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Utility of 2-Chloro-*N*-arylacetamide and 1,1′-(Piperazine-1,4-diyl)bis(2-chloroethanone) as Versatile Precursors for Novel Mono- and Bis[thienopyridines]

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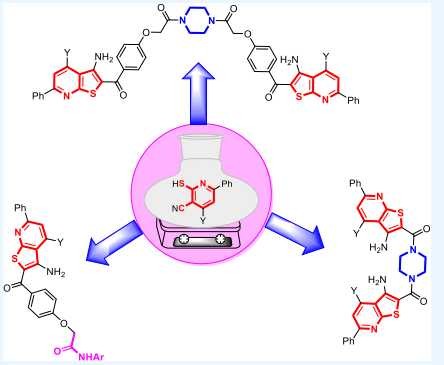
ABSTRACT: A series of novel thieno[2,3-*b*]pyridines linked to *N*-aryl carboxamides or (carbonylphenoxy)-*N*-(aryl)acetamides, as well as bis(thieno[2,3-*b*]pyridines) linked to piperazine core via methanone or carbonylphenoxyethanone units, were synthesized by treating the appropriate chloroacetyl- or bis-bromoacetyl derivatives with 2-mercaptonicotinonitrile derivatives in ethanolic sodium ethoxide at reflux. The spectral data were used to determine the compositions of novel compounds.



INTRODUCTION

Thieno[2,3-*b*]pyridine derivatives occupy a unique position and have received considerable attention due to their diverse pharmacological activities, which include anticancer,[1,2] antiviral,[2,3] anti-inflammatory,[4,5] antimicrobial,[5,6] antidiabetic,[7,8] and osteogenic[9] antiproliferative activity. Furthermore, they can be used as adenosine A1 receptor ligands for the potential treatment of epilepsy[10] and as antiplatelet drugs.[11] Several research publications on this motif as a core in prospective small-molecule medicines have been published (Figure 1).[12,13] Furthermore, several drugs on the market contain thienopyridine nuclei. Prasugrel, and clopidogrel, for example, have all been reported as antiplatelet drugs (Figure 1).[14] The amide group can be found in a wide range of drugs, and many industrial materials, such as polymers, detergents, and lubricants.[15,16] Their biological activities include antitumor, anthelmintic, antispasmodic, antifungal, antibacterial, insecticidal, and herbicidal properties.[17] In terms of medicine, roughly one-quarter of all marketed drugs (and two-thirds of all drug candidates) contain at least one amide bond.[18] Furthermore, molecules with an acetamide linkage or its derivatives as core structures have received significant attention due to their potential therapeutic applications as anti-inflammatory,[19] anticancer,[20] analgesic,[21] antimicrobial,[21−23] anticonvulsant,[24] antituberculosis agents,[25] and anti-COVID-19 agents.[26] Some acetamide derivatives, such as paracetamol V[27] (Figure 1), have been shown to have analgesic or sedative properties. Furthermore, AdipoRon VI[28] (Figure 1), a phenoxyacetamide drug, has received considerable attention as a potential treatment for cardiovascular disease, obesity, diabetes, and nonalcoholic fatty liver disease. Moreover, compounds with a 2-phenoxy-*N*-phenylacetamide core structure have garnered a lot of attention due to their antibacterial, antiparasitic, anticancer, and antiviral properties.[23,29] The piperazine scaffold has also been reported to exhibit antibacterial, antituberculosis, anticancer, antiviral, anti-inflammatory, antipsychotic, anti-Alzheimer's, antifungal, antidiabetic, as well as analgesic, anticonvulsant, and antimalarial properties.[30−39] Figure 1 depicts many medications that have a piperazine core as a fundamental structural feature. Furthermore, over the last few decades, the concept of molecular hybridization has received a lot of attention in the field of drug design. This tool combines two pharmacophoric moieties from different classes of bioactive molecules to create new hybrid molecules with improved biological efficacy and resistance.[40,41]

Considering these findings and our continuous interest in developing heterocycles with improved pharmacophoric characteristics,[42−80] we report the design and synthesis of

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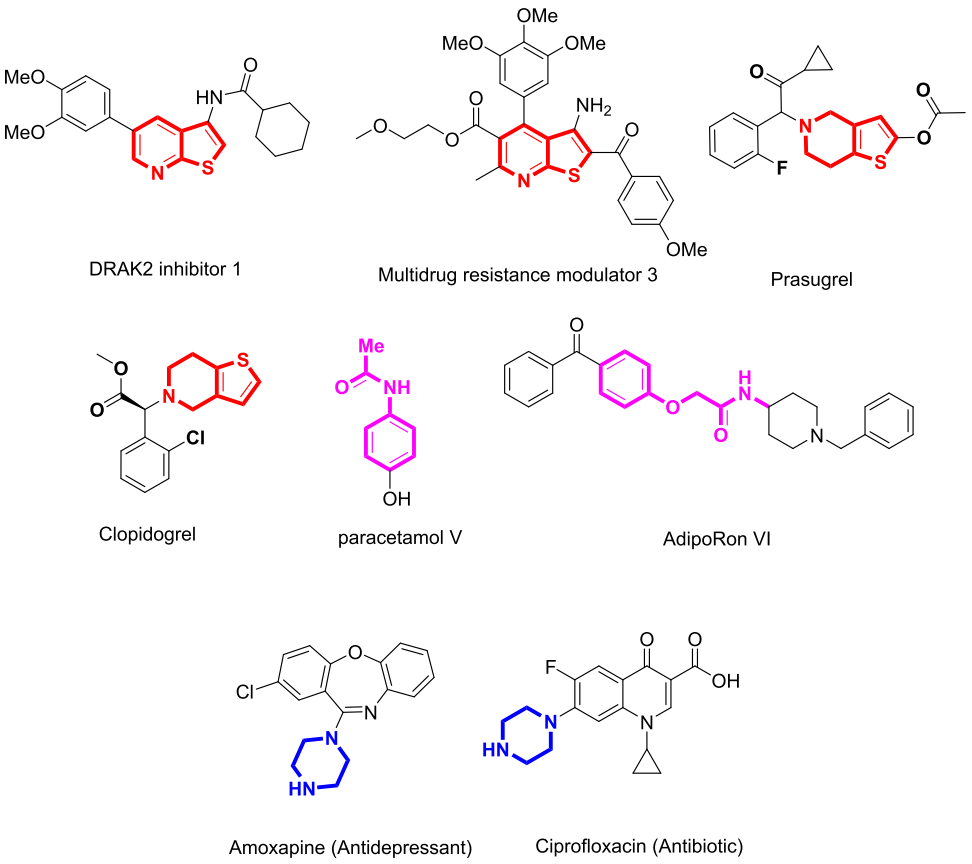
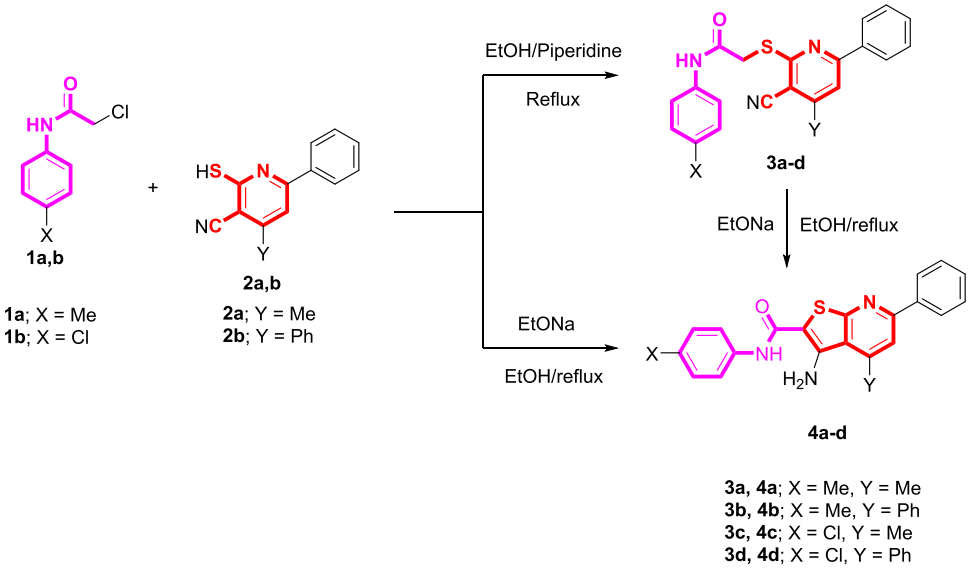


Figure 1. Some medications that have thieno[2,3-*b*]pyridine, acetamide, phenoxyacetamide, and piperazine as fundamental structural features.

Scheme 1. Synthesis of Thienopyridine Linked to *N*-Aryl Carboxamides 4a−d



new hybrid compounds that comprise thieno[2,3-*b*]pyridines linked to piperazine or amide-containing moieties.

RESULTS AND DISCUSSION

As precursors for our targeted synthesis, we chose 2-chloro-*N*-arylylacetamides **1a,b** which were prepared by stirring the appropriate arylamine with 2-chloroacetyl chloride under basic conditions. The synthesis of novel thieno[2,3-*b*]pyridine-2-carboxamide derivatives **4a−d** was performed by the reaction of 6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile **2a,b** with **1a,b** in ethanol containing sodium ethoxide (Scheme 1). The reaction proceeded via the initial formation of 2-((3-cyano-6-phenylpyridin-2-yl)thio)-*N*-phenylacetamide intermediates **3a−d**. The latter compound could be isolated upon treatment of **2a,b** with the appropriate 2-chloro-*N*-arylylacetamides derivatives **1a,b** in ethanol containing piperidine at reflux. Heating of **3a−d** with sodium ethoxide in ethanol at reflux afforded **4a−d** in good yields.

