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Bifunctionalized linked bis-spiro[furo[2,3-d]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3H,3′H,5H)-pentaones derived from one-pot reaction of (thio)barbituric acids with aromatic dialdehydes and BrCN in the presence of Et_3N

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Reaction of pyrimidine-(1H,3H,5H)-2,4,6-trione (barbituric acid), 1,3-dimethyl pyrimidine-(1H,3H,5H)-2,4,6-trione (1,3-dimethyl barbituric acid), and 1,3-diethyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (1,3-diethyl thiobarbituric acid) with cyanogen bromide and aromatic dialdehydes in the presence of triethylamine leads to the selective and efficient formation of a novel class of bifunctionalized stable heterocyclic bis-spiro[furo[2,3-d]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3H,3′ H,5H)pentaones and their sulfur analogues, which are dimeric forms of barbiturate linked by a phenyl ring. A proposed mechanism was suggested for the formation of the products. The reaction of phthalaldehyde with BrCN and (thio)barbituric acids resulted in only monofunctionalized spiro[furo[2,3-d]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3H,3′ H,5H)pentaones, while isophthalaldehyde and terphthalaldehyde resulted in the bifunctionalized form.

Key Words: Barbituric acid, bis-spiro[furo[2,3-d]pyrimidine-6,5′-pyrimidine], diastereomer, rotamer, cyanogen bromide

Introduction

The heterocyclic structures furo[2,3-d]pyrimidines,[1−4] spirobarbituric acids,[5,6] and fused uracils[7,8] are well known due to their wide varieties of pharmaceutical and biological effects.

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Barbituric acid (BA) reacts with cyanogen bromide in the presence of pyridine derivatives through a König-form reaction in which the pyridine derivative reacts with cyanogen bromide and is then coupled with an active methylene to give polymethine dye.[9] For instance, determination of niketamide[10] and niacinamide[11] through the reaction of BA and cyanogen bromide has been used.

BA derivatives can act as nucleophiles and react with different electrophiles such as carbodiimides,[12] benzophenone derivatives,[13] and 2,2′-bipyridil to form 5,5′-(2-pyrilidine)bisbarbituric acid,[14,15] C_{60} molecules,[16] and erythrolactol to obtain spiro-barbituric deoxyribonucleoside,[17] spiro-linked condensed [1,2-*a*]quinolines,[18] π-conjugated systems containing BA, and 1,3-dimethyl barbituric acid (DMBA) derivatives.[19]

More recently, a new class of stable heterocyclic 5-alkyl and/or 5-aryl-1*H*,1′H-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*) pentaones has been reported by our group from one-pot reactions between (thio)barbituric acids and aromatic and aliphatic mono-aldehydes[20,21] and ketones[22] in the presence of cyanogen bromide and triethylamine. Previously, we have also reported the crystal structure of spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*'5*H*)pentaone derivative from the reaction of DMBA and acetone in the presence of cyanogen bromide and Et_3N.[23] Elinson et al. have also reported the reaction of DMBA with aldehydes in the presence of bromine under basic conditions (EtONa/EtOH).[24] Based on these concepts, here we report a one-pot reaction of BA and thiobarbituric acid (TBA) derivatives with aromatic dialdehydes (phthalaldehyde, isophthalaldehyde and terphthalaldehyde) and cyanogen bromide in the presence of triethylamine.

Experimental

General procedures

Melting points were measured using a digital melting point apparatus (Electrothermal) and were uncorrected. IR spectra were recorded in the 4000–400 cm^{-1} region on a NEXUS 670 FT-IR spectrometer through preparing KBr pellets. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker 300 FT-NMR at 300 and 75 MHz, respectively (Urmia University, Urmia, Iran). ^{1}H- and ^{13}C-NMR spectra were obtained using $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. All reactions were monitored by TLC with silica gel-coated plates (AcOEt:AcOH/80:20/v:v). Mass analysis of compounds **3a** and **4b** was performed using a mass spectrometer (Agilent Technology (HP) type, MS Model: 5973 network mass selective detector, electron impact (EI) 70 eV); ion source temperature was 230 °C (Tehran University, Tehran, Iran). Compounds **2a–d** were synthesized and purified in our laboratory as described previously in the literature.[25] Cyanogen bromide was synthesized based on a reported reference.[26] Compounds **1a–c**, triethylamine, and solvents were purchased from Merck and were used without further purification.

Representative physical and spectral data of compounds **3a**–**4c** are given below.

General procedures for the preparation of 3a, 3b, 3c, 3e, 3f, 3h, 4a, 4b, 4c, and 11c

In a 10 mL tube with Teflon-faced screw cap equipped with a magnetic stirrer was dissolved 0.06 g (0.48 mmol) of cyanogen bromide (BrCN), 0.15 g (0.96 mmol) of barbituric acid, and 0.06 g (0.48 mmol) of phthalaldehyde in 10 mL of methanol, and then 0.06 g (0.6 mmol, 0.8 mL) of triethylamine was added to the solution at 0 °C. The

reaction mixture was stirred for 3 h at 0 °C to room temperature. (*Caution! The cyanogen bromide is highly toxic. Reactions should be carried out in a well-ventilated hood*). The Teflon-faced screw cap tube prevents the vaporization of cyanogen bromide during the reaction. The progression of the reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction, a crystalline white solid precipitate appeared, which was filtered off, washed with a few milliliters of methanol, and dried (0.12 g, 70% yield, **4a**).

1,3-bis{[1*H*,1′*H*-Spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)pentaone]-5-yl}benzene (3a)

White solid (85% Yield); mp 320 °C (decomps.); FT-IR (KBr) 3470 (NH), 3047 (CH-ar.), 2825 (CH-aliph.), 1706 (C=O), 1441, 1378 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 4.64, 4.67, 4.70 (s, 2H, 3CH-aliph.), 6.94 (s, 1H, Ph), 7.03 (m, 2H, Ph), 7.17 (m, 1H, Ph), 10.31 (bs, 1H, NH (a shoulder at the peak's left side)), 10.76, 10.80, 10.84 (1H, NH), 11.56, 11.59 (1H, NH), 12.66 (bs, 1H, NH) (an equilibrium mixture of 3 rotamers); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ: 167.2 (CO), 165.0 (CO), 164.8 (CO), 163.7 (CO), 160.7 (CO), 160.6 (CO), 160.3 (CO), 151.2 (Ph), 151.1 (Ph), 149.2 (Ph), 135.4 (Ph), 129.8 (Ph), 129.7 (Ph), 128.4 (Ph), 89.5 (C6 and C6″), 86.6 (**C**$_\alpha$-C4=O), 55.8 (C5 and C5″, minor product), 55.5 (C5 and C5″, major product); MS (m/z, %) 606 (M^+, 1), 493 (6), 438 (12), 294 (6), 279 (10), 246 (15), 203 (50), 190 (18), 177 (20), 164 (12), 149 (24), 85 (16), 71 (32), 57 (66), 43 (100, base peak).

