Synthesis and characterization of novel bis(pyridine-2(1H)-thiones) and their bis(2-methylsulfanylpyridines) incorporating 2,6-dibromophenoxy moiety
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Abstract: The novel 1,4-bis(2,6-dibromo-4-formylphenoxy)butane (3), prepared from 3,5-dibromobenzaldehyde (1), reacted with different hydrazines 4a–4d and active methylene containing compounds 5a–5d to give the corresponding bis(hydrazones) 5a–5d and bis(cinnamondinitriles) 11a–11d, respectively. Both bis(2-cyanoacetic acid hydrazide) derivative 5d and bis(thioacrylamide) derivative 11a were taken as synthetic precursors for the synthesis of the target molecules bis(pyridine-2(1H)-thione) derivative 10 and 13a–13c and their bis(2-methylsulfanylpyridine) derivative 14 and 17a–17c. Another synthetic route was designed to prepare the target molecules 14 and 17a–17c in a better yield using pyridine-2(1H)-thione) derivative 15 and 19a–19c. Characterization of the newly prepared compounds via elemental analyses and spectral data are established.

Key words: bis(aldehyde), cyanoethanethioamide, bis(pyridine-2(1H)-thione), bis(2-methylsulfanylpyridine).

Résumé : Nous avons préparé un nouveau composé, le 1,4-bis(2,6-dibromo-4-formylphenoxy)butane (3), à partir du 3,5-dibromobenzaldéhyde (1), et nous avons fait réagir avec différentes hydrazines (4a–4d) et composés contenant un groupe méthylène actif (9a–9d) pour produire respectivement les bis(hydrazones) 5a–5d et les bis(cinnamondinitriles) 11a–11d correspondants. Les dérivés de bis(2-cyanoacétamidé) 5d et de bis(thioacrylamide) 11a ont été tous deux employés comme précurseurs pour la synthèse des molécules cibles, les dérivés de bis(pyridine-2(1H)-thione) 10 et 13a–13c et les dérivés de bis(2-methylsulfanylpyridine) 14 et 17a–17c. Nous avons élaboré une autre voie de synthèse pour préparer les molécules cibles 14 et 17a–17c avec de meilleurs rendements en utilisant les dérivés de pyridine-2(1H)-thione 15 et 19a–19c. Nous avons caractérisé les composés nouvellement préparés à l’aide des analyses élémentaires et des données spectroscopiques. [Traduit par la Rédaction]

Mots-clés : bis(aldéhyde), cyanoéthanolthioamide, bis(pyridine-2(1H)-thione), bis(2-méthylsulfanylpyridine).

Introduction
Dihydropyridine derivatives show a wide range of bioactivities and are included in many pharmaceutical preparations such as antiarrhythmic, antihypertensive,1–9 and anticanicancer agents.5–9 Moreover, pyridine-2(1H)-thiones show bioactivities such as anti fungal and antibacterial activities.10 On the other hand, 2,6-alkylpyridines show important biological activities such as antiradical,11 cardiovascular,12,13 and antioxidant activities.14 This goal of this study was to design efficient procedures for the synthesis of novel pyridine-2(1H)-thiones 10 and 13a–13c and their bis(2-methylsulfanylpyridine) derivative 14 and 17a–17c incorporating 2,6-dibromophenoxy moiety of expected bioactivity using the bis(aldehyde) 3, bis(hydrazones) 5a–5d, and bis(cinnamondinitriles) 11a–11d as synthetic precursors (Fig. 1).

Experimental
All organic solvents were acquired from commercial sources and used as received unless otherwise stated. All other chemicals were acquired from Merck, Aldrich, or Acros and used without further purification. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile attenuated total reflectance sampling accessory on the Nicolet iS10 FTIR spectrometer. 1H NMR spectra were recorded on Varian Mercury at 300 MHz spectrophotometer using TMS as an internal standard and DMSO-d6 as solvent, and chemical shifts were expressed as δ ppm units. Elemental analyses were carried out on a EuroVector EA3000 series CHNS-O analyzer.

General procedure for synthesis of potassium salts of 1, 8, 16, and 20a–20c
A solution of KOH (5 mmol and 3 mL water) was added to the appropriate aromatic hydroxy compounds 1, 8, 16, and 20a–20c (5 mmol) in 20 mL methanol with stirring at room temperature for 10 min. The solvent was then removed in vacuo, and the solid was triturated with dry ether, collected by filtration, dried, and used in the next reaction without further purification.

