

An expedient synthesis of novel bis[thienopyridines] linked to arene or heteroarene core as novel hybrid molecules

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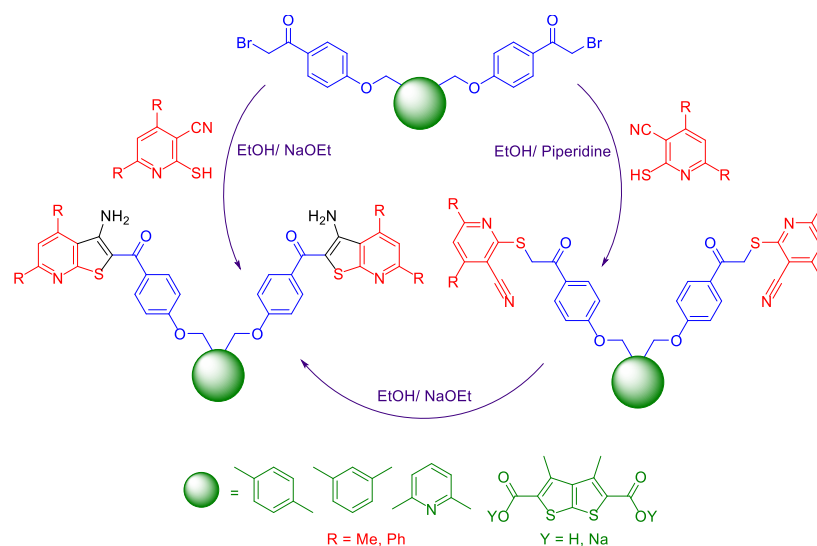
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Abstract

A series of novel bis(thieno[2,3-*b*]pyridines) based arenes or heteroarenes have been synthesized from the appropriate bis-bromoacetyl derivatives upon treatment with the corresponding 2-mercaptonicotinonitrile derivatives in ethanolic sodium ethoxide at reflux. Attempts to synthesize these compounds *via* bis-alkylation of the appropriate phenol derivative with the corresponding dibromo compounds using a mild base were unsuccessful.



Keywords: Pyridinethiones, thieno[2,3-*b*]pyridines, alkylation, cyclization, bis(thieno[2,3-*b*]pyridines).

Introduction

Pyridine is one of the most interesting heterocyclic rings due to their wide range of pharmaceutical properties including anti-inflammatory,^{1,2} antiasthmatic,³ antidepressant,⁴ acetylcholinesterase inhibitors (AChE),⁵ HIV protease inhibitors.⁶ They are also used for treating hypertension⁷ or hypotension,⁸ as well as for inducing or preventing apoptosis.⁹

The pyridine structure is present in many natural compounds like nicotinic acid (vitamin B3) and pyridoxine (vitamin B6) and also in many drugs (Figure 1).

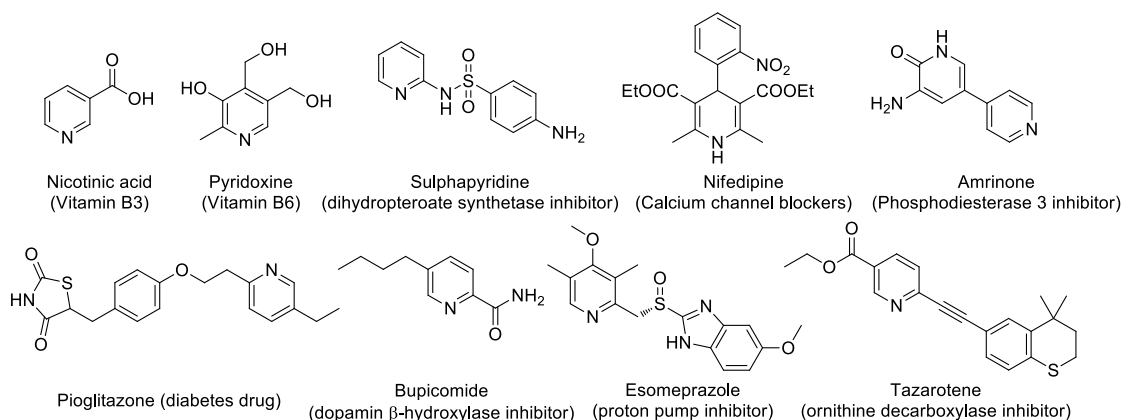


Figure 1. Natural compounds and drugs containing pyridine ring.

Pyridines are also exploited in agrochemistry^{10,11} as well as in materials science.¹² Different methodologies for construction and functionalization of pyridine derivatives have been recently reviewed.^{13,14} Thienopyridines are considered as one of the important fused heterocyclic compounds for their usefulness therapeutic applications.^{15,16}

Moreover, several thienopyridine derivatives are known to possess antiviral,¹⁷ anti-inflammatory,¹⁸ antimicrobial,¹⁹ antidiabetic,²⁰ antihypertensive²¹ and osteogenic activities.²² In particular, thieno[2,3-*b*]pyridines are reported to be useful as anticancer agents.^{23–25}

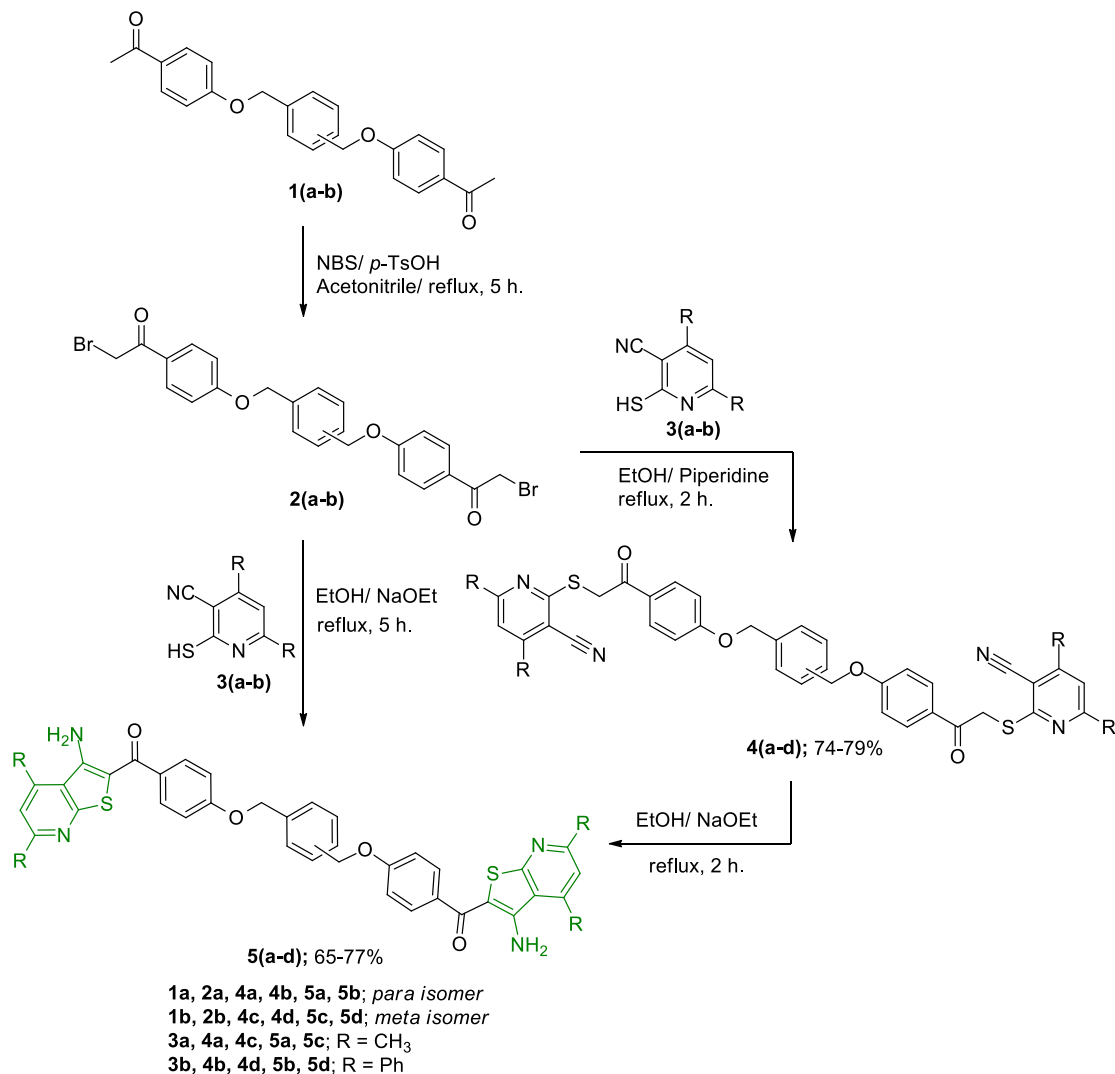
Due to the numerous applications of pyridine as well as thienopyridine systems, exploring novel structures and novel synthetic procedures for this class of compounds is still in need.

Motivated by these findings and in conjunction with recent interest on molecular hybridization concept as well as on the chemistry of bis-heterocyclic compounds,^{26–39} we report herein on the synthesis of novel bis[thienopyridines] linked to arene or heteroarene spacers.

