a**,**b**, and **17a**,**b**, respectively.

1,4-Bis(2,6-dibromo-4-[5-acetyl-3-amino-2-carbamoyl-6-methylthieno[2,3-b]pyridin-4-yl]phenoxy)butane (13a). Yellow crystals (dioxane/ethanol mixture, 89%); m.p. 322–324°C; IR (υ cm^{-1}): 3453, 3328, 3140 (NH_2), 1682,

1653 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.10 (s, 6H, 2 $COCH_3$), 2.13 (s, 4H, $OCH_2CH_2CH_2CH_2O$), 2.51 (s, 6H, 2 CH_3), 4.17 (m, 4H, $OCH_2CH_2CH_2CH_2O$), 5.85 (s, br, 4H, 2 NH_2), 7.28 (s, br, 4H, 2 $CONH_2$), 7.74 (s, 4H, ArH's); Anal. for $C_{38}H_{32}Br_4N_6O_6S_2$ (1052.45): C, 43.37; H, 3.06; N, 7.99; S, 6.09; found: C, 43.09; H, 3.15; N, 8.12; S, 5.90%.

1,4-Bis(2,6-dibromo-4-[3-amino-2-carbamoyl-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridin-4-yl]phenoxy) butane (13b). Yellow crystals (dioxane, 91%); m.p. 278–280°C; IR (υ cm^{-1}): 3470, 3361, 3138 (NH_2), 1723, 1658 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.92 (t, J = 7.0 Hz, 6H, 2 CH_3CH_2), 2.13 (m, 4H, $OCH_2CH_2CH_2CH_2O$), 2.58 (s, 6H, 2 CH_3), 4.02–4.14 (m, 8H, $OCH_2CH_2CH_2CH_2O$ and 2 CH_3CH_2), 5.86 (s, br, 4H, 2 NH_2), 7.30 (s, br, 4H, 2 $CONH_2$), 7.72 (s, 4H, ArH's); Anal. for $C_{40}H_{36}Br_4N_6O_8S_2$ (1112.50): C, 43.18; H, 3.15; N, 7.55; S, 5.76; found: C, 43.02; H, 3.04; N, 7.78; S, 5.92%.

Ethyl 5-acetyl-3-amino-4-(3,5-dibromo-4-ethoxycarbonylmethoxyphenyl)-6-methylthieno[2,3-b]pyridine-2-carboxylate (14a). Pale yellow crystals (ethanol, 88%); m.p. 100–102°C; IR (υ cm^{-1}): 3347, 3189 (NH_2), 1728, 1684 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.18–1.23 (m, 6H, 2 CH_3CH_2O), 2.07 (s, 3H, $COCH_3$), 2.52 (s, 3H, CH_3), 4.12–4.19 (m, 4H, 2 CH_3CH_2), 4.82 (s, 2H, OCH_2CO), 5.82 (s, 2H, NH_2), 7.63 (s, 2H, ArH's); Ms m/z (%): 616 (36.2, M^++4), 614 (74.5, M^++2), 612 (35.8, M^+), 599 (48.9), 571 (27.0), 525 (5.7), 496 (28.6), 494 (27.0), 484 (43.7); Anal. for $C_{23}H_{22}Br_2N_2O_6S$ (614.31): C, 44.97; H, 3.61; N, 4.56; S, 5.22; found: C, 44.88; H, 3.50; N, 4.78; S, 5.40%.