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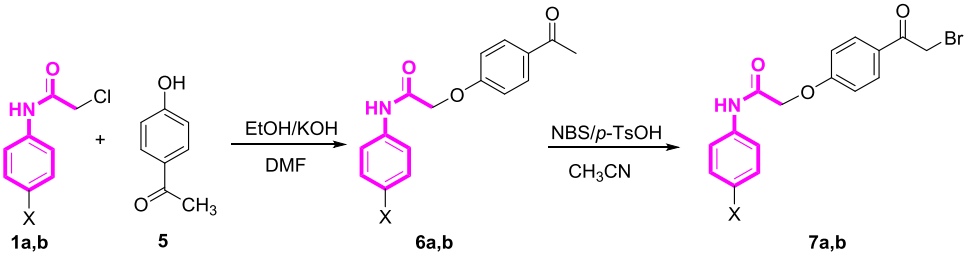
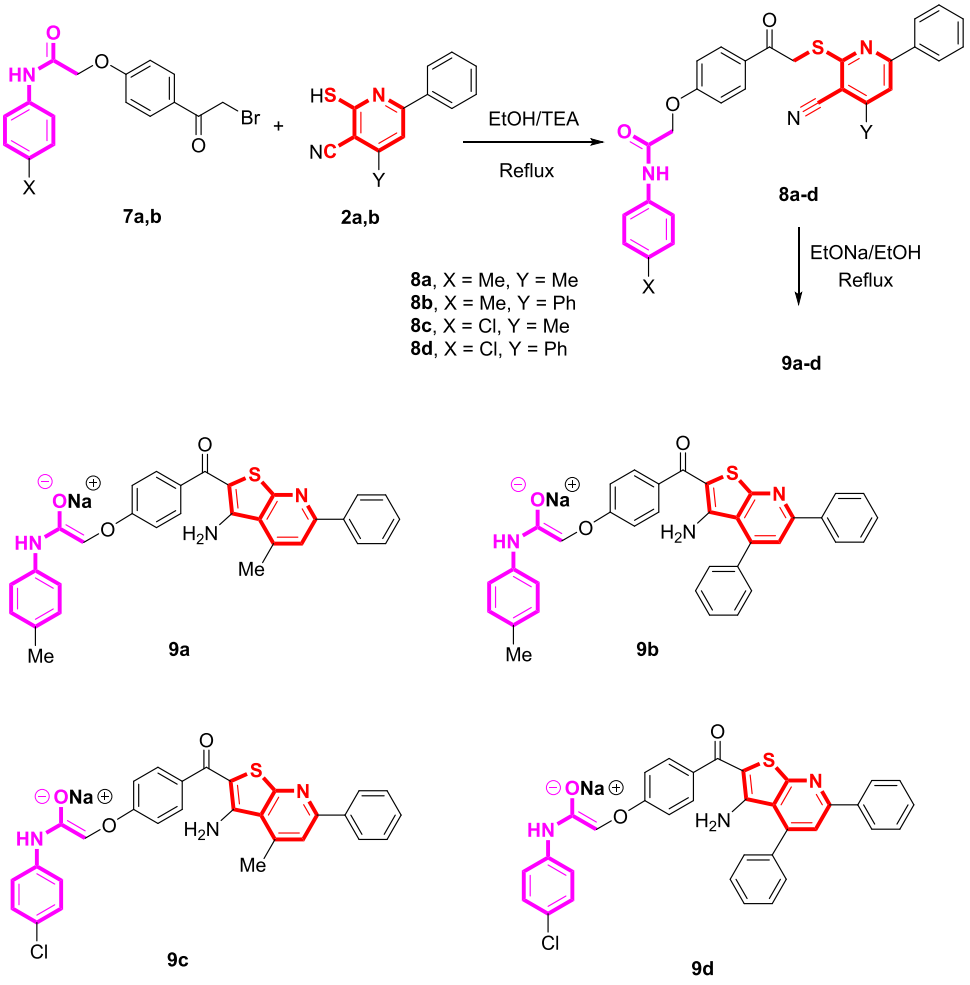
Scheme 2. Synthesis of α-Bromoketones Linked to *N*-Arylacetamide 7a,b



Scheme 3. Synthesis of Thienopyridines (Sod. Salts) Linked to *N*-Arylacetamide 9a−d



The structures of compounds **4a−d** were established based on their spectral data and elemental analyses. Thus, the mass spectrum of **3c** as a representative example reveals a molecular ion peak at m/z 393 that corresponds to its molecular mass. Compound **4c**'s IR spectra revealed the existence of absorption bands at 3427, 3278, and 1640 cm^{-1}, which correspond to the amino group and carbonyl band, respectively. The effective ring closure of compound **3c** into **4c** is confirmed by the absence of absorption bands typical of the cyano group in compound **4c** and the presence of this band in compound **3c**. Furthermore, the ring closure of **3c** to **4c** is further supported by the ^{1}H NMR spectra. Therefore, compound **3c** showed a singlet signal integrating two protons at δ 4.26 ppm, indicating the existence of SCH_2 protons, but compound **4c** lacks this signal. The remaining protons were seen at the anticipated integral values and chemical shifts (see the Experimental Section). The scope of our research was expanded to encompass the synthesis of novel thieno[2,3-*b*]pyridines coupled to *N*-arylacetamide units via carbonylphenoxy groups. Bromoacetyl derivatives **7a,b**[81] were employed as flexible precursors for this purpose. They were successfully obtained from the corresponding 2-(acetylylphenoxy)-*N*-arylacetamides **6a,b** upon treatment with *N*-bromosuccinimide (NBS) in the presence of *p*-TsOH. Compounds **6a,b**[81] were produced via the reaction of the potassium salt of *para*-hydroxyacetophe-

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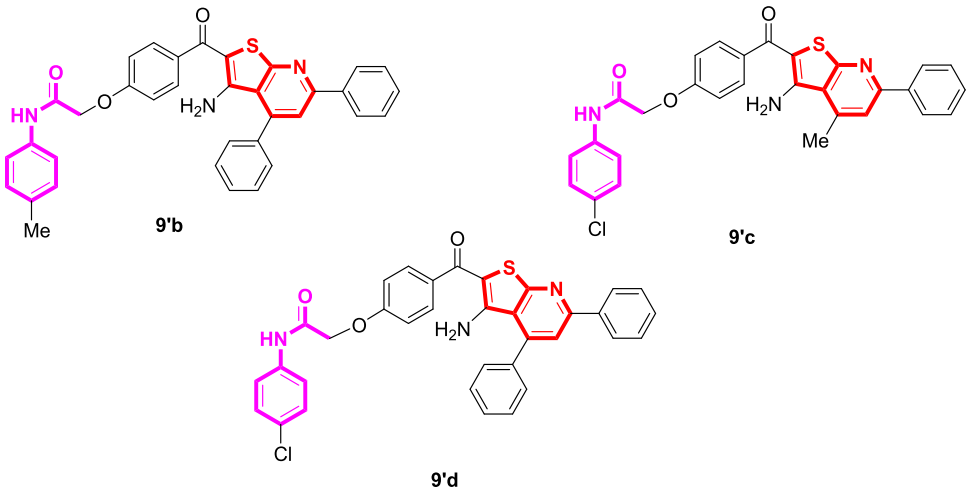
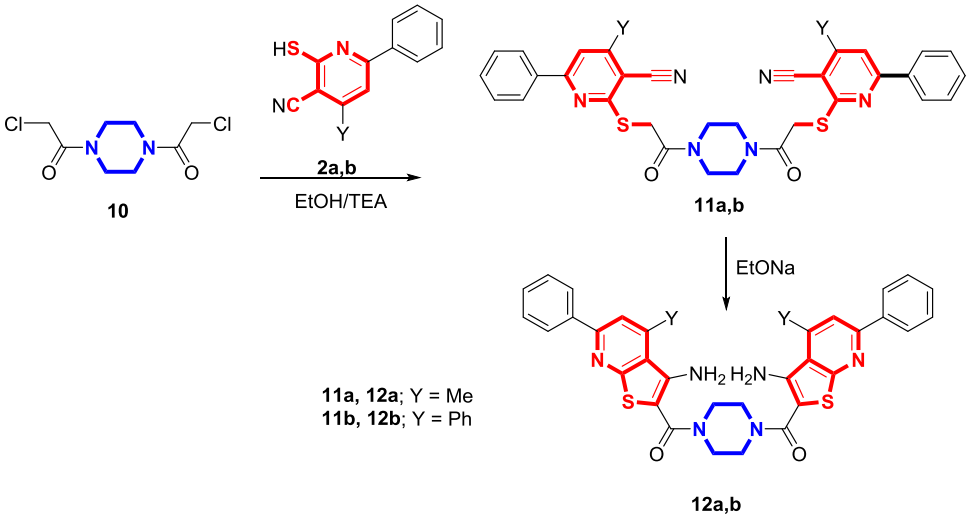


Figure 2. Structures of thienopyridines linked to *N*-arylacetamide.

Scheme 4. Synthesis of Bis(thienopyridines) Linked to Piperazine Core 12a,b



none **5** with the corresponding 2-chloro-*N*-arylacetamide derivatives **1a,b** in boiling DMF (Scheme 2).

Thus, the reaction of 6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitriles **2a,b** with 2-(4-(2-bromoacetyl)phenoxy)-*N*-arylacetamides **7a,b** in ethanol containing piperidine at reflux afforded 2-(4-(2-((3-cyano-6-phenylpyridin-2-yl)thio)acetyl)-phenoxy)-*N*-arylacetamide intermediates **8a−d** in 81−88% yields. Cyclization of the latter compounds in an ethanolic solution containing sodium ethoxide at reflux afforded the corresponding thienopyridine derivatives **9a−d** as sodium salts in 81−84% yields (Scheme 3).

It is worth mentioning that cyclization of 6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitriles **2a,b** with 2-(4-(2-bromoacetyl)phenoxy)-*N*-arylacetamides **7a,b** in an ethanolic solution containing K_2CO_3 at reflux afforded the corresponding thienopyridine derivatives **9′b−d** in 76−77% yields (Figure 2).

The ^{1}H NMR spectrum of **9′b** displayed a singlet signal at 4.81 ppm for the $-OCH_2$ in addition to a signal at 10.19 ppm for the NH group. The other signals appeared at their expected positions. On the other hand, the disappearance of the $-OCH_2$ signal from the spectra of compounds **9a−d** can be observed.

Our investigation was expanded to encompass the preparation of bis(thieno[2,3-*b*]pyridines) **12a,b** connected to the piperazine ring via carbonyl groups. In the first step, 1,1′-(piperazine-1,4-diyl)bis(2-chloroethan-1-one) (**10**) was prepared via the reaction of piperazine with two mole equivalents of chloroacetyl chloride in the presence of anhydrous K_2CO_3. Subsequent reaction of compound **10** with the appropriate 6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitriles **2a,b** in ethanol containing piperidine at reflux afforded bis(sulfanediyl)bis(6-phenylnicotinonitriles) **11a** and **11b** in 74 and 79% yields, respectively. The latter compounds underwent cyclization to give the corresponding piperazine-1,4-diylbis((3-amino-6-phenylthieno[2,3-*b*]pyridin-2-yl)-methanones) **12a,b** in 70−72% yields, respectively, upon heating in ethanolic solution containing sodium ethoxide (Scheme 4).