Results and Discussion

The new bis(thieno[2,3-*b*]pyridines) **5(a-d)**, in which the two thienopyridine moieties are linked *via* aromatic spacers, have been synthesized from the appropriate bis-bromoacetyl derivatives **2(a-b)** upon treatment with the corresponding 2-mercaptopyridonitrile derivatives³⁴ **3a** and **3b** in ethanolic sodium ethoxide at reflux. Compounds **2(a-b)** were obtained by bromination of the appropriate bis(acetyl) derivatives **1(a-b)**⁴⁰ upon treatment with *N*-bromosuccinimide in acetonitrile at reflux.⁴⁰

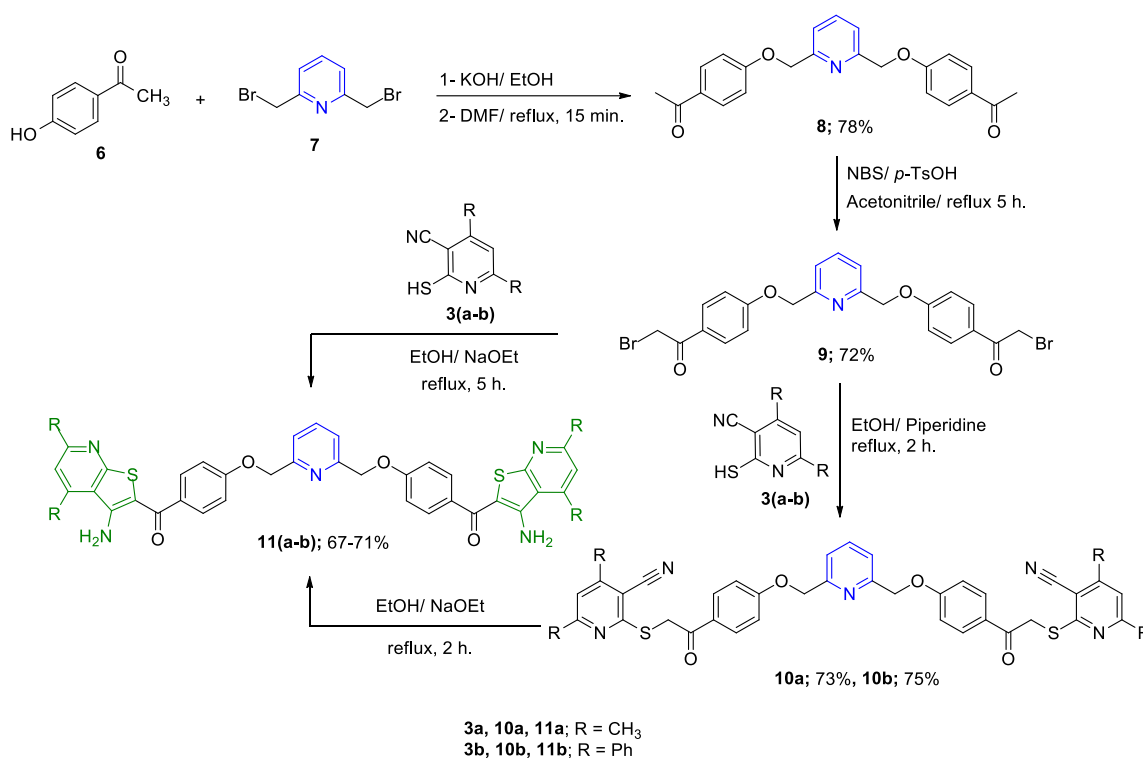
The step-wise synthesis of **5(a-d)** was also performed *via* initial formation of bis(sulfanediyl))bis(nicotinonitriles) **4(a-d)** by the reaction of **2(a-b)** with 2-mercaptonicotinonitriles **3a** and **3b** in ethanol containing few drops of piperidine at reflux. Cyclization of the latter compounds to the corresponding bis(thienopyridines) **5(a-d)** was achieved in 65–77% yields, upon heating at reflux in ethanolic solution containing sodium ethoxide (Scheme 1).



Scheme 1. Synthesis of bis(thieno[2,3-*b*]pyridines) **5(a-d)** linked *via* aromatic spacers.

The structures of compounds **5(a-d)** were established based on their spectral data and elemental analyses. Thus, compound **5c** showed in its IR spectra the presence of absorption bands at 3480, 3436 and 1593 cm^{-1} characteristic for the amino group and the carbonyl band, respectively. The successful ring closure of **4c** is confirmed by the disappearance of absorption bands characteristic for the cyano group in compound **5c** together with the presence of this band in compound **4c**. Moreover, the ^1H NMR spectra provide a further confirmation for the ring closure of **4c** to **5c**. Thus, compound **4c** exhibited the presence of SCH_2 protons, resonated at δ 4.77 ppm as a singlet signal integrating four protons in compound **4c** while that of compound **5c** did not show this signal. Moreover, compounds **4c** and **5c** also featured the methylene ether linkage OCH_2 as a singlet signal at δ 5.2 ppm. All other protons were seen at the expected chemical shifts and integral values (See experimental section).

The same methodology can also be applied for the synthesis of (((pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))bis((3-aminothieno[2,3-*b*]pyridin-2-yl)meth-anones) **11a** and **11b** starting from 1,1'-(((pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))diethanone (**8**). Thus, reaction of 2,6-bis(bromomethyl)pyridine (**7**) with potassium 4-acetylphenolate in DMF at reflux afforded **8** in 78% yield. Subsequent bromination of **8** upon treatment with *N*-bromosuccinimide in acetonitrile at reflux afforded bis(bromoacetyl) product **9** in 72% yield. It is worthy to mention that bis(bromoacetyl) products **9** as well as **2a** and **2b** were isolated as pure single products while no aromatic brominated products under the reaction conditions were detected. Reaction of **9** with 2-mercaptonicotinonitriles **3a** and **3b** in ethanolic solution containing piperidine at reflux gave the corresponding bis(sulfanediyl)bis(nicotinenitriles) **10a** and **10b** which could then be cyclized to the corresponding bis(thienopyridines) **11a** and **11b** upon heating at reflux in ethanolic sodium ethoxide solution (Scheme 2). Reaction of **9** with each of **3a** and **3b** in ethanolic sodium ethoxide at reflux gave the desired bipodals **11a** and **11b** in 70% and 71% yields, respectively.

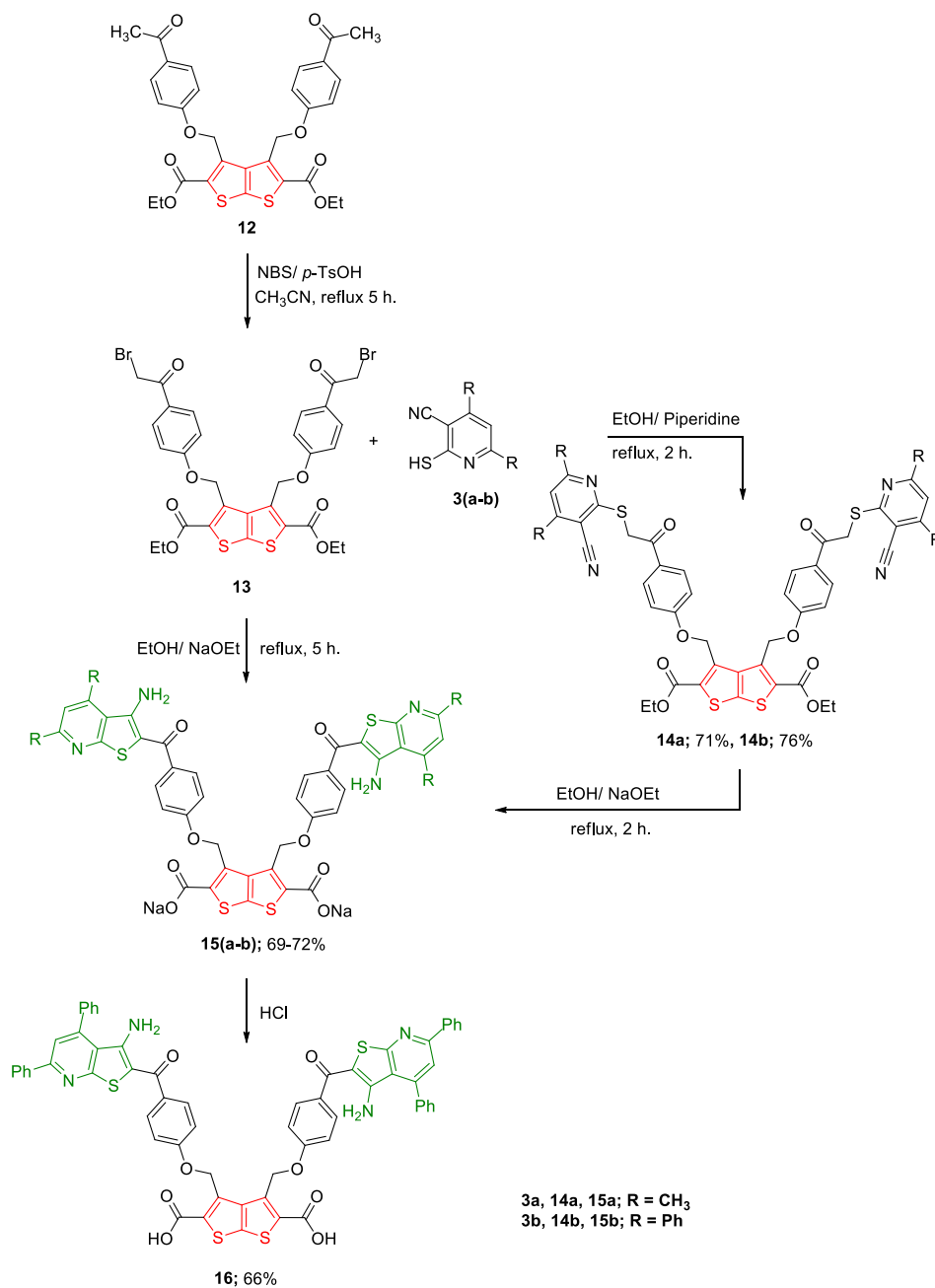


Scheme 2. Synthesis of bis(thieno[2,3-*b*]pyridines) **11(a-b)** linked *via* pyridine spacers.