Diethyl 3-amino-4-(3,5-dibromo-4-ethoxycarbonylmethoxyphenyl)-6-methylthieno[2,3-b]pyridine-2,5-dicarboxylate (14b). Pale yellow crystals (dioxane/ethanol mixture, 86%); m.p. 268–270°C; IR (υ cm^{-1}): 3359, 3225 (NH_2), 1735, 1714 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.96 (t, J = 6.9 Hz, 3H, CH_3CH_2O), 1.20 (m, 6H, 2 CH_3CH_2O), 2.57 (s, 3H, CH_3), 4.04–4.11 (m, 6H, 3 CH_3CH_2), 4.83 (s, 2H, OCH_2CO), 5.79 (s, 2H, NH_2), 7.60 (s, 2H, ArH's); Ms m/z (%): 646 (8.1, M^++4), 644 (15.8, M^++2), 642 (7.5, M^+), 629 (7.5), 628 (7.0), 615 (46.1), 599 (3.0), 571 (4.9), 557 (28.9), 543 (100.0); Anal. for $C_{24}H_{24}Br_2N_2O_7S$ (644.33): C, 44.74; H, 3.75; N, 4.35; S, 4.98; found: C, 44.59; H, 3.88; N, 4.22; S, 5.02%.

1,4-Bis(2,6-dibromo-4-[8-acetyl-7-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-9-yl]phenoxy) butane (15a). Beige crystals (glacial acetic acid, 78% from **13a** or 93% from **16a**); m.p. >350°C; IR (υ cm^{-1}): 3215 (NH), 1680, 1651 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.14 (m, 10H, $OCH_2CH_2CH_2CH_2O$ and 2 $COCH_3$), 2.60 (s, 6H, 2 CH_3), 4.05 (t, 4H, $OCH_2CH_2CH_2CH_2O$), 7.55 (s, 4H, ArH's), 8.14 (s, 2H, 2 pyrimidine-CH), 12.93 (s, 2H, 2 NH); Ms m/z (%): 1076 (11.1, M^++8), 1072 (26.7, M^++4), 1068 (10.1, M^+), 1057 (1.4), 1039 (9.4), 1029 (8.8), 1002 (8.8), 988 (1.7), 952 (7.0), 931 (6.8), 850 (9.6); Anal. for $C_{40}H_{28}Br_4N_6O_6S_2$ (1072.44): C, 44.80; H, 2.63; N, 7.84; S, 5.98; found: C, 44.99; H, 2.50; N, 7.78; S, 5.85%.

1,4-Bis(2,6-dibromo-4-[8-ethoxycarbonyl-7-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-9-yl] phenoxy)butane (15b). Beige crystals (glacial acetic acid, 82% from **13b** or 90% from **16b**); m.p. 348–350°C; IR (υ cm^{-1}): 3231 (NH), 1697, 1655 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.95 (t, J = 7.2 Hz, 6H, 2 CH_3CH_2), 2.15 (m, 4H, $OCH_2CH_2CH_2CH_2O$), 2.66 (s, 6H, 2 CH_3), 4.11–4.16 (m, 8H, $OCH_2CH_2CH_2CH_2O$ and 2 CH_3CH_2), 7.69 (s, 4H, ArH's), 8.13 (s, 2H, 2 pyrimidine CH-2), 12.94 (s, 2H, 2 NH); Anal. for $C_{42}H_{32}Br_4N_6O_8S_2$ (1128.48): C, 44.54; H, 2.85; N, 7.42; S, 5.66; found: C, 44.70; H, 2.98; N, 7.31; S, 5.49%.

1,4-Bis(2,6-dibromo-4-[8-acetyl-7-methyl-4-oxo-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-d][1,2,3]triazin-9-yl] phenoxy)butane (17a). Colorless crystals (dioxane/ethanol mixture, 88% from **13a** or 94% from **18a**); m.p. 292–294°C; IR (υ cm^{-1}): 3222 (NH), 1684, 1654 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.12 (m, 10H, $OCH_2CH_2CH_2CH_2O$ and 2 $COCH_3$), 2.59 (s, 6H, 2 CH_3), 4.09 (m, 4H, $OCH_2CH_2CH_2CH_2O$), 7.58 (s, 4H, ArH's), 15.60 (s, 2H, 2 NH); Ms m/z (%): 1078 (33.9, M^++8), 1074 (69.9, M^++4), 1072 (43.3, M^++2), 1070 (33.0, M^+), 1015 (26.2), 990 (55.6), 930 (26.7), 913 (36.1), 872 (33.4); Anal. for $C_{38}H_{26}Br_4N_8O_6S_2$ (1074.41): C, 42.48; H, 2.44; N, 10.43; S, 5.97; found: C, 42.66; H, 2.69; N, 10.29; S, 5.86%.