1,3-bis{[1,1′,3,3′-Tetramethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)pentaone]-5-yl}benzene (3b)

White solid (90% Yield); mp 251 °C (decomps.); FT-IR (KBr) 3050 (CH-ar.), 2954 (CH-aliph.), 2926 (CH-aliph.), 2856 (CH-aliph.), 1691 (C=O), 1515 (C=C), 1440, 1378, 1041, 753 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.72 (s, 3H, N-CH_3), 3.32 (s, 3H, N-CH_3), 3.38 (s, 3H, N-CH_3), 3.52 (s, 3H, N-CH_3), 4.77 (s, 1H, CH-aliph.), 4.85 (s, 1H, CH-aliph.), 6.84 (s, 1H, Ph), 7.10 (d, 2H, J = 7.5 Hz, Ph), 7.32 (t, 1H, J = 7.5 Hz, Ph); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.4 (CO), 162.9 (CO), 162.6 (CO), 158.2 (CO), 151.2 (CO), 149.2 (CO), 134.6 (Ph), 134.3 (Ph), 129.8 (Ph), 129.3 (Ph), 129.0 (Ph), 128.6 (Ph), 128.2 (Ph), 89.9 (C6 and C6″), 85.9 (**C**$_\alpha$-C4=O), 58.5 (C5 and C5″, major product), 30.1 (N-CH_3, minor product), 30.0 (N-CH_3, major product), 29.5 (N-CH_3, major product), 28.9 (N-CH_3, major product), 28.8 (N-CH_3, minor product), 28.2 (N-CH_3, major product).

1,3-bis{[1,1′,3,3′-Tetraethyl-2,2′-dithioxo-2,2′,3,3′-tetrahydro-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]-4,4′,6′(5*H*)trione]-5-yl}benzene (3c)

White solid (24% Yield); mp 342 °C; FT-IR (KBr) 2980 (CH-aliph.), 1741 (C=O), 1698 (C=O), 1620 (C=C), 1491, 1437, 1385 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.19–1.50 (m, 12H, 4 CH_3), 4.54–4.71 (m, 8H, 4 CH_2), 4.83 (s, 1H, CH-aliph.), 6.85 (s, 1H, CH-aliph.), 7.12 (d, 2H, J = 7.8 Hz, Ph), 7.29 (t, 1H, J = 7.8 Hz, Ph); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 177.5 (CS), 174.6 (CS), 163.7 (CO), 162.1 (CO), 162.0 (CO), 161.0 (CO), 132.3 (Ph), 129.3 (Ph), 127.7 (Ph), 126.7 (Ph), 126.6 (C6 and C6″), 124.3 (**C**$_\alpha$-C4=O), 59.0 (C5 and C5″), 44.6 (N-**C**$H_2$$CH_3$), 44.0 (N-**C**$H_2$$CH_3$), 43.9 (N-**C**$H_2$$CH_3$), 43.6 (N-**C**$H_2$$CH_3$), 12.5 (N-$CH_2$**C**$H_3$), 12.4 (N-$CH_2$**C**$H_3$), 11.8 (N-$CH_2$**C**$H_3$), 11.5 (N-$CH_2$**C**$H_3$).

1,4-bis{[1*H*,1′*H*-Spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)pentaone]-5-yl}benzene (3e)

White solid (93% Yield); mp 386 °C (decomps.); FT-IR (KBr) 3448, 3209 (NH), 3064 (CH-ar.), 2833 (CH-aliph.), 1719 (C=O), 1674 (C=O), 1411, 1357 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 4.68, 4.71, 4.74 (3s, 2H), 6.95, 6.99, 7.01 (3s, 4H), 10.54 (bs, 2H), 10.74, 10.77, 10.80 (3s, 2H), 11.58 (s, 2H), 12.58 (bs, 2H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ: 167.3 (CO), 164.8 (CO), 163.7 (CO), 160.2 (CO), 151.2 (CO), 149.6 (CO), 135.4 (Ph), 128.9 (Ph), 89.4 (C6 and C6″), 86.2 ($\mathbf{C}_\alpha$-C4=O), 55.4 (C5 and C5″).

1,4-bis{[1,1′,3,3′-Tetramethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)pentaone]-5-yl}benzene (3f)

White solid (87% Yield); mp 364 °C (decomps.); FT-IR (KBr) 3050 (CH-ar.), 2965 (CH-aliph.), 1712 (C=O), 1691 (C=O), 1662 (C=O), 1517, 1437, 1374 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.59 (s, 3H), 2.66 (s, 3H), 3.29 (s, 3H), 3.30 (s, 3H), 3.41 (s, 3H), 3.52 (s, 3H), 4.87 (s, 1H), 4.90 (s, 1H), 7.045 (s, 2H), 7.054 (s, 2H) (mixture of 2 rotamers **3fA** and **3fB**); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.4 (CO), 162.8 (CO), 158.3 (CO), 151.2 (CO), 149.5 (CO), 134.6 (Ph), 128.8 (Ph), 89.9 (C6 and C6″), 85.1 ($\mathbf{C}_\alpha$-C4=O), 58.5 (C5 and C5″), 30.0 (N-CH_3), 29.5 (N-CH_3), 28.7 (N-CH_3), 28.5 (N-CH_3).