The study was extended to include the synthesis of novel bis(thieno[2,3-*b*]pyridines) **15(a-b)** which are linked to thienothiophene core (Scheme 3). The bis-bromoacetyl derivative **13**⁴¹ was chosen as precursor and was obtained as previously reported from the corresponding bis(acetyl) derivative **12**⁴¹ upon treatment with *N*-bromosuccinimide in acetonitrile at reflux.⁴¹

Both of two-step and one-step syntheses of **15(a-b)** were performed. Thus, reaction of **13** with 2-mercaptonicotinonitrile derivatives **3a** and **3b** in ethanolic sodium ethoxide at reflux afforded the corresponding sodium 3,4-bis((4-(3-aminothieno[2,3-*b*]pyridine-2-carbonyl)phenoxy)-methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate **15(a-b)** in 69-72% yields. On the other hand, step-wise synthesis of **15(a-b)** was achieved by firstly formation of diethyl 3,4-bis((4-(2-(3-cyanopyridin-2-ylthio)acetyl)phenoxy)-methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate **14(a-b)** by the reaction of **13** with 2-

mercaptocotinonitriles **3(a-b)** in ethanol containing few drops of piperidine at reflux. Subsequent heating of **14(a-b)** at reflux in ethanolic solution containing sodium ethoxide afforded the corresponding sodium 3,4-bis((4-(3-aminothieno[2,3-*b*]pyridine-2-carbonyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate **15(a-b)** in 67 and 69% yields, respectively. The free dicarboxylic acid, 3,4-bis((4-(3-amino-4,6-diphenylthieno[2,3-*b*]pyridine-2-carbonyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylic acid (**16**) was liberated upon neutralization of **15b** with hydrochloric acid (Scheme 3).

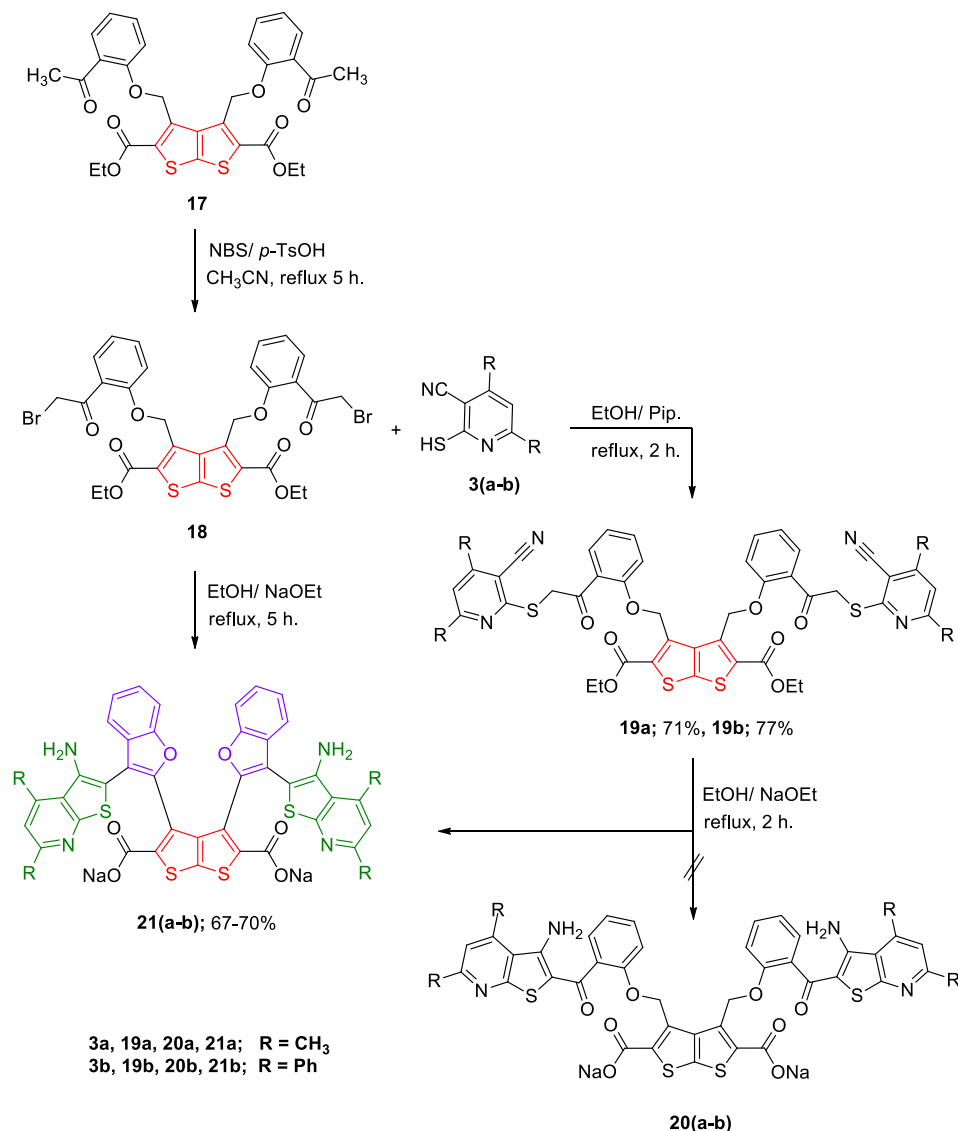


Scheme 3. Synthesis of bis(thieno[2,3-*b*]pyridines) **15(a-b)** linked *via* thienothiophene spacers.

Compound **14a** featured the ethyl ester protons as triplet and quartet signals at δ 1.27 and 4.33 in their ^1H NMR spectra. On the other hand, these signals disappeared in the ^1H NMR spectra of both of the di-sodium salts **15(a-b)** as well as the free dicarboxylic acid **16**. The latter compound showed the presence of broad signal

at δ 3.40 characteristic for the COOH proton. The structure of **16** was further confirmed by IR spectra which showed absorption band at 3430 cm^{-1} characteristic for the OH of the carboxylic acid COOH.

Our study included also the synthesis of novel sodium 3,4-bis((2-(3-aminothieno[2,3-*b*]pyridine-2-carbonyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate **20(a-b)** as outlined in Scheme 4. For this purpose, the bis-bromoacetyl derivative **18**⁴¹ was obtained from the corresponding bis(acetyl) derivative **17**⁴¹ upon treatment with *N*-bromosuccinimide in acetonitrile at reflux.⁴¹ Reaction of **18** with 2-mercaptopyridine derivatives **3a** and **3b** in ethanol containing few drops of piperidine at reflux afforded the corresponding diethyl 3,4-bis((2-(2-((3-cyano-4,6-dimethylpyridin-2-yl)thio)acetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate **19(a-b)** in 71 and 77% yields, respectively. Subsequent heating of **19(a-b)** at reflux in ethanolic solution containing sodium ethoxide did not lead to the formation of sodium 3,4-bis((2-(3-aminothieno[2,3-*b*]pyridine-2-carbonyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate **20(a-b)** but gave instead the corresponding sodium 3,4-bis(3-(3-amino-thieno[2,3-*b*]pyridin-2-yl)benzofuran-2-yl)thieno[2,3-*b*]thiophene-2,5-dicarboxylates **21(a-b)**. The latter compounds could also be obtained in one step by the reaction of bis-bromoacetyl derivative **18** with 2-mercaptopyridine derivatives **3a** and **3b** in ethanolic sodium ethoxide at reflux (Scheme 4).



Scheme 4. Synthesis of bis(thieno[2,3-*b*]pyridines) **20(a-b)**.

The formation of **21a** and **21b** proceeded *via* intramolecular cyclocondensation of the methylene groups at the 3-position of thienothiophene with the ketonic groups of compound **19a** and **19b**, respectively. Similar behavior of some related systems has been previously reported by us as well as by other groups.^{42–45}

The structures of compounds **21(a-b)** were established based on their spectral data and elemental analyses. Thus compound **21a** showed in its IR spectrum the presence of absorption bands at 3432 and 3330 cm^{-1} characteristic for the amino group. Moreover, its ^1H NMR spectrum provide a further confirmation for the ring closure of **19a** to **21a**. Thus, compound **21a** did not revealed the presence of characteristic signals for the methylene ether protons SCH_2 as well as the OCH_2 protons. On the other hand, its precursor **19a** showed two singlet signals each integrating four protons resonated at δ 4.33 and 5.67 ppm characteristic for the SCH_2 and the OCH_2 protons, respectively. All other protons were seen at the expected chemical shifts and integral values (See experimental section).

Motivated by these results, we also attempted to synthesize the novel bis(thieno[2,3-*b*]pyridines) **22** and **23** (Figure 2) which are linked to pyridine and quinoxaline, respectively, as spacers by the reaction of 2-mercaptonicotinonitrile **3(a-b)** with the appropriate bis(bromoacetyl) derivatives using a similar approach.