1,4-Bis(2,6-dibromo-4-[8-ethoxycarbonyl-7-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazin-9-yl] phenoxy)butane (17b). Colorless crystals (dioxane, 81% from **13b** or 92% from **18b**); m.p. >350°C; IR (υ cm^{-1}): 3244 (NH), 1691, 1658 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.97 (t, J = 7.2 Hz, 6H, 2 CH_3CH_2), 2.15 (m, 4H, $OCH_2CH_2CH_2CH_2O$), 2.62 (s, 6H, 2 CH_3), 4.09–4.15 (m, 8H, $OCH_2CH_2CH_2CH_2O$ and 2 CH_3CH_2), 7.64 (s, 4H, ArH's), 15.63 (s, 2H, 2 NH); Anal. for $C_{40}H_{30}Br_4N_8O_8S_2$ (1134.46): C, 42.53; H, 2.67; N, 9.88; S, 5.65; found: C, 42.36; H, 2.90; N, 10.01; S, 5.77%.

General procedure for synthesis of compounds 15a,b and 16a,b. A mixture of each of **13a**,**b** or **10b**,**c** (5 mmol) in formic acid (15 mL) was boiled at reflux for 6 h. The reaction mixture was evaporated to its half volume and cooled. The solid products were filtrated, washed with cold ethanol, and then recrystallized from the proper solvent to yield **15a**,**b** and **16a**,**b**, respectively.

8-Acetyl-9-(3,5-dibromo-4-hydroxyphenyl)-7-methylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (16a). Colorless crystals (glacial acetic acid, 92%); m.p. >350°C; IR (υ cm^{-1}): 3418 (OH), 3211 (NH), 1683, 1656 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.13 (s, 3H, $COCH_3$), 2.58 (s, 3H, CH_3), 7.54 (s, 2H, ArH's), 8.13 (s,

1H, pyrimidine CH-2), 10.32 (s, 1H, OH), 12.93 (s, 1H, NH); Anal. for $C_{18}H_{11}Br_2N_3O_3S$ (509.17): C, 42.46; H, 2.18; N, 8.25; S, 5.30; found: C, 42.02; H, 2.39; N, 8.50; S, 5.03%.

Ethyl 9-(3,5-dibromo-4-hydroxyphenyl)-7-methyl-4-oxo-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (16b). Colorless crystals (glacial acetic acid, 87%); m.p. 304–306°C; IR (υ cm^{-1}): 3428 (OH), 3218 (NH), 1697, 1655 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.96 (t, J = 7.2 Hz, 3H, C<u>H</u>$_3$CH$_2$), 2.64 (s, 3H, CH$_3$), 4.11 (q, J = 7.2 Hz, 2H, CH$_3$C<u>H</u>$_2$), 7.54 (s, 2H, ArH's), 8.13 (s, 1H, pyrimidine CH-2), 10.32 (s, 1H, OH), 12.93 (s, 1H, NH); Ms m/z (%): 541 (41.2, M^++4), 539 (80.9, M^++2), 537 (43.0, M^+), 522 (16.3), 492 (73.6), 466 (51.8), 449 (63.6), 432 (7.2); Anal. for $C_{19}H_{13}Br_2N_3O_4S$ (539.20): C, 42.32; H, 2.43; N, 7.79; S, 5.95; found: C, 42.06; H, 2.78; N, 7.99; S, 5.71%.