General procedure for compounds 3, 6, 14, and 17a–17c
A mixture of 1,4-dibromobutane (2; 5 mmol) and each of the appropriate potassium salt of 1, 8, 16, and 20a–20c (10 mmol) in DMF (25 mL) was heated under reflux for 15 min. The reaction mixture was cooled to room temperature and poured onto iced water. The products were collected by filtration, washed with cold ethanol, dried, and recrystallized from the proper solvent to yield 3, 6, 14, and 17a–17c, respectively.

1,4-Bis(2,6-dibromo-4-formylphenoxy)butane (3)
Colorless crystals recrystallized from dioxane–ethanol mixture (85%); mp 188–190 °C; IR (υ cm⁻¹): 2848, 2750 (ald. H stretch), 2818, 2770 (ald. H stretch), 1730, 1698 (C=O), 1480, 1420 (C=C), 1384, 1365 (C–O-C), 1265, 1225, 1185, 1095, 1070 (C–O), 755, 685 (C–H).
Fig. 1. Structure of the synthetic precursors bis(alddehyde) 3, bis(hydrazone) 5a–5d, and bis(cinnamonomitile) 11a–11d and the target materials pyridine-2(1H)/thiones 10 and 13a–13c and their bis(2-methylsulfanylpyridine) derivative 14 and 17a–17c.

1689 (CO); $^1$H NMR (DMSO-d$_6$): δ 2.10 (t, 4H, J = 7.2 Hz, OCH$_2$CH$_2$CH$_2$CH$_2$O), 4.16 (t, 4H, J = 7.2 Hz, OCH$_2$CH$_2$CH$_2$O), 8.18 (s, 4H, ArH), and 9.90 (s, 2H, 2 CHO); Anal. Calcd for C$_{18}$H$_{14}$Br$_4$O$_4$ (613.92): C, 35.22; H, 2.30; found: C, 35.10; H, 2.39.

1,4-Bis(2,6-dibromo-4-[(2-amino-5-cyano-6-methylsulfanyl-pyridin-4-yl]-phenoxy)-butane (17a)

Brown crystals recrystallized from dioxane–ethanol mixture (50% from 14 or 75% from 20); mp 154–156 °C; IR (υ cm$^{-1}$): 3355, 3190 (NH$_2$), 2216 (CN); $^1$H NMR (DMSO-d$_6$): δ 2.13 (t, 4H, J = 7.2 Hz, OCH$_2$CH$_2$CH$_2$O), 2.57 (s, 6H, 2 SCH$_3$), 4.02 (t, 4H, J = 7.2 Hz, OCH$_2$CH$_2$CH$_2$O), 7.77 (s, 4H, ArH); MS m/z: 1030 (63.56%, M$^+$ + 8), 1010 (58.06%), 998 (60.36%), 973 (0.60%), 966 (61.12%), 928 (45.03%), 865 (20.05%); Anal. Calcd for C$_{38}$H$_{34}$Br$_4$N$_8$O$_2$S$_2$ (1022.45): C, 44.46; H, 3.34; N, 12.80; S, 5.36; found: C, 44.92; H, 2.98; N, 12.80; S, 5.36.

Procedure for 1,4-bis(2,6-dibromo-4-(2-phenylhydrazinylidene)methyl)-phenoxy)butane (17a)

A solution of 3 (5 mmol) and hydrazine hydrate 99% (4a, 5 mL) in pyridine (30 mL) was heated under reflux for 2 h. The reaction mixture was evaporated to its half volume, cooled to room temperature, and then, 2 mL of ethanol was added dropwise. The solid product was collected by filtration, washed with cold ethanol, and recrystallized from dioxane–ethanol mixture as colorless crystals (50%); mp 182–184 °C; IR (υ cm$^{-1}$): 3374, 3185 (NH$_2$); $^1$H NMR (DMSO-d$_6$): δ 2.04 (t, 4H, J = 7.2 Hz, OCH$_2$CH$_2$CH$_2$O), 4.03 (t, 4H, J = 7.2 Hz, OCH$_2$CH$_2$CH$_2$O), 7.08 (s, 4H, ArH), 7.57 (s, 2H, 2 CH=N); Anal. Calcd for C$_{36}$H$_{30}$Br$_4$N$_4$O$_4$S$_2$ (962.39): C, 44.74; H, 3.13; N, 5.80; S, 6.64; found: C, 44.98; H, 2.88; N, 5.41; S, 6.32.