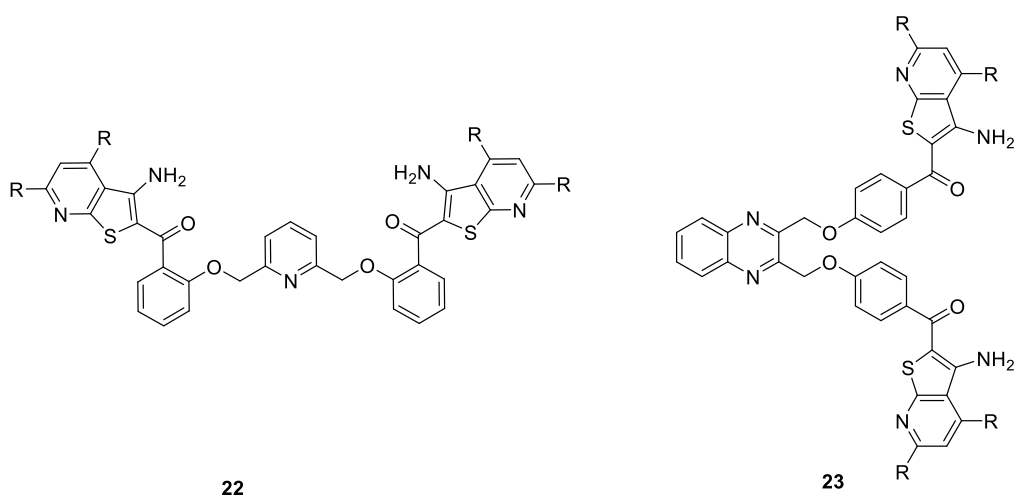
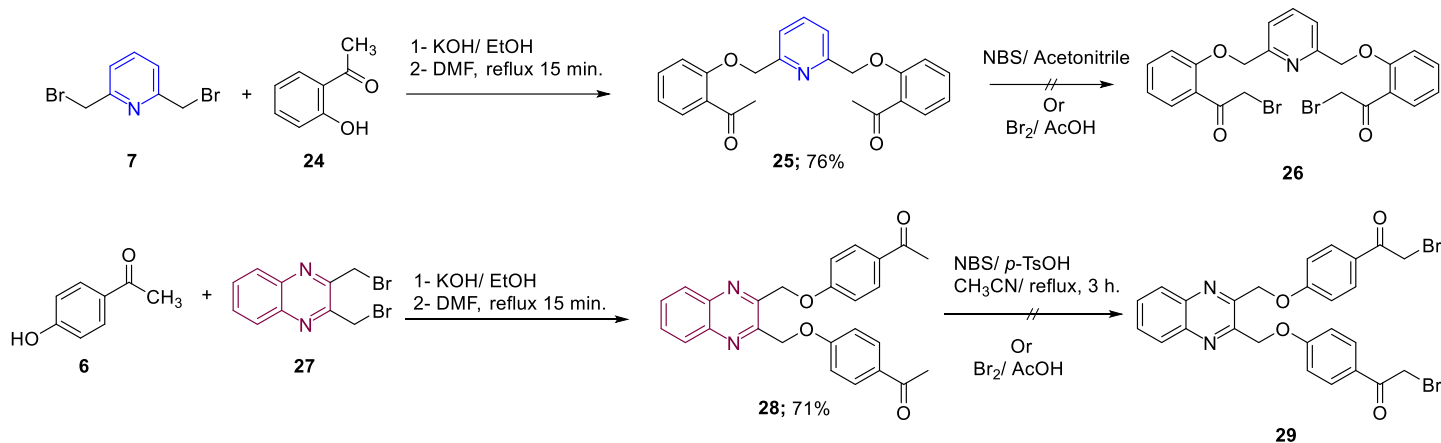


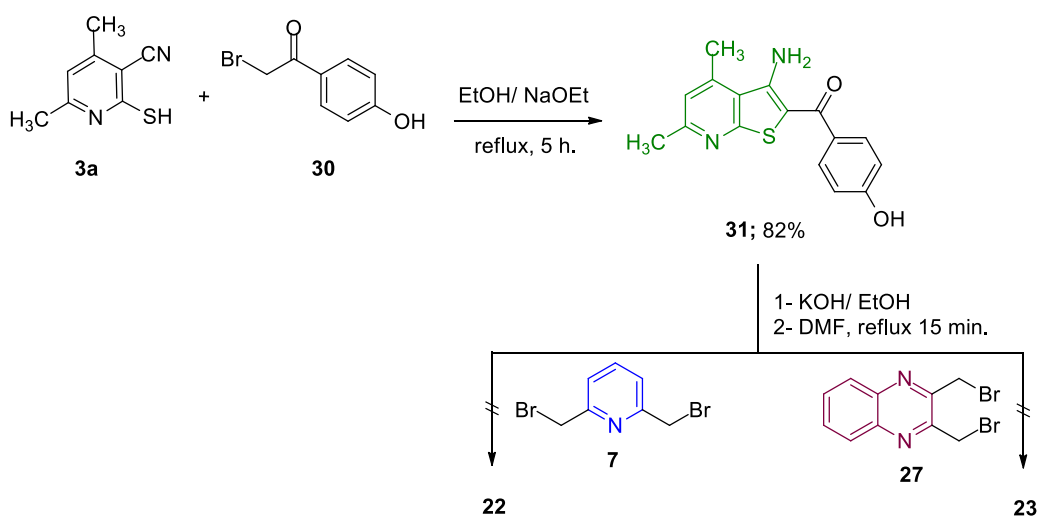
Figure 2. Structures of bis(thieno[2,3-*b*]pyridines) linked to pyridine and quinoxaline **22** and **23**.

To achieve this goal we studied the synthesis of bis(acetyl)pyridine **25** by the reaction of 2,6-bis(bromomethyl)pyridine (**7**) with potassium 2-acetylphenolate in DMF at reflux. Likewise, bis(acetyl)quinoxaline **28** were also obtained by the reaction of 2,3-bis(bromomethyl)quinoxalines (**27**) with potassium 4-acetylphenolate in DMF at reflux. Attempted bromination of **25** and **28** to give the corresponding bis(bromoacetyl) derivatives **26** and **29**, respectively, either by reaction with Br_2 in acetic acid or upon treatment with *N*-bromosuccinimide in acetonitrile at reflux were unsuccessful. In all trials, the reactions gave a mixture of products that were not easily handled and have not been characterized as yet (Scheme 5).



Scheme 5. Attempted Synthesis of bis(bromoacetyl) derivatives **26** and **29**.

Aiming at synthesizing compounds **22** and **23**, which could not be prepared by the above method, we then turned to another strategy. For this purpose, (3-amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)(4-hydroxyphenyl)methanone (**31**)⁴⁶ have initially been synthesized by the reaction of 2-bromo-1-(4-hydroxyphenyl)ethanone (**30**) with **3a**. Compound **31** was then allowed to react with each of bis(bromomethylquinoxaline) **7** and **27** in the presence of ethanolic solution containing sodium ethoxide aiming at obtaining **22** and **23**, respectively. Unfortunately, the ¹H-NMR of the reaction products indicated the presence of the target compounds **22** and **23** together with other non-isolable products which may be formed as a result of competing *N*-alkylation reaction (Scheme 6). It is worthy mentioned that repeated attempts to get the target products **22** or **23** by carrying out the alkylation reactions under different basic conditions were also unsuccessful.



Scheme 6. Attempts to Synthesis of bis(thieno[2,3-*b*]pyridines) **22** and **23**.

Conclusions

We developed an efficient synthesis of previously unreported bis(thienopyridines) which are linked to arene or heteroarene *via* phoxymethyl groups. The structures of the newly synthesized compounds were fully characterized by both spectral data and elemental analyses. Trials to synthesize these compounds by alkylation of thieno[2,3-*b*]pyridin-2-yl(4-hydroxyphenyl)methanone with the appropriate dibromo-compounds were unsuccessful. The main advantages of these reactions include mild reaction conditions, good yields, easily accessible starting materials and straightforward product isolation. The newly synthesized compounds achieved the “hybrid molecules” concept which aims at combining two promising pharmacophores in one molecule.

Experimental Section

General. Melting points were determined in open glass capillaries with a Gallenkamp apparatus and were not corrected. Infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP3-300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer operating at 300 MHz (^1H NMR) and 75 MHz (^{13}C NMR), a Varian VXR spectrometer operating at 400 MHz (^1H NMR) and 101 MHz (^{13}C NMR) and a Varian VXR spectrometer operating at 500 MHz (^1H NMR) and 126 MHz (^{13}C NMR) using TMS as an internal standard and DMSO-*d*₆ as a solvent. Mass spectra were measured on a GC MS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The starting **1(a-b)**,⁴⁰ **2(a-b)**,⁴⁰ **3(a-b)**,³⁴ **12**,⁴¹ **13**,⁴¹ **17**,⁴¹ **18**⁴¹ and **31**⁴⁶ were prepared following literature procedures.

Synthesis of 2,2'-(2,2'-(4,4'-(phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyl))bis(4,6-disubstituted nicotinonitrile) 4(a-d). To a solution of the appropriate bis-bromoacetyls **2a** or **2b** (5 mmol) in ethanol (25 mL) containing 2-3 drops piperidine, the appropriate 2-mercapto-4,6-disubstituted nicotinonitriles **3a** or **3b** (10 mmol) was added. The reaction mixture was heated at reflux for 3–4 h. The solid product obtained upon cooling was filtered off and recrystallized from ethanol/DMF to afford the title compounds **4(a-d)**.

