Received: 28 March 2020 | Revised: 17 April 2020 | Accepted: 30 April 2020

DOI: 10.1002/jhet.4021

ARTICLE

WILEY

Piperazine-mediated tandem synthesis of bis(thieno[2,3-*b*]pyridines): Versatile precursors for related fused [1,2,4]triazolo[4,3-*a*]pyrimidines

Sherif M. H. Sanad | **Ahmed E. M. Mekky**

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

Correspondence
Sherif M. H. Sanad, Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt.
Email: sherif_hamed1980@yahoo.com

Abstract

In this study, we discuss the utility of bis(cyanoacetamides) as versatile precursors to the piperazine-mediated synthesis of a wide spectrum of bis(thieno[2,3-*b*]pyridine) derivatives, linked to aliphatic spacers via thioethers. The proposed tandem protocol involved the reaction of bis(cyanoacetamides) with two equivalents of the appropriate cinnamonitriles in dioxane in the presence of six equivalents of piperazine at reflux for 4 hours. Then, two equivalents of the appropriate halogen-containing reagents were added and the reaction was heated at reflux for further 3 hours. The bis(thieno[2,3-*b*]pyridines) were taken as a key intermediates to new bis(4-oxopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines). The above derivatives were reacted with the appropriate hydrazonyl chloride derivatives in dioxane in the presence of triethylamine to yield the corresponding bis([1,2,4]triazoles) with a related fused pyridothienopyrimidine moiety. The new structures were elucidated by IR, NMR spectral data, as well as elemental analyses.

1 | INTRODUCTION

Heterocyclic derivatives incorporating thienopyridine moieties show excellent medicinal activities such as antimicrobial,[1,2] antiviral,[3,4] anti-inflammatory,[5–7] antidiabetic,[8,9] antihypertensive,[10,11] and Osteogenic.[12,13] Thienopyridine derivatives also act as good inhibitors for DNA gyrase,[14] glycine site antagonist of the *N*-methyl-*D*-aspartate (NMDA) receptor,[15] selective and orally bioavailable CHK1,[16] and eukaryotic elongation factor-2 kinase eEF2-K.[17] Thienopyridines act also as inhibitors of eicosanoid biosynthesis through their binding with COX enzymes.[18] Moreover, heterocyclic compounds incorporating thieno[2,3-*b*]pyridine moiety gave act promising results as pim-1 kinase inhibitors as well as anticancer and antiproliferative agents.[19–23]

[1,2,4]Triazolopyrimidines, as analogues to purine derivatives, possess a wide range of medicinal activities including antileishmanial, anticonvulsant, selective ATP site directed inhibition of the EGF-receptor protein tyrosine kinase.[24–27] Also, they inhibit tubulin by promotion of its polymerization and currently important in agricultural chemistry and as antiparasitic.[28–30] In addition, they act as antimicrobial, anti-influenza, antifungal, antioxidant, anti-inflammatory, antimalarial, analgesic, antitumor, antihypertensive, and cardiovascular agents.[31–41]

In connection to our efforts in the synthesis of biologically potent thienopyridine and their related fused heterocyclic derivatives,[42–46] we report herein an efficient procedure for the synthesis of new bis(thienopyridine) and their related fused [1,2,4]triazolo[4,3-*a*]pyrimidines linked to aliphatic spacers via thioethers.

2 | RESULTS AND DISCUSSION

The bis(cyanoacetamide) derivatives **5** were prepared by two-step reaction protocol.[47] The protocol involved the

reaction of 2-aminobenzenethiol **1** with the appropriate 1,ω-dibromoalkanes **2** in the presence of potassium hydroxide and tetrabutylammonium bromide to give the corresponding bis(2-aminophenylthio)alkane derivatives **3**[48] followed by their reaction with cyanoacetyl derivative **4** (Scheme 1).

The bis(cyanoacetamide) derivatives were used as versatile precursors to the piperazine-mediated synthesis of a wide spectrum of bis(3,6-diaminothieno[2,3-*b*]pyridine-5-carboxamide) derivatives, linked to aliphatic spacers via thioethers.

At first, compound **5a** reacted with two equivalents of cinnamonitrile **6a** in ethanol in the presence of an equivalent amount of piperazine at reflux for 4 hours to afford a sole reaction product. The ^{1}H-NMR spectrum of such product showed the presence of four singlet signals at δ 3.81, 6.72, 10.80, and 13.12 ppm assigned for OCH_3, NH_2, NH, and pyridine-NH protons, respectively (see experimental section). Based on the above, the structure of such product was assigned as the corresponding bis(2-amino-5-cyano-6-thioxopyridine-3-carboxamide) **10** and not bis (2-amino-5-cyano-6-oxopyridine-3-carbothioamide) **8**. The reaction may proceed by the initial Michael addition of active methylene groups in **5a** to the olefinic bond in two molecules of **6a** followed by consecutive cyclization and auto-oxidation to afford **10** through the non-isolable intermediates **7** and **9** (Scheme 2).[49]

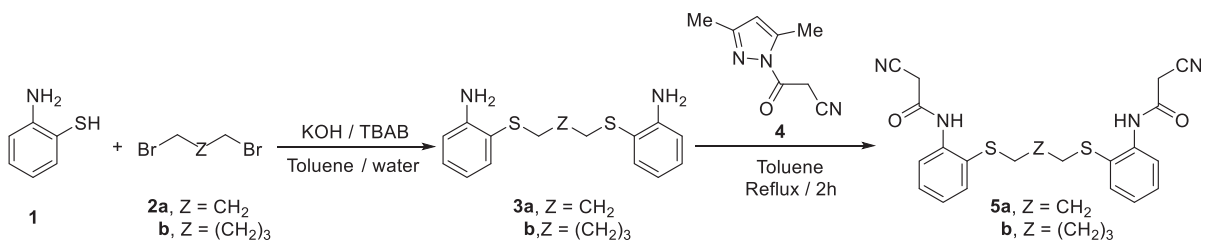
The structure of bis(pyridine-2[1*H*]-thione) **10** was more confirmed via its reaction with chloroacetone **11a** to prepare the corresponding bis(thieno[2,3-*b*]pyridine). Thus, compound **10** reacted with two equivalents of **11a** in ethanol in the presence of two equivalent of piperazine at reflux for 3 hours to afford the corresponding bis (2-acetyl-3,6-diaminothieno[2,3-*b*]pyridine-5-carboxamide) **13a** (Scheme 3).[50] The IR spectrum of **13a** showed the absence of nitrile function. Its ^{1}H-NMR spectrum showed the presence of four singlet signals at δ 2.38, 3.83, 6.70, and 10.69 ppm assigned for CH_3, OCH_3, NH_2, and NH protons, respectively. In addition, it showed two signals at δ 1.85 and 3.05 ppm attributed to propane spacer and a multiplet signal at the range of 6.96 to 7.58 corresponding to two NH_2 and 16 aromatic protons (see experimental section). The synthesis of **13a** may proceed by the initial formation of bis(nicotinonitrile) **12** followed by piperazine-catalyzed intramolecular cyclization (Scheme 3).

Next, we examine the synthesis of bis(thieno[2,3-*b*] pyridine) via four-component one-pot method. Therefore, bis(cyanoacetamide) **5a** reacted with two equivalents of each of cinnamonitrile **6a** and chloroacetone **11a** in ethanol in the presence of three equivalents of piperazine at reflux for 8 hours. Unfortunately, we could not isolate a pure sample of **13a** using this route. Instead, we obtained an inseparable mixture of products.