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product that formed was collected by filtration and washed with cold ethanol recrystallized from glacial acetic acid as colorless crystals (48%); mp 206–208 °C; IR (ν cm⁻¹): 3292 (NH); 1H NMR (DMSO-d6): δ 2.05 (t, 4H, J = 7.2 Hz, OCH₂CH₂CH₂CH₂O), 4.05 (t, 4H, J = 7.2 Hz, OCH₂CH₂CH₂CH₂O), 10.50 (s, 2H, 2 NH), 7.05–7.90 (m, 16H, 14 ArH and 2 CH=N); MS m/z: 798 (38.56%, M⁺ + 8), 794 (46.85%, M⁺ + 4), 704 (59.46%, 686 (54.05%), 673 (71.17%), 608 (80.18%), 606 (51.33%); Anal. Calcd for C₂₆H₂₀Br₄N₆O₄: C, 33.45; H, 1.98; N, 7.45; found: C, 33.45; H, 1.98; N, 7.45.

Procedure for 1,4-bis(2,6-dibromo-4-[2-thiocarbamoyl-3-phenylacryloyl]hydrazineylidene)methyl(phenoxo)butane (5c)

A solution of 3 (5 mmol) and thiocarbamoylacryloylhydrazide (7)

A solution of each of 1,4-bis(2,6-dibromo-4-[2-thiocarbamoyl-3-phenylacryloyl]hydrazineylidene)methyl(phenoxo)butane (5c) in methanolic sodium methoxide solution (prepared from 10 mmol of sodium metal in 30 mL of methanol) was heated under reflux for 5 h. The reaction mixture was cooled, poured onto ice-cold water, and then neutralized (pH = 7) with diluted HCl. The so formed product was collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent to yield 10 and 15, respectively.

1,4-Bis(2,6-dibromo-4-[[2-amino-5-cyano-4-phenyl-6-thioxo-1,6-dihydro-pyridin-3-yl]-carbonylhydrazineylidene)methyl(phenoxo)butane (10)

Yellow crystals recrystallized from ethanol (58%); mp > 360 °C; IR (ν cm⁻¹): 3410 (OH), 3209 (NH), 2219 (CN), 1628 (CN); 1H NMR (DMSO-d6): δ 6.75 (s, 2H, NH₂), 7.12–7.89 (m, 7H, ArH), 8.24 (s, 1H, CH=N), 10.40 (s, 1H, OH), 11.72 (s, 1H, NH), 14.07 (s, 1H, pyridine NH); MS m/z: 549 (6.75%, M⁺ + 4), 547 (5.27%, M⁺ + 2), 545 (6.47%, M⁺), 531 (8.50%), 519 (7.58%), 503 (6.75%), 490 (4.99%), 472 (5.27%), 456 (5.73%), 77 (25.32%); Anal. Calcd for C₂₀H₁₅Br₂N₄O₂S: 45.41; H, 2.81; N, 12.20; S, 5.58; found: C, 45.43; H, 2.82; N, 12.38; S, 5.40.

General procedure for compounds 10 and 15

A mixture of each of 6 or 8 (5 mmol) and 2-cyanoethioamide (9a; 10 mmol for 6 or 5 mmol for 8) in methanolic sodium methoxide solution (prepared from 10 mmol of sodium metal in 30 mL of methanol) was heated under reflux for 5 h. The reaction mixture was cooled, poured onto ice-cold water, and then neutralized (pH = 7) with diluted HCl. The so formed product was collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent to yield 10 and 15, respectively.

1,4-Bis(2,6-dibromo-4-{[(2-aminoo-5-cyano-4-phenyl-6-thioxo-1,6-dihydro-pyridin-3-yl)-carbonylhydrazineylidene)methyl(phenoxo)butane (10)

Yellow crystals recrystallized from toluene–ethanol mixture (61%); mp 224–226 °C; IR (ν cm⁻¹): 3315, 3194 (NH₂), 2219 (CN), 1628 (CN); 1H NMR (DMSO-d6): δ 6.75 (s, 2H, NH₂), 14.07 (s, 1H, pyridine NH); MS m/z: 549 (6.75%, M⁺ + 4), 547 (5.27%, M⁺ + 2), 545 (6.47%, M⁺), 531 (8.50%), 519 (7.58%), 503 (6.75%), 490 (4.99%), 472 (5.27%), 456 (5.73%), 77 (25.32%); Anal. Calcd for C₂₀H₁₅Br₂N₄O₂S: 45.41; C, 43.90; H, 2.33; N, 12.80; S, 5.86; found: C, 43.45; H, 2.82; N, 12.38; S, 5.40.

