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ARTICLE

# Synthesis and characterization of novel bis(pyridine-2(1*H*)-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 **9a–9d** to give the corresponding bis(hydrazones) **5a–5d** and bis(cinnamonitriles) **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(1*H*)-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(1*H*)-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(1*H*)-thione), bis(2-methylsulfanylpyridine).

**Résumé :** Nous avons préparé un nouveau composé, le 1,4-bis(2,6-dibromo-4-formylphénoxy)butane (**3**), à partir du 3,5-dibromobenzaldéhyde (**1**), et nous l'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(cinnamonitriles) **11a–11d** correspondants. Les dérivés de bis(2-cyanoacétohydrazide) **5d** et de bis(thioacrylamide) **11a** ont été tous les deux employés comme précurseurs pour la synthèse des molécules cibles, les dérivés de bis(pyridine-2(1*H*)-thione) **10** et **13a–13c** et les dérivés de bis(2-méthylsulfanylpyridine) **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(1*H*)-thione) **15** et **19a–19c**. Nous avons caractérisé les composés nouvellement s[illegible] ›lligé leurs données spectrales. [Traduit par la Rédaction]



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

## Introduction

Dihydropyridine derivatives show a wide range of bioactivities and are included in many pharmaceutical preparations such as antiarrhythmic, antihypertensive,[1–4] and anticancer agents.[5–9] Moreover, pyridine-2(1*H*)-thiones show bioactivities such as antifungal and antibacterial activities.[10] On the other hand, 2-*S*-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(1*H*)-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(cinnamonitriles) **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. $^1$H NMR spectra were recorded on Varian Mercury at 300 MHz spectrophotometer 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 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 ice-cold 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),

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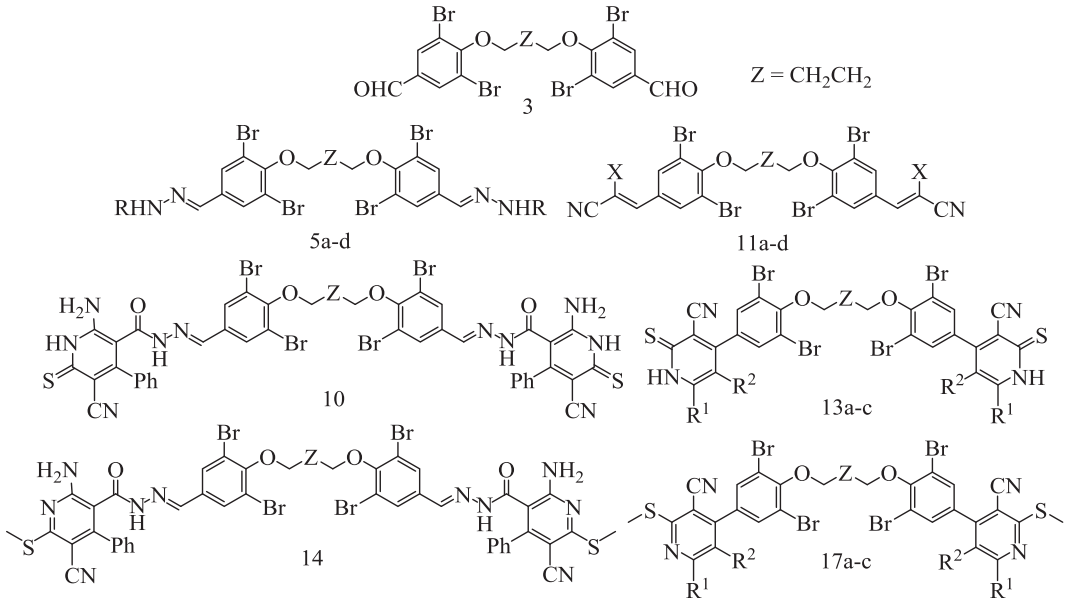
**Fig. 1.** Structure of the synthetic precursors bis(aldehyde) **3**, bis(hydrazones) **5a–5d**, and bis(cinnamonitriles) **11a–11d** and the target materials pyridine-2(1*H*)-thiones **10** and **13a–13c** and their bis(2-methylsulfanylpyridine) derivative **14** and **17a–17c**.




1689 (CO); $^1$H NMR (DMSO-$d_6$): δ 2.10 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 4.16 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 8.18 (s, 4H, ArH), and 9.90 (s, 2H, 2 C<u>H</u>O); Anal. Calcd for $C_{18}H_{14}Br_4O_4$ (613.92): C, 35.22; H, 2.30; found: C, 35.10; H, 2.39.

***1,4-Bis(2,6-dibromo-4-[((2-cyano-3-phenylacryloyl) hydrazineylidene)methyl]phenoxy)-butane (6)***

Yellowish white crystals recrystallized from DMF–ethanol mixture (55% from **5d** or 82% from **8**); mp 256–258 °C; IR (υ cm$^{-1}$): 3273 (NH), 2210 (CN), 1684 (CO); $^1$H NMR (DMSO-$d_6$): δ 2.07 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 4.07 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 7.17–7.98 (m, 18H, 14 ArH, 2 CH=C and 2 CH=N), 11.76 (s, 2H, 2 NH); MS *m*/*z*: 956 (45.65%, M$^+$ + 8), 952 (74.64%, M$^+$ + 4), 951 (44.93%, M$^+$ + 3), 949 (43.48%, M$^+$ + 1), 928 (47.83%), 927 (72.46%), 898 (59.42%), 879 (59.42%), 803 (57.25%), 797 (41.30%); Anal. Calcd for $C_{38}H_{28}Br_4N_6O_4$ (948.28): C, 47.93; H, 2.96; N, 8.83; found: C, 48.25; H, 2.60; N, 8.52.