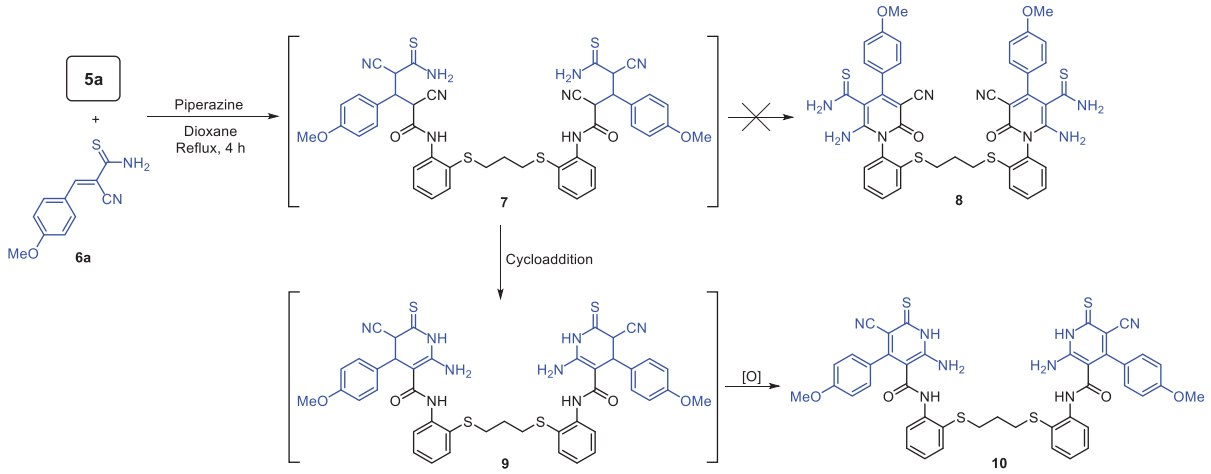
The aforementioned results stimulate us to prepare the bis(thieno[2,3-*b*]pyridine) derivatives using another tandem reaction. Thus, bis(cyanoacetamide) **5a** was treated at first with two equivalents of **6a** in ethanol in the presence of three equivalents of piperazine at reflux for 4 hours, then two equivalents of chloroacetone **11a** were added to the reaction mixture. The reaction mixture was further heated at reflux for 3 hours to afford a sole product. The product of such reaction was found identical with the bis(thieno[2,3-*b*]pyridine) **13a** in all characteristics (Scheme 4).

The possibility and generality of the above tandem reaction were established by using bis(cyanoacetamides) **5a,b**, cinnamonitriles **6a,b**, and several of halogen-containing reagents **11a-d** in ethanol in the presence of piperazine under the above conditions to prepare a novel series of bis(thieno[2,3-*b*]pyridines) **13b-13l** (Scheme 4).

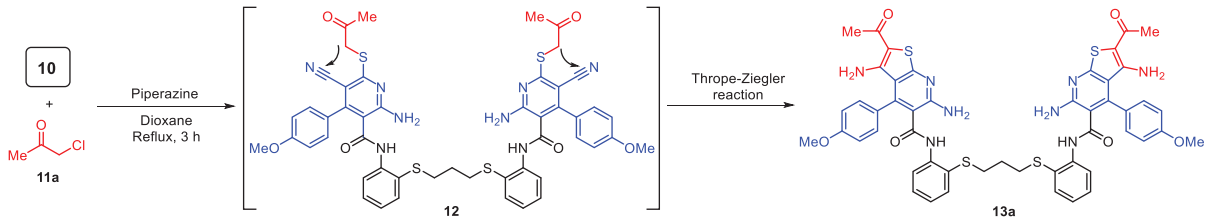
Encouraged by these findings, our efforts were extended to synthesize novel bis([1,2,4]triazolo[4,3-*a*] pyrimidines) bearing a related fused thieno[2,3-*b*]pyridine moiety. Thus, bis(2-carbamoylthieno[2,3-*b*]pyridine-5-carboxamide) derivative **13c** reacted with formic acid **14a** at reflux to give the corresponding bis(4-oxopyrido [3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide) derivative **15a** (Scheme 5 and experimental section).[46] In the same way, bis(2-carbamoylthieno[2,3-*b*]pyridine-5-carboxamides) **13e** and **13i** reacted with formic acid **14a** at reflux to give the corresponding bis(pyridothieno[3,2-*d*] pyrimidines) **15b** and **15c**, respectively (Scheme 5).



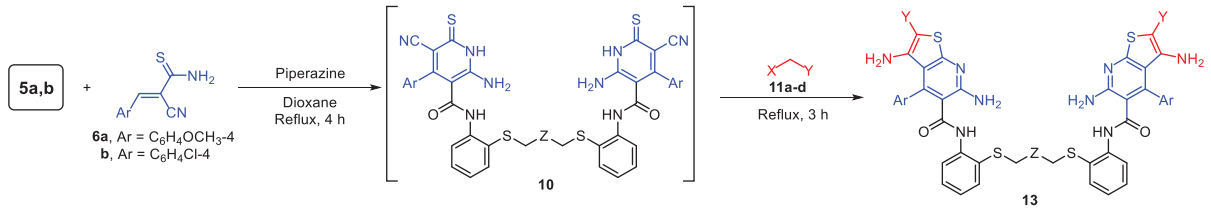
SCHEME 1 Synthesis of the starting precursors bis(cyanoacetamides) **5**



SCHEME 2 Synthesis of bis(pyridine-2[1*H*]-thione) **10** [Colour figure can be viewed at wileyonlinelibrary.com]



SCHEME 3 Synthesis of bis(thieno[2,3-*b*]pyridine) **13a** [Colour figure can be viewed at wileyonlinelibrary.com]