General procedure for compounds 11a and 18

A solution of each of 3 or 1 (5 mmol) and 9a (10 mmol for 3 or 5 mmol for 1) in 50 mL ethanol containing 3 drops of piperidine was heated at 40–50 °C (for 3 h or for 5 min for 1). The reaction mixture was then stirred overnight at room temperature, the solid that formed was collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent to yield 11a and 18, respectively.

1,4-Bis(2,6-dibromo-4-{[2-cyano-2-thiocarbamoylvinyl]phenoxo}butane (11a)

Yellow crystals recrystallized from dioxane–ethanol mixture (70%); mp 244–246 °C; IR (ν cm⁻¹): 3315, 3194 (NH₂), 2219 (CN), 1554 (CN); 1H NMR (DMSO-d6): δ 2.12 (t, 4H, J = 7.2 Hz, OCH₂CH₂CH₂CH₂O), 4.15 (t, 4H, J = 7.2 Hz, OCH₂CH₂CH₂CH₂O), 7.65 (s, 2H, 2 CH=C), 7.91 (s, 1H, CH=CH=N), 8.07 (s, 2H, ArH), 10.61 (s, br, 1H, OH), 11.98 (s, 1H, NH); MS m/z: 549 (6.75%, M⁺ + 4), 547 (5.27%, M⁺ + 2), 545 (6.47%, M⁺), 531 (8.50%), 519 (7.58%), 503 (6.75%), 490 (4.99%), 472 (5.27%), 456 (5.73%), 77 (25.32%); Anal. Calcd for C₂₀H₁₅Br₂N₄O₂S: 45.41; C, 43.90; H, 2.33; N, 12.80; S, 5.86; found: C, 43.45; H, 2.82; N, 12.38; S, 5.40.

2-Cyano-3-(3,5-dibromo-4-hydroxybenzylidene)-3-phenylacryloylacetic acid hydrazide (8)

Yellowish white crystals recrystallized from dioxane–ethanol mixture (84%); mp 260–262 °C; IR (ν cm⁻¹): 3315, 3194 (NH₂), 2219 (CN), 1554 (CN); 1H NMR (DMSO-d6): δ 7.05 (s, br, 4H, 2 NH₂), 7.59 (s, 2H, 2 CH=N), 7.79 (s, 4H, ArH), 10.70 (s, br, 1H, OH); MS m/z: 364 (66.46%, M⁺ + 4), 362 (96.84%, M⁺ + 2), 360 (36.08%, M⁺), 346 (32.28%), 345 (29.11%), 338 (18.35%), 301 (23.42%), 276 (1.90%), 264 (7.28%); Anal. Calcd for C₁₇H₁₁Br₂N₂O₂S: 360.04; C, 33.18; H, 1.67; N, 7.74; S, 8.86; found: C, 33.45; H, 1.98; N, 7.45; S, 8.67.

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General procedure for compounds 11b–11d

A solution of 3 (5 mmol) and the proper active methylene reagent 9b–9d (10 mmol) in 50 mL ethanol containing 3 drops of piperidine was heated under reflux for 3 h. The reaction mixture was then cooled at room temperature, and the solid that formed was collected by filtration and recrystallized from the proper solvent to yield 11b–11d, respectively.

1.4-Bis(2,6-dibromo-4-[2,4-dicyano-1-phenoxyl]phenyl)butane (11b)

Colorless crystals recrystallized from dioxane (75%); mp 236–238 °C; IR (ν cm⁻¹): 2223 (CN, NH); 1709 (CO); 1H NMR (DMSO-d₆): δ 2.10 (t, 4H, J = 7.2 Hz, OCH₂CH₂CH₂CH₂O), 4.11 (t, 4H, J = 7.2 Hz, OCH₂CH₂CH₂CH₂O), 7.78 (s, 2H, 2 CH=O), 7.99 (s, 4H, 4 ArH), MS m/z: 714 (13.23%, M⁺ + 8), 713 (8.10%, M⁺ + 7), 707 (7.69%, M⁺ + 1), 657 (7.02%), 647 (7.69%), 608 (7.83%), 576 (8.50%); Anal. Calcd for C₂₄H₁₄Br₄N₄O₂ (706.01): C, 40.60; H, 1.99; N, 7.89; found: C, 40.21; H, 2.41; N, 7.53.