2,2'-(2,2'-(4,4'-(1,4-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyl))bis(4,6-dimethylnicotinonitrile) (4a). Pale yellow powder, mp 227–229 °C; yield 78%, IR (KBr disc) $\nu = 3064, 2948, 2215, 1678, 1599, 1422 \text{ cm}^{-1}$. ^1H NMR (300 MHz, DMSO) δ 2.19 (s, 6H, CH₃), 2.39 (s, 6H, CH₃), 4.77 (s, 4H, SCH₂), 5.25 (s, 4H, OCH₂), 7.04 (s, 2H, pyridine-5-H), 7.15 (d, 4H, *J* 8.7 Hz), 7.50 (s, 4H, ArH), 8.04 (d, 4H, *J* 8.7 Hz). MS (*m/z*) 698 (M^+). Anal. Calcd. For C₄₀H₃₄N₄O₄S₂: C, 68.75; H, 4.90; N, 8.02; S, 9.18. Found: C, 68.48; H, 4.79; N, 8.19; S, 9.24.

2,2'-(2,2'-(4,4'-(1,4-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))-bis(2-oxoethane-2,1-diyl))bis(sulfanediyl))bis(4,6-diphenylnicotinonitrile) (4b). Pale yellow powder, mp 231–233 °C; yield 79%, IR (KBr disc) $\nu = 3057, 2917, 2214, 1686, 1597, 1461 \text{ cm}^{-1}$. ^1H NMR (300 MHz, DMSO) δ 4.79 (s, 4H, SCH₂), 5.34 (s, 4H, OCH₂), 7.06 (s, 2H, pyridine-5-H), 7.09–7.43 (m, 10H, ArH), 7.53–7.82 (m, 10H, ArH), 7.85 (s, 4H, ArH), 7.90 (d, 4H, *J* 8.7 Hz), 8.08 (d, 4H, *J* 8.7 Hz). ^{13}C NMR (126 MHz, DMSO): 37.8, 69.4, 102.8, 115.2, 116.0, 116.4, 127.7, 128.2, 128.9, 129.0, 129.1, 129.2, 129.4, 130.5, 130.9, 136.0, 136.4, 136.9, 154.5, 157.9, 162.1, 162.6, 191.3. MS (*m/z*) 947 (M^+). Anal. Calcd. For C₆₀H₄₂N₄O₄S₂: C, 76.09; H, 4.47; N, 5.92; S, 6.77. Found: C, 76.34; H, 4.33; N, 5.69; S, 6.44.

2,2'-(2,2'-(4,4'-(1,3-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyl))bis(4,6-dimethylnicotinonitrile) (4c). Pale yellow powder, mp 171–173 °C; yield 74%, IR (KBr disc) ν 3062, 2916, 2215, 1680, 1598, 1421 cm^{-1} . ^1H NMR (300 MHz, DMSO) δ 2.20 (s, 6H, CH_3), 2.39 (s, 6H, CH_3), 4.77 (s, 4H, SCH_2), 5.26 (s, 4H, OCH_2), 7.04 (s, 2H, pyridine-5-H), 7.16 (d, 4H, J 9 Hz), 7.45–7.46 (m, 3H, ArH), 7.58 (s, 1H, ArH), 8.04 (d, 4H, J 8.7 Hz). ^{13}C NMR (75 MHz, DMSO): 19.5, 23.9, 36.7, 69.3, 103.5, 114.7, 115.0, 120.3, 127.0, 127.4, 128.7, 129.3, 130.6, 136.7, 152.4, 159.9, 161.1, 162.3, 191.9. MS (m/z) 698 (M^+). Anal. Calcd. For $\text{C}_{40}\text{H}_{34}\text{N}_4\text{O}_4\text{S}_2$: C, 68.75; H, 4.90; N, 8.02; S, 9.18. Found: C, 68.58; H, 4.66; N, 8.15; S, 9.10.

2,2'-(2,2'-(4,4'-(1,3-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyl))bis(4,6-diphenylnicotinonitrile) (4d). Pale yellow powder, mp 229–231 °C; yield 77%, IR (KBr disc) ν 3055, 2917, 2211, 1674, 1596, 1445 cm^{-1} . ^1H NMR (300 MHz, DMSO) δ 4.95 (s, 4H, SCH_2), 5.32 (s, 4H, OCH_2), 7.12 (s, 2H, pyridine-5-H), 7.15–7.47 (m, 10H, ArH), 7.51–7.73 (m, 10H, ArH), 7.74–7.75 (m, 3H, ArH), 7.84 (s, 1H, ArH), 7.89 (d, 4H, J 7.8 Hz), 8.08 (d, 4H, J 9 Hz). MS (m/z) 947 (M^+). Anal. Calcd. For $\text{C}_{60}\text{H}_{42}\text{N}_4\text{O}_4\text{S}_2$: C, 76.09; H, 4.47; N, 5.92; S, 6.77. Found: C, 76.32; H, 4.28; N, 5.77; S, 6.57.

Synthesis of (4,4'-(phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis((3-amino-4,6-disubstituted-thieno[2,3-*b*]pyridin-2-yl)methanone) 5(a-d)

Method A. A mixture of the appropriate bis-bromoacetyl **2a** or **2b** (5 mmol) in ethanol (25 mL) containing sodium ethoxide (10 mmol) and the appropriate 2-mercapto-4,6-disubstituted nicotinonitrile **3a** or **3b** (10 mmol) was added. The reaction mixture was heated at reflux for 5 h. The solid products obtained upon cooling were filtered off and recrystallized from DMF to afford the title compounds **5(a-d)**.

Method B. A solution of the appropriate 2,2'-(2,2'-(4,4'-(phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyl))bis(4,6-disubstitutednicotinonitrile) intermediates **4(a-d)** (2 mmol) in ethanol (25 mL) containing sodium ethoxide (4 mmol) was heated at reflux for 3 h. The reaction mixture was then cooled, and the solvent was evaporated in *vacuo*. The solid residue was collected and recrystallized from DMF to afford **5(a-d)**.

(4,4'-(1,4-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis((3-amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)methanone) (5a). Yellow powder, mp 295–297 °C; yield (A) 72%; (B) 65%, IR (KBr disc) ν 3489, 3437, 3070, 2972, 1593, 1554, 1462 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ 2.52 (s, 6H, CH_3), 2.77 (s, 6H, CH_3), 5.24 (s, 4H, OCH_2), 7.11 (s, 2H, pyridine-5-H), 7.16 (d, 4H, J 8.8 Hz), 7.54 (s, 4H, ArH), 7.79 (d, 4H, J 8.8 Hz), 7.98 (br. s, 4H, NH_2). ^{13}C NMR (101 MHz, DMSO): 20.5, 24.4, 69.6, 102.8, 114.9, 122.1, 122.4, 128.4, 130.0, 130.9, 134.0, 136.8, 146.3, 152.8, 161.0, 161.8, 188.4. MS (m/z) 698 (M^+). Anal. Calcd. For $\text{C}_{40}\text{H}_{34}\text{N}_4\text{O}_4\text{S}_2$: C, 68.75; H, 4.90; N, 8.02; S, 9.18. Found: C, 68.49; H, 4.61; N, 8.24; S, 9.32.

(4,4'-(1,4-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis((3-amino-4,6-diphenylthieno[2,3-*b*]pyridin-2-yl)methanone) (5b). Yellow powder, mp 263–265 °C; yield (A) 73%; (B) 70%, IR (KBr disc) ν 3466, 3257, 2918, 1593, 1543, 1432 cm^{-1} . ^1H NMR (300 MHz, DMSO) δ 5.25 (s, 4H, OCH_2), 6.84 (br. s, 4H, NH_2), 7.18 (d, 4H, J 8.7 Hz), 7.50–7.63 (m, 20H, ArH), 7.82 (s, 2H, pyridine-5-H), 7.83 (d, 4H, J 8.7 Hz), 8.22–8.25 (m, 4H, ArH). ^{13}C NMR (101 MHz, DMSO): 69.6, 103.9, 113.4, 115.0, 118.8, 120.3, 127.7, 128.4, 128.9, 129.4, 129.5, 130.1, 130.9, 133.8, 136.6, 136.9, 137.6, 149.2, 150.2, 157.6, 161.2, 162.4, 188.4. MS (m/z) 947 (M^+). Anal. Calcd. For $\text{C}_{60}\text{H}_{42}\text{N}_4\text{O}_4\text{S}_2$: C, 76.09; H, 4.47; N, 5.92; S, 6.77. Found: C, 76.23; H, 4.26; N, 5.80; S, 6.60.

(4,4'-(1,3-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis((3-amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)methanone) (5c). Yellow powder, mp 230–231 °C; yield (A) 72%; (B) 67%, IR (KBr disc) ν 3480, 3436, 3038, 2972, 1593, 1552, 1463 cm^{-1} . ^1H NMR (300 MHz, DMSO) δ 2.48 (s, 6H, CH_3), 2.76 (s, 6H, CH_3), 5.24 (s, 4H, OCH_2), 7.08 (s, 2H, pyridine-5-H), 7.15 (d, 4H, J 8.7 Hz), 7.47 (s, 3H, ArH), 7.61 (s, 1H, ArH), 7.78 (d, 4H, J 8.4 Hz), 7.94 (br. s, 4H, NH_2). ^{13}C NMR (75 MHz, DMSO): 20.1, 24.0, 69.3, 102.4, 114.5, 120.6, 121.6, 121.9,

127.1, 127.4, 128.7, 129.5, 133.6, 137.0, 145.8, 152.3, 160.5, 161.3, 187.9. MS (m/z) 698 (M⁺). Anal. Calcd. For C₄₀H₃₄N₄O₄S₂: C, 68.75; H, 4.90; N, 8.02; S, 9.18. Found: C, 68.57; H, 4.77; N, 8.19; S, 9.08.