5-(4-(1′,3-Dimethyl-2,2′,4,4′,6′-pentaoxo-2,2′,3,3′,4,4′,5,6′-octahydro-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidin]-5-yl)phenyl)-1,1′-dimethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]-2,2′,4,4′,6′(3*H*,3′*H*,5*H*)pentaone (3h)

White solid (80% Yield); mp 232 °C (decomps.); FT-IR (KBr) 3470 (NH), 3047 (CH-ar.), 2825 (CH-aliph.), 1706 (C=O), 1650 (C=O), 1550, 1513, 1441, 1378, 1022, 757, 567 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.32 (s, 3H), 3.03 (s, 3H), 3.05 (s, 3H), 3.29 (s, 3H), 4.84, 4.89, 4.93 (s, 2H, mixture of at least 3 diastereomers and equilibrium mixtures of tautomers), 7.00 (m, 4H), 10.76, 11.43 (bs, 1H), 11.13 (s, 1H), 11.82 (bs, 1H), 12.98 (bs, 1H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ: 167.2 (CO), 165.1 (CO), 164.4 (CO), 163.3 (CO), 159.6 (CO), 159.1 (CO), 151.4 (CO), 151.0 (CO), 150.0 (CO), 136.0 (Ph), 135.03 (Ph), 135.0 (Ph), 129.0 (Ph), 128.8 (Ph), 90.05 (C6 and C6″), 90.00 ($\mathbf{C}_\alpha$-C4=O), 49.0 (C5 and C5″), 46.1 (N-$\mathbf{CH}_2$$CH_3$, triethyl ammonium salt), 29.2 (N-CH_3), 28.7 (N-CH_3), 27.27 (N-CH_3), 27.26 (N-CH_3), 9.0 (N-$CH_2$$\mathbf{CH}_3$, triethyl ammonium salt).

5-(2-Formylphenyl)-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)pentaone (4a)

White solid (70% Yield); mp 287 °C (decomps.); FT-IR (KBr) 3224 (NH), 2991 (CH-aliph.), 2787 (COH), 2687 (COH), 1736 (C=O), 1688 (C=O), 1587 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 5.88 (s, 1H, CH-aliph.), 7.31 (d, 1H, J = 5.7 Hz, Ph), 7.59 (m, 2H, Ph), 7.95 (d, 1H, J = 6.3 Hz, Ph), 10.06 (s, 1H, COH), 10.88 (s, 1H, NH), 11.10 (s, 1H, NH), 11.74 (s, 1H, NH), 12.66 (bs, 1H, NH); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ: 191.5 (CO), 171.8 (CO), 164.5 (CO), 163.0 (CO), 157.6 (CO), 151.2 (CO), 149.8 (CO), 139.8 (Ph), 134.4 (Ph), 134.2 (Ph), 133.6 (Ph), 131.5 (Ph), 129.4 (Ph), 90.5 (C6), 86.6 ($\mathbf{C}_\alpha$-C4=O), 51.5 (C5).

5-(2-Formylphenyl)-1,1′,3,3′-tetramethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)pentaone (4b)

White solid (90% Yield); mp 388 °C (decomps.); FT-IR (KBr) 3050 (CH-ar.), 2926 (CH-aliph.), 2854 (CH-aliph.), 2738 (CH-aliph.), 1691 (C=O), 1518 (C=C), 1438, 1382 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.64 (s, 3H, N-CH_3), 3.31 (s, 3H, N-CH_3), 3.46 (s, 3H, N-CH_3), 3.50 (s, 3H, N-CH_3), 6.10 (s, 1H, CH-aliph.), 7.39 (d, 1H, J = 7.2 Hz, Ph), 7.60 (m, 2H, Ph), 7.77 (d, 1H, J = 6.9 Hz, Ph), 9.94 (s, 1H, COH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 194.4 (CH=O), 165.6 (CO), 163.4 (CO), 162.6 (CO), 158.6 (CO), 151.2 (CO), 149.8 (CO), 136.0 (Ph), 134.4 (Ph), 134.2 (Ph), 133.6 (Ph), 131.5 (Ph), 129.4 (Ph), 88.6 (C6), 86.8 (**C**$_\alpha$-C4=O), 52.3 (C5), 29.9 (N-CH_3), 29.5 (N-CH_3), 28.2 (N-CH_3), 28.2 (N-CH_3); MS (m/z, %) 426 (M^+, 6), 397 (4), 310 (90), 280 (6), 253 (65), 222 (100, base peak), 197 (30), 183 (50), 156 (15), 138 (16), 111 (10), 83 (18), 69 (80), 58 (60), 53 (28), 43 (28).

2-(1,1′,3,3′-Tetraethyl-4,4′,6′-trioxo-2,2′-dithioxo-2,2′,3,3′,4,4′,5,6′-octahydro-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]-5-yl)benzaldehyde (4c)

White solid (85% Yield); mp 212 °C (decomps.); FT-IR (KBr) 3050 (CH-ar.), 2979 (CH-aliph.), 2930 (CH-aliph.), 2856 (CH-aliph.), 2748 (COH), 1738 (C=O), 1696 (C=O), 1666 (C=C), 1493, 1401, 1111 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.68 (t, 3H, J = 6.9 Hz, N-CH_2**C**$\mathbf{H}_3$), 1.27 (t, 3H, J = 6.9 Hz, N-CH_2**C**$\mathbf{H}_3$), 1.37 (t, 3H, J = 6.9 Hz, N-CH_2**C**$\mathbf{H}_3$), 1.47 (t, 3H, J = 6.9 Hz, N-CH_2**C**$\mathbf{H}_3$), 3.49 (m, 1H, N-**C**$\mathbf{H}_2$$CH_3$), 3.85 (sextet, 1H, J = 6.9 Hz, N-**C**$\mathbf{H}_2$$CH_3$), 4.43-4.67 (m, 6H, 2 N-**C**$\mathbf{H}_2$$CH_3$), 6.34 (s, 1H, CH-aliph.), 7.36 (d, 1H, J = 7.2 Hz, Ph), 7.55-7.64 (m, 2H, Ph), 7.73 (d, 1H, J = 6.6 Hz, Ph), 9.92 (s, 1H, COH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 193.7 (CH=O), 177.2 (CS), 175.8 (CS), 163.8 (CO), 162.0 (CO), 161.6 (CO), 157.0 (CO), 136.2 (Ph), 134.1 (Ph), 133.8 (Ph), 133.6 (Ph), 131.4 (Ph), 129.4 (Ph), 91.5 (C6), 88.5 (**C**$_\alpha$-C4=O), 51.9 (C5), 45.1 (N-**C**$\mathbf{H}_2$$CH_3$), 44.8 (N-**C**$\mathbf{H}_2$$CH_3$), 43.7 (N-**C**$\mathbf{H}_2$$CH_3$), 43.6 (N-**C**$\mathbf{H}_2$$CH_3$), 12.5 (N-$CH_2$**C**$\mathbf{H}_3$), 12.1 (N-$CH_2$**C**$\mathbf{H}_3$), 11.7 (N-$CH_2$**C**$\mathbf{H}_3$), 11.5 (N-$CH_2$**C**$\mathbf{H}_3$).