1.4-Bis(2,6-dibromo-4-[2-cyano-1-phenoxyl]phenyl)butane (11c)

Yellowish white crystals recrystallized from dioxane–ethanol mixture (80%); mp 216–218 °C; IR (ν cm⁻¹): 2222 (CN, CO); 1719 (CO); 1H NMR (DMSO-d₆): δ 1.82 (t, 4H, J = 7.0 Hz, 2 CH₂CH₃), 2.10 (t, 4H, J = 7.2 Hz, OCH₂CH₂CH₂CH₂O), 4.18 (t, 4H, J = 7.2 Hz, OCH₂CH₂CH₂CH₂O), 4.33 (q, J = 7.0 Hz, 4H, 2 CH₂CH₃), 8.36 (s, 6H, 2 ArH and 2 CH=O); Anal. Calcd for C₁₆H₁₂Br₂N₂O₂ (518.22): C, 40.75; H, 2.28; N, 6.34; found: C, 41.09; H, 2.28; N, 6.30.

General procedure for compounds 13a, 13b, 19a, and 19b

A mixture of each of 11a or 11b (5 mmol) and each of 12a and 12b (10 mmol for 11a or 5 mmol for 11b) or 4 mmol for 12a and 12b (5 mmol) in pyridine (20 mL) and ethanol (10 mL) was heated under reflux for 5 h. The reaction mixture was heated to evaporate half its volume, cooled, poured onto ice-cold water, and then neutralized (pH = 7) with drops of glacial acetic acid. The products so formed were collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent to yield 13a and 19a, respectively.

1.4-Bis(2,6-dibromo-4-[5-acetyl-3-cyano-6-methyl-2-thioxo-1,2-dihydropyridine-3-carboxylate (19b)

Yellow crystals recrystallized from dioxane–ethanol mixture (70% from 11b or 68% from ternary mixture); mp 270–272 °C; IR (ν cm⁻¹): 3417 (NH), 2213 (CN), 1708 (CO), 1558 (CS); 1H NMR (DMSO-d₆): δ 7.40 (s, br, 4H, 2 NH2), 7.68 (s, 2H, 2 CH=C), 7.94 (s, 4H, ArH); MS m/z: 910 (92.79%, M⁺ + 8), 909 (55.86%, M⁺ + 7), 902 (51.35%, M⁺ + 5), 890 (63.06%), 868 (16.45%), 856 (70.27%), 802 (58.56%), 772 (73.87%), 728 (56.76%); Anal. Calcd for C₁₅H₁₀Br₂N₂O₂ (440.13): C, 40.70; H, 2.56; N, 5.53; S, 6.79; found: C, 40.48; H, 2.96; N, 6.30; S, 6.36.

General procedure for compounds 13c and 19c

A mixture of each of 11b or 11c (5 mmol) and each of 14, 16, 17a–17c, and 20a–20c (10 mmol) or after cooling 11b or 11c (5 mmol) and each of 15, 19a–19c (10 mmol) in pyridine (20 mL) and ethanol (10 mL) was heated under reflux for 5 h. The reaction mixture was heated to evaporate half its volume, cooled, poured onto ice-cold water, and then neutralized (pH = 7) with drops of glacial acetic acid. The products so formed were collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent to yield 13c and 19c, respectively.

1.4-Bis(2,6-dibromo-4-[6-amino-3,5-dicyano-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (19c)

Yellow crystals recrystallized from dioxane–ethanol mixture (51% from 9a or 48% from 9b); mp 254–256 °C; IR (ν cm⁻¹): 3438, 3342, 3164 (NH and NH2), 2214 (CN), 1559 (CO); 1H NMR (DMSO-d₆): δ 8.36 (s, 6H, ArH and 2 CH=C); Anal. Calcd for C₁₃H₆Br₂N₄O₂S (702.27): C, 40.48; H, 2.08; N, 7.90.

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Scheme 1. Synthesis of bis(hydrazone)methylphenoxy)butanes 5a–5d.