(4,4'-(1,3-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis((3-amino-4,6-diphenylthieno[2,3-b]pyridin-2-yl)methanone) (5d). Yellow powder, mp 241–243 °C; yield (A) 77%; (B) 68%, IR (KBr disc) ν 3469, 3257, 2955, 1603, 1543, 1462 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ 5.27 (s, 4H, OCH₂), 6.63 (d, 4H, *J* 7.5 Hz), 6.84 (br. s, 4H, NH₂), 6.95 (d, 4H, *J* 8.7 Hz), 7.18 (d, 2H, *J* 8.1 Hz), 7.48–7.63 (m, 14H, ArH), 7.81 (s, 1H, ArH), 7.84 (s, 2H, pyridine-5-H), 8.21–8.51 (m, 7H, ArH). MS (m/z) 947 (M⁺). Anal. Calcd. For C₆₀H₄₂N₄O₄S₂: C, 76.09; H, 4.47; N, 5.92; S, 6.77. Found: C, 75.93; H, 4.31; N, 5.76; S, 6.88.

Synthesis of 1,1'-(4,4'-(pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))diethanone (8). A solution of potassium 4-acetylphenolate (20 mmol) and 2,6-bis(bromo-methyl)pyridine (**7**) (10 mmol) in DMF (20 mL) was heated under reflux for 15 min., during which time, KBr precipitated. The solvent was then removed in *vacuo*, and the remaining material was washed with water (50 mL) and purified by crystallization from ethanol.

1,1'-(4,4'-(Pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))diethanone (8). Pale yellow crystals, mp 145–148 °C; yield 78%, IR (KBr disc) ν 3073, 2962, 1673, 1598, 1471 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ 2.51 (s, 6H, CH₃), 5.30 (s, 4H, OCH₂), 7.14 (d, 4H, *J* 9.0 Hz), 7.49 (d, 2H, *J* 7.8 Hz), 7.89 (t, 1H, *J* 7.8 Hz), 7.93 (d, 4H, *J* 9.0). MS (m/z) 375 (M⁺). Anal. Calcd. For C₂₃H₂₁NO₄: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.36; H, 5.49; N, 3.65.

Synthesis of 1,1'-(4,4'-(pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-bromoethanone) (9). To a stirred solution of 1,1'-(4,4'-(pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))diethanone (**8**) (10 mmol) and *p*-TsOH (20 mmol) in acetonitrile (50 mL), NBS (20 mmol) was slowly added. After complete addition of NBS, the reaction mixture was heated at reflux with stirring for 5 h. The solvent was then evaporated in *vacuo* and the residue was stirred with water (50 mL) for 1 h. and then filtered. After filtration the resulting solid was recrystallized from acetone to afford compound **9**.

1,1'-(4,4'-(Pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-bromoethanone) (9). White crystals, mp 116–118 °C; yield 72%, IR (KBr disc) ν 3069, 2992, 1694, 1597, 1445 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 4.40 (s, 4H, CH₂Br), 5.35 (s, 4H, OCH₂), 7.07 (d, 4H, *J* 8.7 Hz), 7.53 (d, 2H, *J* 7.8 Hz), 7.86 (t, 1H, *J* 7.8 Hz), 7.99 (d, 4H, *J* 8.7). MS (m/z) 533 (M⁺). Anal. Calcd. For C₂₃H₁₉Br₂NO₄: C, 51.81; H, 3.59; Br, 29.97; N, 2.63. Found: C, 51.66; H, 3.40; Br, 29.81; N, 2.47.

Synthesis of 2,2'-(2,2'-(4,4'-(pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyl))bis(4,6-disubstituted nicotinonitrile) 10(a-b). To a solution of 1,1'-(4,4'-(pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-bromoethanone) (**9**) (5 mmol) in ethanol (25 mL) containing few drops piperidine, the appropriate 2-mercapto-4,6-disubstituted nicotinonitriles **3a** or **3b** (10 mmol) was added. The reaction mixture was heated at reflux for 2 h. The solid product obtained upon cooling was filtered off and recrystallized from ethanol/ DMF to afford the title compounds **10(a-b)**.

2,2'-(2,2'-(4,4'-(Pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyl))bis(4,6-dimethylnicotinonitrile) (10a). Pale yellow powder, mp 179–181 °C; yield 73%, IR (KBr disc) ν 3065, 2964, 2216, 1668, 1594, 1437 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ 2.19 (s, 6H, CH₃), 2.39 (s, 6H, CH₃), 4.76 (s, 4H, SCH₂), 5.33 (s, 4H, OCH₂), 7.03 (s, 2H, pyridine-5-H), 7.19 (d, 4H, *J* 6.9 Hz), 7.51 (d, 2H, *J* 8.1 Hz) 7.91 (t, 1H, *J* 7.5 Hz), 8.05 (d, 4H, *J* 7.2 Hz). MS (m/z) 699 (M⁺). Anal. Calcd. For C₃₉H₃₃N₅O₄S₂: C, 66.93; H, 4.75; N, 10.01; S, 9.16. Found: C, 66.82; H, 4.67; N, 10.15; S, 9.09.

2,2'-(2,2'-(4,4'-(Pyridine-2,6-diylbis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyl))bis(4,6-diphenylnicotinonitrile) (10b). Pale yellow powder, mp 198–200 °C; yield 75%, IR (KBr disc) ν 3056, 2897, 2211, 1674, 1596, 1451 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ 4.96 (s, 4H, SCH₂), 5.39 (s, 4H,

OCH₂), 7.12 (s, 2H, pyridine-5-H), 7.16 (d, 2H, *J* 8.1 Hz), 7.21 (d, 4H, *J* 8.7 Hz), 7.36 (t, 1H, *J* 7.2 Hz), 7.52–7.9 (m, 20H, ArH), 8.11 (d, 4H, *J* 9 Hz). ¹³C NMR (75 MHz, DMSO): 37.6, 70.4, 102.5, 113.1, 114.9, 115.7, 116.1, 118.3, 121.1, 127.3, 128.5, 129.2, 130.5, 131.5, 135.5, 136.1, 138.1, 154.1, 155.9, 157.8, 161.9, 162.2, 191.2. MS (*m/z*) 948 (M⁺). Anal. Calcd. For C₅₉H₄₁N₅O₄S₂: C, 74.74; H, 4.36; N, 7.39; S, 6.76. Found: C, 74.56; H, 4.29; N, 7.21; S, 6.67.

Synthesis of (4,4'-(pyridine-2,6-diylbis(methylene))bis(oxy)bis(4,1-phenylene))bis((3-amino-4,6-disubstituted thieno[2,3-*b*]pyridin-2-yl)methanone) 11(a-b). **Method A:** A mixture of 1,1'-(4,4'-(pyridine-2,6-diylbis(methylene))bis(oxy)bis(4,1-phenylene))bis(2-bromoethanone) (**9**) (5 mmol) in ethanol (25 mL) containing sodium ethoxide (10 mmol) and the appropriate 2-mercapto-4,6-disubstituted nicotinonitrile **3a** or **3b** (10 mmol) was added. The reaction mixture was heated at reflux for 5 h. The solid products obtained upon cooling were filtered off and recrystallized from DMF to afford the title compounds **11(a-b)**.

Method B. A solution of 2,2'-(2,2'-(4,4'-(pyridine-2,6-diylbis(methylene))bis(oxy)bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyl))bis(4,6-disubstituted-nicotinonitrile) intermediates **10a** or **10b** (2 mmol) in ethanol (25 mL) containing sodium ethoxide (4 mmol) was heated at reflux for 2 h. The reaction mixture was then cooled, and the solvent was evaporated in *vacuo*. The solid residue was collected and recrystallized from DMF to afford **11(a-b)**.

(4,4'-(Pyridine-2,6-diylbis(methylene))bis(oxy)bis(4,1-phenylene))bis((3-amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)methanone) (11a). Yellow powder, mp 276–278 °C; yield (A) 70%; (B) 68%, IR (KBr disc) ν 3496, 3306, 3069, 2976, 1593, 1556, 1440 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ 2.48 (s, 6H, CH₃), 2.75 (s, 6H, CH₃), 5.31 (s, 4H, OCH₂), 7.07 (s, 2H, pyridine-5-H), 7.18 (d, 4H, *J* 8.4 Hz), 7.54 (d, 2H, *J* 7.8 Hz), 7.79 (d, 4H, *J* 8.7 Hz), 7.93–7.94 (m, 5H, ArH & NH₂). MS (*m/z*) 699 (M⁺). Anal. Calcd. For C₃₉H₃₃N₅O₄S₂: C, 66.93; H, 4.75; N, 10.01; S, 9.16. Found: C, 66.72; H, 4.57; N, 10.19; S, 9.00.