The structures of compounds **12a** and **12b** were established based on their spectral data and elemental analyses. Thus, compound **12a** showed in its IR spectra the presence of absorption bands at 3415, 34260, and 1633 cm^{-1} characteristic for the amino group and the carbonyl band, respectively. The piperazine and NH_2 appeared as two broad signals at 3.75 and 6.03 ppm. All other protons were seen at the expected

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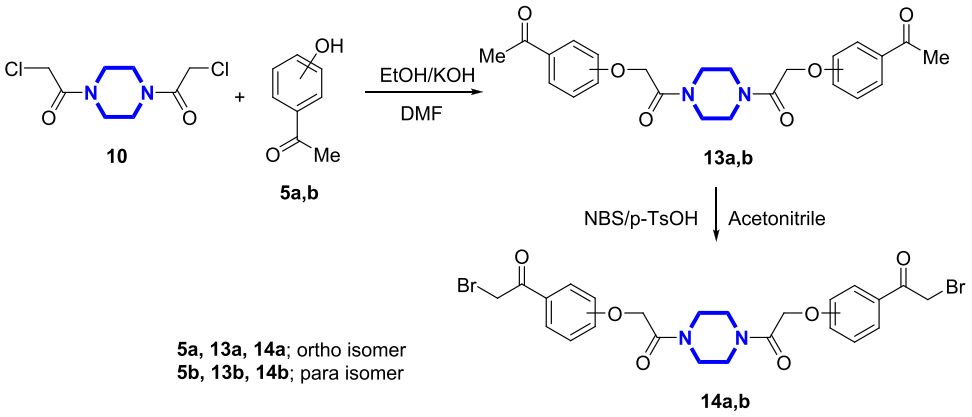
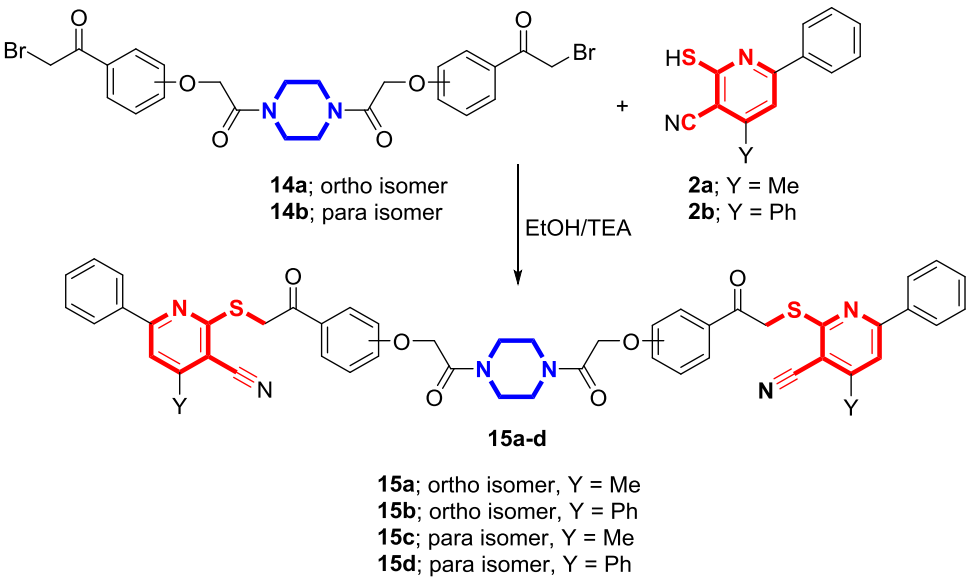
Scheme 5. Synthesis of Bis(α-bromoketones) Linked to Piperazine Core 14a,b



Scheme 6. Synthesis of Bis(sulfanediyl)bis(6-phenylnicotinonitriles) 15a−d



chemical shifts and integral values (see the Experimental Section). The structures of compounds **12a** and **12b** were determined using their elemental analyses and spectrum data. As a result, compound **12a** displayed absorption peaks in its infrared spectra at 3415, 34260, and 1633 cm^{-1}, which are indicative of the amino group and the carbonyl band, respectively. ^1H NMR revealed the piperazine and NH_2 protons as two broad signals at 3.75 and 6.03 ppm. Other protons were seen at the anticipated integral values and chemical shifts (see the Experimental Section). Thieno[2,3-*b*]pyridines 16a,b linked to piprazine core via carbonylphenoxyacetyl linker could also be prepared in good yields starting from 1,1′-(piperazine-1,4-diyl)bis(2-(4-(2-bromoacetyl)phenoxy)ethanones) **14a,b**. The latter compounds were prepared in 69−71% yields by reacting 1,1′-(piperazine-1,4-diyl)bis(2-(4-acetylphenoxy)ethanone) **13a,b** with *N*-bromosuccinimide in the presence of *p*-toluenesulfonic acid (PTSA) in acetonitrile. Compounds **13a and b** were successfully obtained in 77 and 79% yields, respectively, by the reaction of 1,1′-(piperazine-1,4-diyl)bis(2-chloroethanone) with the potassium salts of *ortho*- and *para*-hydroxyacetophenone **5a,b** in DMF at reflux (Scheme 5). The ^1H NMR spectra of **14b** indicated the presence of CH_2−Br protons, resonated at δ 4.82 as singlet signals integrating four protons.

The interaction of the 6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitriles **2a,b** with the relevant bromoacetyl derivatives **14a,b** in ethanol containing piperidine at reflux yielded bis(sulfanediyl)bis(6-phenylnicotinonitriles) **15a−d** in 76−78% yields (Scheme 6).

Subsequent cyclization of **15c** and **15d** in ethanol containing sodium ethoxide at reflux afforded the corresponding bis-(thieno[2,3-*b*]pyridines) **16a** and **16b** in 68 and 69% yields, respectively (Scheme 7). Analytical and spectral evidence confirmed the structure of **16a** and **16b**. Compound **16a** had IR bands at 3420, 3315, 1695, and 1650 cm^{-1} that were representative of the NH_2 and the ketonic and amide C═O groups, respectively. The ^1H NMR spectra of compound **16a** exhibited a singlet signal at δ 5.02, indicating the presence of OCH_2 protons. Furthermore, the mass spectra of **16a** revealed the appropriate molecular ion peaks at m/z = 886.

On the other hand, an attempt to synthesize bis(thieno[2,3-*b*]pyridine) **17** through cyclization of **15b** in ethanol containing sodium ethoxide at reflux was unsuccessful. Instead, the reactions gave 2-((benzofuran-3-ylmethyl)thio)-4,6-diphenylnicotinonitrile **19** in 82% yield (Scheme 8). It is suggested that compound **17** was formed initially and then intramolecular cyclocondensation of the methylene group with the ketonic groups at the 2-position of thienopyridine leading to

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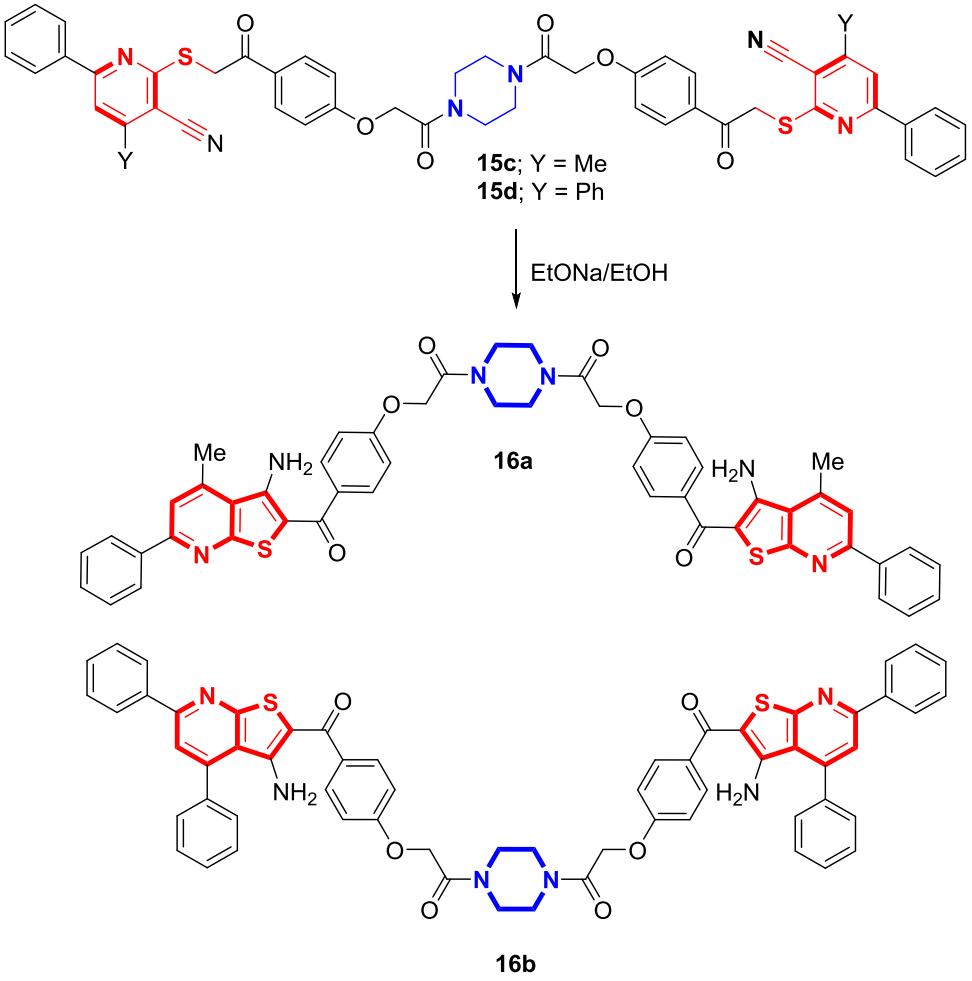
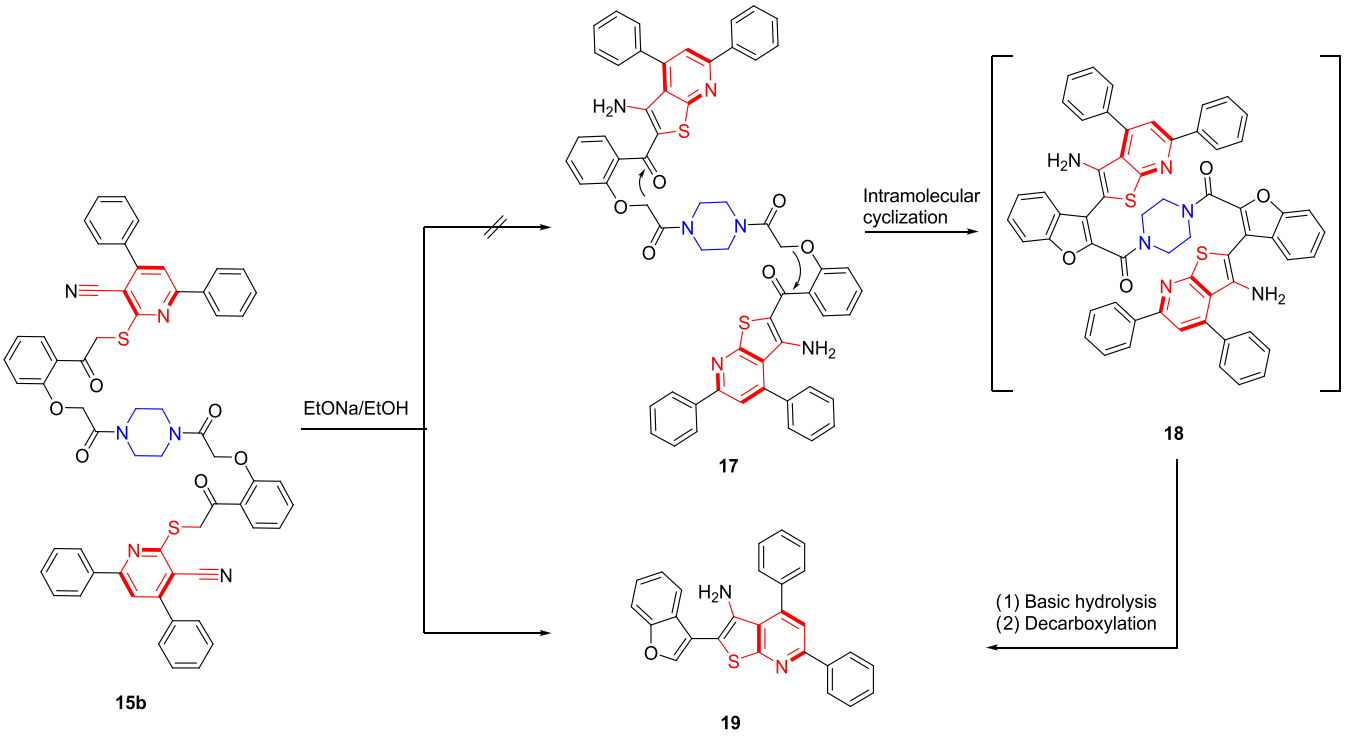
Scheme 7. Synthesis of Bis(thieno[2,3-*b*]pyridines) 16a and 16b