![Scheme 1](image)

2-Amino-5-cyano-6-methylsulfonyl-4-phenyl-N-’(3,5-dibromo-4-hydroxybenzylidene)-pyridine-3-carbohydrazide (16)

Brown crystals recrystallized from toluene–ethanol mixture (71%); mp 250–252 °C; IR (ν cm⁻¹): 3457 (OH), 3330, 3210 (NH), 2211 (CN), 1633 (CO); δ 2.32 (s, 3H, CH₃), 6.92–7.64 (m, 9H, 7 ArH and NH₂), 8.24 (s, 1H, CH=N), 10.46 (s, 1H, OH), 11.78 (s, 1H, NH); MS m/z: 563 (8.93%, M⁺ + 4), 561 (3.07%, M⁺ + 2), 559 (1.64%, M⁺), 558 (26.12%, M⁺ – 1), 548 (15.20%), 542 (12.85%), 516 (14.13%), 500 (11.56%), 494 (12.85%), 486 (14.13%), 485 (12.21%); Anal. Calcd for C₂₁H₁₅Br₂N₅O₂S (563.11): C, 38.63; H, 1.99; N, 12.40; S, 7.02.

5-Acetyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-6-methylsulfanylnicotinonitrile (20a)

Colourless crystals recrystallized from ethanol as (88%); mp 228–230 °C; IR (ν cm⁻¹): 3445 (OH), 2218 (CN), 1680 (CO); ¹H NMR (DMSO-d₆): δ 2.10 (s, 3H, COCH₃), 2.52 (s, 3H, CH₃), 2.68 (s, 3H, SCH₃), 7.78 (s, 2H, ArH), 10.75 (s, 1H, OH); MS m/z: 458 (76.70%, M⁺ + 4), 456 (58.25%, M⁺ + 2), 453 (61.17%, M⁺ + 1), 443 (75.73%), 428 (46.17%), 415 (71.84%), 400 (73.79%), 370 (64.08%); Anal. Calcd for C₁₃H₁₀Br₂N₂O₅S (456.15): C, 42.13; H, 2.65; N, 6.14; S, 7.03; found: C, 42.42; H, 2.96; N, 5.86; S, 6.60.

Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-6-methylsulfanylnicotinate (20b)

Colourless crystals recrystallized from ethanol (74%); mp 160–162 °C; IR (ν cm⁻¹): 3427 (OH), 2222 (CN), 1693 (CO); ¹H NMR (DMSO-d₆): δ 1.05 (t, 3H, J = 7.0 Hz, CH₂CH₂), 2.58 (s, 3H, CH₃), 2.67 (s, 3H, SCH₃), 4.05 (q, 2H, J = 7.0 Hz, CH₂CH₂), 7.79 (s, 2H, ArH), 10.68 (s, 1H, OH); MS m/z: 488 (16.11%, M⁺ + 4), 486 (57.42%, M⁺ + 2), 484 (100.00%, M⁺), 473 (6.46%), 469 (2.27%), 457 (43.98%), 441 (9.60%), 437 (13.79%), 413 (1.92%); Anal. Calcd for C₁₅H₁₂Br₂N₂O₄S (484.18): C, 42.00; H, 2.90; N, 5.76; S, 6.60; found: C, 42.35; H, 2.53; N, 5.99; S, 6.36.

2-Amino-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylsulfonylpyridine-3,5-dicarboxonitrile (20c)

Colourless crystals recrystallized from ethanol (85%); mp 323–334 °C; IR (ν cm⁻¹): 3433 (OH), 3365, 3190 (NH), 2219 (CN); ¹H NMR (DMSO-d₆): δ 2.58 (s, 3H, SCH₃), 7.95 (s, 2H, ArH), 8.10 (s, br, 2H, NH₂), 10.56 (s, br, 1H, OH); MS m/z: 442 (34.70%, M⁺ + 4), 440 (67.03%, M⁺ + 2), 438 (39.44%, M⁺), 425 (21.12%), 424 (17.89%), 416 (11.85%), 396 (16.38%), 393 (3.88%), 388 (11.21%), 374 (1.08%); Anal. Calcd for C₁₅H₁₀Br₂N₂O₅S (442.11): C, 38.21; H, 1.83; N, 12.73; S, 7.29; found: C, 38.63; H, 1.99; N, 12.40; S, 7.02.