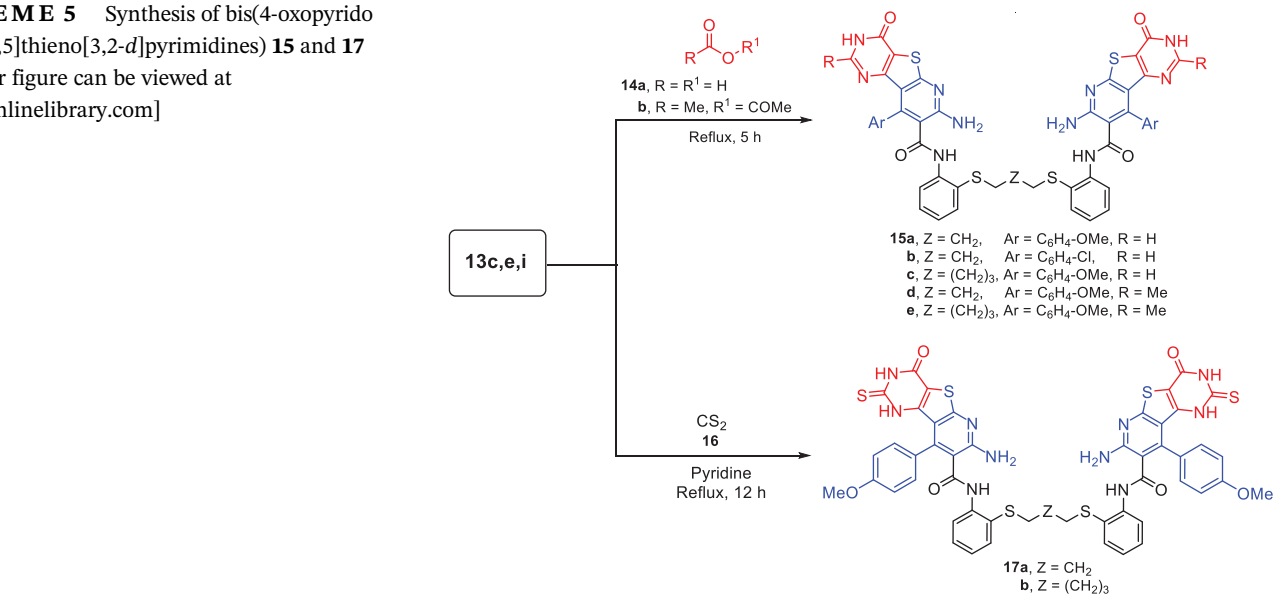


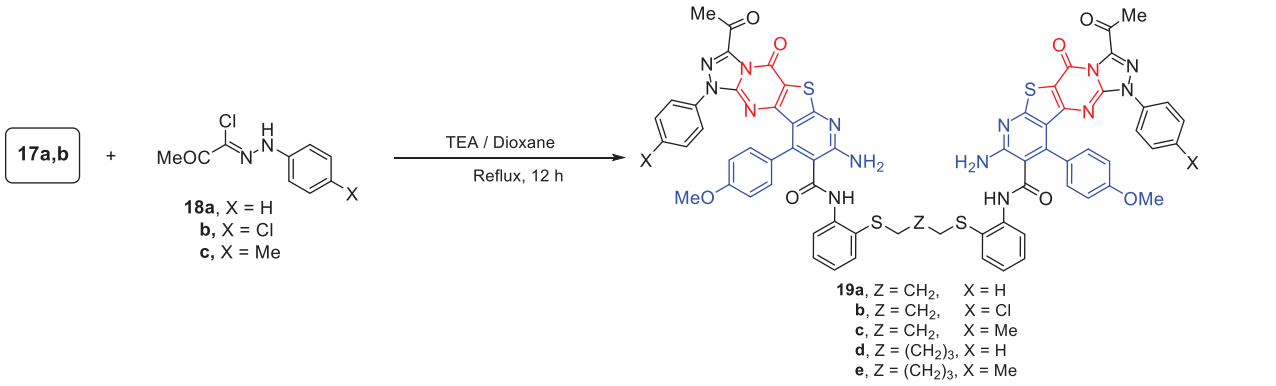
SCHEME 4 Tandem synthesis of bis(thieno[2,3-*b*]pyridines) **13** [Colour figure can be viewed at wileyonlinelibrary.com]

On the other hand, bis(2-carbamoylthieno[2,3-*b*]pyridine-5-carboxamides) **13c** and **13i** reacted with acetic anhydride **14b** or carbon disulfide **16** in pyridine at reflux to afford the corresponding bis(2-methyl-4-oxopyrimidines) **15d,e** and bis(4-oxo-2-thioxopyrimidines) **17a,b**, respectively (Scheme 5 and experimental section).[46]

Preparation of [1,2,4]triazole ring with a related fused pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine moiety was accomplished by the reaction of bis(4-oxo-2-thioxopyrimidines) **17** with the appropriate hydrazonyl chloride derivatives **18**.[51] Thus, **17a** was reacted with hydrazonyl chloride **18a** in dioxane in the presence of triethylamine. The reaction mixture was heated at reflux till no hydrogen sulfide gases were evolved. After refluxing the reaction mixture for 12 hours, TLC analysis revealed the presence of a sole product which formulated as bis(3-acetylpyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine) derivative **19a** (Scheme 6). The structure of **19a** was confirmed by elucidation of its elemental and spectral analyses. Thus, its ^{1}H NMR spectrum

SCHEME 5 Synthesis of bis(4-oxopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines) **15** and **17** [Colour figure can be viewed at wileyonlinelibrary.com]





SCHEME 6 Synthesis of bis(3-acetylpyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,4]triazolo[4,3-*a*]pyrimidines) **19** [Colour figure can be viewed at wileyonlinelibrary.com]

revealed four singlet signals at δ 2.73, 3.84, 6.72, and 10.65 ppm assigned to CH_3CO, OCH_3, NH_2, and NH protons, respectively (see experimental section). In the same manner, compounds **17a,b** reacted with hydrazonyl chlorides **18a-c** to give the corresponding bis([1,2,4]triazoles) **19b-e**, respectively (Scheme 6).

3 | CONCLUSIONS

The bis(cyanoacetamides) were prepared and used as key intermediates to the piperazine-mediated synthesis of a wide spectrum of bis(thieno[2,3-*b*]pyridine) derivatives, linked to aliphatic spacers via thioethers. The bis(thieno[2,3-*b*]pyridines) were taken as versatile precursors to novel bis(4-oxopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine) derivatives. The above derivatives were reacted with the appropriate hydrazonyl chloride derivatives in dioxane in the presence of triethylamine to yield the corresponding bis([1,2,4]triazoles) with a related fused pyridothienopyrimidine moiety.

4 | EXPERIMENTAL

4.1 | Introduction

All solvents were acquired from commercial sources and used as received unless otherwise stated. All other chemicals were acquired from Merck or Aldrich. These chemicals were used without further purification. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, which is an ultrahigh performance, versatile attenuated total reflectance (ATR) sampling accessory on the Nicolet iS10 FT-IR spectrometer manufactured. NMR spectra were recorded on a Bruker

Avance III 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using TMS as an internal standard and DMSO-d_6 as solvent, and chemical shifts were expressed as δ ppm units. Elemental analyses were carried out on a EuroVector instrument C, H, N analyzer EA3000 Series.

4.2 | Synthesis of *N,N′*-((propane-1,3-diylbis[sulfanediyl])bis(2,1-phenylene)) bis(2-amino-5-cyano-4-[4-methoxyphenyl]-6-thioxo-1,6-dihydropyridine-3-carboxamide) (8)

A mixture of bis(2-cyanoacetamide) **5a** (5 mmol), cinnamonitrile **6a** (10 mmol), and piperazine (5 mmol) in dioxane (30 mL) was heated at reflux for 4 hours. The solid product was isolated and recrystallized from dioxane as yellow crystals (71%); m.p. 272°C to 274°C; IR (υ cm^{-1}): 3362, 3208 (NH), 2218 (CN), and 1642 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.88 (m, 2H, $SCH_2CH_2CH_2S$), 3.07 (t, 4H, $SCH_2CH_2CH_2S$), 3.81 (s, 6H, 2 OCH_3), 6.72 (s, br, 4H, 2 NH_2), 6.99 to 7.48 (m, 16H, ArH′s), 10.80 (s, br, 2H, 2 NH), and 13.12 (s, br, 2H, 2 pyridine NH); Anal. calcd. For $C_{43}H_{36}N_8O_4S_4$ (857.0): C, 60.26; H, 4.23; N, 13.07; found: C, 60.38; H, 4.09; N, 13.22%.

4.3 | General procedure for bis(thieno [2,3-*b*]pyridines) 13a-13l

A mixture of bis(2-cyanoacetamides) **5a,b** (5 mmol)), cinnamonitrile **6a** (10 mmol), and piperazine (15 mmol) in dioxane (30 mL) was heated at reflux for 4 hours. Then, each of chloroacetone **13a**, chloroacetonitrile **13b**, 2-bromo-1-(4-chlorophenyl)ethanone **13c**, or chloroacetonitrile **13d** (10 mmol) was added and the reaction was heated further at reflux for 3 hours. The product that formed was collected by filtration, washed with cold ethanol, dried, and then recrystallized from the proper solvent.

4.3.1 | *N,N′*-((Propane-1,3-diylbis [sulfanediyl])bis(2,1-phenylene))bis (2-acetyl-3,6-diamino-4-[4-methoxyphenyl] thieno[2,3-*b*]pyridine-5-carboxamide) (13a)

Orange solid recrystallized from DMF (78%); m.p. 292°C to 293°C; IR (υ cm^{-1}): 3442, 3347, 3184 (NH), and 1652 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.85 (t, 2H, $SCH_2CH_2CH_2S$), 2.38 (s, 6H, 2 CH_3), 3.05 (t, 4H, $SCH_2CH_2CH_2S$), 3.83 (s, 6H, 2 OCH_3), 6.70 (s, br, 4H, 2 NH_2), 6.96 to 7.58 (m, 20H, 16 ArH's, and 2 NH_2), and 10.69 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 27.8, 29.4, 31.7, 55.3, 105.8, 112.7, 113.9, 120.8, 120.9, 126.4, 127.5, 129.5, 129.8, 130.4, 132.7, 135.6, 140.8, 146.8, 156.2, 159.2, 161.2, 163.6, and 192.1; Anal. calcd. For $C_{49}H_{44}N_8O_6S_4$ (969.1): C, 60.73; H, 4.58; N, 11.56; found: C, 60.80; H, 4.47; N, 11.75%.