2-(bis(2,4,6-Trioxohexahydropyrimidin-5-yl)methyl)benzaldehyde (10a)

White solid (75% Yield); mp 260 °C (decomps.); FT-IR (KBr) 3224 (NH), 3100 (CH-ar.), 2990 (CH-aliph.), 1738 (C=O), 1687 (C=O), 1586, 1460, 1377, 1048, 775, 533 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 4.82, 4.98 (2s, 1H), 5.17, 5.32 (2s, 1H), 6.78-7.10 (m, 4H, Ph), 9.17 (s, 1H, COH), 10.54, 10.83 (2 bs, 4H, NH); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ: 191.0 (CHO), 165.1 (CO), 151.5 (CO), 145.2 (Ph), 142.6 (Ph), 127.1 (Ph), 125.6 (Ph), 124.2 (Ph), 122.6 (Ph), 52.8 (CH-aliph.), 48.9 (OC-**C**H-CO).

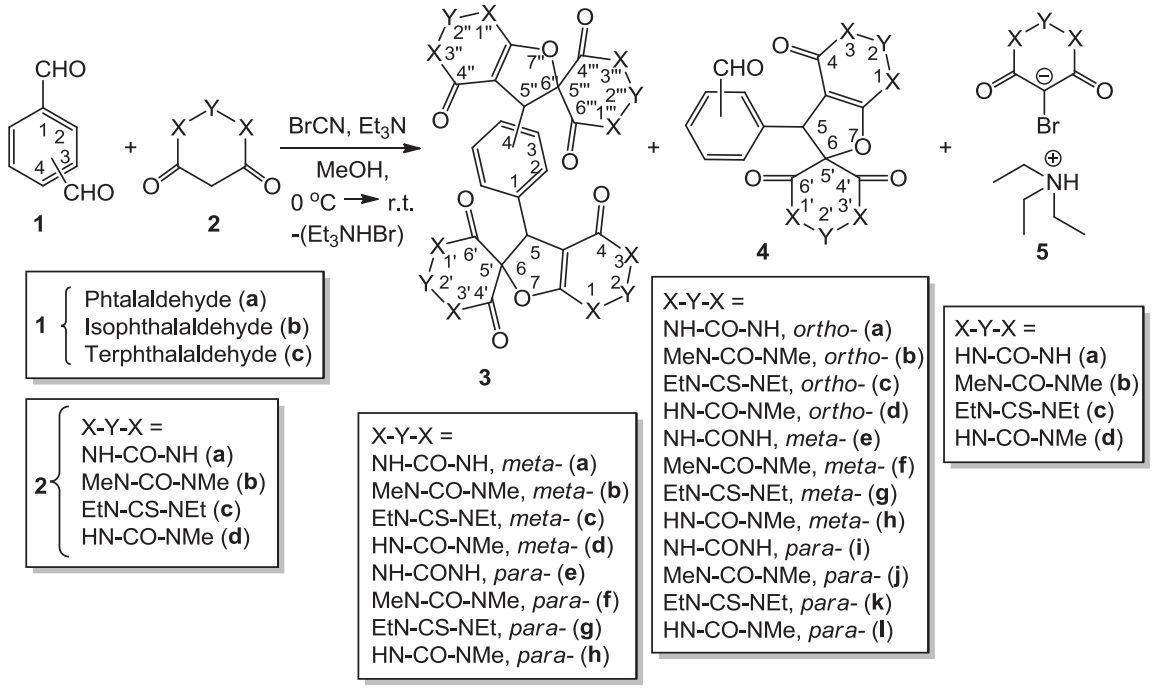
5,5′5″5‴-(1,3-Phenylenebis(methanetriyl))tetrakis(1,3-diethyl-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)one) (11c)

White solid (76% Yield); mp 197–198 °C (decomps.); FT-IR (KBr) 3437 (OH), 3100 (CH-ar.), 2980 (CH-aliph.), 1741 (C=O), 1698 (C=O), 1620, 1437, 1385, 1267, 1111 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, 8 × 3H, J = 6.9 Hz), 4.51 (q, 8 × 2H, J = 6.9 Hz), 5.51 (s, 1H), 5.70 (s, 2H), 6.75 (s, 1H), 7.05 (d, 2H, J = 7.5 Hz), 7.29 (t, 1H, J = 7.8 Hz), 9.0 (bs, 2H), 14.0 (bs, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 174.3 (CS), 163.6

(CO), 162.2 (CO), 136.8 (Ph), 136.0 (Ph), 128.6 (Ph), 125.0 (Ph), 97.3 (HO-C=**C**-C=O), 45.1 (Ph-**CH**-aliph.), 44.4 (N-$\mathbf{CH_2}$CH$_3$), 35.0 (N-$\mathbf{CH_2}$CH$_3$), 12.1 (N-CH$_2$$\mathbf{CH_3}$), 12.0 (N-CH$_2$$\mathbf{CH_3}$).

Results and discussion

This article describes the reaction of aromatic dialdehydes such as isophthalaldehyde (**1b**) and terphthalaldehyde (**1c**) with BAs such as BA (**2a**), DMBA (**2b**), and DETBA (**2c**) as representative symmetric BAs and 1-methyl barbituric acid (1-MBA, **2d**) as an unsymmetric BA in the presence of cyanogen bromide and Et$_3$N affording a new class of stable heterocyclic bis-spiro[furo[2,3-*d*]pyrimidine barbiturate derivatives (**3a**–**3h**) as major products. In contrast, the reaction of phthalaldehyde (**1a**) with **2a**–**d** and cyanogen bromide afforded mono-functionalized spiro[furo[2,3-*d*]pyrimidine barbiturate (**4a**–**d**) that reacted with only one aldehyde group under the same conditions (Scheme 1).



Scheme 1. Reaction of aromatic dialdehydes (**1a**–**c**) with (thio)barbituric acids (**2a**–**d**) and cyanogen bromide in the presence of Et$_3$N in methanol.

More recently, we have reported the reaction mechanism for the formation of stable mono-functionalized heterocyclic 5-alkyl and/or 5-aryl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)pentaones (**8a, 8b**) and their sulfur analogues from the reaction of aldehydes[20,21] and ketones[22] with **2a** and **2b** in the presence of cyanogen bromide and triethylamine (Figure 1). Another mechanism has also been proposed for the formation of triethylammonium-5-bromo-barbiturate salts (**5a** and **5b**).[20–22] These salts play a major role in the synthesis of **3a**–**h** through **4a**–**d** as major products and **4e**–**l** as minor products (Scheme 1).

