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

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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, antiasthmatic, antidepressant, acetylcholinesterase inhibitors (AChE), HIV protease inhibitors. They are also used for treating hypertension or hypotension, as well as for inducing or preventing apoptosis.

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).

![Pyridine derivatives](image)

Figure 1. Natural compounds and drugs containing pyridine ring.

Pyridines are also exploited in agrochemistry as well as in materials science. Different methodologies for construction and functionalization of pyridine derivatives have been recently reviewed. Thienopyridines are considered as one of the important fused heterocyclic compounds for their usefulness therapeutic applications.

Moreover, several thienopyridine derivatives are known to possess antiviral, anti-inflammatory, antimicrobial, antidiabetic, antihypertensive and osteogenic activities. In particular, thieno[2,3-b]pyridines are reported to be useful as anticancer agents.

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, 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-mercaptopnicotinonitrile derivatives 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) upon treatment with N-bromosuccinimide in acetonitrile at reflux.
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-mercaptanicotinonitriles 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 \(^1\)H 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 \(\delta 4.77\) 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 \(\delta 5.2\) 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-y1)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 worth mentioning 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(sulfanediy1)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 was chosen as precursor and was obtained as previously reported from the corresponding bis(acetyl) derivative 12 upon treatment with N-bromosuccinimide in acetonitrile at reflux.

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-y1thio)acetyl)phenoxy)-methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate 14(a-b) by the reaction of 13 with 2-
mercaptocotonitriles 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).


Compound 14a featured the ethyl ester protons as triplet and quartet signals at δ 1.27 and 4.33 in their $^1$H NMR spectra. On the other hand, these signals disappeared in the $^1$H 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 ban 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 was obtained from the corresponding bis(acetyl) derivative 17 upon treatment with N-bromosuccinimide in acetonitrile at reflux. Reaction of 18 with 2-mercaptocotinonitrile derivatives 3a and 3b in ethanol containing few drops of piperidine at reflux afforded the corresponding diethyl 3,4-bis((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 obtained in one step by the reaction of bis-bromoacetyl derivative 18 with 2-mercaptophtiononitrile derivatives 3a and 3b in ethanolic sodium ethoxide at reflux (Scheme 4).
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 SCH₂ as well as the OCH₂ 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 SCH₂ and the OCH₂ 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-mercaptopenicotinonitrile 3(a-b) with the appropriate bis(bromoacetyl) derivatives using a similar approach.

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 Br₂ 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).

Aiming at synthesizing compounds 22 and 23, which could not 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.

![Figure 2. Structures of bis(thieno[2,3-b]pyridines) linked to pyridine and quinoxaline 22 and 23.](image-url)
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 5. Attempted Synthesis of bis(bromoacetyl) derivatives 26 and 29.

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 phenoxy methyl groups. The structures of the newly synthesized compounds were full 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 PyeUnicam 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 (13C NMR), a Varian VXR spectrometer operating at 400 MHz (1H NMR) and 101 MHz (13C NMR) and a Varian VXR spectrometer operating at 500 MHz (1H NMR) and 126 MHz (13C NMR) using TMS as an internal standard and DMSO-d6 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 compounds achieved the “hybrid molecules” concept which aims at combining two promising pharmacophores in one molecule.