4.3.2 | *N,N′*-((Propane-1,3-diylbis [sulfanediyl])bis(2,1-phenylene))bis (3,6-diamino-2-(4-chlorobenzoyl)-4-(4-methoxyphenyl)thieno[2,3-*b*]pyridine-5-carboxamide) (13b)

Yellow solid recrystallized from DMF/ ethanol mixture (74%); m.p. above 300°C; IR (υ cm^{-1}): 3458, 3332, 3204 (NH), and 1644 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.87 (t, 2H, $SCH_2CH_2CH_2S$), 3.08 (t, 4H, $SCH_2CH_2CH_2CH_2S$), 3.82 (s, 6H, 2 OCH_3), 6.66 (s, br, 4H, 2 NH_2), 6.97 to 7.79 (m, 28H, 24 ArH's, and 2 NH_2), and 10.72 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 27.7, 31.7, 55.2, 103.7, 111.8, 114.2, 119.3, 120.7, 126.5, 127.6, 129.1, 129.5, 129.8, 130.0, 130.5, 132.6, 135.5, 135.9, 136.2, 141.6, 150.8, 156.4, 159.0, 162.2, 162.9, and 187.6; Anal. calcd. For $C_{59}H_{46}Cl_2N_8O_6S_4$ (1162.2): C, 60.97; H, 3.99; N, 9.64; found: C, 61.14; H, 4.07; N, 9.51%.

4.3.3 | *N,N′*-((Propane-1,3-diylbis [sulfanediyl])bis(2,1-phenylene))bis (3,6-diamino-2-carbamoyl-4-(4-methoxyphenyl)thieno[2,3-*b*]pyridine-5-carboxamide) (13c)

Orange solid recrystallized from DMF/ethanol mixture (65%); m.p. 276°C to 278°C; IR (υ cm^{-1}): 3456, 3339, 3224 (NH), and 1652 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.86 (t, 2H, $SCH_2CH_2CH_2S$), 3.07 (t, 4H, $SCH_2CH_2CH_2S$), 3.82 (s, 6H, 2 OCH_3), 6.21 (s, br, 4H, 2 NH_2), 6.78 (s, br, 4H, 2 NH_2), 6.96 to 7.59 (m, 20H, 16 ArH's and 2 NH_2), and 10.69 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 27.7, 31.6, 55.1, 106.2, 113.5, 114.1, 120.6, 120.7, 126.6, 127.7, 129.4, 129.8, 130.6, 132.4, 135.7, 140.5, 151.9, 156.8, 158.9, 162.1, 162.9, and 168.6; Anal. calcd. For $C_{47}H_{42}N_{10}O_6S_4$ (971.1): C, 58.13; H, 4.36; N, 14.42; found: C, 58.24; H, 4.31; N, 14.66%.

4.3.4 | *N,N′*-((Propane-1,3-diylbis [sulfanediyl])bis(2,1-phenylene))bis (3,6-diamino-2-(4-chlorobenzoyl)-4-(4-chlorophenyl)thieno[2,3-*b*]pyridine-5-carboxamide) (13d)

Yellow solid recrystallized from DMF (69%); m.p. above 300°C; IR (υ cm^{-1}): 3458, 3332, 3204 (NH), and 1644 (CO);

^{1}H-NMR (DMSO-d_6): δ 1.87 (t, 2H, $SCH_2CH_2CH_2S$), 3.08 (t, 4H, $SCH_2CH_2CH_2CH_2S$), 3.82 (s, 6H, 2 OCH_3), 6.66 (s, br, 4H, 2 NH_2), 7.22 to 7.77 (m, 28H, 24 ArH's, and 2 NH_2), and 10.72 (s, br, 2H, 2 NH); Anal. calcd. For $C_{57}H_{40}Cl_4N_8O_4S_4$ (1171.0): C, 58.46; H, 3.44; N, 9.57; found: C, 58.31; H, 3.49; N, 9.42%.

4.3.5 | *N,N′*-((Propane-1,3-diylbis [sulfanediyl])bis(2,1-phenylene))bis (3,6-diamino-2-carbamoyl-4-(4-chlorophenyl)thieno[2,3-*b*]pyridine-5-carboxamide) (13e)

Orange solid recrystallized from DMF/ethanol mixture (69%); m.p. above 300°C; IR (υ cm^{-1}): 3451, 3332, 3218 (NH), and 1656 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.87 (t, 2H, $SCH_2CH_2CH_2S$), 3.08 (t, 4H, $SCH_2CH_2CH_2S$), 6.19 (s, br, 4H, 2 NH_2), 6.75 (s, br, 4H, 2 NH_2), 7.21 to 7.50 (m, 20H, 16 ArH's, and 2 NH_2), and 10.72 (s, br, 2H, 2 NH); Anal. calcd. For $C_{45}H_{36}Cl_2N_{10}O_4S_4$ (979.9): C, 55.15; H, 3.70; N, 14.29; found: C, 55.23; H, 3.58; N, 14.44%.

4.3.6 | *N,N′*-((Propane-1,3-diylbis [sulfanediyl])bis(2,1-phenylene))bis (3,6-diamino-4-(4-chlorophenyl)-2-cyanothieno[2,3-*b*]pyridine-5-carboxamide) (13f)

Yellow crystals recrystallized from DMF (75%); m.p. above 300°C; IR (υ cm^{-1}): 3466, 3330, 3225 (NH), 2224 (CN), and 1644 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.84 (t, 2H, $SCH_2CH_2CH_2S$), 3.04 (t, 4H, $SCH_2CH_2CH_2S$), 5.94 (s, br, 4H, 2 NH_2), 6.74 (s, br, 4H, 2 NH_2), 7.21 to 7.50 (m, 16H, and ArH's), and 10.67 (s, br, 2H, and 2 NH); Anal. calcd. For $C_{45}H_{32}Cl_2N_{10}O_2S_4$ (943.9): C, 57.26; H, 3.42; N, 14.84; found: C, 57.39; H, 3.51; N, 14.98%.

4.3.7 | *N,N′*-((Pentane-1,5-diylbis [sulfanediyl])bis(2,1-phenylene))bis (2-acetyl-3,6-diamino-4-(4-methoxyphenyl) thieno[2,3-*b*]pyridine-5-carboxamide) (13g)

Orange solid recrystallized from DMF (72%); m.p. 284°C to 286°C; IR (υ cm^{-1}): 3433, 3357, 3202 (NH), and 1645 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.55 to 1.58 (t, 6H, $SCH_2CH_2CH_2CH_2CH_2S$), 2.39 (s, 6H, 2 CH_3), 2.95 (t, 4H, $SCH_2CH_2CH_2CH_2CH_2S$), 3.81 (s, 6H, 2 OCH_3), 6.68 (s, br, 4H, 2 NH_2), 6.94 to 7.61 (m, 20H, 16 ArH's, and 2 NH_2), and 10.77 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 27.2, 27.9, 29.6, 31.7, 55.2, 106.0, 113.2, 114.1, 120.9, 121.1, 126.5, 127.4, 129.6, 129.7, 130.7, 132.6, 135.4, 140.8, 146.8, 155.9, 159.5, 161.3, 163.8, and 192.2; Anal. calcd. For $C_{51}H_{48}N_8O_6S_4$ (997.2): C, 61.43; H, 4.85; N, 11.24; found: C, 61.66; H, 4.92; N, 11.13%.

4.3.8 | *N,N′*-((Pentane-1,5-diylbis [sulfanediyl])bis(2,1-phenylene))bis (3,6-diamino-2-(4-chlorobenzoyl)-4-(4-chlorophenyl)thieno[2,3-*b*]pyridine-5-carboxamide) (13h)

Yellow solid recrystallized from DMF (66%); m.p. above 300°C; IR (υ cm^{-1}): 3454, 3336, 3209 (NH), and 1646 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.55 to 1.58 (t, 6H, $SCH_2CH_2CH_2CH_2CH_2S$), 2.96 (t, 4H, $SCH_2CH_2CH_2CH_2CH_2S$), 6.69 (s, br, 4H, 2 NH_2), 7.20 to 7.75 (m, 28H, 24 ArH's and 2 NH_2), and 10.80 (s, br, 2H, 2 NH); Anal. calcd. For $C_{59}H_{44}Cl_4N_8O_4S_4$ (1199.0): C, 59.10; H, 3.70; N, 9.35; found: C, 59.10; H, 3.70; N, 9.35%.