Scheme 8. Synthesis of 2-((Benzofuran-3-ylmethyl)thio)-4,6-diphenylnicotinonitrile 19



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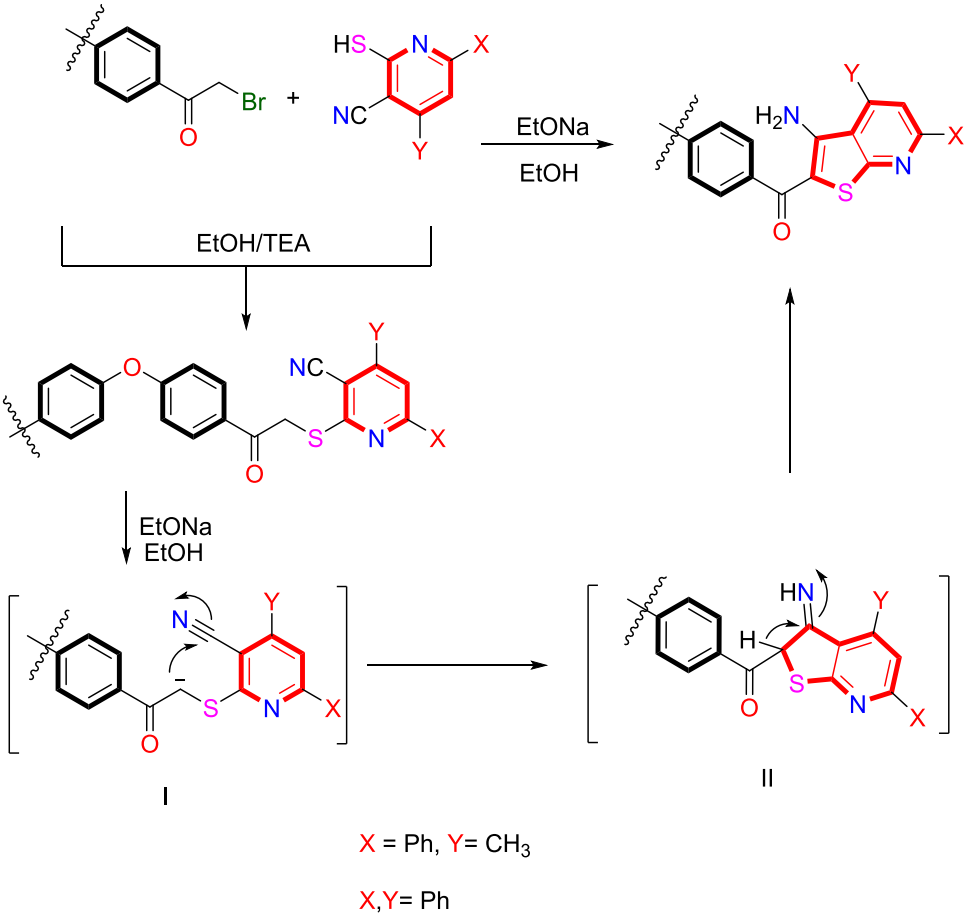
Scheme 9. Plausible Mechanism for the Formation of Thieno[2,3-*b*]pyridines



the formation of the corresponding 2-bezofuranyl derivative **18** followed by hydrolysis and subsequent decarboxylation under the reaction conditions to give **19**. Similar behavior of some related systems has been previously reported.[82]

It is worth mentioning that treatment of **15a** under similar conditions gave a mixture of nonisolable products.

A plausible mechanism of the formation of thieno[2,3-*b*]pyridines is outlined in Scheme 9. The reaction of the appropriate *α*-haloketone with the corresponding pyridinethione results in the formation of thienopyridines via an initial nucleophilic substitution reaction of the appropriate *α*-haloketone with the corresponding thienopyridines to give the intermediate *S*-alkylated product. Base-catalyzed intramolecular cyclization was used on the latter compounds to efficiently prepare the target thieno[2,3-*b*]pyridines via intermediates **I** and **II**. After treating pyridinethione with the appropriate *α*-halokeone in an ethanolic solution containing TEA in a catalytic amount, the intermediate *S*-alkylated product was successfully isolated.

CONCLUSIONS

We established an effective synthesis of hitherto unknown thienopyridines and bis(thienopyridines) connected to arene or heteroarene via phenoxymethyl groups. The newly synthesized compounds fulfilled the "hybrid molecules" idea, which seeks to combine two potential pharmacophores in a single molecule. We think that the inclusion of two pharmacophoric units in the newly synthesized compounds will increase their biological activity. Our present study attempts to widen the use of the stated technique by synthesizing more hybrid compounds with useful biological potency.

EXPERIMENTAL SECTION

Melting points were determined in open glass capillaries with a Gallenkamp apparatus. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Infrared spectra were recorded as potassium bromide disks on a Pye Unicam SP 3-300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR, and 125.65 MHz for ^{13}C NMR. Chemical shifts were reported downfield from TMS (= 0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMQP 1000 EX spectrometer. Analytical thin-layer chromatography was performed using precoated silica gel 60,778 plates (Fluka), and the spots were visualized with UV light at 254 nm.

General Procedure for the Synthesis of 2-((3-Cyano-4-alkyl-6-phenylpyridin-2-yl)thio)-*N*-(aryl)acetamide 3a−d. The proper 2-mercapto-4,6-disubstituted nicotinonitrile **2a** or **2b** (10 mmol) was added to a solution of 2-chloro-*N*-arylacetamides **1a,b** (10 mmol) in ethanol (25 mL) containing 0.2 mL of TEA. The reaction mixture was heated at reflux for 3 h. The title compounds **3a−d** were produced by filtering out and recrystallizing the solid that was formed after cooling from ethanol/DMF".

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*2-((3-Cyano-4-methyl-6-phenylpyridin-2-yl)thio)-N-(p-tolyl)acetamide (**3a**).* Off-white powder (89% Yield), mp 197−199 °C; IR (cm^{-1}): 3387 (NH), 2214 (CN), 1674 (CO); ^{1}H NMR (DMSO): δ 2.31 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.23 (s, 2H, SCH_2), 7.09 (d, J = 10 Hz, 2H, ArH), 7.28−7.48 (m, 5H, ArH), 7.80 (s, 1H, pyridine-5-H), 8.09 (d, J = 10 Hz, 2H, ArH), 10.33 (s, 1H, NH); ^{13}C NMR: δ 20.0, 22.6, 43.5, 105.4, 122.3, 127.0, 127.7, 128.4, 129.1, 132.4, 135.8, 137.5, 146.5, 149.6, 150.0, 153.4, 170.4; MS: m/z (%) 373 (M^+). Anal. Calcd For $C_{22}H_{19}N_3OS$: C, 70.75; H, 5.13; N, 11.25; S, 8.58. Found: C, 70.71; H, 5.14; N, 11.23; S, 8.57%.

*2-((3-Cyano-4,6-diphenylpyridin-2-yl)thio)-N-(p-tolyl)-acetamide (**3b**).* Creamy powder (83% Yield), mp 266−268 °C; IR (cm^{-1}): 3325 (NH), 2224 (CN), 1671 (CO); ^{1}H NMR (DMSO): δ 2.25 (s, 3H, CH_3), 4.31 (s, 2H, SCH_2), 7.11 (d, J = 8.1 Hz, 2H, ArH), 7.31−7.76 (m, 10H, ArH), 7.89 (s, 1H, pyridine-5-H), 8.22 (d, J = 8.1 Hz, 2H, ArH), 10.35 (s, 1H, NH); MS: m/z (%) 435 (M^+). Anal. Calcd For $C_{27}H_{21}N_3OS$: C, 74.46; H, 4.86; N, 9.65; S, 7.36. Found: C, 74.48; H, 4.83; N, 9.64; S, 7.37%.