(4,4'-(Pyridine-2,6-diylbis(methylene))bis(oxy)bis(4,1-phenylene))bis((3-amino-4,6-diphenylthieno[2,3-*b*]pyridin-2-yl)methanone) (11b). Yellow powder, mp 258–260 °C; yield (A) 71%; (B) 67%, IR (KBr disc) ν 3467, 3257, 3055, 2919, 1590, 1533, 1434 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ 5.34 (s, 4H, OCH₂), 6.83 (br. s, 4H, NH₂), 7.22 (d, 4H, *J* 9.0 Hz), 7.50–7.53 (m, 8H, ArH), 7.56 (d, 2H, *J* 7.5 Hz), 7.63–7.85 (m, 12H, ArH), 7.86 (s, 2H, pyridine-5-H), 7.95 (t, 1H, *J* 7.5 Hz), 8.23 (d, 4H, *J* 7.8 Hz), MS (*m/z*) 948 (M⁺). Anal. Calcd. For C₅₉H₄₁N₅O₄S₂: C, 74.74; H, 4.36; N, 7.39; S, 6.76. Found: C, 74.63; H, 4.13; N, 7.66; S, 6.69.

Synthesis of diethyl 3,4-bis((4-(2-(3-cyano-4,6-disubstituted pyridin-2-ylthio)acetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate 14(a-b). To a solution of diethyl 3,4-bis((4-(2-bromoacetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (**13**) (5 mmol) in ethanol (25 mL) containing few drops piperidine, the appropriate 2-mercapto-4,6-disubstituted nicotinonitriles **3a** or **3b** (10 mmol) was added. The reaction mixture was heated at reflux for 2 h. The solid product obtained upon cooling was filtered off and recrystallized from ethanol/ DMF to afford the title compounds **14(a-b)**.

Diethyl 3,4-bis((4-(2-(3-cyano-4,6-dimethylpyridin-2-ylthio)acetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (14a). Yellow powder, mp 201–203 °C; yield 71%, IR (KBr disc) ν 3072, 2979, 2216, 1694, 1600, 1578, 1448 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ 1.27 (t, 6H, *J* 6.9 Hz), 2.16 (s, 6H, CH₃), 2.36 (s, 6H, CH₃), 4.33 (q, 4H, *J* 6.9 Hz), 4.65 (s, 4H, SCH₂), 5.70 (s, 4H, OCH₂), 6.97 (s, 2H, pyridine-5-H), 6.99 (d, 4H, *J* 8.4 Hz), 7.87 (d, 4H, *J* 8.4 Hz). MS (*m/z*) 905 (M⁺). Anal. Calcd. For C₄₆H₄₀N₄O₈S₄: C, 61.04; H, 4.45; N, 6.19; S, 14.17. Found: C, 61.15; H, 4.29; N, 6.02; S, 14.25.

Diethyl 3,4-bis((4-(2-(3-cyano-4,6-diphenylpyridin-2-ylthio)acetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (14b). Yellow powder, mp 215–218 °C; yield 76%, IR (KBr disc) ν 3057, 2976, 2214, 1706, 1676, 1598, 1447 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ 1.31 (t, 6H, *J* 7.2 Hz), 4.37 (q, 4H, *J* 7.2 Hz), 4.63 (s, 4H, SCH₂), 5.70 (s, 4H, OCH₂), 6.90 (d, 4H, *J* 8.8 Hz), 7.16–7.72 (m, 16H, ArH), 7.75 (d, 4H, *J* 8.8 Hz), 7.81 (s, 2H,

pyridine-5-H), 7.85-7.87 (m, 4H, ArH). ^{13}C NMR (126 MHz, DMSO): 14.4, 37.8, 40.5, 62.2, 102.9, 114.6, 116.0, 116.6, 127.9, 129.0, 129.06, 129.1, 129.2, 129.4, 130.5, 130.9, 135.5, 135.9, 136.8, 145.8, 146.1, 154.5, 158.3, 161.7, 162.1, 162.3, 191.3. Anal. Calcd. For $\text{C}_{66}\text{H}_{48}\text{N}_4\text{O}_8\text{S}_4$: C, 68.73; H, 4.19; N, 4.86; S, 11.12. Found: C, 68.59; H, 4.11; N, 4.70; S, 11.21.

Synthesis of sodium 3,4-bis((4-(3-amino-4,6-disubstitutedthieno[2,3-*b*]-pyridine-2-carbonyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate 15(a-b). **Method A.** A mixture of diethyl 3,4-bis((4-(2-bromoacetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (**13**) (5 mmol) in ethanol (25 mL) containing sodium ethoxide (10 mmol) and the appropriate 2-mercapto-4,6-disubstituted nicotinonitrile **3a** or **3b** (10 mmol) was added. The reaction mixture was heated at reflux for 5 h. The solid products obtained upon cooling were filtered off and recrystallized from DMF to afford the title compounds **15(a-b)**.

Method B. A solution of diethyl 3,4-bis((4-(2-(3-cyano-4,6-disubstitutedpyridin-2-ylthio)acetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate **14a** or **14b** (2 mmol) in ethanol (25 mL) containing sodium ethoxide (4 mmol) was heated at reflux for 2 h. The reaction mixture was then cooled, and the solvent was evaporated in *vacuo*. The solid residue was collected and recrystallized from DMF to afford **15(a-b)**.

Sodium 3,4-bis((4-(3-amino-4,6-dimethylthieno[2,3-*b*]pyridine-2-carbonyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (15a). Yellow powder, mp > 300 °C; yield (A) 69%; (B) 67%, IR (KBr disc) ν 3431, 3330, 2965, 1599, 1550, 1502, 1442 cm^{-1} . ^1H NMR (500 MHz, DMSO) 2.47 (s, 6H, CH_3), 2.72 (s, 6H, CH_3), 5.99 (s, 4H, OCH_2), 7.00 (s, 2H, pyridine-5-H), 7.13 (d, 4H, J 8.5Hz), 7.65 (d, 4H, J 8.5 Hz), 7.84 (br. s, 4H, NH_2). ^{13}C NMR (126 MHz, DMSO): 20.5, 24.3, 61.7, 102.9, 114.6, 121.9, 122.1, 129.2, 129.9, 133.2, 137.2, 145.9, 148.0, 149.3, 152.5, 160.6, 161.0, 161.6, 165.2, 188.2. MS (m/z) 892 (M^+). Anal. Calcd. For $\text{C}_{42}\text{H}_{30}\text{N}_4\text{Na}_2\text{O}_8\text{S}_4$: C, 56.49; H, 3.39; N, 6.27; S, 14.36. Found: C, 56.32; H, 3.25; N, 6.11; S, 14.31.

Sodium 3,4-bis((4-(3-amino-4,6-diphenylthieno[2,3-*b*]pyridine-2-carbonyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (15b). Yellow powder, mp > 300°C; yield (A) 72%; (B) 69%, IR (KBr disc) ν 3469, 3277, 2919, 1583, 1534, 1500, 1440 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ 6.03 (s, 4H, OCH_2), 6.73 (br. s, 4H, NH_2), 7.19 (d, 4H, J 8.8 Hz), 7.47–7.71 (m, 20H, ArH), 7.73 (s, 2H, pyridine-5-H), 8.17-8.32 (m, 4H, ArH). ^{13}C NMR (126 MHz, DMSO): 61.8, 104.1, 114.7, 118.5, 120.2, 127.6, 128.9, 129.1, 129.2, 129.4, 129.8, 130.0, 130.4, 133.0, 136.6, 137.3, 137.6, 148.0, 148.8, 149.3, 149.9, 157.2, 161.3, 162.3, 165.2, 188.3. Anal. Calcd. For $\text{C}_{62}\text{H}_{38}\text{N}_4\text{Na}_2\text{O}_8\text{S}_4$: C, 65.25; H, 3.36; N, 4.91; S, 11.24. Found: C, 65.03; H, 3.16; N, 4.73; S, 11.14.

Synthesis of 3,4-bis((4-(3-amino-4,6-diphenylthieno[2,3-*b*]pyridine-2-carbonyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylic acid (16). To a stirred a solution of sodium 3,4-bis((4-(3-amino-4,6-diphenylthieno[2,3-*b*]-pyridine-2-carbonyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (**15b**) (2 mmol) in 25 ml water, few drops of conc. HCl were add with stirring. After 1 h. the obtained solid product was filtrated to give compound **16**.

3,4-Bis((4-(3-amino-4,6-diphenylthieno[2,3-*b*]pyridine-2-carbonyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylic acid (16). Yellow powder, mp 286-288 °C; yield 66%, IR (KBr disc) ν 3430, 2918, 1597, 1500, 1434 cm^{-1} . ^1H NMR (300 MHz, DMSO) δ 3.4 (br. s, 2H, OH), 5.72 (s, 4H, OCH_2), 6.72 (br. s, 4H, NH_2), 6.99 (d, 4H, J 8.4 Hz), 7.41–7.67 (m, 20H, ArH), 7.70 (s, 2H, pyridine-5-H), 8.08-8.11 (m, 4H, ArH). Anal. Calcd. For $\text{C}_{62}\text{H}_{40}\text{N}_4\text{O}_8\text{S}_4$: C, 67.87; H, 3.67; N, 5.11; S, 11.69. Found: C, 67.76; H, 3.59; N, 4.98; S, 11.49.

Synthesis of diethyl 3,4-bis((2-(2-(3-cyano-4,6-disubstitutedpyridin-2-ylthio)acetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate 19(a-b). To a solution of diethyl 3,4-bis((2-(2-bromoacetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (**18**) (5 mmol) in ethanol (25 mL) containing few drops piperidine, the appropriate 2-mercapto-4,6-disubstituted nicotinonitriles **3a** or **3b** (10

mmol) was added. The reaction mixture was heated at reflux for 2 h. The solid product obtained upon cooling was filtered off and recrystallized from ethanol/ DMF to afford the title compounds **19(a-b)**.