**Synthesis of 2,2’-(2,2’-(4,4’-(phenylenebis(methylene))bis(oxy)bis(4,1-phenylene))bis(2-oxoethane-2,1-diyli))bis(sulfanediyl))bis(4,6-disubstituted nicotinonitrile) 4(a-d).** To a solution of the appropriate bis-bromoacetyl 2a or 2b (5 mmol) in ethanol (25 mL) containing 2-3 drops piperidine, the appropriate 2-mercapto-4-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-diyli))bis(sulfanediyl))bis(4,6-dimethyl nicotinonitrile) (4a). Pale yellow powder, mp 227–229 °C; yield 78%, IR (KBr disc) ν = 3064, 2948, 2215, 1678, 1599, 1422 cm⁻¹. 1H NMR (300 MHz, DMSO) δ 2.19 (s, 6H, CH2), 2.39 (s, 6H, CH3), 4.77 (s, 4H, CH2), 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 C40H36N6O4S2: C, 76.85; H, 4.90; N, 8.02; S, 9.18. Found: C, 76.48; 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-diyli))bis(sulfanediyl))bis(4,6-diphenylnicotinonitrile) (4b). Pale yellow powder, mp 231–233 °C; yield 79%, IR (KBr disc) ν = 3057, 2917, 2214, 1686, 1597, 1461 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), 8.03 (d, 4H, J 8.7 Hz). 13C 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 C60H42N6O4S2: 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-diyli))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, CH3), 2.39 (s, 6H, CH3), 4.77 (s, 4H, SCH2), 5.26 (s, 4H, OCH2), 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). 13C 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 C60H42N6O4S2: C, 76.34; H, 4.47; N, 5.92; S, 6.77. Found: C, 76.09; H, 4.47; N, 5.92; S, 6.77.
2,2’-(2,2’-(4,4’-(1,3-Phenylenbis(methylene))bis(oxy)bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyI))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, SCH₂), 5.32 (s, 4H, OCH₂), 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 C₆₀H₄₂N₂O₄S₂: 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-bromocetyl 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(sulfanediyI))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-Phenylenbis(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, CH₃), 2.77 (s, 6H, CH₃), 5.24 (s, 4H, OCH₂), 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, NH₂). ¹³C 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 C₄₀H₃₄N₂O₄S₂: 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-Phenylenbis(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, OCH₂), 6.84 (br. s, 4H, NH₂), 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). ¹³C 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 C₄₀H₃₄N₂O₄S₂: C, 68.75; 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-Phenylenbis(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, CH₃), 2.76 (s, 6H, CH₃), 5.24 (s, 4H, OCH₂), 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, NH₂). ¹³C 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 C₃₀H₃₄N₂O₄S₂: 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-Phenylenbis(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 C₆₀H₄₂N₂O₄S₂: 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-diylibis(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-diylibis(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-diylibis(methylene))bis(oxy)bis(4,1-phenylene))bis(2-bromoethanone) (9). To a stirred solution of 1,1’-(4,4’-(pyridine-2,6-diylibis(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 acetonitrile to afford compound 9.

1,1’-(4,4’-(Pyridine-2,6-diylibis(methylene))bis(oxy)bis(4,1-phenylene))bis(2-bromoethanone) (9). White crystals, mp 116–118 °C; yield 72%, IR (KBr disc) ν 3069, 2929, 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-diylibis(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-diylibis(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-diylibis(methylene))bis(oxy)bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyl)bis(4,6-dimethylnicotinonitritile) (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, OCH₂), 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 C₃₉H₃₉N₅O₄S₂: 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-diylibis(methylene))bis(oxy)bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis(sulfanediyl)bis(4,6-diphenylnicotinonitritile) (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, CH₂Br), 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, 133.5, 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-diylibis(methylene))bis(oxy)bis(4,1-phenylene))bis((3-amino-4,6-disubstituted thieno[2,3-b]pyridin-2-yl)methanonene) 11(a-b). Method A: A mixture of 1,1’-(4,4’-(pyridine-2,6-diylibis(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-diyllbis(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-diyllbis(methylene))bis(oxy)bis(4,1-phenylene))bis(3-amino-4,6-dimethylthieno[2,3-b]pyridinyl-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 1.02 (t, 6H, CH₃), 2.67 (s, 6H, CH₃), 2.68 (s, 6H, CH₃), 3.18 (q, 4H, CH₂), 5.70 (s, 4H, NH₂), 6.83 (br. s, 4H, NH), 7.07 (d, 2H, 8.7 Hz), 7.54 (d, 2H, 7.8 Hz), 7.93–7.94 (m, 5H, ArH & NH₂), MS (m/z) 699 (M⁺). Anal. Calcd. For C₉₃H₅₃N₅O₄S₂: C, 69.12; H, 4.56; N, 7.66; S, 6.69. Found: C, 66.72; H, 4.57; N, 4.19; S, 6.90.