***1,4-Bis(2,6-dibromo-4-[((2-amino-5-cyano-6-methylsulfanyl-4-phenyl-pyridin-3-yl)carbonyl-hydrazineylidene)methyl] phenoxy)butane (14)***

Brown crystals recrystallized from toluene–ethanol mixture (47% from **10** or 70% from **16**); mp 226–228 °C; IR (υ cm$^{-1}$): 3340, 3204 (NH), 2215 (CN), 1630 (CO); $^1$H NMR (DMSO-$d_6$): δ 2.18 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 2.30 (s, 6H, 2 $CH_3$), 3.98 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 6.72 (s, br, 4H, 2 $NH_2$), 7.10–7.91 (m, 14H, Ars), 8.21 (s, 2H, 2 CH=N), 11.68 (s, 2H, 2 NH); Anal. Calcd for $C_{46}H_{36}Br_4N_{10}O_4S_2$ (1172.59): C, 46.96; H, 3.08; N, 11.90; S, 5.45; found: C, 47.32; H, 3.41; N, 11.58; S, 5.12.

***1,4-Bis(2,6-dibromo-4-[5-acetyl-3-cyano-6-methyl-2-methylsulfanylpyridin-4-yl]phenoxy)-butane (17a)***

Colorless crystals recrystallized from dioxane–ethanol mixture as white crystals (45% from **13a** or 76% from **20a**); mp 220–222 °C; IR (υ cm$^{-1}$): 2217 (CN), 1692 (CO); $^1$H NMR (DMSO-$d_6$): δ 2.11 (m, 10H, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$ and 2 $COCH_3$), 2.53 (s, 6H, 2 $CH_3$), 2.66 (s, 6H, 2 $SCH_3$), 4.15 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 7.79 (s, 4H, ArH); Anal. Calcd for $C_{36}H_{30}Br_4N_4O_4S_2$ (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.

***1,4-Bis(2,6-dibromo-4-[5-cyano-3-ethoxycarbonyl-2-methyl-6-methylsulfanylpyridin-4-yl]-phenoxy)butane (17b)***

Yellowish white crystals recrystallized from dioxane–ethanol mixture (40% from **13b** or 67% from **20b**); mp 172–174 °C; IR (υ cm$^{-1}$): 2214 (CN), 1705 (CO); $^1$H NMR (DMSO-$d_6$): δ 1.01 (t, 6H, *J* = 7.0 Hz, 2 $C\underline{H}_3CH_2$), 2.16 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 2.57 (s, 6H, 2 $CH_3$), 2.66 (s, 6H, 2 $SCH_3$), 4.02 (m, 8H, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$ and 2 $CH_3C\underline{H}_2$), 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 $C_{38}H_{34}Br_4N_4O_6S_2$ (1022.45): C, 44.46; H, 3.34; N, 12.48; S, 5.71; found: C, 44.92; H, 2.98; N, 12.80; S, 5.36.

***1,4-Bis(2,6-dibromo-4-[6-amino-3,5-dicyano-2-methylsulfanylpyridin-4-yl]phenoxy)butane (17c)***

Brown crystals recrystallized from dioxane–ethanol mixture (50% from **13c** or 75% from **20c**); 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, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 2.58 (s, 6H, 2 $SCH_3$), 4.16 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 7.95 (s, 4H, ArH), 8.10 (s, br, 4H, 2 $NH_2$); Anal. Calcd for $C_{32}H_{22}Br_4N_8O_2S_2$ (930.32): C, 41.14; H, 2.37; N, 11.99; S, 6.86; found: C, 41.60; H, 2.05; N, 11.60; S, 7.12.

**Procedure for 1,4-bis(2,6-dibromo-4-(hydrazineylidenemethyl) phenoxy)butane (5a)**

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, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 4.03 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 7.08 (s, br, 4H, 2 $NH_2$), 7.57 (s, 2H, 2 CH=N), 7.76 (s, 4H, ArH); Anal. Calcd for $C_{18}H_{18}Br_4N_4O_2$ (637.98): C, 33.68; H, 2.83; N, 8.73; found: C, 33.24; H, 2.99; N, 8.50.

**Procedure for 1,4-bis(2,6-dibromo-4-((2-phenylhydrazineylidene) methyl)phenoxy)butane (5b)**

A solution of **3** (5 mmol) and phenyl hydrazine (**4b**, 10 mmol) in glacial acetic acid (30 mL) was heated under reflux for 3 h. The reaction mixture was cooled to room temperature, and the solid

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 (υ $cm^{-1}$): 3292 (NH); $^1$H NMR (DMSO-$d_6$): δ 2.05 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 4.05 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 10.50 (s, 2H, 2 NH), 7.05–7.90 (m, 16H, 14 ArH and 2 CH=N); MS *m*/*z*: 798 (58.56%, $M^+$ + 8), 794 (46.85%, $M^+$ + 4), 704 (59.46%), 702 (59.46%), 686 (54.05%), 673 (71.17%), 608 (80.18%), 606 (51.35%); Anal. Calcd for $C_{30}H_{26}Br_4N_4O_2$ (790.17): C, 45.37; H, 3.30; N, 7.05; found: C, 45.70; H, 3.62; N, 6.61.