Results and discussion

The novel 1,4-bis(2,6-dibromo-4-formylphenoxy)butane (3) was prepared via reacting the potassium salt of 3,5-dibromobenzaldehyde (1) with 1,4-dibromobutane (2) in refluxing DMF. The IR spectrum (cm⁻¹) of 3 showed the absorption bands of CH stretching of formyl group at 2848 and 2750 in addition to CO group at 1689. Its ¹H NMR spectrum revealed the signals of OCH₂CH₂CH₂CH₂O (t, 4H, J = 7.2 Hz, δ = 2.10 ppm), OCH₂CH₂CH₂CH₂O (t, 4H, J = 7.2 Hz, δ = 4.16 ppm), aromatic protons (s, 4H, δ = 8.18 ppm), and CHO (s, 2H, δ = 9.90 ppm) (Scheme 1; see also the Experimental section).

The chemical potentiality of the bis(aldehyde) 3 was investigated via its reaction with different hydrazines 4a–4d to give the corresponding bis(hydrazone)s 5a–5d. It has been found that compound 3 reacted with two molecules of hydrazine hydride (4a) in pyridine under reflux to afford the corresponding bis(hydrazineylidenemethylphenoxy)butane derivative 5a in a moderate yield. The IR spectrum (cm⁻¹) of 5a showed the absorption bands of NH₂ groups at 3374 and 3185. Its ¹H NMR spectrum revealed the presence of the signals of NH₂ (s, 2H, 4H, δ = 7.08 ppm) and CH=N (s, 2H, δ = 7.57 ppm). In the same manner, compound 3 condensed with two molecules of phenyl hydrazine (4b), thiosemicarbazide (4c), in glacial acetic acid under reflux, and 2-cyanoacetic acid hydrazide (4d), in ethanol under reflux, to afford the corresponding bis(hydrazineylidenemethylphenoxy)butane derivatives 5b–5d, respectively (Scheme 1; see also the Experimental section).

In a further investigation, the bis(2-cyanoacetic acid hydrazide) derivative 5d reacted with benzaldehyde in ethanol containing a few drops of piperidine under reflux to give the corresponding bis(3-phthalaldehyde hydrazide) derivative 6, in 55% yield, whose IR spectrum (cm⁻¹) showed the absorption bands of NH at 3273, CN at 2210, and CO at 1684. Its ¹H NMR spectrum revealed the signals of NH₂ (s, 4H, δ = 8.18 ppm) and CHO (s, 2H, δ = 9.90 ppm). In the same manner, compound 3 condensed with two molecules of phenyl hydrazine (4b), in glacial acetic acid under reflux, and 2-cyanoacetic acid hydrazide (4d), in ethanol under reflux, to afford the corresponding bis(hydrazineylidenemethylphenoxy)butane derivatives 5b–5d, respectively (Scheme 1; see also the Experimental section).

The target molecule bis(pyridine-2(1H)-thione) derivative 10 was prepared via reacting bis(3-phthalaldehyde hydrazide) derivative 6 with two molecules of 2-cyanoethanolthioamide (9a) in refluxing...
methanolic sodium methoxide solution. The IR spectrum (cm⁻¹) of 10 showed the absorption bands of NH at 3361 and 3205, CN at 2215, CO at 1640, and CS at 1550. Its ¹H NMR spectrum revealed the signals of 2 CH=N (s, 2H, δ = 8.25 ppm), 2 NH (s, 2H, δ = 11.70 ppm), and 2 pyridine NH (s, br, 2H, δ = 14.05 ppm) (Scheme 2; see also the Experimental section).

The chemical potentiality of the bis(aldehyde) 3 was investigated via its reaction with different active methylene containing compounds 9a–9d to give the corresponding bis(cinnamonitrile) derivatives 11a–11d. Thus, it has been found that compound 3 reacted with two molecules of 2-cyanoethanethioamide (9a) in ethanol containing piperidine to afford the corresponding bis(thioacrylamide) derivative 11a through the elimination of two molecules of water. The IR spectrum of 11a showed the absorption bands of NH₂ at 3315 and 3194, CN at 2213, and CS at 1554. Its ¹H NMR spectrum revealed the signals of CH=N (s, 2H, δ = 7.65 ppm) and NH₂ (s, br, 4H, δ = 8.22 ppm). In a similar manner, compound 3 reacted with two molecules of malononitrile (9b), ethyl cyanoacetate (9c), and 2-cyanoethanamide (9d) to afford the corresponding ylidene derivatives 11b–11d, respectively. The structures of 11b–11d were elucidated via using of spectral data and elemental analyses (Scheme 3; see also the Experimental section).