*N-(4-Chlorophenyl)-2-((3-cyano-4-methyl-6-phenylpyridin-2-yl)thio)acetamide (**3C**).* Off-white powder (85% Yield), mp 200−202 °C; IR (cm^{-1}): 3364 (NH), 2214 (CN), 1658 (CO); ^{1}H NMR (DMSO): δ 2.52 (s, 3H, CH_3), 4.26 (s, 2H, SCH_2), 7.33 (d, J = 6.9 Hz, 2H, ArH), 7.35−7.65 (m, 5H, ArH), 7.84 (s, 1H, pyridine-5-H), 8.10 (d, J = 7.2 Hz, 2H, ArH), 10.55 (s, 1H, NH); ^{13}C NMR: δ 20.0, 35.0, 104.6, 115.1, 117.2, 120.5, 126.8, 127.3, 128.4, 128.9, 130.5, 136.5, 138.0, 153.5, 157.7, 160.9, 166.0; MS: m/z (%) 393 (M^+). Anal. Calcd For $C_{21}H_{16}ClN_3OS$: C, 64.04; H, 4.09; N, 10.67; S, 8.14. Found: C, 64.02; H, 4.06; N, 10.69; S, 8.13%.

*N-(4-Chlorophenyl)-2-((3-cyano-4,6-diphenylpyridin-2-yl)thio)acetamide (**3d**).* Creamy powder (81% Yield), mp 250−252 °C; IR (cm^{-1}): 3331 (NH), 2221 (CN), 1667 (CO); ^{1}H NMR (DMSO): δ 4.32 (s, 2H, SCH_2), 7.33 (d, J = 8.1 Hz, 2H, ArH), 7.36−7.76 (m, 10H, ArH), 7.90 (s, 1H, pyridine-5-H), 8.20 (d, J = 8.4 Hz, 2H, ArH), 10.60 (s, 1H, NH); MS: m/z (%) 455 (M^+). Anal. Calcd For $C_{26}H_{18}ClN_3OS$: C, 68.49; H, 3.98; N, 9.22; S, 7.03. Found: C, 68.49; H, 3.97; N, 9.22; S, 7.01. %.

General Procedure for the Synthesis of *N*-Arylthieno-[2,3-*b*]pyridine-2-carboxamide Derivatives 4a−d. A solution of 2-(3-cyanopyridin-2-ylthio)-*N*-arylacetamides **3a−d** (10 mmol) in ethanol (25 mL) containing sodium ethoxide (10 mmol) was heated at reflux for 2 h. After cooling the reaction mixture, the solvent was vacuum-evaporated. The solid residue was collected and recrystallized from DMF to afford **4a−d**".

*3-Amino-4-methyl-6-phenyl-N-(p-tolyl)thieno[2,3-b]-pyridine-2-carboxamide (**4a**).* Yellow powder (83% Yield), mp 249−251 °C; IR (cm^{-1}): 3441, 3289 (NH_2), 1635 (CO); ^{1}H NMR (DMSO): δ 2.25 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 6.95 (s, 2H, NH_2), 7.11 (d, J = 10 Hz, 2H, ArH), 7.44−7.54 (m, 5H, ArH), 7.97 (s, 1H, pyridine-5-H), 8.12 (d, J = 10 Hz, 2H, ArH), 9.43 (s, 1H, NH); ^{13}C NMR: δ 17.0, 20.9, 120.0, 121.6, 122.5, 124.1, 128.0, 128.8, 129.7, 133.1, 136.4, 142.7, 146.8, 151.5, 155.6, 166.6, 167.3; MS: m/z (%) 373 (M^+). Anal. Calcd For $C_{22}H_{19}N_3OS$: C, 70.75; H, 5.13; N, 11.25; S, 8.58. Found: C, 70.71; H, 5.12; N, 11.23; S, 8.55%.

*3-Amino-4,6-diphenyl-N-(p-tolyl)thieno[2,3-b]pyridine-2-carboxamide (**4b**).* Orange powder (80% Yield), mp > 300 °C; IR (cm^{-1}): 3448, 3291 (NH_2), 1629 (CO); ^{1}H NMR (DMSO): δ 2.38 (s, 3H, CH_3), 7.34 (d, J = 8.4 Hz, 2H, ArH), 7.40−7.73 (m, 10H, ArH), 7.78 (s, 2H, NH_2), 8.03 (s, 1H, pyridine-5-H), 8.22 (d, J = 8.4 Hz, 2H, ArH), 9.58 (s, 1H, NH); MS: m/z (%) 435 (M^+). Anal. Calcd For $C_{27}H_{21}N_3OS$: C, 74.46; H, 4.86; N, 9.65; S, 7.36. Found: C, 74.46; H, 4.85; N, 9.63; S, 7.34%.

*3-Amino-N-(4-chlorophenyl)-4-methyl-6-phenylthieno-[2,3-b]pyridine-2-carboxamide (**4c**).* Yellow powder (79% Yield), mp 240−242 °C; IR (cm^{-1}): 3427, 3278 (NH_2), 1640 (CO); ^{1}H NMR (DMSO): δ 2.86 (s, 3H, CH_3), 7.01 (s, 2H, NH_2), 7.33 (d, J = 8.4 Hz, 2H, ArH), 7.47−7.72 (m, 5H, ArH), 7.97 (s, 1H, pyridine-5-H), 8.16 (d, J = 8.4 Hz, 2H, ArH), 9.60 (s, 1H, NH); ^{13}C NMR: δ 20.2, 118.7, 122.8, 124.0, 127.0, 127.1, 128.3, 128.9, 129.8, 137.6, 138.0, 145.8, 149.2, 156.2, 159.6, 164.2; MS: m/z (%) 393 (M^+). Anal. Calcd For $C_{21}H_{16}ClN_3OS$: C, 64.04; H, 4.09; N, 10.67; S, 8.14. Found: C, 64.03; H, 4.09; N, 10.66; S, 8.10%.

*3-Amino-N-(4-chlorophenyl)-4,6-diphenylthieno[2,3-b]-pyridine-2-carboxamide (**4d**).* Orange powder (76% Yield), mp 267−269 °C; IR (cm^{-1}): 3421, 3277 (NH_2), 1631 (CO); ^{1}H NMR (DMSO): δ 7.34 (d, J = 8.7 Hz, 2H, ArH), 7.49−7.72 (m, 12H, ArH, NH_2), 7.78 (s, 1H, pyridine-5-H), 8.23 (d, J = 8.1 Hz, 2H, ArH), 9.21 (s, 1H, NH); MS: m/z (%) 455 (M^+). Anal. Calcd For $C_{26}H_{18}ClN_3OS$: C, 68.49; H, 3.98; N, 9.22; S, 7.03. Found: C, 68.49; H, 3.96; N, 9.22; S, 7.02%.

General Procedure for the Synthesis of 8a−d. The 2-mercapto-4,6-disubstituted nicotinonitrile **2a** or **2b** (10 mmol) was added to a solution of the appropriate 2-(2-bromoacetyl)-phenoxy-*N*-arylcetamide **7a,b** (10 mmol) in ethanol (25 mL) containing a few drops TEA. For 3 h, the reaction mixture was heated at reflux. The solid obtained upon cooling was filtered off and recrystallized from ethanol/DMF to afford the title compounds **8a−d**.

*2-(4-(2-((3-Cyano-4-methyl-6-phenylpyridin-2-yl)thio)-acetyl)phenoxy)-N-(p-tolyl)acetamide (**8a**).* Colorless powder (88% Yield), mp 210−212 °C; IR (cm^{-1}): 3460 (NH), 2214 (CN), 1674 (CO), 1643 (CO); ^{1}H NMR (DMSO): δ 2.26 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.85 (s, 2H, SCH_2), 4.94 (s, 2H, OCH_2), 7.12−7.54 (m, 9H, ArH), 7.79−7.81 (m, 3H, pyridine-5-H, ArH), 8.11 (d, J = 8.1 Hz, 2H, ArH), 10.07 (s, 1H, NH); MS: m/z (%) 507 (M^+). Anal. Calcd For $C_{30}H_{25}N_3O_3S$: C, 70.99; H, 4.96; N, 8.28; S, 6.32. Found: C, 70.97; H, 4.95; N, 8.25; S, 6.33%.

*2-(4-(2-((3-Cyano-4,6-diphenylpyridin-2-yl)thio)acetyl)-phenoxy)-N-(p-tolyl)acetamide (**8b**).* Creamy powder (85% Yield), mp 184−186 °C; IR (cm^{-1}): 3425 (NH), 2219 (CN), 1671 (CO), 1650 (CO); ^{1}H NMR (DMSO): δ 2.26(s, 3H, CH_3), 4.87 (s, 2H, SCH_2), 5.00 (s, 2H, OCH_2), 7.12−7.74 (m, 14H, ArH), 7.85 (s, 1H, pyridine-5-H), 7.91 (d, J = 7.8 Hz, 2H, ArH), 8.15 (d, J = 8.7 Hz, 2H, ArH), 10.11 (s, 1H, NH); MS: m/z (%) 569 (M^+). Anal. Calcd For $C_{35}H_{27}N_3O_3S$: C, 73.79; H, 4.78; N, 7.38; S, 5.63. Found: C, 73.77; H, 4.78; N, 7.35; S, 5.60%.

*N-(4-Chlorophenyl)-2-(4-(2-((3-cyano-4-methyl-6-phenyl-pyridin-2-yl)thio)acetyl)phenoxy)acetamide (**8C**).* Colorless powder (83% Yield), mp 214−216 °C; IR (cm^{-1}): 3464 (NH), 2215 (CN), 1670 (CO), 1658 (CO); ^{1}H NMR (DMSO): δ 2.51 (s, 3H, CH_3), 4.85 (s, 2H, SCH_2), 4.94 (s, 2H, OCH_2), 7.15−7.41 (m, 8H, ArH), 7.69 (d, J = 8.7 Hz, 2H, ArH), 7.79−7.81 (m, 2H, pyridine-5-H, ArH), 8.11 (d, J = 8.7 Hz, 2H, ArH), 10.30 (s, 1H, NH); MS: m/z (%) 527 (M^+). Anal. Calcd For $C_{29}H_{22}ClN_3O_3S$: C, 65.97; H, 4.20; N, 7.96; S, 6.07. Found: C, 65.97; H, 4.21; N, 7.93; S, 6.05%.