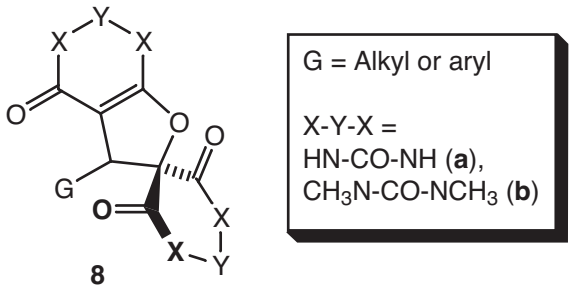
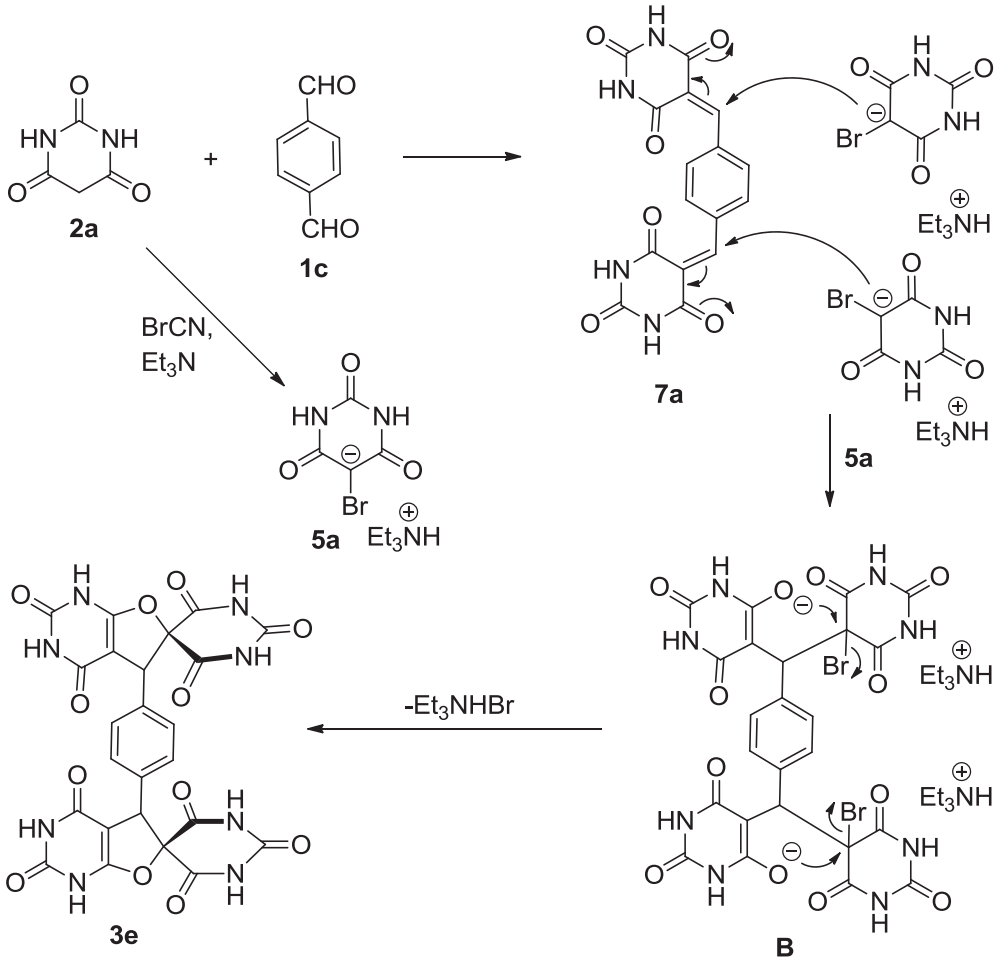


Figure 1. The structures of (**8a, b**)[20–23].

Representatively, the reaction of **2b** with cyanogen bromide and **1a** afforded **4b** in 90% yield in the presence of triethylamine in methanol. Owing to the hindrance effect in **1a**, only one aldehyde functional group reacted with **2b** and cyanogen bromide (Scheme 1). The reaction of **2b** and **1b** with cyanogen bromide afforded **3b** as major product (96%) and **4f** as minor product (4%) (Figures 2a and 3). The reaction of **2b** with **1c** also afforded **3f** as major product (92%) and **4j** as minor product (8%) (Figure 2b). Representatively, a proposed



Scheme 2. Proposed mechanism for the formation of **3e** as representative.

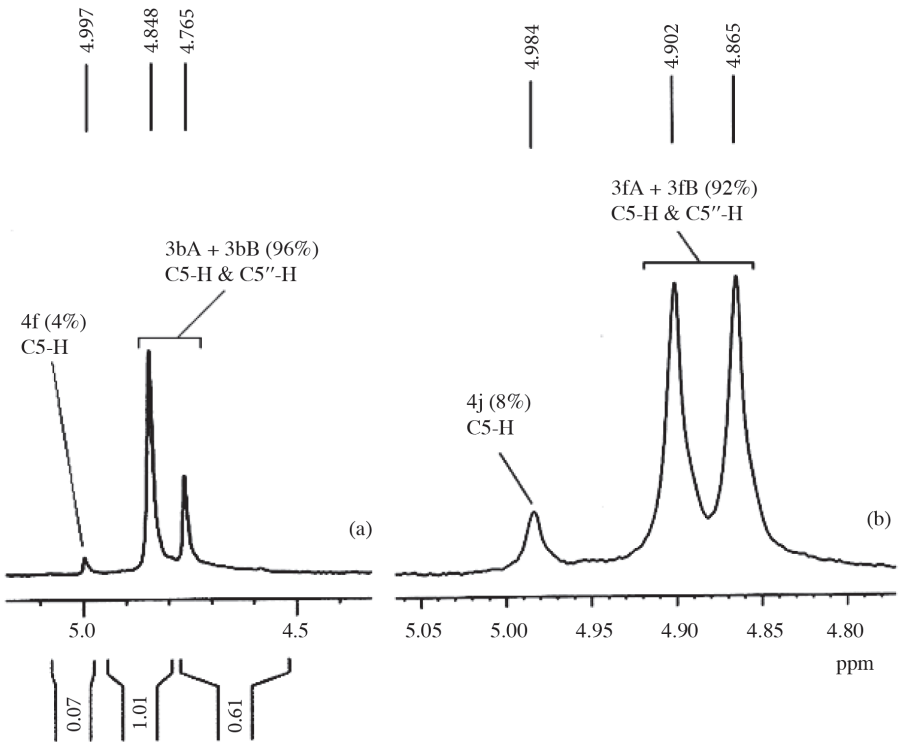


Figure 2. Expanded ^{1}H-NMR spectra and the percentage of each structure in the equilibrium mixture of **3b** and **4f** (a) and mixture of **3f** and **4j** (b).