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

A solution of **3** (5 mmol) and thiosemicarbzide (**4c**, 10 mmol) in glacial acetic acid (30 mL) was heated under reflux for 3 h. The reaction mixture was cooled to room temperature, and the solid product was collected by filtration, washed with cold ethanol, and recrystallized from glacial acetic acid as colorless crystals (74%) m.p. 276–278 °C; IR (υ $cm^{-1}$): 3424, 3261, 3155 (NH and $NH_2$), 1541 (CS); $^1$H NMR (DMSO-$d_6$): δ 2.06 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 4.07 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 7.93 (s, 2H, 2 CH=N), 8.16 (s, 4H, ArH), 8.26 (s, br, 4H, 2 $NH_2$), 11.52 (s, 2H, 2 NH); Anal. Calcd for $C_{20}H_{20}Br_4N_6O_2S_2$ (756.16): C, 31.60; H, 2.65; N, 11.06; S, 8.44; found: C, 31.98; H, 2.21; N, 10.89; S, 8.80.

**General procedure for compounds 5d and 7**

A solution of each of **3** or **1** (5 mmol) and 2-cyanoacetic acid hydrazide (**4d**, 5 mmol for **3** or 10 mmol for **1**) in 50 mL ethanol was heated under reflux for 30 min. 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 **5d** and **7**, respectively.

***1,4-Bis(2,6-dibromo-4-[(2-(cyanoacetyl)hydrazineylidene) methyl]phenoxy)butane (5d)***

Colorless crystals recrystallized from DMF–ethanol mixture (86%); m.p. 234–236 °C; IR (υ $cm^{-1}$): 3211 (NH), 2261 (CN), 1693 (CO); $^1$H NMR (DMSO-$d_6$): δ 2.07 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 4.07 (t, 4H, *J* = 7.2 Hz, $O\underline{C}H_2CH_2CH_2\underline{C}H_2O$), 4.28 (s, 4H, 2 $CH_2$), 7.91 (s, 2H, 2 CH=N), 8.03 (s, 4H, ArH), 11.96 (s, 2H, 2 NH); Anal. Calcd for $C_{24}H_{20}Br_4N_6O_4$ (772.07): C, 37.14; H, 2.60; N, 10.83; found: C, 36.80; H, 2.89; N, 11.12.

***2-Cyanoacetic acid* N′*-(3,5-dibromo-4-hydroxybenzylidene) hydrazide (7)***

Colorless crystals recrystallized from dioxane (88%); mp 238–240 °C; IR (υ $cm^{-1}$): 3294 (OH), 3200 (NH), 2277 (CN), 1694 (CO); $^1$H NMR (DMSO-$d_6$): δ 4.29 (s, 2H, $CH_2$), 7.92 (s, 1H, CH=N), 8.07 (s, 2H, ArH), 10.61 (s, br, 1H, OH), 11.98 (s, 1H, NH); MS *m*/*z*: 363 (9.92%, $M^+$ + 4), 361 (20.11%, $M^+$ + 2), 359 (10.09%, $M^+$), 321 (0.94%), 293 (2.28%), 278 (27.99%), 264 (0.83%), 83 (2.07%); Anal. Calcd for $C_{10}H_7Br_2N_3O_2$ (358.99): C, 33.27; H, 1.95; N, 11.64; found: C, 32.99; H, 2.32; N, 11.40.

**General procedure for compounds 6 and 8**

A solution of each of **5d** or **7** (5 mmol) and benzaldehyde (10 mmol for **5d** or 5 mmol for **7**) in 40 mL of ethanol containing 2 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, washed by cold ethanol, and recrystallized from the proper solvent to yield **6** and **8**, respectively.

***2-Cyano-*N′*-(3,5-dibromo-4-hydroxybenzylidene)-3-phenylacrylic acid hydrazide (8)***

Yellowish white crystals recrystallized from dioxane (84%); mp 274–276 °C; IR (υ $cm^{-1}$): 3411 (OH), 3276 (NH), 2209 (CN), 1689 (CO); $^1$H NMR (DMSO-$d_6$): δ 7.17–7.95 (m, 9H, 7 ArH, CH=C and CH=N), 10.52 (s, br, 1H, OH), 11.76 (s, 1H, NH); MS *m*/*z*: 451 (3.56%, $M^+$ + 4), 449 (6.26%, $M^+$ + 2), 447 (3.10%, $M^+$), 370 (22.12%), 185 (4.89%), 171 (100.00%), 156 (44.01%), 128 (35.24%), 77 (21.87%); Anal. Calcd for $C_{17}H_{11}Br_2N_3O_2$ (447.10): C, 45.47; H, 2.47; N, 9.36; found: C, 45.89; H, 2.12; N, 9.62.

**General procedure for compounds 10 and 15**

A mixture of each of **6** or **8** (5 mmol) and 2-cyanoethanethioamide (**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-amino-5-cyano-4-phenyl-6-thioxo-1,6-dihydro-pyridin-3-yl)-carbonylhydrazineylidene) methyl]phenoxy)butane (10)***

Yellow crystals recrystallized from ethanol (58%); mp > 360 °C; IR (υ $cm^{-1}$): 3361, 3205 (NH), 2215 (CN), 1640 (CO), 1550 (CS); $^1$H NMR (DMSO-$d_6$): δ 2.20 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 3.95 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 6.70 (s, br, 4H, 2 $NH_2$), 7.15–7.85 (m, 14H, ArH), 8.25 (s, 2H, 2 CH=N), 11.70 (s, 2H, 2 NH), 14.05 (s, br, 2H, 2 pyridine NH); Anal. Calcd for $C_{44}H_{32}Br_4N_{10}O_4S_2$ (1144.54): C, 46.01; H, 2.81; N, 12.20; S, 5.58; found: C, 46.31; H, 2.50; N, 11.84; S, 5.94.