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*N-(4-Chlorophenyl)-2-(4-(2-((3-cyano-4,6-diphenylpyridin-2-yl)thio)acetyl)phenoxy)acetamide (**8d**).* Creamy powder (81% Yield), mp 198−200 °C; IR (cm^{-1}): 3431 (NH), 2221 (CN), 1667 (CO), 1647 (CO); ^{1}H NMR (DMSO): δ 4.90 (s, 2H, SCH_2), 5.00 (s, 2H, OCH_2), 7.16−7.75 (m, 14H, ArH), 7.85 (s, 1H, pyridine-5-H), 7.90 (d, J = 7.8 Hz, 2H, ArH), 8.15 (d, J = 8.7 Hz, 2H, ArH), 10.32 (s, 1H, NH); MS: m/z (%) 589 (M^+). Anal. Calcd For $C_{34}H_{24}ClN_3O_3S$: C, 69.20; H, 4.10; N, 7.12; S, 5.43. Found: C, 69.21; H, 4.07; N, 7.11; S, 5.41. %.

General Procedure for the Synthesis of Sodium 2-(4-(3-amino-4-alkyl-6-phenylthieno[2,3-*b*]pyridine-2-carbonyl)phenoxy)-1-(*p*-arylamino)ethen-1-olate Derivatives 9a−d. A solution of the suitable 2-(4-(2-((3-cyano-4-alkyl-6-phenylpyridin-2-yl)thio)acetyl)phenoxy)-*N*-(aryl)-acetamide **8a−d** (10 mmol) in ethanol (25 mL) containing sodium ethoxide (10 mmol) was heated at reflux for 2 h. The solid was collected on heating to provide **9a−d**.

*Sodium 2-(4-(3-Amino-4-methyl-6-phenylthieno[2,3-b]-pyridine-2-carbonyl)phenoxy)-1-(p-tolylamino)ethen-1-olate (**9a**).* Yellow powder (83% Yield), mp > 300 °C; IR (cm^{-1}): 3433, 3224 (NH_2), 1675 (CO); ^{1}H NMR (DMSO): δ 2.27 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 7.05 (d, J = 7.5 Hz, 2H, ArH), 7.09−7.77 (m, 10H, ArH), 7.84 (s, 1H, pyridine-5-H), 7.88(s, 2H, NH_2), 8.17 (d, J = 6.6 Hz, 2H, ArH), 8.58 (s, 1H, NH); ^{13}C NMR: δ 20.4, 23.6, 103.4, 113.5, 118.5, 119.6, 123.0, 127.0, 128.8, 129.7, 129.9, 130.4, 130.8, 137.4, 138.8, 146.7, 147.6, 151.6, 157.0, 161.5, 187,6; MS: m/z (%) 529 (M^+). Anal. Calcd For $C_{30}H_{24}N_3NaO_3S$: C, 68.04; H, 4.57; N, 7.93; S, 6.05. Found: C, 68.02; H, 4.56; N, 7.91; S, 6.05%.

*Sodium 2-(4-(3-Amino-4,6-diphenylthieno[2,3-b]pyridine-2-carbonyl)phenoxy)-1-(p-tolylamino)ethen-1-olate (**9b**).* Orange powder (81% Yield), mp > 300 °C; IR (cm^{-1}): 3425, 3260 (NH_2), 1671 (CO); ^{1}H NMR (DMSO): δ 2.27 (s, 3H, CH_3), 6.76 (s, 2H, NH_2), 7.06 (d, J = 8.7 Hz, 2H, ArH), 7.10−7.63 (m, 13H, ArH), 7.76 (d, J = 8.7 Hz, 2H, ArH), 7.82 (s, 1H, pyridine-5-H), 8.23−8.26 (m, 2H, ArH), 8.61 (s, 1H, NH); MS: m/z (%) 591 (M^+). Anal. Calcd For $C_{35}H_{26}N_3NaO_3S$: C, 71.05; H, 4.43; N, 7.10; S, 5.42. Found: C, 71.05; H, 4.42; N, 7.11; S, 5.41%.

*Sodium 2-(4-(3-Amino-4-methyl-6-phenylthieno[2,3-b]-pyridine-2-carbonyl)phenoxy)-1-((4-chlorophenyl)amino)-ethen-1-olate (**9c**).* Yellow powder (83% Yield), mp > 300 °C; IR (cm^{-1}): 3456,3260 (NH_2), 1666 (CO); ^{1}H NMR (DMSO): δ 2.89 (s, 3H, CH_3), 7.13 (d, J = 8.4 Hz, 2H, ArH), 7.19−7.53 (m, 8H, ArH), 7.78 (d, J = 8.4 Hz, 2H, ArH), 7.83 (s, 1H, pyridine-5-H), 7.92 (s, 2H, NH_2), 8.17 (d, J = 7.2 Hz, 2H, ArH), 8.82 (s, 1H, NH); ^{13}C NMR: δ 20.4, 103.4, 113.5, 118.5, 119.6, 123.0, 127.0, 128.8, 129.7, 129.9, 130.4, 130.7, 137.4, 138.8, 146.7, 147.6, 151.6, 157.0, 161.5, 187,6; MS: m/z (%) 549 (M^+). Anal. Calcd For $C_{29}H_{21}ClN_3NaO_3S$: C, 63.33; H, 3.85; N, 7.64; S, 5.83. Found: C, 63.33; H, 3.83; N, 7.63; S, 5.82%.

*Sodium 2-(4-(3-Amino-4,6-diphenylthieno[2,3-b]pyridine-2-carbonyl)phenoxy)-1-((4-chlorophenyl)amino)ethen-1-olate (**9d**).* Orange powder (84% Yield), mp > 300 °C; IR (cm^{-1}): 3425,3255 (NH_2), 1667 (CO); ^{1}H NMR (DMSO): δ 6.79 (s, 2H, NH_2), 7.14 (d, J = 8.7 Hz, 2H, ArH), 7.20−7.63 (m, 13H, ArH), 7.79 (d, J = 8.7 Hz, 2H, ArH), 7.82 (s, 1H, pyridine-5-H), 8.22−8.24 (m, 2H, ArH), 8.88 (s, 1H, NH); MS: m/z (%) 611 (M^+). Anal. Calcd For $C_{34}H_{23}ClN_3NaO_3S$: C, 66.72; H, 3.79; N, 6.87; S, 5.24. Found: C, 66.71; H, 3.79; N, 6.88; S, 5.21. %.

General Procedure for the Synthesis of 2-(3-Amino-4-alkyl-6-phenylthieno[2,3-*b*]pyridine-2-carbonyl)-phenoxy-*N*-arylacetamide Derivatives 9′b−d. A solution of the appropriate 2-(4-(2-((3-cyano-4-alkyl-6-phenylpyridin-2-yl)thio)acetyl)phenoxy)-*N*-(aryl)acetamide **8a−d** (10 mmol) in ethanol (25 mL) containing potassium carbonate (10 mmol) was heated at reflux for 2 h. The reaction mixture was then cooled, and the solvent was evaporated in *a vacuum*. The solid residue was collected and recrystallized from DMF to afford **9a−d.**

*2-(4-(3-Amino-4,6-diphenylthieno[2,3-b]pyridine-2-carbonyl)phenoxy)-N-(p-tolyl)acetamide (**9′b**).* Orange powder (77% Yield), mp 226−228 °C; IR (cm^{-1}): 3425, 3253 (NH_2), 1671 (CO), 1645 (CO); ^{1}H NMR (DMSO): δ 2.26 (s, 3H, CH_3), 4.81 (s, 2H, OCH_2), 6.86 (s, 2H, NH_2), 7.12−8.25 (m, 19H, ArH, pyridine-5-H), 10.19 (s, 1H, NH); MS: m/z (%) 569 (M^+). Anal. Calcd For $C_{35}H_{27}N_3O_3S$: C, 73.79; H, 4.78; N, 7.38; S, 5.63. Found: C, 73.77; H, 4.78; N, 7.35; S, 5.60%.

*2-(4-(3-Amino-4-methyl-6-phenylthieno[2,3-b]pyridine-2-carbonyl)phenoxy)-N-(4-chlorophenyl)acetamide (**9′c**).* Yellow powder (76% Yield), mp 240−242 °C; IR (cm^{-1}): 3414,3233 (NH_2), 1668 (CO), 1643 (CO); ^{1}H NMR (DMSO): δ 2.89 (s, 3H, CH_3), 3.32 (s, 1H, NH DMSO moisture), 4.85 (s, 2H, OCH_2), 7.13−7.81 (m, 11H, ArH), 7.85 (s, 1H, pyridine-5-H), 7.92 (s, 2H, NH_2), 8.16−8.17 (m, 2H, ArH); MS: m/z (%) 527 (M^+). Anal. Calcd For $C_{29}H_{22}ClN_3O_3S$: C, 65.97; H, 4.20; N, 7.96; S, 6.07. Found: C, 65.97; H, 4.21; N, 7.93; S, 6.05%.

*2-(4-(3-Amino-4,6-diphenylthieno[2,3-b]pyridine-2-carbonyl)phenoxy)-N-(4-chlorophenyl)acetamide (**9′d**).* Orange powder (77% Yield), mp 229−231 °C; IR (cm^{-1}): 3430,3253 (NH_2), 1667 (CO), 1443 (CO); ^{1}H NMR (DMSO): δ 3.38 (s, 1H, NH DMSO moisture), 4.83 (s, 2H, OCH_2), 6.84 (s, 2H, NH_2), 7.13−7.82 (m, 16H, ArH), 7.84 (s, 1H, pyridine-5-H), 8.22−8.24 (m, 2H, ArH); ^{13}C NMR: δ 67.0, 103.4, 114.5, 118.5, 119.9, 121.2, 127.3, 128.6, 128.7, 129.0, 129.1, 129.5, 129.6, 130.2, 133.7, 136.2, 137.2, 137.4, 148.9, 149.9, 157.2, 160.2, 162.0, 166.4; 188.0; m/z (%) 589 (M^+). Anal. Calcd For $C_{34}H_{24}ClN_3O_3S$: C, 69.20; H, 4.10; N, 7.12; S, 5.43. Found: C, 69.21; H, 4.07; N, 7.11; S, 5.41. %.

General Procedure for the Synthesis of 2,2′-((Piperazine-1,4-diylbis(2-oxoethane-2,1-diyl))bis-(sulfanediyl))bis(4-alkyl-6-phenylnicotinonitrile) 11a,b. To a solution of the appropriate 1,1′-(piperazine-1,4-diyl)bis-(2-chloroethanone) **10** (5 mmol) in ethanol (25 mL) containing 0.2 mL of TEA, the appropriate 2-mercapto-4,6-disubstituted nicotinonitrile **2a** or **2b** (10 mmol) was added. The reaction mixture was heated at reflux for 3h. The solid obtained upon cooling was filtered off and recrystallized from ethanol/DMF to afford the title compounds **11a,b**.