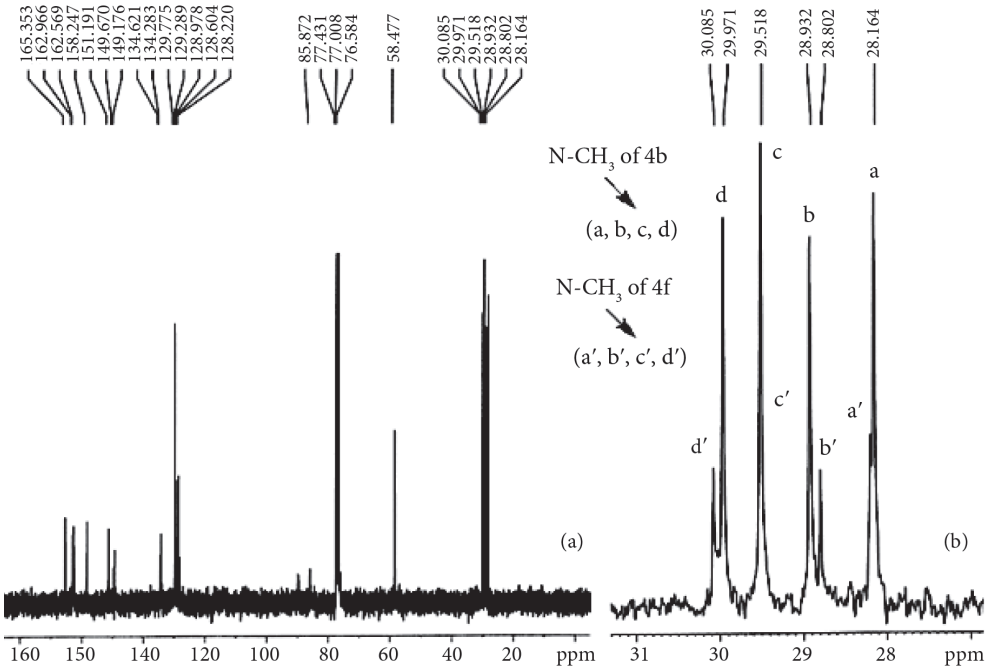
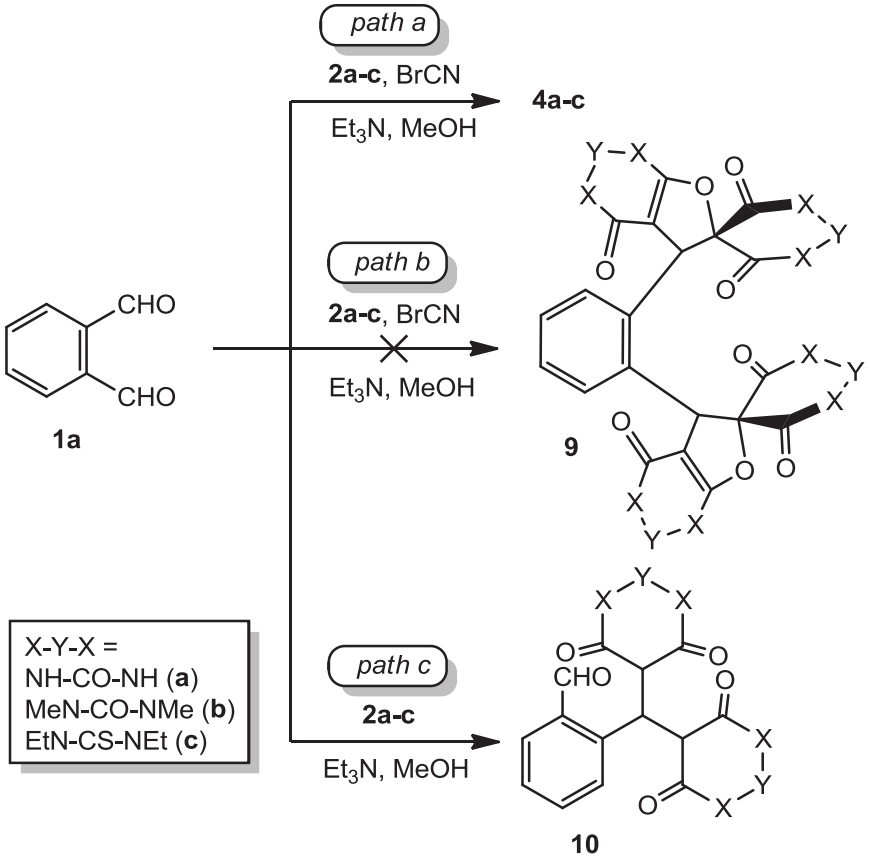


Figure 3. ^{13}C-NMR spectrum of the mixture of **3b** (major) and **4f** (minor) (a) and expanded N-CH_3 aliphatic region (b) in $CDCl_3$.

mechanism for the formation of **3e** is shown in Scheme 2. The IR spectrum of **3e** shows frequencies at 3448 and 3209 cm^{-1} that correspond to NH groups and at 3064 and 2833 cm^{-1} that are of CH frequencies of the aromatic phenyl ring and aliphatic groups. Frequencies at 1719 and 1674 cm^{-1} correspond to carbonyl groups. The ^{1}H-NMR spectrum of this compound shows 3 peaks at δ 4.74, 4.71, and 4.68 ppm related to C_5-H and/or $C_{5''}$-H aliphatic protons. The phenyl protons also show 3 peaks at δ 7.01, 6.99, and 6.95 ppm. There are 4 broadened peaks at δ 12.58, 11.58, 10.77, and 10.57 ppm (see Experimental). These data demonstrate the formation of the mixture of **3e** diastereomers (similar to **3f** in Figure 6).

Bifunctionalized products (**9a–c**) were not observed in the reaction of **1a** and **2a–c** in the presence of BrCN and triethylamine. In this reaction, the compounds **10a–c** were obtained in the absence of BrCN under the same conditions (Scheme 3). In contrast, new compounds **4a–c** were obtained in excellent yields due to the hindrance effect at the *ortho*-position on the phenyl ring (Schemes 1 and 3).