4.3.9 | *N,N′*-((Pentane-1,5-diylbis [sulfanediyl])bis(2,1-phenylene))bis (3,6-diamino-2-carbamoyl-4-(4-methoxyphenyl)thieno[2,3-*b*]pyridine-5-carboxamide) (13i)

Orange solid recrystallized from DMF (71%); m.p. above 300°C; IR (υ cm^{-1}): 3448, 3342, 3226 (NH), and 1647 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.55 to 1.57 (t, 6H, $SCH_2CH_2CH_2CH_2CH_2S$), 2.95 (t, 4H, $SCH_2CH_2CH_2CH_2CH_2S$), 3.83 (s, 6H, 2 OCH_3), 6.18 (s, br, 4H, 2 NH_2), 6.67 (s, br, 4H, 2 NH_2), 6.95 to 7.58 (m, 20H, 16 ArH's, and 2 NH_2), and 10.76 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 27.1, 27.8, 31.7, 55.3, 106.5, 113.4, 114.0, 120.4, 120.7, 126.7, 127.6, 129.5, 129.8, 130.5, 132.6, 135.7, 140.4, 151.7, 156.9, 159.3, 162.5, 164.0, and 168.9; Anal. calcd. For $C_{49}H_{46}N_{10}O_6S_4$ (999.2): C, 58.90; H, 4.64; N, 14.02; found: C, 59.12; H, 4.47; N, 14.14%.

4.3.10 | *N,N′*-((Pentane-1,5-diylbis [sulfanediyl])bis(2,1-phenylene))bis (3,6-diamino-2-cyano-4-(4-methoxyphenyl) thieno[2,3-*b*]pyridine-5-carboxamide) (13j)

Yellow crystals recrystallized from DMF (72%); m.p. 262°C to 265°C; IR (υ cm^{-1}): 3470, 3341, 3224 (NH), 2222 (CN), and 1646 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.56 to 1.58 (m, 6H, $SCH_2CH_2CH_2CH_2CH_2S$), 2.95 (t, 4H,

SCH_2CH$_2$CH$_2$CH$_2$CH_2S), 3.83 (s, 6H, 2 OCH$_3$), 5.95 (s, br, 4H, 2 NH$_2$), 6.76 (s, br, 4H, 2 NH$_2$), 6.98 to 7.59 (m, 16H, ArH's), 10.64 (s, br, 2H, 2 NH); Anal. calcd. For $C_{49}H_{42}N_{10}O_4S_4$ (963.1): C, 61.10; H, 4.40; N, 14.54; found: C, 60.94; H, 4.52; N, 14.69%.

4.3.11 | *N,N′*-((Pentane-1,5-diylbis [sulfanediyl])bis(2,1-phenylene))bis (2-acetyl-3,6-diamino-4-(4-chlorophenyl) thieno[2,3-*b*]pyridine-5-carboxamide) (13k)

Orange solid recrystallized from DMF (72%); m.p. 284°C to 286°C; IR (υ cm^{-1}): 3445, 3350, 3206 (NH), and 1649 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.55 to 1.58 (t, 6H, SCH$_2$CH_2CH_2CH_2CH$_2$S), 2.39 (s, 6H, 2 CH$_3$), 2.95 (t, 4H, SCH_2CH$_2$CH$_2$CH$_2$CH_2S), 6.73 (s, br, 4H, 2 NH$_2$), 6.86 (s, br, 4H, 2 NH$_2$), 7.18 to 7.51 (m, 16H, ArH's), and 10.77 (s, br, 2H, 2 NH); Anal. calcd. For $C_{49}H_{42}Cl_2N_8O_4S_4$ (1006.0): C, 58.50; H, 4.21; N, 11.14; found: C, 58.50; H, 4.21; N, 11.14%.

4.3.12 | *N,N′*-((Pentane-1,5-diylbis [sulfanediyl])bis(2,1-phenylene))bis (3,6-diamino-4-(4-chlorophenyl)-2-cyanothieno[2,3-*b*]pyridine-5-carboxamide) (13l)

Yellow solid recrystallized from DMF (78%); m.p. above 300°C; IR (υ cm^{-1}): 3472, 3338, 3217 (NH), 2223 (CN), and 1643 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.56 to 1.59 (m, 6H, SCH$_2$CH_2CH_2CH_2CH$_2$S), 2.93 (t, 4H, SCH_2CH$_2$CH$_2$CH$_2$CH_2S), 5.93 (s, br, 4H, 2 NH$_2$), 6.81 (s, br, 4H, 2 NH$_2$), 7.22 to 7.48 (m, 16H, ArH's), and 10.86 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 27.2, 27.9, 31.8, 74.1, 110.6, 115.6, 119.1, 120.8, 126.4, 129.0, 129.6, 129.8, 130.2, 132.6, 135.5, 135.6, 135.7, 140.4, 140.8, 155.2, 156.4, and 163.2; Anal. calcd. For $C_{47}H_{36}Cl_2N_{10}O_2S_4$ (972.0): C, 58.08; H, 3.73; N, 14.41; found: C, 58.22; H, 4.01; N, 14.56%.

4.4 | General procedure for synthesis of bis(4-oxopyrimidines) 15a-15e

A mixture of bis(2-carbamoylthieno[2,3-*b*]pyridine-5-carboxamides) **13c,e,i** (5 mmol) and each of formic acid **14a** or acetic anhydride **14b** (25 mL) was heated at reflux for 5 hours. The solvent was evaporated to its half volume and cooled. The solid product was collected by filtration, washed with cold ethanol, dried, and then recrystallized from the proper solvent.

4.4.1 | *N,N′*-((Propane-1,3-diylbis [sulfanediyl])bis(2,1-phenylene))bis (7-amino-9-(4-methoxyphenyl)-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*] pyrimidine-8-carboxamide) (15a)

Colorless solid recrystallized from glacial acetic acid (63%); m.p. above 300°C; IR (υ cm^{-1}): 3412, 3324, 3192 (NH), and 1646 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.87 (t, 2H, SCH$_2$CH_2CH$_2$S), 3.06 (t, 4H, SCH_2CH$_2$CH_2S), 3.81 (s, 6H, 2 OCH$_3$), 6.62 (s, br, 4H, 2 NH$_2$), 6.94 to 7.55 (m, 16H, ArH's), 8.13 (s, 2H, 2 pyrimidine-H2), 10.52 (s, br, 2H, 2 NH), and 12.80 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 27.8, 31.8, 55.3, 104.6, 114.2, 116.7, 120.6, 121.1, 126.3, 127.5, 129.4, 129.6, 130.5, 132.6, 135.4, 142.9, 147.1, 151.0, 155.7, 157.1, 159.5, 162.8, and 166.6; Anal. calcd. For $C_{49}H_{38}N_{10}O_6S_4$ (991.1): C, 59.38; H, 3.86; N, 14.13; found: C, 59.22; H, 3.97; N, 14.01%.

4.4.2 | *N,N′*-((Propane-1,3-diylbis [sulfanediyl])bis(2,1-phenylene))bis (7-amino-9-(4-chlorophenyl)-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*] pyrimidine-8-carboxamide) (15b)

Colorless solid recrystallized from DMF/ethanol mixture (70%); m.p. above 300°C; IR (υ cm^{-1}): 3419, 3322, 3197 (NH), and 1646 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.86 (t, 2H, SCH$_2$CH_2CH$_2$S), 3.06 (t, 4H, SCH_2CH$_2$CH_2S), 6.66 (s, br, 4H, 2 NH$_2$), 7.21 to 7.49 (m, 16H, ArH's), 8.10 (s, 2H, 2 pyrimidine-H2), 10.48 (s, br, 2H, 2 NH), and 12.78 (s, br, 2H, 2 NH); Anal. calcd. For $C_{47}H_{32}Cl_2N_{10}O_4S_4$ (999.9): C, 56.45; H, 3.23; N, 14.01; found: C, 56.29; H, 3.46; N, 13.84%.