*2,2′-((Piperazine-1,4-diylbis(2-oxoethane-2,1-diyl))bis-(sulfanediyl))bis(4-methyl-6-phenylnicotinonitrile) (**11a**).* Colorless powder (79% Yield), mp 178−180 °C; IR (cm^{-1}): 2214 (CN), 1643 (CO); ^{1}H NMR (DMSO): δ 2.47 (s, 6H, CH_3), 3.56−3.75 (m, 8H, NCH_2), 4.43 (s, 4H, SCH_2), 7.46−7.61 (m, 6H, ArH), 7.83 (s, 2H, pyridine-5-H), 8.11 (s, 4H, ArH); MS: m/z (%) 618 (M^+). Anal. Calcd For $C_{34}H_{30}N_6O_2S_2$: C, 66.00; H, 4.89; N, 13.58; S, 10.36. Found: C, 66.02; H, 4.83; N, 13.58; S, 10.37%.

*2,2′-((Piperazine-1,4-diylbis(2-oxoethane-2,1-diyl))bis-(sulfanediyl))bis(4,6-diphenylnicotinonitrile) (**11b**).* Off-white powder (74% Yield), mp 198−200 °C; IR (cm^{-1}): 2211 (CN),

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1645 (CO); ^{1}H NMR (DMSO): δ 3.49−3.83 (m, 8H, NCH_2), 4.53 (s, 4H, SCH_2), 7.50−7.78 (m, 16H, ArH), 7.91 (s, 2H, pyridine-5-H), 8.22−8.24 (m, 4H, ArH); MS: *m*/*z* (%) 742 (M^+). Anal. Calcd For $C_{44}H_{34}N_6O_2S_2$: C, 71.14; H, 4.61; N, 11.31; S, 8.63. Found: C, 71.13; H, 4.63; N, 11.29; S, 8.60%.

General Procedure for the Synthesis of Piperazine-1,4-diylbis((3-amino-4-alkyl-6-phenylthieno[2,3-*b*]-pyridin-2-yl)methanone) 12a,b. A solution of the appropriate 2,2′-(2,2′-(piperazine-1,4-diyl)bis(2-oxoethane-2,1-diyl))bis(sulfanediyl)bis(4-alkyl-6-phenylnicotinonitrile) **11a,b** (5 mmol) in ethanol (25 mL) containing sodium ethoxide (10 mmol) was heated at reflux for 2 h. The reaction mixture was then cooled, and the solvent was evaporated in *a vacuum*. The solid residue was collected and recrystallized from DMF to afford **12a,b.**

*Piperazine-1,4-diylbis((3-amino-4-methyl-6-phenylthieno[2,3-b]pyridin-2-yl)methanone) (**12a**).* Yellow powder (72% Yield), mp 245−247 °C; IR (cm^{-1}): 4415−3260 (NH_2), 1633 (CO); ^{1}H NMR (DMSO): δ 2.86 (s, 6H, CH_3), 3.75 (s, 8H, NCH_2), 6.03 (s, 4H, NH_2), 7.49−7.51 (m, 6H, ArH), 7.78 (s, 2H, pyridine-5-H), 8.13−8.16 (m, 4H, ArH); ^{13}C NMR: δ 25.5, 47.7, 116.7, 120.6, 122.7, 124.8, 127.6, 129.0, 130.4, 135.4, 144.4, 151.0, 156.4, 168.0; MS: *m*/*z* (%) 618 (M^+). Anal. Calcd For $C_{34}H_{30}N_6O_2S_2$: C, 66.00; H, 4.89; N, 13.58; S, 10.36. Found: C, 66.00; H, 4.83; N, 13.58; S, 10.37%.

*Piperazine-1,4-diylbis((3-amino-4,6-diphenylthieno[2,3-b]pyridin-2-yl)methanone) (**12b**).* Orange powder (70% Yield), mp 288−290 °C; IR (cm^{-1}): 2425−2271 (NH_2), 1625 (CO); ^{1}H NMR (DMSO): δ 3.70 (s, 8H, NCH_2), 7.01 (s, 4H, NH_2), 7.48−7.60 (m, 16H, ArH), 7.78 (s, 2H, pyridine-5-H), 8.20−8.23 (m, 4H, ArH); MS: *m*/*z* (%) 742 (M^+). Anal. Calcd For $C_{44}H_{34}N_6O_2S_2$: C, 71.14; H, 4.61; N, 11.31; S, 8.63. Found: C, 71.14; H, 4.64; N, 11.29; S, 8.61%.

General Procedure for the Synthesis of 1,1′-(Piperazine-1,4-diyl)bis(2-acetylphenoxy)ethanone Derivatives 13a,b. 2-Hydroxyacetophenone **5a** or 4-hydroxyacetophenone **5b** (10 mmol) was dissolved in hot ethanolic KOH solution (prepared by dissolving 0.56 g (10 mmol) of KOH in 10 mL of absolute ethanol), and the solvent was then removed in vacuo. The remaining material was dissolved in DMF (10 mL) and 1,1′-(piperazine-1,4-diyl)bis(2-chloroethan-1-one) (**10**) (5 mmol) was added. The reaction mixture was refluxed for 10 min during which KCl was separated. The solvent was then removed in vacuo, and the remaining materials were poured onto crushed ice. The crude precipitate of **6** was recrystallized from ethanol **13a** as off-white crystals and DMF **13b** as a white powder.

*1,1′-(Piperazine-1,4-diyl)bis(2-(2-acetylphenoxy)ethan-1-one) (**13a**).* Off-white crystals, (77% yield), mp 260 °C; IR (KBr) 1702 (C═O), 1682 (C═O) cm^{-1}; ^{1}H NMR: δ 2.63 (s, 6H, CH_3), 3.50−3.56 (m, 8H, NCH_2), 5.06 (s, 4H, OCH_2), 7.00−7.58 (m, 8H, ArH); MS: *m*/*z* (%) 438 (M^+). Anal. Calcd for $C_{24}H_{26}N_2O_6$; C, 65.74; H, 5.98; N, 6.39. Found: C, 65.71; H, 5.97; N, 6.38%

*1,1′-(Piperazine-1,4-diyl)bis(2-(4-acetylphenoxy)ethan-1-one) (**13b**).* White crystals, (79% yield), mp 240 °C; IR (KBr) 1698 (C ═ O), 1677 (C═O) cm^{-1}; ^{1}H NMR: δ 2.51 (s, 6H, CH_3), 3.47−3.54 (m, 8H, NCH_2), 5.00 (s, 4H, OCH_2), 7.02 (d, *J* = 8.7 Hz, 4H, ArH), 7.91 (d, *J* = 8.7 Hz, 4H, ArH); MS: *m*/*z* (%) 438 (M^+). Anal. Calcd for $C_{24}H_{26}N_2O_6$; C, 65.74; H, 5.98; N, 6.39. Found: C, 65.71; H, 5.97; N, 6.38%

General Procedure for the Synthesis of 1,1′-(Piperazine-1,4-diyl)bis(2-(2-bromoacetyl)phenoxy)ethanone Derivatives 14a,b. To a stirred solution of the bis-(acetophenone) derivatives **13a,b** (l0 mmol) and *p*-TsOH (5.6 g, 20 mmol) in acetonitrile (50 mL) was slowly added NBS (3.6 g, 20 mmol). After NBS was added, the reaction mixture was heated at reflux with stirring for 2−3 h then left to cool to room temperature. The solvent was evaporated in *vacuo*, and the residue was dissolved in chloroform (50 mL), washed with water (20 mL), and dried over $MgSO_4$. After evaporation of the solvent, the resulting solid was recrystallized from ethyl acetate to afford the bis(α-bromoketone) derivatives **14a,b**.

*1,1′-(Piperazine-1,4-diyl)bis(2-(2-(2-bromoacetyl)-phenoxy)ethan-1-one) (**14a**).* Creamy crystals, (69% yield), mp 180 °C; IR (KBr) 1692 (C═O), 1660 (C═O) cm^{-1}; ^{1}H NMR: δ 3.50−3.56 (m, 8H, NCH_2), 5.03 (s, 4H, CH_2Br), 5.12 (s,4H, OCH_2), 7.06−7.67 (m, 8H, ArH); MS: *m*/*z* (%) 596 (M^+). Anal. Calcd for $C_{24}H_{24}Br_2N_2O_6$; C, 48.34; H, 4.06; N, 4.70. Found: C, 48.34; H, 4.07; N, 4.67%.

*1,1′-(Piperazine-1,4-diyl)bis(2-(4-(2-bromoacetyl)-phenoxy)ethan-1-one) (**14b**).* White powder, (71% yield), mp 136 °C; IR (KBr) 1697 (C═O), 1659 (C═O) cm^{-1}; ^{1}H NMR: δ 3.48−3.55 (m, 8H, NCH_2), 4.82 (s, 4H, CH_2Br), 5.03 (s,4H, OCH_2), 7.05 (d, *J* = 8.4 Hz, 4H, ArH), 7.96 (d, *J* = 8.4 Hz, 4H, ArH); MS: *m*/*z* (%) 596 (M^+). Anal. Calcd for $C_{24}H_{24}Br_2N_2O_6$; C, 48.34; H, 4.06; N, 4.70. Found: C, 48.33; H, 4.05; N, 4.67%.

General Procedure for the Synthesis of 2,2′-(((((Piperazine-1,4-diylbis(2-oxoethane-2,1-diyl))bis-(oxy))bis(*n*,1-phenylene))bis(2-oxoethane-2,1-diyl))bis-(sulfanediyl))bis(4-alkyl-6-phenylnicotinonitrile) 15a−d. To a solution of the appropriate bis-bromoacetyls **14a,b** (5 mmol) in ethanol (25 mL) containing 0.2 mL of TEA, the appropriate 2-mercapto-4,6-disubstituted nicotinonitrile **2a** or **2b** (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 compounds **15a−d.**

*2,2′-(((((Piperazine-1,4-diylbis(2-oxoethane-2,1-diyl))bis-(oxy))bis(2,1-phenylene))bis(2-oxoethane-2,1-diyl))bis-(sulfanediyl))bis(4-methyl-6-phenylnicotinonitrile) (**15a**).* Yellowish white powder (76% Yield), mp 226−228 °C; IR (cm^{-1}): 2217 (CN), 1690 (CO), 1643 (CO); ^{1}H NMR (DMSO): δ 2.34 (s, 6H, CH_3), 3.46−3.54 (m, 8H, NCH_2), 4.98 (s, 4H, SCH_2), 5.13 (s, 4H, OCH_2), 6.99 (t, *J* = 7.2 Hz, 2H, ArH), 7.23−7.59 (m, 12H, ArH), 7.81 (s, 2H, pyridine-5-H), 7.95 (d, *J* = 7.8 Hz, 4H, ArH); MS: *m*/*z* (%) 886 (M^+). Anal. Calcd For $C_{50}H_{42}N_6O_6S_2$: C, 67.70; H, 4.77; N, 9.47; S, 7.23. Found: C, 67.69; H, 4.75; N, 9.47; S, 7.21%.