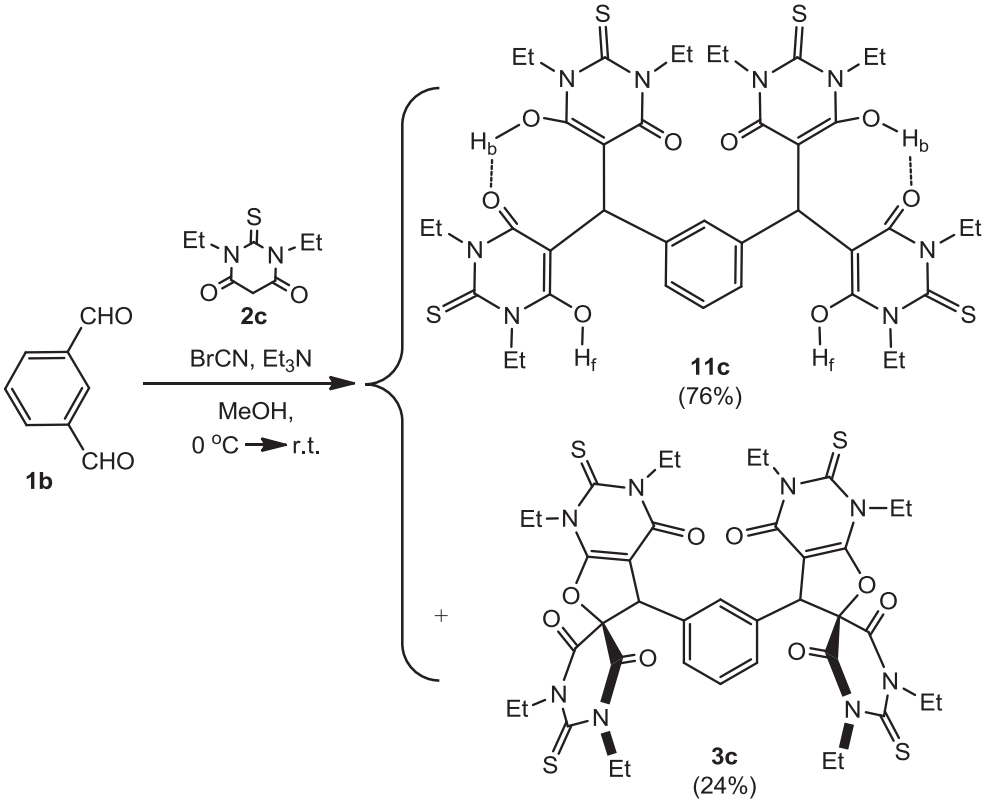


Scheme 3. Reaction between phthalaldehyde (**1a**) and (thio)barbituric acids (**2a–c**) in the presence (path *a*) and in the absence of BrCN (path *c*) in methanol, respectively.

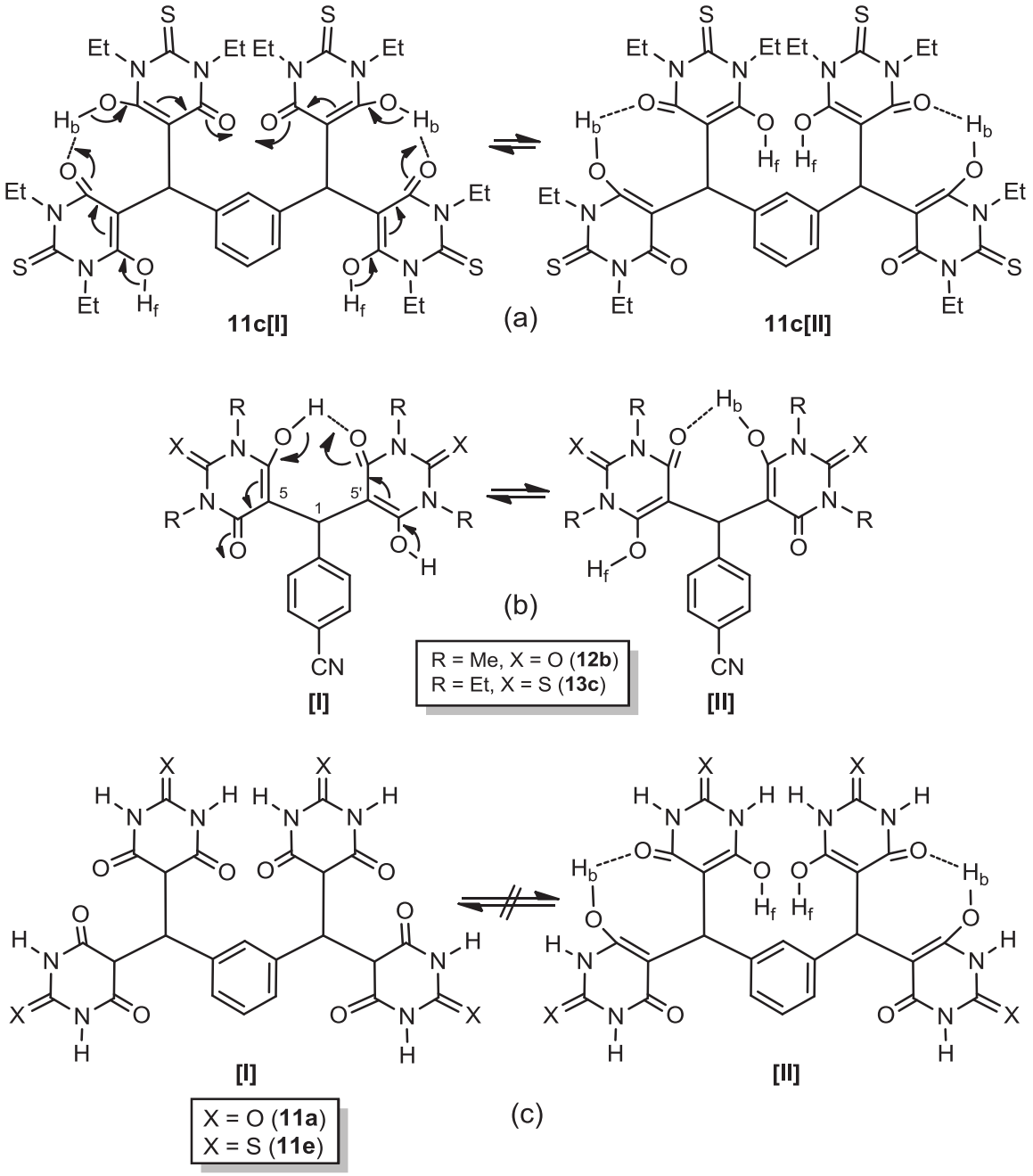
On the other hand, in the reaction of **1b** or **1c** with **2a–d** and BrCN, the compounds **3a–d** and **3e–h** were obtained as major products (more than 85%), while the minor products **4e–h** and **4i–l** were afforded under 15%. These observations about **1b** and **1c** are attributed to the lower hindrance effect between 2 neighboring aldehyde groups on the phenyl ring.