General procedure for synthesis of compounds 17a,b and 18a,b. A solution of each of **13a,b** or **10b,c** (5 mmol) in glacial acetic acid (20 mL) and concentrated hydrochloric acid (4 mL) was added drop by drop to cold solution of sodium nitrite (10 mmol for compounds **13a,b** or 5 mmol for compounds **10b,c** in 5 mL of water) with constant stirring at 0–5°C. Then stirring was continued for 3 h. The reaction mixture was then allowed to stand at room temperature for 30 min. The solid obtained was filtrated and recrystallized from the proper solvent to yield **17a,b** and **18a,b**, respectively.

8-Acetyl-9-(3,5-dibromo-4-hydroxyphenyl)-7-methylpyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazin-4(3H)-one (18a). Colorless crystals (dioxane, 93%); m.p. 320–322°C; IR (υ cm^{-1}): 3423 (OH), 3214 (NH), 1680, 1657 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.10 (s, 3H, COCH$_3$), 2.57 (s, 3H, CH$_3$), 7.58 (s, 2H, ArH's), 10.20 (s, 1H, OH), 15.60 (s, 1H, NH); Ms m/z (%): 512 (17.2, M^++4), 511 (18.0, M^++3), 477 (17.2), 466 (18.5), 436 (21.4), 405 (18.3), 349 (20.1); Anal. for $C_{17}H_{10}Br_2N_4O_3S$ (510.16): C, 40.02; H, 1.98; N, 10.98; S, 6.29; found: C, 40.26; H, 2.14; N, 11.20; S, 6.01%.

Ethyl 9-(3,5-dibromo-4-hydroxyphenyl)-7-methyl-4-oxo-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine-8-carboxylate (18b). Colorless crystals (dioxane, 90%); m.p. 310–312°C; IR (υ cm^{-1}): 3432 (OH), 3247 (NH), 1695, 1660 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.97 (t, J = 7.2 Hz, 3H, C<u>H</u>$_3$CH$_2$), 2.63 (s, 3H, CH$_3$), 4.12 (q, J = 7.2 Hz, 2H, CH$_3$C<u>H</u>$_2$), 7.63 (s, 2H, ArH's), 10.23 (s, 1H, OH), 15.62 (s, 1H, NH); Ms m/z (%): 542 (1.2, M^++4), 540 (2.5, M^++2), 538 (1.2, M^+), 511 (0.8), 510 (0.7), 454 (0.8), 433 (0.7); Anal. for $C_{18}H_{12}Br_2N_4O_4S$ (540.19): C, 40.02; H, 2.24; N, 10.37; S, 5.94; found: C, 40.19; H, 2.05; N, 10.56; S, 5.70%.

General procedure for synthesis of compounds 19a,b. A mixture of each of **10b,c** (5 mmol) and carbon disulfide (5 mL) in pyridine (25 mL) was boiled at reflux for 10 h. The reaction mixture was cooled and poured onto ice-cold water, and the products were filtrated, washed with cold ethanol, and recrystallized from the proper solvent to afford **19a,b**, respectively.

8-Acetyl-9-(3,5-dibromo-4-hydroxyphenyl)-7-methyl-2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(1H)-one (19a). Colorless crystals (dioxane, 88%); m.p. >350°C; IR (υ cm^{-1}): 3411 (OH), 3178 (NH), 1682, 1659 (CO), 1540 (CS); ^{1}H-NMR (DMSO-d_6): δ 0.96 (t, J = 7.2 Hz, 3H, C<u>H</u>$_3$CH$_2$), 2.57 (s, 3H, CH$_3$), 4.12 (q, J = 7.2 Hz, 2H, CH$_3$C<u>H</u>$_2$), 7.55 (s, 1H, NH), 7.71 (s, 2H, ArH's), 10.25 (s, 1H, OH), 12.66 (s, 1H, NH); Anal. for $C_{18}H_{11}Br_2N_3O_3S_2$ (541.24): C, 39.94; H, 2.05; N, 7.76; S, 11.85; found: C, 40.12; H, 2.31; N, 7.99; S, 11.59%.