*2,2′-(((((Piperazine-1,4-diylbis(2-oxoethane-2,1-diyl))bis-(oxy))bis(2,1-phenylene))bis(2-oxoethane-2,1-diyl))bis-(sulfanediyl))bis(4,6-diphenylnicotinonitrile) (**15b**).* Yellow powder (77% Yield), mp 233−235 °C; IR (cm^{-1}): 2223(CN), 1698 (CO), 1651 (CO); ^{1}H NMR (DMSO): δ 3.48−3.56 (m, 8H, NCH_2), 5.06 (s, 4H, SCH_2), 5.15 (s, 4H, OCH_2), 7.01 (t, *J* = 7.5 Hz, 2H, ArH), 7.25−7.75 (m, 22H, ArH), 7.87 (s, 2H, pyridine-5-H), 8.05 (d, *J* = 7.8 Hz, 4H, ArH); ^{13}C NMR: δ 35.8, 42.0, 66.2, 102.5, 113.7, 115.7, 116.0, 121.0, 126.5, 127.5, 128.6, 128.8, 130.1, 130.6, 134.1, 135.6, 136.2, 154.1, 157.3, 157.8, 162.1, 165.6;, 194.7; MS: *m*/*z* (%) 1010 (M^+). Anal. Calcd For $C_{60}H_{46}N_6O_6S_2$: C, 71.27; H, 4.59; N, 8.31; S, 6.34. Found: C, 71.26; H, 4.59; N, 8.29; S, 6.36%.

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*2,2′-(((((Piperazine-1,4-diylbis(2-oxoethane-2,1-diyl))bis-(oxy))bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis-(sulfanediyl))bis(4-methyl-6-phenylnicotinonitrile) (**15c**).* Yellow powder (78% Yield), mp 198−200 °C; IR (cm^{-1}): 2214 (CN), 1695 (CO), 1650 (CO); ^{1}H NMR (DMSO): δ 2.51 (s, 6H, CH_3), 3.52−3.59 (m, 8H, NCH_2), 4.92 (s, 4H, SCH_2), 5.07 (s, 4H, OCH_2), 7.09 (d, J = 8.4 Hz, 4H, ArH), 7.22−7.80(m, 10H, ArH), 7.82 (s, 2H, pyridine-5-H), 8.07 (d, J = 8.4 Hz, 4H, ArH); MS: m/z (%) 886 (M^+). Anal. Calcd For $C_{50}H_{42}N_6O_6S_2$: C, 67.70; H, 4.77; N, 9.47; S, 7.23. Found: C, 67.70; H, 4.76; N, 9.45; S, 7.22%.

*2,2′-(((((Piperazine-1,4-diylbis(2-oxoethane-2,1-diyl))bis-(oxy))bis(4,1-phenylene))bis(2-oxoethane-2,1-diyl))bis-(sulfanediyl))bis(4,6-diphenylnicotinonitrile) (**15d**).* Yellow powder (77% Yield), mp 239−241 °C; IR (cm^{-1}): 2217(CN), 1691 (CO), 1644 (CO); ^{1}H NMR (DMSO): δ 3.53−3.61 (m, 8H, NCH_2), 4.99 (s, 4H, SCH_2), 5.09 (s, 4H, OCH_2), 7.12 (d, J = 8.1 Hz, 4H, ArH), 7.22−7.85 (m, 16H, ArH), 7.86 (s, 2H, pyridine-5-H), 7.91 (d, J = 7.8 Hz, 4H, ArH), 8.10 (d, J = 8.1 Hz, 4H, ArH); MS: m/z (%) 1010 (M^+). Anal. Calcd For $C_{60}H_{46}N_6O_6S_2$: C, 71.27; H, 4.59; N, 8.31; S, 6.34. Found: C, 71.26; H, 4.57; N, 8.30; S, 6.34%.

General Procedure for the Synthesis of 1,1′-(Piperazine-1,4-diyl)bis(2-(*n*-(3-amino-4-alkyl-6-phenylthieno[2,3-*b*]pyridine-2-carbonyl)phenoxy)-ethanone) (16a, 16b, and 18). A solution of the appropriate 2,2′-(((((piperazine-1,4-diylbis(2-oxoethane-2,1-diyl))bis-(oxy))bis(n,1-phenylene))bis(2-oxoethane-2,1-diyl))bis-(sulfanediyl))bis(4-alkyl-6-phenylnicotinonitriles) **15a, 15b,** and **15d** (5 mmol) in ethanol (25 mL) containing sodium ethoxide (10 mmol) was heated at reflux for 2 h. The reaction mixture was then cooled, and the solvent was evaporated in a vacuum. The solid residue was collected and recrystallized from DMF to afford **16a, 16b,** and **18**.

*1,1′-(Piperazine-1,4-diyl)bis(2-(4-(3-amino-4-methyl-6-phenylthieno[2,3-b]pyridine-2-carbonyl)phenoxy)ethan-1-one) (**16a**).* Yellow powder (68% Yield), mp > 300 °C; IR (cm^{-1}): 3420, 3315 (NH_2), 1695 (CO), 1650 (CO); ^{1}H NMR (DMSO): δ 2.89 (s, 6H, CH_3), 3.53−3.59 (m, 8H, NCH_2), 5.02 (s, 4H, OCH_2), 7.09 (d, J = 8.7 Hz, 4H, ArH), 7.50−7.82 (m, 10H, ArH), 7.85 (s, 2H, pyridine-5-H), 7.99 (s, 4H, NH_2), 8.07 (d, J = 6.3 Hz, 4H, ArH); MS: m/z (%) 886 (M^+). Anal. Calcd For $C_{50}H_{42}N_6O_6S_2$: C, 67.70; H, 4.77; N, 9.47; S, 7.23. Found: C, 67.70; H, 4.76; N, 9.45; S, 7.22%.

*1,1′-(Piperazine-1,4-diyl)bis(2-(4-(3-amino-4,6-diphenylthieno[2,3-b]pyridine-2-carbonyl)phenoxy)ethan-1-one) (**16b**).* Yellow powder (69% Yield), mp > 300 °C; IR (cm^{-1}): 3425, 3326 (NH_2), 1677 (CO), 1648 (CO); ^{1}H NMR (DMSO): δ 3.53−3.60 (m, 8H, NCH_2), 5.03 (s, 4H, OCH_2), 6.85 (s, 4H, NH_2), 7.22−7.85 (m, 30H, ArH, pyridine-5-H); MS: m/z (%) 1010 (M^+). Anal. Calcd For $C_{60}H_{46}N_6O_6S_2$: C, 71.27; H, 4.59; N, 8.31; S, 6.34. Found: C, 71.26; H, 4.57; N, 8.30; S, 6.34%.

*2-((Benzofuran-3-ylmethyl)thio)-4,6-diphenylnicotinonitrile (**18**).* Yellow powder (77% Yield), mp 233−235 °C; IR (cm^{-1}): 2223(CN), 1698 (CO), 1651 (CO); ^{1}H NMR (DMSO): δ 7.45−7.56 (m, 10H, NH_2, ArH), 7.72−7.81 (m, 5H, ArH, pyridine-5-H), 8.02 (d, J = 7.8 Hz, 1H, ArH), 8.24 (d, J = 7.2 Hz, 2H, ArH); MS: m/z (%) 418 (M^+). Anal. Calcd For $C_{27}H_{18}N_2OS$: C, 77.49; H, 4.34; N, 6.69; S, 7.66. Found: C, 77.47; H, 4.33; N, 6.68; S, 7.64%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c06653.

^{1}H NMR spectrum of compound **3a**; ^{13}C NMR spectrum of compound **3a**; ^{1}H NMR spectrum of compound **3b**; ^{1}H NMR spectrum of compound **3c**; ^{13}C NMR spectrum of compound **3c**; ^{1}H NMR spectrum of compound **3d**; ^{1}H NMR spectrum of compound **4a**; ^{13}C NMR spectrum of compound **4a**; ^{1}H NMR spectrum of compound **4b**; ^{1}H NMR spectrum of compound **4c**; ^{13}C NMR spectrum of compound **4c**; ^{1}H NMR spectrum of compound **4d**; ^{1}H NMR spectrum of compound **8a**; ^{1}H NMR spectrum of compound **8b**; ^{1}H NMR spectrum of compound **8c**; ^{1}H NMR spectrum of compound **8d**; ^{1}H NMR spectrum of compound **9a**; ^{13}C NMR spectrum of compound **9a**; ^{1}H NMR spectrum of compound **9b**; ^{1}H NMR spectrum of compound **9c**; ^{13}C NMR spectrum of compound **9c**; ^{1}H NMR spectrum of compound **9d**; ^{1}H NMR spectrum of compound **9′b**; ^{1}H NMR spectrum of compound **9′c**; ^{1}H NMR spectrum of compound **9′d**; ^{13}C NMR spectrum of compound **9′d**; ^{1}H NMR spectrum of compound **11a**; ^{1}H NMR spectrum of compound **11b**; ^{1}H NMR spectrum of compound **12a**; ^{13}C NMR spectrum of compound **12a**; ^{1}H NMR spectrum of compound **12b**; ^{1}H NMR spectrum of compound **13a**; ^{1}H NMR spectrum of compound **13b**; ^{1}H NMR spectrum of compound **14a**; ^{1}H NMR spectrum of compound **14b**; ^{1}H NMR spectrum of compound **15a**; ^{1}H NMR spectrum of compound **15b**; ^{13}C NMR spectrum of compound **15b**; ^{1}H NMR spectrum of compound **15c**; ^{1}H NMR spectrum of compound **15d**; ^{1}H NMR spectrum of compound **′6a**; ^{1}H NMR spectrum of compound **16b**; and ^{1}H NMR spectrum of compound **18** (PDF)

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