***2-Amino-5-cyano-4-phenyl-6-thioxo-*N′*-(3,5-dibromo-4-hydroxybenzylidene)-1,6-dihydro-pyridine-3-carbohydrazide (15)***

Yellow crystals recrystallized from toluene–ethanol mixture (61%); mp 224–226 °C; IR (υ $cm^{-1}$): 3410 (OH), 3324, 3198 (NH), 2218 (CN), 1628 (CO), 1553 (CS); $^1$H NMR (DMSO-$d_6$): δ 6.75 (s, br, 2H, $NH_2$), 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 $C_{20}H_{13}Br_2N_5O_2S$ (545.22): C, 43.90; H, 2.39; 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 for **3** 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]phenoxy) butane (11a)***

Yellow crystals recrystallized from dioxane–ethanol mixture (70%); mp 244–246 °C; IR (υ $cm^{-1}$): 3315, 3194 ($NH_2$), 2213 (CN), 1554 (CS); $^1$H NMR (DMSO-$d_6$): δ 2.12 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 4.15 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 7.65 (s, 2H, 2 CH=C), 7.91 (s, 4H, ArH), 8.22 (s, br, 4H, 2 $NH_2$); Anal. Calcd for $C_{24}H_{18}Br_4N_4O_2S_2$ (774.17): C, 37.04; H, 2.33; N, 7.20; S, 8.24; found: C, 37.36; H, 2.54; N, 7.02; S, 8.56.

***2-Cyano-3-(3,5-dibromo-4-hydroxyphenyl)prop-2-enethioamide (18)***

Yellow crystals recrystallized from dioxane–ethanol mixture as (84%); m.p. 260–262 °C; IR (υ $cm^{-1}$): 3315, 3194 ($NH_2$), 2213 (CN), 1554 (CS); $^1$H NMR (DMSO-$d_6$): δ 7.05 (s, br, 4H, 2 $NH_2$), 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 $C_{10}H_6Br_2N_2OS$ (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.

**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-[2,2-dicyanovinyl]phenoxy)butane (11b)***

Colorless crystals recrystallized from dioxane (75%); mp 236–238 °C; IR (υ $cm^{-1}$): 2223 (CN); $^1$H NMR (DMSO-$d_6$): δ 2.10 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 4.11 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 7.78 (s, 2H, 2 CH=C), 7.99 (s, 4H, 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 $C_{24}H_{14}Br_4N_4O_2$ (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-2-ethoxycarbonylvinyl]phenoxy) butane (11c)***

Colorless crystals recrystallized from dioxane (80%); mp 216–218 °C; IR (υ $cm^{-1}$): 2222 (CN), 1719 (CO); $^1$H NMR (DMSO-$d_6$): δ 1.32 (t, *J* = 7.0 Hz, 6H, 2 $CH_2\underline{CH}_3$), 2.10 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 4.18 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 4.33 (q, *J* = 7.0 Hz, 4H, 2 $C\underline{H}_2CH_3$), 8.36 (s, 6H, ArH and 2 CH=C); Anal. Calcd for $C_{28}H_{24}Br_4N_2O_6$ (800.12): C, 41.82; H, 3.01; N, 3.48; found: C, 41.99; H, 3.22; N, 3.06.

***1,4-Bis(2,6-dibromo-4-[2-cyano-2-carbamoylvinyl]phenoxy)butane (11d)***

Yellowish white crystals recrystallized from dioxane–ethanol (72%); mp 296–298 °C; IR (υ $cm^{-1}$): 3337, 3192 ($NH_2$), 2212 (CN), 1645 (CO); $^1$H NMR (DMSO-$d_6$): δ 2.16 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 4.18 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 7.40 (s, br, 4H, 2 $NH_2$), 7.68 (s, 2H, 2 CH=C), 7.94 (s, 4H, ArH); MS *m*/*z*: 750 (3.75%, $M^+$ + 8), 742 (3.89%, $M^+$), 724 (4.04%), 716 (3.94%), 702 (3.56%), 672 (3.37%), 663 (4.42%), 656 (3.89%); Anal. Calcd for $C_{24}H_{18}Br_4N_4O_4$ (742.04): C, 38.64; H, 2.43; N, 7.51; found: C, 38.26; H, 2.08; N, 7.90.

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

A mixture of each of **11a** or **18** (5 mmol) and each of **12a** and **12b** (10 mmol for **11a** or 5 mmol for **18**) or a ternary mixture of **1** (5 mmol), **9a** (5 mmol), and **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 **13b** and **19a** and **19b**, respectively.

***1,4-Bis(2,6-dibromo-4-[5-acetyl-3-cyano-6-methyl-2-thioxo-1,2-dihydro-pyridin-4-yl]-phenoxy)butane (13a)***

Yellow crystals recrystallized from dioxane–ethanol mixture (58%); mp 234–236 °C; IR (υ $cm^{-1}$): 3443 (NH), 2217 (CN), 1692 (CO), 1565 (CS); $^1$H NMR (DMSO-$d_6$): δ 1.94 (s, 6H, 2 $COCH_3$), 2.10 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 2.40 (s, 6H, 2 $CH_3$), 4.14 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 7.78 (s, 4H, ArH), 14.40 (s, 2H, 2 NH); Anal. Calcd for $C_{34}H_{26}Br_4N_4O_4S_2$ (934.34): C, 43.52; H, 2.79; N, 5.97; S, 6.83; found: C, 43.84; H, 2.96; N, 5.56; S, 6.54.