(4,4’-(Pyridine-2,6-diyllbis(methylene))bis(oxy)bis(4,1-phenylene))bis(4,6-diphenylthieno[2,3-b]pyridinyl-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), 5.30 (d, 4H, J 8.4 Hz), 7.18 (d, 4H, J 8.8 Hz), 7.55 (d, 2H, 7.5 Hz), 7.75–7.85 (m, 12H, ArH), 8.23 (d, 4H, 7.8 Hz), MS (m/z) 948 (M⁺). Anal. Calcd. For C₉₅H₆₅N₅O₄S₂: 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 1.02 (t, 6H, CH₃), 2.16 (s, 6H, CH₃), 2.37 (s, 6H, CH₃), 4.33 (q, 4H, J 6.9 Hz), 6.45 (s, 4H, SCH₂), 5.70 (s, 4H, OCH₂), 6.97 (d, 4H, 7.8 Hz), 7.87 (d, 4H, 8.4 Hz). MS (m/z) 905 (M⁺). Anal. Calcd. For C₆₈H₄₅N₄O₉S₄: 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). ¹³C NMR (126 MHz, DMSO): 34.4, 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 C₆₈H₄₈N₄O₉: 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.
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) v 3431, 3330, 2965, 1599, 1550, 1502, 1442 cm⁻¹. ¹H NMR (500 MHz, DMSO) 2.47 (s, 6H, CH₃), 2.72 (s, 6H, CH₃), 5.99 (s, 4H, OCH₂), 7.00 (s, 2H, pyridine-5-H), 7.13 (d, 4H, J 8.5 Hz), 7.65 (d, 4H, J 8.0 Hz), 7.84 (br. s, 4H, NH₂). ¹³C NMR (126 MHz, DMSO): 20.5, 24.3, 61.7, 102.9, 114.6, 121.9, 122.1, 129.2, 129.9, 132.2, 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 C₄₂H₃₀N₄Na₂O₆S₄: 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) v 3469, 3277, 2919, 1583, 1534, 1500, 1440 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ 6.03 (s, 4H, OCH₂), 6.73 (br. s, 4H, NH₂), 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). ¹³C 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 C₆₂H₃₈N₄Na₂O₆S₄: 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 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 added 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) v 3430, 2918, 1597, 1500, 1434 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ 3.4 (br. s, 2H, OH), 5.72 (s, 4H, OCH₂), 6.72 (br. s, 4H, NH₂), 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 C₆₂H₄₀N₄O₆S₄: 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).** 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) v 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, CH₃), 2.35 (s, 6H, CH₃), 4.26 (q, 4H, J 6.8 Hz), 4.33 (s, 4H, SCH₂), 5.67 (s, 4H, OCH₂), 6.94 (s, 2H, pyridine-5-H), 6.95–7.59 (m, 8H, ArH). MS (m/z) 905 (M⁺). Anal. Calcd. For C₄₆H₄₀N₄O₈S₄: 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) v = 3058, 2978, 2215,
1706, 1595, 1569, 1446 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO) \(\delta\) 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 C\(_{68}\)H\(_{48}\)N\(_4\)O\(_8\)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 (21a-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) v 3432, 3330, 2960, 1598, 1551, 1445 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 2.48 (s, 6H, CH\(_2\)), 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 C\(_{62}\)H\(_{34}\)N\(_4\)O\(_8\)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) v 3466, 3277, 2918, 1596, 1535, 1442 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO) \(\delta\) 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 C\(_{62}\)H\(_{34}\)N\(_4\)O\(_8\)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) v 3074, 2926, 1666, 1593, 1439 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO) \(\delta\) 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 C\(_{23}\)H\(_{21}\)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) v 3061, 2934, 1670, 1598, 1451 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO) \(\delta\) 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 C\(_{26}\)H\(_{22}\)N\(_2\)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, CH₃), 2.76 (s, 3H, CH₃), 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, NH₂), 11.01 (s, 1H, OH). MS (m/z) 298 (M⁺). Anal. Calcd. For C₁₆H₁₄N₂O₂S: 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 ¹³C 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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