4.4.3 | *N,N′*-((Pentane-1,5-diylbis [sulfanediyl])bis(2,1-phenylene))bis (7-amino-9-(4-methoxyphenyl)-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*] pyrimidine-8-carboxamide) (15c)

Colorless solid recrystallized from glacial acetic acid (68%); m.p. above 300°C; IR (υ cm^{-1}): 3412, 3324, 3192 (NH), and 1646 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.55 to 1.58 (m, 6H, SCH$_2$CH_2CH_2CH_2CH$_2$S), 2.95 (t, 4H, SCH_2CH$_2$CH$_2$CH$_2$CH_2S), 3.82 (s, 6H, 2 OCH$_3$), 6.58 (s, br, 4H, 2 NH$_2$), 6.96 to 7.56 (m, 16H, ArH's), 8.12 (s, 2H, 2 pyrimidine-H2), 10.60 (s, br, 2H, 2 NH), and 12.69 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 27.2, 27.8, 31.6, 55.2, 105.1, 114.1, 116.2, 120.7, 121.3, 126.4, 127.5, 129.5,

129.7, 130.4, 132.6, 135.6, 142.6, 147.3, 151.5, 155.4, 157.2, 159.2, 162.9, and 165.8; Anal. calcd. For $C_{51}H_{42}N_{10}O_6S_4$ (1019.2): C, 60.10; H, 4.15; N, 13.74; found: C, 59.87; H, 4.23; N, 13.82%.

4.4.4 | *N*,*N*′-((Propane-1,3-diylbis[sulfanediyl])bis(2,1-phenylene))bis(7-amino-9-(4-methoxyphenyl)-2-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide) (15d)

Colorless solid recrystallized from DMF (63%); m.p. above 300°C; IR (υ cm^{-1}): 3420, 3327, 3196 (NH), and 1648 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.87 (t, 2H, $SCH_2CH_2CH_2S$), 2.20 (s, 6H, 2 CH_3), 3.07 (t, 4H, $SCH_2CH_2CH_2S$), 3.83 (s, 6H, 2 OCH_3), 6.54 (s, br, 4H, 2 NH_2), 6.94 to 7.58 (m, 16H, ArH's), 10.52 (s, br, 2H, 2 NH), and 12.80 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 24.6, 27.6, 31.7, 55.2, 105.6, 114.0, 117.8, 120.7, 126.2, 126.5, 127.4, 129.6, 129.8, 130.4, 132.8, 135.6, 142.5, 146.7, 155.5, 155.8, 157.4, 159.3, 163.0, and 166.8; Anal. calcd. For $C_{51}H_{42}N_{10}O_6S_4$ (1019.2): C, 60.10; H, 4.15; N, 13.74; found: C, 60.28; H, 4.01; N, 13.64%.

4.4.5 | *N*,*N*′-((Pentane-1,5-diylbis[sulfanediyl])bis(2,1-phenylene))bis(7-amino-9-(4-methoxyphenyl)-2-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide) (15e)

Colorless solid recrystallized from DMF/ethanol mixture (63%); m.p. above 300°C; IR (υ cm^{-1}): 3419, 3334, 3201 (NH), and 1649 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.55 to 1.58 (m, 6H, $SCH_2CH_2CH_2CH_2CH_2S$), 2.23 (s, 6H, 2 CH_3), 2.93 (t, 4H, $SCH_2CH_2CH_2CH_2CH_2S$), 3.81 (s, 6H, 2 OCH_3), 6.70 (s, br, 4H, 2 NH_2), 6.95 to 7.58 (m, 16H, ArH's), 10.57 (s, br, 2H, 2 NH), and 12.62 (s, br, 2H, 2 NH); Anal. calcd. For $C_{53}H_{46}N_{10}O_6S_4$ (1047.2): C, 60.79; H, 4.43; N, 13.37; found: C, 60.65; H, 4.48; N, 13.21%.

4.5 | General procedure for synthesis of bis(4-oxo-2-thioxopyrimidines) 17a,b

A mixture of bis(2-carbamoylthieno[2,3-*b*]pyridine-5-carboxamides) **13c,i** (5 mmol) and carbon disulfide **16** (8 mL) in pyridine (30 mL) was heated at reflux for 12 hours. The solvent was evaporated to its half volume and cooled. The product was collected by filtration, washed with cold ethanol, dried, and recrystallized from the proper solvent.

4.5.1 | *N*,*N*′-((Propane-1,3-diylbis[sulfanediyl])bis(2,1-phenylene))bis(7-amino-9-(4-methoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide) (17a)

Yellow solid recrystallized from DMF (66%); m.p. above 300°C; IR (υ cm^{-1}): 3410, 3327, 3199 (NH), and 1656 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.84 (t, 2H, $SCH_2CH_2CH_2S$), 3.04 (t, 4H, $SCH_2CH_2CH_2S$), 3.83 (s, 6H, 2 OCH_3), 6.69 (s, br, 4H, 2 NH_2), 6.97 to 7.68 (m, 16H, ArH's), 10.33 (s, br, 2H, 2 NH), 10.85 (s, br, 2H, 2 NH), and 12.92 (s, br, 2H, 2 NH); Anal. calcd. For $C_{49}H_{38}N_{10}O_6S_6$ (1055.2): C, 55.77; H, 3.63; N, 13.27; found: C, 55.53; H, 3.51; N, 13.42%.

4.5.2 | *N*,*N*′-((Pentane-1,5-diylbis[sulfanediyl])bis(2,1-phenylene))bis(7-amino-9-(4-methoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide) (17b)

Yellow solid recrystallized from DMF/ethanol mixture (62%); m.p. above 300°C; IR (υ cm^{-1}): 3415, 3330, 3202 (NH), and 1650 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.57 to 1.59 (m, 6H, $SCH_2CH_2CH_2CH_2CH_2S$), 2.96 (t, 4H, $SCH_2CH_2CH_2CH_2CH_2S$), 3.84 (s, 6H, 2 OCH_3), 6.58 (s, br, 4H, 2 NH_2), 6.98 to 7.65 (m, 16H, ArH's), 10.41 (s, br, 2H, 2 NH), 10.92 (s, br, 2H, 2 NH), and 12.98 (s, br, 2H, 2 NH); Anal. calcd. For $C_{51}H_{42}N_{10}O_6S_6$ (1083.3): C, 56.54; H, 3.91; N, 12.93; found: C, 56.67; H, 4.04; N, 12.75%.

4.6 | General procedure for synthesis of bis(3-acetylpyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-9-carboxamides) 19a-e

A mixture of bis(4-oxo-2-thioxopyrimidines) **17a,b** (5 mmol) and the appropriate hydrazonyl chlorides **18a-c** (10 mmol) in the presence of triethylamine (2 mL) in dioxane (30 mL) was heated at reflux for 12 hours. The solvent was evaporated to its half volume and cooled. The solid products were collected by filtration, washed

with cold ethanol, dried, and then recrystallized from the proper solvent.