***1,4-Bis(2,6-dibromo-4-[5-cyano-3-ethoxycarbonyl-2-methyl-6-thioxo-1,6-dihydropyridin-4-yl]phenoxy)butane (13b)***

Yellow crystals recrystallized from dioxane/ethanol mixture (53%); mp > 350 °C; IR (υ $cm^{-1}$): 3417 (NH), 2213 (CN), 1708 (CO), 1558 (CS); $^1$H NMR (DMSO-$d_6$): δ 1.01 (t, 6H, *J* = 7.0 Hz, 2 $\underline{CH}_3CH_2$), 2.16 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 2.58 (s, 6H, 2 $CH_3$), 4.02 (m, 8H, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$ and 2 $CH_3\underline{CH}_2$), 7.77 (s, 4H, ArH), 14.40 (s, 2H, 2 NH); MS *m*/*z*: 1002 (17.57%, $M^+$ + 8), 998 (32.57%, $M^+$ + 4), 994 (17.73%), 915 (16.45%), 768 (17.57%), 748 (16.29%), 737 (20.77%), 560 (24.12%); Anal. Calcd for $C_{36}H_{30}Br_4N_4O_6S_2$ (994.39): C, 43.31; H, 3.03; N, 5.61; S, 6.42; found: C, 43.02; H, 2.69; N, 5.98; S, 6.88.

***5-Acetyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (19a)***

Yellow crystals recrystallized from dioxane (74% from **18** or 70% from ternary mixture); mp 284–286 °C; IR (υ $cm^{-1}$): 3410 (OH), 3207 (NH), 2228 (CN), 1682 (CO), 1571 (CS); $^1$H NMR (DMSO-$d_6$): δ 1.91 (s, 3H, $COCH_3$), 2.36 (s, 3H, $CH_3$), 7.62 (s, 2H, ArH), 10.70 (s, br, 1H, OH), 14.28 (s, br, 1H, NH); Anal. Calcd for $C_{15}H_{10}Br_2N_2O_2S$ (440.13): C, 40.75; H, 2.28; N, 6.34; S, 7.25; found: C, 40.50; H, 1.95; N, 6.61; S, 7.01.

***Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxylate (19b)***

Yellow crystals recrystallized from dioxane (70% from **18** or 68% from ternary mixture); mp 270–272 °C; IR (υ $cm^{-1}$): 3427 (OH), 3218 (NH), 2230 (CN), 1697 (CO), 1577 (CS); $^1$H NMR (DMSO-$d_6$): δ 0.86 (t, 3H, *J* = 6.9 Hz, $C\underline{H}_3CH_2$), 2.57 (s, 3H, $CH_3$), 3.97 (q, 2H, *J* = 6.9 Hz, $CH_3C\underline{H}_2$), 7.58 (s, 2H, ArH), 10.57 (s, br, 1H, OH), 14.40 (s, br, 1H, NH); Anal. Calcd for $C_{16}H_{12}Br_2N_2O_3S$ (470.15): C, 40.70; H, 2.56; N, 5.93; 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 **11a** and **11b** or **18** (5 mmol) and each of **9a** (10 mmol for **11a** and **11b** or 5 mmol for **18**) or a mixture of **1** (5 mmol) and **9a** (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-dihydropyridin-4-yl]phenoxy)-butane (13c)***

Yellow crystals recrystallized from dioxane–ethanol mixture (51% from **9a** or 48% from **9b**); mp 254–256 °C; IR (υ $cm^{-1}$): 3438, 3342, 3164 (NH and $NH_2$), 2214 (CN), 1559 (CS); $^1$H NMR (DMSO-$d_6$): δ 2.13 (t, 4H, *J* = 7.2 Hz, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 3.91 (t, 4H, *J* = 7.2 Hz, $OC\underline{H}_2CH_2CH_2C\underline{H}_2O$), 7.80 (s, 4H, ArH), 8.00 (s, br, 4H, 2 $NH_2$), 14.40 (s, 2H, 2 NH); MS *m*/*z*: 910 (92.79%, $M^+$ + 8), 909 (55.86%, $M^+$ + 7), 902 (51.35%, $M^+$), 890 (63.06%), 868 (16.45%), 856 (70.27%), 802 (58.56%), 772 (73.87%), 728 (56.76%); Anal. Calcd for $C_{30}H_{18}Br_4N_8O_2S_2$ (902.26): C, 39.76; H, 2.00; N, 12.36; S, 7.08; found: C, 39.98; H, 2.36; N, 12.08; S, 6.78.