Ethyl 9-(3,5-dibromo-4-hydroxyphenyl)-7-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (19b). Colorless crystals (dioxane, 85%); m.p. 296–298°C; IR (υ cm^{-1}): 3436 (OH), 3205 (NH), 1719, 1665 (CO), 1540 (CS); ^{1}H-NMR (DMSO-d_6): δ 2.13 (s, 3H, COCH$_3$), 2.60 (s, 3H, CH$_3$), 7.53 (s, br, 1H, NH), 7.70 (s, 2H, ArH's), 10.12 (s, 1H, OH), 12.68 (s, 1H, NH); Ms m/z (%): 573 (2.2, M^++4), 571 (4.5, M^++2), 569 (2.7, M^+), 556 (1.0), 540 (1.3), 526 (5.1), 496 (3.0), 481 (7.9), 467 (3.0); Anal. for $C_{19}H_{13}Br_2N_3O_4S_2$ (571.26): C, 39.95; H, 2.29; N, 7.36; S, 11.23; found: C, 39.62; H, 1.98; N, 7.09; S, 11.52%.

General procedure for synthesis of compounds 21a,b. A mixture of each of **10b,c** (5 mmol) and acetic anhydride (15 mL) was boiled at reflux for 6 h. The reaction mixture was evaporated to its half volume and cooled. The solid products were filtrated, washed with cold ethanol, and then recrystallized from the proper solvent to yield **21a,b**, respectively.

4-(8-Acetyl-2,7-dimethyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]-pyrimidin-9-yl)-2,6-dibromophenyl acetate (21a). Colorless crystals (glacial acetic acid, 85%); m.p. 306–308°C; IR (υ cm^{-1}): 3319 (NH), 1718, 1652 (CO); ^{1}H-NMR (DMSO-d_6): δ 2.16 (s, 3H, CH$_3$), 2.24 (s, 3H, COCH$_3$), 2.44 (s, 3H, OCOCH$_3$), 2.64 (s, 3H, CH$_3$), 7.74 (s, 2H, ArH's), 12.70 (s, 1H, NH); Ms m/z (%): 567 (44.6, M^++4), 565 (89.7, M^++2), 563 (42.1, M^+), 522 (2.9), 504 (1.4), 483 (15.5), 471 (15.1), 474 (0.4), 453 (42.2), 422 (32.0); Anal. for $C_{21}H_{15}Br_2N_3O_4S$ (565.23): C, 44.62; H, 2.67; N, 7.43; S, 5.67; found: C, 44.39; H, 2.90; N, 7.62; S, 5.41%.

Ethyl 9-[4-(acetyloxy)-3,5-dibromophenyl]-2,7-dimethyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (21b). Colorless crystals (glacial acetic acid, 90%); m.p. 336–338°C; IR (υ cm^{-1}): 3342 (NH), 1724, 1657 (CO); ^{1}H-NMR (DMSO-d_6): δ 0.96 (t, J = 7.2 Hz, 3H, OCH$_2$C<u>H</u>$_3$), 2.16 (s, 3H, CH$_3$), 2.44 (s, 3H, COCH$_3$), 2.68 (s, 3H, CH$_3$), 4.14 (q, J = 7.2 Hz, 2H, OC<u>H</u>$_2$CH$_3$), 7.75 (s, 2H, ArH's), 12.82 (s, 1H, NH); Ms

m/z (%): 597 (21.6, M^++4), 595 (43.2, M^++2), 593 (23.4, M^+), 583 (16.9), 553 (19.2), 524 (16.7), 431 (15.7); Anal. for $C_{22}H_{17}Br_2N_3O_5S$ (595.26): C, 44.39; H, 2.88; N, 7.06; S, 5.39; found: C, 44.02; H, 2.99; N, 7.36; S, 5.02%.

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