4.6.1 | *N,N′*-((Propane-1,3-diylbis[sulfanediyl])bis(2,1-phenylene))bis(3-acetyl-8-amino-10-(4-methoxyphenyl)-5-oxo-1-phenyl-1,5-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-9-carboxamide) (19a)

Yellow solid recrystallized from DMF (59%); m.p. 294°C to 296°C; IR (υ cm^{-1}): 3396, 3322, 3174 (NH), and 1686 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.85 (t, 2H, $SCH_2CH_2CH_2S$), 2.73 (s, 6H, 2 CH_3), 3.07 (t, 4H, $SCH_2CH_2CH_2S$), 3.84 (s, 6H, 2 OCH_3), 6.72 (s, br, 4H, 2 NH_2), 6.98 to 7.72 (m, 26H, ArH's), and 10.65 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 27.4, 27.6, 31.7, 55.3, 113.7, 113.9, 119.8, 120.2, 120.3, 120.8, 124.9, 126.5, 127.7, 129.6, 129.8, 130.6, 132.5, 135.6, 135.7, 140.8, 144.8, 151.2, 151.6, 153.5, 156.7, 157.8, 159.4, 163.6, 164.8, and 194.0; Anal. calcd. For $C_{67}H_{50}N_{14}O_8S_4$ (1307.4): C, 61.55; H, 3.85; N, 15.00; found: C, 61.72; H, 3.93; N, 15.11%.

4.6.2 | *N,N′*-((Propane-1,3-diylbis[sulfanediyl])bis(2,1-phenylene))bis(3-acetyl-8-amino-1-(4-chlorophenyl)-10-(4-methoxyphenyl)-5-oxo-1,5-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-9-carboxamide) (19b)

Yellow solid recrystallized from DMF (59%); m.p. above 300°C; IR (υ cm^{-1}): 3391, 3330, 3179 (NH), and 1686 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.86 (t, 2H, $SCH_2CH_2CH_2S$), 2.74 (s, 6H, 2 CH_3), 3.06 (t, 4H, $SCH_2CH_2CH_2S$), 3.82 (s, 6H, 2 OCH_3), 6.82 (s, br, 4H, 2 NH_2), 6.98 to 7.81 (m, 24H, ArH's), and 10.74 (s, br, 2H, 2 NH); Anal. calcd. For $C_{67}H_{48}Cl_2N_{14}O_8S_4$ (1376.3): C, 58.47; H, 3.52; N, 14.25; found: C, 58.36; H, 3.47; N, 14.38%.

4.6.3 | *N,N′*-((Propane-1,3-diylbis[sulfanediyl])bis(2,1-phenylene))bis(3-acetyl-8-amino-10-(4-methoxyphenyl)-5-oxo-1-(*p*-tolyl)-1,5-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-9-carboxamide) (19c)

Yellow solid recrystallized from DMF/ethanol mixture (59%); m.p. 290°C to 293°C; IR (υ cm^{-1}): 3398, 3328, 3170 (NH), and 1682 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.86 (t, 2H, $SCH_2CH_2CH_2S$), 2.31 (s, 6H, 2 *p*-CH_3), 2.74 (s, 6H, 2 CH_3), 3.06 (t, 4H, $SCH_2CH_2CH_2S$), 3.82 (s, 6H, 2 OCH_3), 6.59 (s, br, 4H, 2 NH_2), 6.97 to 7.70 (m, 24H, ArH's), and 10.58 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 21.2, 27.4, 27.7, 31.7, 55.4, 113.7, 114.1, 119.9, 120.3, 120.7, 126.6, 127.5, 128.8, 129.7, 129.8, 129.9, 130.4, 132.7, 134.2, 135.5, 141.2, 144.7, 151.5, 151.9, 153.3, 156.2, 157.4, 159.8, 163.9, 164.4, and 194.1; Anal. calcd. For $C_{69}H_{54}N_{14}O_8S_4$ (1335.5): C, 62.06; H, 4.08; N, 14.68; found: C, 61.85; H, 4.14; N, 14.57%.

4.6.4 | *N,N′*-((Pentane-1,5-diylbis[sulfanediyl])bis(2,1-phenylene))bis(3-acetyl-8-amino-10-(4-methoxyphenyl)-5-oxo-1-phenyl-1,5-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-9-carboxamide) (19d)

Yellow solid recrystallized from DMF (59%); m.p. 294°C to 296°C; IR (υ cm^{-1}): 3396, 3322, 3174 (NH), and 1686 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.57 to 1.60 (m, 6H, $SCH_2CH_2CH_2CH_2CH_2S$), 2.75 (s, 6H, 2 CH_3), 2.95 (t, 4H, $SCH_2CH_2CH_2CH_2CH_2S$), 3.83 (s, 6H, 2 OCH_3), 6.68 (s, br, 4H, 2 NH_2), 6.97 to 7.74 (m, 26H, ArH's), and 10.54 (s, br, 2H, 2 NH); Anal. calcd. For $C_{69}H_{54}N_{14}O_8S_4$ (1335.5): C, 62.06; H, 4.08; N, 14.68; found: C, 62.01; H, 4.02; N, 14.81%.

4.6.5 | *N,N′*-((Pentane-1,5-diylbis[sulfanediyl])bis(2,1-phenylene))bis(3-acetyl-8-amino-10-(4-methoxyphenyl)-5-oxo-1-(*p*-tolyl)-1,5-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-9-carboxamide) (19e)

Yellow solid recrystallized from DMF/ethanol mixture (59%); m.p. 290°C to 293°C; IR (υ cm^{-1}): 3398, 3328, 3170 (NH), and 1682 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.55 to 1.58 (m, 6H, $SCH_2CH_2CH_2CH_2CH_2S$), 2.32 (s, 6H, 2 *p*-CH_3), 2.73 (s, 6H, 2 CH_3), 2.94 (t, 4H, $SCH_2CH_2CH_2CH_2CH_2S$), 3.81 (s, 6H, 2 OCH_3), 6.64 (s, br, 4H, 2 NH_2), 6.98 to 7.71 (m, 24H, ArH's), and 10.71 (s, br, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 21.3, 27.2, 27.4, 27.8, 31.5, 55.2, 113.6, 114.0, 119.6, 120.5, 120.6, 126.7, 127.9, 128.7, 129.6, 129.6, 129.7, 130.6, 132.7, 134.3, 135.6, 141.3, 144.7, 151.8, 152.3, 153.6, 155.9, 157.7, 160.1, 163.6, 164.2, and 194.0; Anal. calcd. For $C_{71}H_{58}N_{14}O_8S_4$ (1363.5): C, 62.54; H, 4.29; N, 14.38; found: C, 62.48; H, 4.17; N, 14.50%.

ORCID

Sherif M. H. Sanad https://orcid.org/0000-0002-0186-6418

Ahmed E. M. Mekky https://orcid.org/0000-0002-8226-010X

REFERENCES

[1] S. A. Al-Trawneh, M. M. El-Abadelah, J. A. Zahra, S. A. Al-Taweel, F. Zani, M. Incerti, A. Cavazzoni, P. Vicini, *Bioorg. Med. Chem.* **2011**, *19*, 2541.

[2] A. M. Bernardino, L. C. da Silva Pinheiro, C. R. Rodrigues, N. I. Loureiro, H. C. Castro, A. Lanfredi-Rangel, J. Sabatini-Lopes, J. C. Borges, J. M. Carvalho, G. A. Romeiro, V. F. Ferreira, I. C. Frugulhetti, M. A. Vannier-Santos, *Bioorg. Med. Chem.* **2006**, *14*, 5765.

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

[4] M. E. Schnute, D. J. Anderson, R. J. Brideau, F. L. Ciske, S. A. Collier, M. M. Cudahy, M. Eggen, M. J. Genin, T. A. Hopkins, T. M. Judge, E. J. Kim, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3349.

[5] K. Madhusudana, B. Shireesha, V. G. Naidu, S. Ramakrishna, B. Narsaiah, A. R. Rao, P. V. Diwan, *Eur. J. Pharmacol.* **2012**, *678*, 48.

[6] D. H. Boschelli, B. Wu, A. C. Barrios Sosa, J. Chen, M. Asselin, D. C. Cole, J. Lee, X. Yang, D. Chaudhary, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2850.

[7] L. N. Tumey, D. H. Boschelli, J. Lee, D. Chaudhary, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4420.

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

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

[10] I. Adachi, T. Yamamori, Y. Hiramatsu, K. Sakai, S. Mihara, M. Kawakami, M. Masui, O. Uno, M. Ueda, *Chem. Pharm. Bull.* **1988**, *36*, 4389.