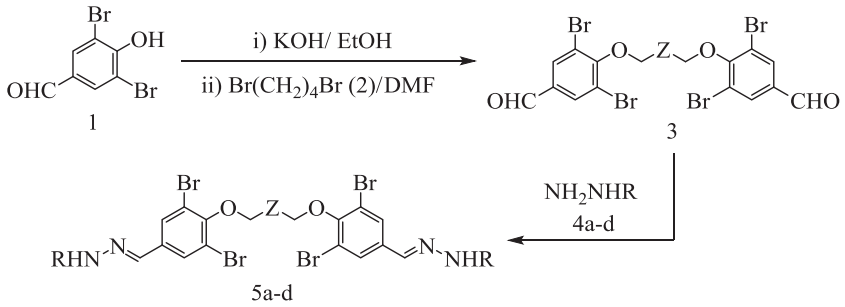
***6-Amino-4-(3,5-dibromo-4-hydroxyphenyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (19c)***

Yellow crystals recrystallized from ethanol (84% from **18** or 80% from ternary mixture); mp 170–172 °C; IR (υ $cm^{-1}$): 3450, 3415, 3355, 3177 (OH, NH and $NH_2$), 2217 (CN), 1565 (CS); $^1$H NMR (DMSO-$d_6$): δ 7.85 (s, 2H, ArH), 8.25 (s, br, 2H, $NH_2$), 10.75 (s, br, 1H, OH), 12.95 (s, br, 1H, NH); Anal. Calcd for $C_{13}H_6Br_2N_4OS$ (424.09): C, 36.64; H, 1.42; N, 13.15; S, 7.53; found: C, 36.89; H, 1.85; N, 13.62; S, 7.23.

**General procedure for compounds 14, 16, 17a–17c, and 20a–20c**

A mixture of each of **10, 15, 13a–13c**, or **19a–19c** (5 mmol) and iodomethane (10 mmol for **10, 13a–13c** or 5 mmol for **15, 19a–19c**) in methanolic sodium methoxide solution (10 mmol of sodium metal in 20 mL of methanol) was heated under reflux for 1 h. The products so formed (after cooling for **10, 13a–13c** or after cooling and neutralization to pH = 7 for **15, 19a–19c**) were collected by filtration, washed with cold ethanol, and then recrystallized from the proper solvent to yield **14, 16, 17a–17c**, and **20a–20c**, respectively.

**Scheme 1.** Synthesis of bis(hydrazonomethylphenoxy)butanes **5a–5d**.




| 4, 5 | R |
|---|---|
| a | H |
| b | Ph |
| c | $CSNH_2$ |
| d | $COCH_2CN$ |

$Z = CH_2CH_2$

***2-Amino-5-cyano-6-methylsulfanyl-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 (υ $cm^{-1}$): 3457 (OH), 3330, 3210 (NH), 2211 (CN), 1633 (CO); δ 2.32 (s, 3H, $CH_3$), 6.92–7.64 (m, 9H, 7 ArH and $NH_2$), 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%), 458 (12.21%); Anal. Calcd for $C_{21}H_{15}Br_2N_5O_2S$ (559.25): C, 44.94; H, 2.69; N, 12.48; S, 5.71; found: C, 44.56; H, 2.25; N, 12.82; S, 5.99.

***5-Acetyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-2-methylsulfanylnicotinonitrile (20a)***

Colourless crystals recrystallized from ethanol as (88%); mp 228–230 °C; IR (υ $cm^{-1}$): 3445 (OH), 2218 (CN), 1680 (CO); $^1$H NMR (DMSO-$d_6$): δ 2.10 (s, 3H, $COCH_3$), 2.52 (s, 3H, $CH_3$), 2.68 (s, 3H, $SCH_3$), 7.78 (s, 2H, ArH), 10.75 (s, br, 1H, OH); MS *m*/*z*: 458 (76.70%, $M^+ + 4$), 456 (58.25%, $M^+ + 2$), 453 (61.17%, $M^+ - 1$), 443 (75.73%), 428 (61.17%), 415 (71.84%), 400 (73.79%), 370 (64.08%); Anal. Calcd for $C_{16}H_{12}Br_2N_2O_2S$ (454.15): 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)-2-methyl-6-methylsulfanylnicotinate (20b)***

Colourless crystals recrystallized from ethanol (74%); mp 160–162 °C; IR (υ $cm^{-1}$): 3427 (OH), 2222 (CN), 1693 (CO); $^1$H NMR (DMSO-$d_6$): δ 1.05 (t, 3H, $J$ = 7.0 Hz, $CH_3CH_2$), 2.58 (s, 3H, $CH_3$), 2.67 (s, 3H, $SCH_3$), 4.05 (q, 2H, $J$ = 7.0 Hz, $CH_3CH_2$), 7.79 (s, 2H, ArH), 10.68 (s, br, 1H, OH); MS *m*/*z*: 488 (11.17%, $M^+ + 4$), 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 $C_{17}H_{14}Br_2N_2O_3S$ (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-methylsulfanylpyridine-3,5-dicarbonitrile (20c)***

Colourless crystals recrystallized from ethanol (85%); mp 332–334 °C; IR (υ $cm^{-1}$): 3433 (OH), 3365, 3190 ($NH_2$), 2219 (CN); $^1$H NMR (DMSO-$d_6$): δ 2.58 (s, 3H, $SCH_3$), 7.95 (s, 2H, ArH), 8.10 (s, br, 2H, $NH_2$), 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 $C_{14}H_8Br_2N_4OS$ (438.11): 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