Diethyl 3,4-bis((2-(2-(3-cyano-4,6-dimethylpyridin-2-ylthio)acetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (19a). Pale yellow powder, mp 116–118 °C; yield 71%, IR (KBr disc) ν 3066, 2979, 2216, 1709, 1594, 1580, 1447 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ 1.21 (t, 6H, J 6.8 Hz), 2.06 (s, 6H, CH_3), 2.35 (s, 6H, CH_3), 4.26 (q, 4H, J 6.8 Hz), 4.33 (s, 4H, SCH_2), 5.67 (s, 4H, OCH_2), 6.94 (s, 2H, pyridine-5-H), 6.95–7.59 (m, 8H, ArH). MS (m/z) 905 (M^+). Anal. Calcd. For $\text{C}_{46}\text{H}_{40}\text{N}_4\text{O}_8\text{S}_4$: C, 61.04; H, 4.45; N, 6.19; S, 14.17. Found: C, 60.81; H, 4.29; N, 6.10; S, 14.05.

Diethyl 3,4-bis((2-(2-(3-cyano-4,6-diphenylpyridin-2-ylthio)acetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (19b). Pale yellow powder, mp 190–192 °C; yield 77%, IR (KBr disc) ν = 3058, 2978, 2215, 1706, 1595, 1569, 1446 cm^{-1} . ^1H NMR (300 MHz, DMSO) δ 1.05 (t, 6H, J 7.2 Hz), 4.06 (q, 4H, J 7.2 Hz), 4.51 (s, 4H, SCH_2), 5.62 (s, 4H, OCH_2), 6.59–7.74 (m, 22H, ArH), 7.77 (s, 2H, pyridine-5-H), 7.88–8.09 (m, 6H, ArH). Anal. Calcd. For $\text{C}_{66}\text{H}_{48}\text{N}_4\text{O}_8\text{S}_4$: C, 68.73; H, 4.19; N, 4.86; S, 11.12. Found: C, 68.52; H, 4.13; N, 4.69; S, 10.98.

Synthesis of sodium 3,4-bis(3-(3-amino-4,6-disubstituted thieno[2,3-*b*]pyridin-2-yl)benzofuran-2-yl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate 21(a-b). **Method A.** A mixture of diethyl 3,4-bis((2-(2-bromoacetyl)phenoxy)methyl)-thieno[2,3-*b*]thiophene-2,5-dicarboxylate (**18**) (5 mmol) in ethanol (25 mL) containing sodium ethoxide (10 mmol) and the appropriate 2-mercapto-4,6-disubstituted nicotinonitriles **3a** or **3b** (10 mmol) was added. The reaction mixture was heated at reflux for 5 h. The solid products obtained upon cooling were filtered off and recrystallized from DMF to afford the title compounds **21(a-b)**.

Method B. A solution of diethyl 3,4-bis((2-(2-(3-cyano-4,6-disubstitutedpyridin-2-ylthio)acetyl)phenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate **19a** or **19b** (2 mmol) in ethanol (25 mL) containing sodium ethoxide (4 mmol) was heated at reflux for 2 h. The reaction mixture was then cooled, and the solvent was evaporated in *vacuo*. The solid residue was collected and recrystallized from DMF to afford **21(a-b)**.

Sodium 3,4-bis(3-(3-amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)benzofuran-2-yl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (21a). Yellow powder, mp > 300 °C; yield (A) 69%; (B) 67%, IR (KBr disc) ν 3432, 3330, 2960, 1598, 1551, 1445 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ 2.48 (s, 6H, CH_3), 2.74 (s, 6H, CH_3), 6.77–6.81 (m, 2H, ArH), 7.01–7.05 (m, 4H, pyridine-5-H & ArH), 7.15–7.39 (m, 4H, ArH), 7.79 (br. s, 4H, NH_2). MS (m/z) 856 (M^+). Anal. Calcd. For $\text{C}_{42}\text{H}_{26}\text{N}_4\text{Na}_2\text{O}_6\text{S}_4$: C, 58.87; H, 3.06; N, 6.54; S, 14.97. Found: C, 58.73; H, 2.89; N, 6.43; S, 14.77.

Sodium 3,4-bis(3-(3-amino-4,6-diphenylthieno[2,3-*b*]pyridin-2-yl)benzofuran-2-yl)thieno[2,3-*b*]thiophene-2,5-dicarboxylate (21b). Yellow powder, mp > 300 °C; yield (A) 70%; (B) 68%, IR (KBr disc) ν 3466, 3277, 2918, 1596, 1535, 1442 cm^{-1} . ^1H NMR (300 MHz, DMSO) δ 6.76–7.65 (m, 28H, NH_2 & ArH), 7.73 (s, 2H, pyridine-5-H), 8.18–8.20 (m, 4H, ArH). Anal. Calcd. For $\text{C}_{62}\text{H}_{34}\text{N}_4\text{Na}_2\text{O}_6\text{S}_4$: C, 67.38; H, 3.10; N, 5.07; S, 11.61. Found: C, 67.19; H, 2.95; N, 4.99; S, 11.50.

Synthesis of 1,1'-(2,2'-(pyridine-2,6-diylbis(methylene))bis(oxy))bis(2,1-phenylene)diethanone (25). A solution of potassium 2-acetylphenolate (20 mmol) and 2,6-bis(bromomethyl)pyridine (**7**) (10 mmol) in DMF (20 mL) was heated under reflux for 15 min., during which time, KBr precipitated. The solvent was then removed in *vacuo*, and the remaining material was washed with water (50 mL) and purified by crystallization from Ethanol to give **25**.

1,1'-(2,2'-(Pyridine-2,6-diylbis(methylene))bis(oxy))bis(2,1-phenylene)diethanone (25). Pale yellow crystals, mp 120–122 °C; yield 76%, IR (KBr disc) ν 3074, 2926, 1666, 1593, 1439 cm^{-1} . ^1H NMR (300 MHz, DMSO) δ 2.53 (s, 6H, CH_3), 5.29 (s, 4H, OCH_2), 7.00–7.05 (m, 2H, ArH), 7.18 (d, 2H, J 8.4 Hz), 7.44–7.59 (m, 6H, ArH), 7.90 (t, 1H, J 8.1 Hz). MS (m/z) 375 (M^+). Anal. Calcd. For $\text{C}_{23}\text{H}_{21}\text{NO}_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.40; H, 5.51; N, 3.65.

Synthesis of 1,1'-(4,4'-(quinoxaline-2,3-diylbis(methylene))bis(oxy))bis(4,1-phenylene)diethanone (28).

A solution of potassium 4-acetylphenolate (20 mmol) and 2,3-bis(bromomethyl)quinoxaline (**27**) (10 mmol) in DMF (20 mL) was heated under reflux for 15 min., during which time, KBr precipitated. The solvent was then removed in *vacuo*, and the remaining material was washed with water (50 mL) and purified by crystallization from ethanol to give **28**.

1,1'-(4,4'-(Quinoxaline-2,3-diylbis(methylene))bis(oxy))bis(4,1-phenylene)diethanone (28). Pale yellow crystals, mp 156–158 °C; yield 71%, IR (KBr disc) ν 3061, 2934, 1670, 1598, 1451 cm^{-1} . ^1H NMR (300 MHz, DMSO) δ 2.49 (s, 6H, CH_3), 5.67 (s, 4H, OCH_2), 7.14 (d, 4H, J 8.4 Hz), 7.89 (d, 4H, J 8.4 Hz), 7.90–7.92 (m, 2H, quinoxaline-H), 8.10–8.13 (m, 2H, quinoxaline-H). MS (m/z) 426 (M^+). Anal. Calcd. For $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_4$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.05; H, 5.14; N, 6.42.

Synthesis of (3-amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)(4-hydroxyphenyl)methanone (31). A mixture of 2-bromo-1-(4-hydroxyphenyl)ethanone (**30**) (10 mmol) in ethanol (25 mL) containing sodium ethoxide (10 mmol) and 2-mercapto-4,6-dimethylnicotinonitrile **3a** (10 mmol) was added. The reaction mixture was heated at reflux for 5 h. The solid products obtained upon cooling were filtered off and recrystallized from DMF to afford **31**.

(3-Amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)(4-hydroxyphenyl)methanone (31). Yellow powder, mp 211–213 °C; yield 82%, IR (KBr disc) ν 3482, 3276, 3085, 2967, 1595, 1443 cm^{-1} . ^1H NMR (300 MHz, DMSO) δ 2.49 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 7.07 (d, 2H, J 8.4 Hz), 7.10 (s, 1H, pyridine-5-H), 7.68 (d, 2H, J 8.4 Hz), 7.90 (br. s, 2H, NH_2), 11.01 (s, 1H, OH). MS (m/z) 298 (M^+). Anal. Calcd. For $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 64.41; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.33; H, 4.63; N, 9.23; S, 10.68.

Supplementary Material

Supplementary material related to this article, including Nuclear Magnetic Resonance (^1H and ^{13}C NMR) figures for compounds **4a-d**, **5a-d**, **8**, **9**, **10a** and **b**, **11a** and **b**, **14a** and **b**, **15a** and **b**, **16**, **19a** and **b**, **21a** and **b**, **25**, **28**, and **31** are available in the online version of the text.

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