[11] M. Ueda, S. Matsumura, M. Masui, E. Matsuura, M. Kawakami, H. Fujitomo, T. Umeda, H. Kagawa, S. Hirohata, K. Shima, *Arzneimittelforschung* **1993**, *43*, 1282.

[12] S. Ohba, K. Nakajima, Y. Komiyama, F. Kugimiya, K. Igawa, K. Itaka, T. Moro, K. Nakamura, H. Kawaguchi, T. Takato, U. I. Chung, *Biochem. Biophys. Res. Commun.* **2007**, *357*, 854.

[13] K. Saito, A. Nakao, T. Shinozuka, K. Shimada, S. Matsui, K. Oizumi, K. Yano, K. Ohata, D. Nakai, Y. Nagai, S. Naito, *Bioorg. Med. Chem.* **2013**, *21*, 1628.

[14] E. M. Mohi El-Deen, E. A. Abd El-Meguid, S. Hasabelnaby, E. A. Karam, E. S. Nossier, *Molecules* **2019**, *24*(20), 3650.

[15] H. P. Buchstaller, C. D. Siebert, R. Steinmetz, I. Frank, M. L. Berger, R. Gottschlich, J. Leibrock, M. Krug, D. Steinhilber, C. R. Noe, *J. Med. Chem.* **2006**, *49*(3), 864.

[16] S. A. Said, H. A. El-Sayed, A. E. Amr, M. M. Abdalla, *Int. J. Pharm.* **2015**, *11*, 659.

[17] J. W. Lockman, M. D. Reeder, K. Suzuki, K. Ostanin, R. Hoff, L. Bhoite, H. Austin, V. Baichwal, J. A. Willardsen, *Bioorg. Med. Chem. Lett.* **2010**, *20*(7), 2283.

[18] M. S. Mohamed, Y. E. Mansour, H. K. Amin, M. E. El-Araby, *J. Enzyme Inhib. Med. Chem.* **2018**, *33*(1), 755.

[19] B. H. Naguib, H. B. El-Nassan, *J. Enzyme Inhib. Med. Chem.* **2016**, *31*(6), 1718.

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

[21] I. Pevet, C. Brulé, A. Tizot, A. Gohier, F. Cruzalegui, J. A. Boutin, S. Goldstein, *Bioorg. Med. Chem.* **2011**, *19*, 2517.

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

[23] C. Willemann, R. Grünert, P. J. Bednarski, R. Troschütz, *Bioorg. Med. Chem.* **2009**, *17*, 4406.

[24] R. Magan, C. Marin, M. J. Rosales, J. M. Salas, M. Sánchez-Moreno, *Pharmacology* **2005**, *73*, 41.

[25] S. Pandey, S. N. Suryawanshi, S. Gupta, V. M. L. Srivastava, *Eur. J. Med. Chem.* **2004**, *39*, 969.

[26] B. Deyanov, R. K. Niyazov, F. Y. Nazmetdivov, B. Y. Syropyatov, V. E. Kolla, M. E. Konshin, *J. Pharm. Chem.* **1991**, *25*, 248.

[27] P. M. Traxler, P. Furet, H. Mett, E. Buchdunger, T. Meyer, N. J. Lydon, *J. Med. Chem.* **1996**, *39*, 2285.

[28] N. Zhang, S. Ayral-Kaloustian, T. Nguyen, J. Afragola, R. Hernandez, J. Lucas, J. Gibbons, C. Beyer, *J. Med. Chem.* **2007**, *50*(2), 319.

[29] C. N. Chen, L. L. Lv, F. Q. Ji, Q. Chen, H. Xu, C. W. Niu, Z. Xi, G. F. Yang, *Bioorg. Med. Chem.* **2009**, *17*(8), 3011.

[30] M. A. H. Triana, M. H. Huynh, M. F. Garavito, B. A. Fox, D. J. Bzik, V. B. Carruthers, M. Löffler, B. H. Zimmermann, *Mol. Biochem. Parasitol.* **2012**, *184*, 71.

[31] A. A. Abu-Hashem, H. A. R. Hussein, K. M. Abu-zied, *Med. Chem. Res.* **2017**, *26*, 120.

[32] Y. Kotaiah, K. Nagaraju, N. Harikrishna, C. V. Rao, L. Yamini, M. Vijjulatha, *Eur. J. Med. Chem.* **2014**, *75*, 195.

[33] H. M. Ashour, O. G. Shaaban, O. H. Rizk, I. M. El-Ashmawy, *Eur. J. Med. Chem.* **2013**, *62*, 341.

[34] Q. Chen, X. L. Zhu, L. L. Jiang, Z. M. Liu, G. F. Yang, *Eur. J. Med. Chem.* **2008**, *43*, 595.

[35] S. Massari, G. Nannetti, J. Desantis, G. Muratore, S. Sabatini, G. Manfroni, B. Mercorelli, V. Cecchetti, G. Pal, G. Cruciani, A. Loregian, L. Goracci, O. Tabarrini, *J. Med. Chem.* **2015**, *58*, 3830.

[36] L. H. Huang, Y. F. Zheng, Y. Z. Lu, C. J. Song, Y. G. Wang, B. Yu, M. Hong-Liu, *Steroids* **2012**, *77*, 710.

[37] M. Ahmed, S. Mohamed, T. A. Farghaly, *Lett. Org. Chem.* **2018**, *15*(3), 183.

[38] I. Abbas, S. Gomha, M. A. A. Elneairy, M. Elaasser, B. Mabrouk, *Turk. J. Chem.* **2015**, *39*(3), 510.

[39] K. A. Ali, E. A. Ragab, M. M. Abdalla, *Acta Pol. Pharm.* **2011**, *68*, 237.

[40] V. J. Ram, D. N. Upadhyay, *Indian J. Chem.* **1999**, *38B*, 1173.

[41] V. J. Ram, U. K. Singha, P. Y. Guru, *Eur. J. Med. Chem.* **1990**, *25*, 533.

[42] A. E. M. Mekky, S. M. H. Sanad, *Polycycl. Aromat. Compd.* **2019**. https://doi.org/10.1080/10406638.2019.1631194.

[43] S. M. H. Sanad, A. E. M. Mekky, *Synth. Commun.* **2020**, *50*(10), 1468. https://doi.org/10.1080/00397911.2020.1743318.

[44] A. A. M. Ahmed, A. E. M. Mekky, A. H. M. Elwahy, S. M. H. Sanad, *Synth. Commun.* **2020**, *50*(6), 796.

[45] S. M. H. Sanad, A. A. M. Ahmed, A. E. M. Mekky, *Arch. Pharm.* **2020**, *353*(4), 1900309.

[46] S. M. H. Sanad, A. A. M. Ahmed, A. E. M. Mekky, *J. Heterocyclic Chem.* **2020**, *57*, 590.

[47] S. M. H. Sanad, A. H. M. Elwahy, I. A. Abdelhamid, *ARKIVOC* **2018**, *2018*(7), 39.
[48] R. Anandhan, A. Kannan, P. Rajakumar, *Synth. Commun.* **2017**, *47*(7), 671.
[49] S. M. H. Sanad, A. M. Abdel Fattah, F. A. Attaby, M. A. A. Elneairy, *Can. J. Chem.* **2019**, *97*(1), 53.
[50] V. P. Litvinov, V. V. Dotsenko, S. G. Krivokolysko, *Russ. Chem. Bull.* **2005**, *54*, 864.
[51] N. M. Elwan, E. M. Awad, H. M. Hassaneen, *Helv. Chim. Acta* **2003**, *86*, 739.

How to cite this article: Sanad SMH, Mekky AEM. Piperazine-mediated tandem synthesis of bis(thieno[2,3-*b*]pyridines): Versatile precursors for related fused [1,2,4]triazolo[4,3-*a*] pyrimidines. *J Heterocyclic Chem*. 2020;57: 3142–3152. https://doi.org/10.1002/jhet.4021