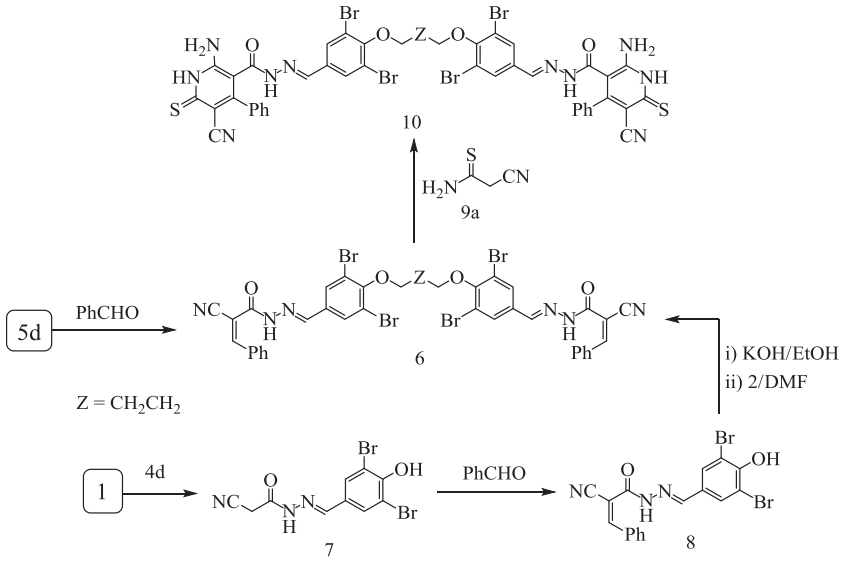
The novel 1,4-bis(2,6-dibromo-4-formylphenoxy)butane (**3**) was prepared via reacting the potassium salt of 3,5-dibromobenzaldehyde (**1**) with 1,4-dibromobutane (**2**) in refluxing DMF. The IR spectrum ($cm^{-1}$) of **3** showed the absorption bands of C<u>H</u> stretching of formyl group at 2848 and 2750 in addition to CO group at 1689. Its $^1$H NMR spectrum revealed the signals of $OCH_2\underline{CH_2}\underline{CH_2}CH_2O$ (t, 4H, $J$ = 7.2 Hz, δ = 2.10 ppm), $O\underline{CH_2}CH_2CH_2\underline{CH_2}O$ (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(hydrazones) **5a–5d**. It has been found that compound **3** reacted with two molecules of hydrazine hydrate (**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 $NH_2$ groups at 3374 and 3185. Its $^1$H NMR spectrum revealed the presence of the signals of $NH_2$ (s, br, 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).

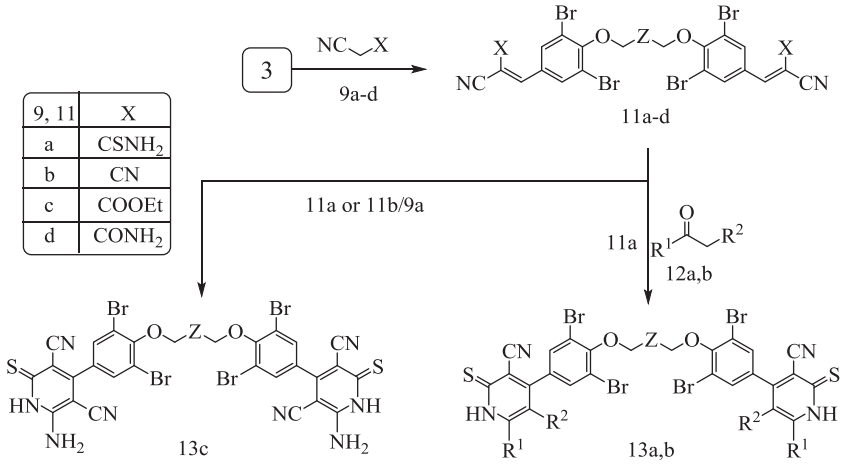
In a further investigation, the bis(2-cyanoacetic acid hydrazide) derivative **5d** reacted with benzaldehyde in ethanol containing a few drops of piperidine under reflux to give the corresponding bis(3-phenylacrylic acid hydrazide) derivative **6**, in 55% yield, whose IR spectrum ($cm^{-1}$) showed the absorption bands of NH at 3273, CN at 2210, and CO at 1684. Its $^1$H NMR spectrum revealed the presence of the signals of 14 aromatic and 4 olefinic protons (m, 18H, δ = 7.17–7.98 ppm) and 2 NH protons 11.76 (s, 2H, δ = 11.76 ppm). Compound **6** could be authentically prepared via another route by reacting aldehyde **1** with 2-cyanoacetic acid hydrazide (**4d**) to give compound **7**, which condensed with benzaldehyde to afford the corresponding 3-phenylacrylic acid hydrazide derivative **8** whose potassium salt reacted with 1,4-dibromobutane (**2**) in refluxing DMF (Scheme 2; see also the Experimental section).

The target molecule bis(pyridine-2(1*H*)-thione) derivative **10** prepared via reacting bis(3-phenylacrylic acid hydrazide) derivative **6** with two molecules of 2-cyanoethanethioamide (**9a**) in refluxing

**Scheme 2.** Synthesis of bis(pyridine-2(1*H*)-thione) derivative **10**.




**Scheme 3.** Synthesis of bis(pyridine-2(1*H*)-thione) derivatives **13a–13c**.




| 9, 11 | X |
|---|---|
| a | $CSNH_2$ |
| b | CN |
| c | COOEt |
| d | $CONH_2$ |