The chemical potentiality of the bis(thioacrylamide) derivative 11a was investigated via its reaction with β-dicarbonyl compounds 12a and 12b to give the corresponding target molecules bis(pyridine-2(1H)-thione) derivatives 13a and 13b. Therefore, it has been found that compound 11a reacted with acetylacetone (12a) in ethanol-pyridine mixture under reflux to afford the corresponding bis(4-[2-thioxo-dihydropyridin-4-yl]phenoxy)butane derivative 13a whose IR spectrum (cm⁻¹) showed the absorption bands of NH at 3443, CN at 2217, CO at 1692, and CS at 1565. Its ¹H NMR spectrum revealed the signals of COCH₃ (s, 6H, δ = 1.94 ppm), CH₃ (s, 6H, δ = 2.40 ppm), and NH (s, 2H, δ = 14.40 ppm). Similarly, the bis(4-[3-ethoxycarbonyl-6-thioxopyridin-4-yl]phenoxy)butane derivative 13b could be prepared via the reaction between 11a and
Moreover, the target molecule bis(4-[(6-amino-3,5-dicyano-2-thioxopyridin-4-yl)phenoxy]butane derivative 13c could be prepared either by the reaction of compound 11a or 11b with 9a in ethanol–pyridine mixture under reflux to afford such reaction product whose IR spectrum (cm⁻¹) showed the absorption bands of NH and NH₂ at 3438, 3342 and 3164, CN at 2214, and CS at 1559. Its ¹H NMR spectrum revealed the signals of NH₂ (s, br, 4H, /H = 8.00 ppm) and NH (s, 2H, /H = 14.40 ppm) (Scheme 3; see also the Experimental section).

The target molecule bis(4-[(6-methylsulfanylpyridin-3-yl)carbonyl-hydrazineylidene)methyl]phenoxy)butane derivative 14 was prepared in a moderate yield, by the reaction of bis(pyridine-2(1H)-thione) derivative 10 and iodomethane in methanolic sodium methoxide solution whose ¹H NMR spectrum revealed the absence of pyridine NH signal and the presence of the signal corresponding to 2 CH₃ groups (s, 6H, /H = 2.30 ppm). Another solid evidence for the structure of 14 came from its independent synthesis, in a good yield, by performing the reaction between compound 8 and 9a in methanolic sodium methoxide solution to give the corresponding pyridine-2(1H)-thione derivative 15, which reacted with iodomethane in methanolic sodium methoxide solution methylsulfanylpyridine derivative 16 whose potassium salt reacted with 2 in DMF under reflux (Scheme 4; see also the Experimental section).

In a similar manner, two synthetic routes were designed to prepare the target molecules bis(methylsulfanylpyridines) 17a–17c. The first route came from the direct methylation of bis(pyridine-2(1H)-thione) derivatives 13a–13c via their reaction with iodomethane in methanolic sodium methoxide solution. Among the above series, compound 17a was prepared in, 45% yield, and its ¹H NMR spectrum revealed the absence of pyridine NH signal and the presence of the signal corresponding to two SCH₃ groups (s, 6H, /H = 2.66 ppm). The second route came from the synthesis of pyridine-2(1H)-thiones 19a–19c by the reaction of aldehyde 1 with 9a to give the corresponding 2-cyanoprop-2-enethioamide derivative 18, which reacted with each of 12a and 12b or another molecule of 9a. Compounds 19a–19c could also be prepared by the reaction of a ternary mixture of 1, 9a, and each of 12a and 12b or 1 with two molecules of 9a. Among the above series, the ¹H NMR spectrum of compound 19a revealed the presence of a signal corresponding to the COCH₃ group (s, 3H, /H = 1.91 ppm), CH₃ group (s, 3H, /H = 2.36 ppm), and NH group (s, br, 1H, /H = 14.28 ppm). Then, compounds 19a–19c are methylated, using iodomethane in methanolic sodium methoxide solution, and their potassium salts were reacted with 2 in refluxing DMF to afford identical reaction products, in good yields, to 17a–17c, which were prepared via the first route (Scheme 5; see also the Experimental section).
References