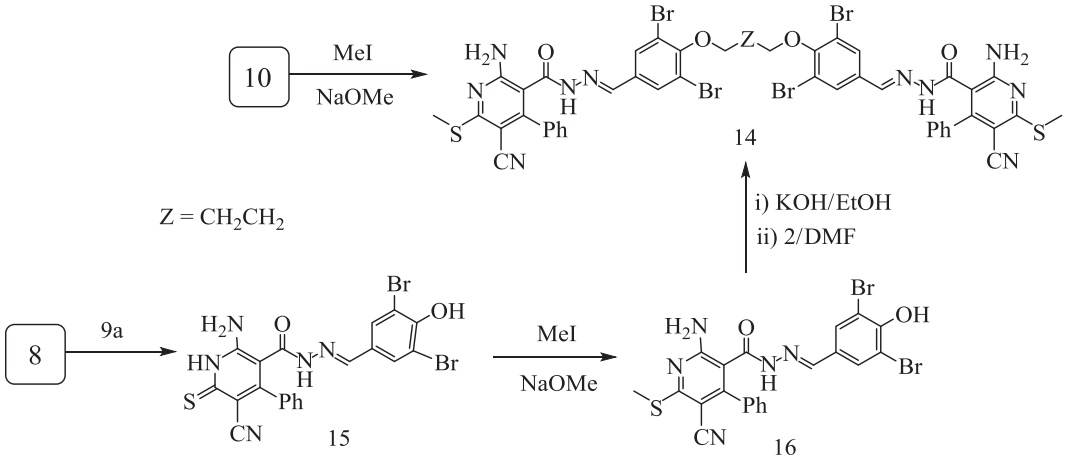
| 12, 13 | $R^1$ | $R^2$ |
|---|---|---|
| a | Me | COMe |
| b | Me | COOEt |

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 $^1$H 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).

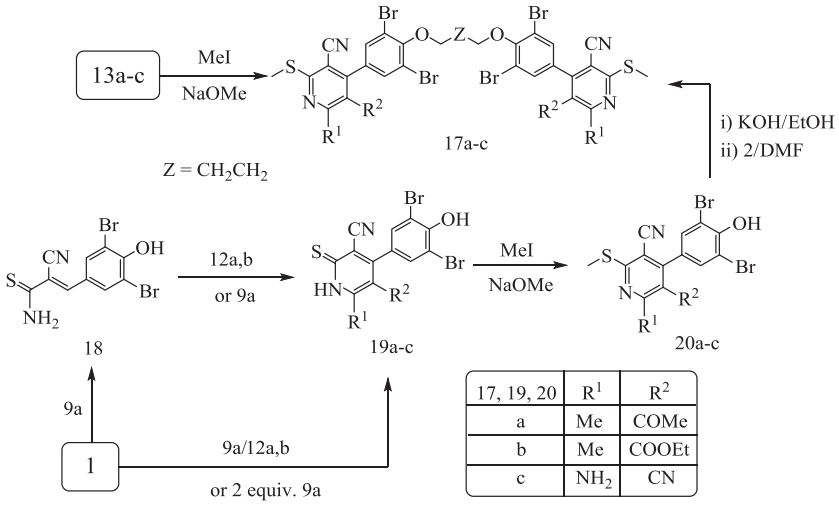
The chemical potentiality of the bis(aldehyde) **3** was investigated via its reaction with different active methylene containing compounds **9a–9d** to give the corresponding bis(cinnamonitrile) derivatives **11a–11d**. Thus, it has been found that compound **3** reacted with two molecules of 2-cyanoethanethioamide (**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 $NH_2$ at 3315 and 3194, CN at 2213, and CS at 1554. Its $^1$H NMR spectrum revealed the signals of CH=N (s, 2H, δ = 7.65 ppm) and $NH_2$ (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(1*H*)-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 $^1$H NMR spectrum revealed the signals of $COCH_3$ (s, 6H, δ = 1.94 ppm), $CH_3$ (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

**Scheme 4.** Synthesis of bis(4-[((6-methylsulfanylpyridin-3-yl)carbonyl-hydrazineylidene)methyl]phenoxy)butane derivative **14**.




**Scheme 5.** Synthesis of bis(2-methylsulfanylpyridin-4-ylphenoxy)butane derivative **17a–17c**.




| 17, 19, 20 | $R^1$ | $R^2$ |
|---|---|---|
| a | Me | COMe |
| b | Me | COOEt |
| c | $NH_2$ | CN |

ethyl acetoacetate (**12b**) (Scheme 3; see also the Experimental section).

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 $NH_2$ at 3438, 3342 and 3164, CN at 2214, and CS at 1559. Its $^1$H NMR spectrum revealed the signals of $NH_2$ (s, br, 4H, δ = 8.00 ppm) and NH (s, 2H, δ = 14.40 ppm) (Scheme 3; see also the Experimental section).

The target molecule bis(4-[((6-methylsulfanylpyridin-3-yl) carbonylhydrazine-ylidene)methyl]phenoxy)butane derivative **14** was prepared, in a moderate yield, by the reaction of bis(pyridine-2(1*H*)-thione) derivative **10** and iodomethane in methanolic sodium methoxide solution whose $^1$H NMR spectrum revealed the absence of pyridine NH signal and the presence of the signal corresponding to 2 $CH_3$ groups (s, 6H, δ = 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(1*H*)-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(1*H*)-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 $^1$H NMR spectrum revealed the absence of pyridine NH signal and the presence of the signal corresponding to two $SCH_3$ groups (s, 6H, δ = 2.66 ppm). The second route came from the synthesis of pyridine-2(1*H*)-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 β-dicarbonyl compounds **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 $^1$H NMR spectrum of compound **19a** revealed the presence of a signal corresponding to the $COCH_3$ group (s, 3H, δ = 1.91 ppm), $CH_3$ group (s, 3H, δ = 2.36 ppm), and NH group (s, br, 1H, δ = 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).

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