In the reaction of **1b** and **2c**, compound **11c** was afforded as major product (76%) and **3c** as minor product (24%) (Scheme 4). This compound **11c** shows 2 intramolecular H-bonds between the carbonyl group of thiobarbituric acid ring moiety with the hydroxyl group of the enolic form of the other thiobarbituric acid ring moiety (these protons were assigned as H_b) (Schemes 4 and 5a). The formation of **11c** was attributed to the strong nucleophilicity of **2c** rather than **5c**. Therefore, the nucleophilic attack of **2c** is faster than **5c** on the Michael adduct of **7c** and it has a competitive reaction with **5c** for the formation of corresponding compounds (**11c** and **3c**, respectively).

The ^{1}H-NMR spectrum of this compound shows 2 broad singlets at δ 9.0 and 14.0 ppm that correspond to 2 types of exchangeable protons (the exchangeability was examined by adding 2 drops of D_2O). The peak at δ 14.0 ppm corresponds to the 8-membered intramolecular H-bond (H_b and H_f were assigned as intramolecular H-bonded and H-free, respectively, in Schemes 4 and 5). Similarly, 2 mono-functionalized compounds **12b** and **13c** also showed the same structures including an intramolecular H-bond (Scheme 5b). The chemical shifts of the H-bonded and H-free of compounds **11c**, **12b**, and **13c** are summarized in the Table. These types of barbiturates having amidic (-CO-NH-) and/or thioamidic protons (-CS-NH-) do not show 8-membered intramolecular H-bonds, and so only *N*-alkylated barbiturates show this behavior (Scheme 5c). It seems that this phenomenon arose from tautomerization of (thio)barbituric acids (lactam-thiolactam $\rightleftharpoons$ lactim-thiolactim forms) that occurred prior to formation of the intramolecular H-bond. Another compound consisting of 8-membered intramolecular H-bonds has also been reported.[27]



Scheme 4. Reaction of **1b** with **2c** for the formation of the mixture of **3c** and **11c** in the presence of BrCN and Et_3N in methanol.



Scheme 5. Tautomeric forms and intramolecular H-bonding in **11c** (H_b: H-bonding and H_f: H-free).

An interesting situation occurred in the molecules **3a**, **3b** and **3c**, and **3e**–**h**, which have C-H protons on the phenyl ring. For instance, the ^{1}H-NMR spectrum of crude **3b** shows 4 distinct methyl groups at δ 2.72, 3.31, 3.38, and 3.52 ppm. Another 4 methyl peaks were also observed in the ^{1}H-NMR spectrum of **3b** at δ 2.68, 3.32, 3.42, and 3.55 ppm. Two singlets also appeared at δ 4.77 and 4.85 ppm for C_5-H and/or $C_{5''}$-H with integration ratio of 1.01:0.61 in the ^{1}H-NMR spectrum of **3b** assigned as **3bA** and **3bB**, respectively (Figure 2a). These observations indicated that the equilibrium mixture of 2 diastereomers and/or rotamers **3bA** and

3bB existed with the exact ratio of ≈60%:≈36%, (Figure 2a). In contrast, obviously, the ^{1}H- and ^{13}C-NMR spectra of pure **3a** were complicated and showed the equilibrium mixtures of at least 3 distinct diastereomers and/or rotamers (Figures 4 and 5). For example, the expanded ^{1}H-NMR spectrum of **3a** showed 3 singlets at δ 4.64, 4.67, and 4.70 ppm for C_5-H and/or $C_{5''}$-H, respectively. This observation agrees with the existence of more than 13 distinct peaks for **3a** in its ^{13}C-NMR spectrum. Representatively, possible diastereomers and/or rotamers that existed for **3a** are shown in Figure 5.

Table. The chemical shifts of the exchangeable protons of H_b (H-bonded) and H_f (H-free) in compounds **11c**, **12b**, and **13c**.

Compd.	H_b	H_f
11c	14.00	9.00
12b	13.46	10.13
13c	13.90	8.50

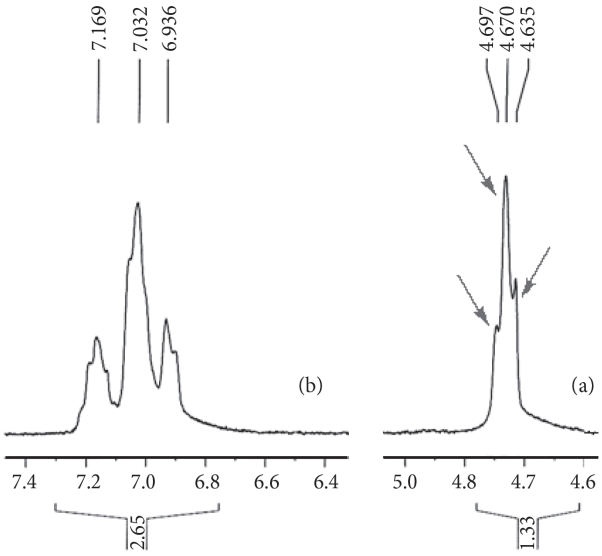


Figure 4. Expanded ^{1}H-NMR spectrum of **3a** at aliphatic (a) and aromatic regions (b) that confirms the mixture of at least 3 diastereomers and/or rotamers in **3a**.

On the other hand, the ^{1}H-NMR spectrum of **3f** shows 2 singlets at δ 7.045 and 7.054 ppm for the phenyl ring protons and 2 singlets at δ 4.87 and 4.90 ppm for C_5-H and $C_{5''}$-H protons, respectively. The H_a, H_b, and H_c protons on the phenyl ring in each diastereomer and/or rotamer have equivalent chemical shift because of a plane of symmetry (σ) (in **3fA** form) and an axis of symmetry (C_2) (in **3fB** form) and also the free rotation about the single bond between C_5-C_1 and $C_{5''}$-C_4 (on phenyl ring) (Figures 2b and 6). The experimental results (^{1}H- and ^{13}C-NMR data) confirm the structures of **3fA** and **3fB** diastereomers and/or rotamers in equilibrium mixture, because 2 singlets were observed in the aromatic region (a singlet for each of

3fA and **3fB** phenyl ring). The ^{1}H-NMR spectrum of **3f** shows 4 methyl groups at δ 2.61, 3.29, 3.41, and 3.52 ppm and also other peaks at δ 2.66, 3.00, 3.41, and 3.52 ppm for methyl groups. Two singlets at δ 4.87 and 4.90 ppm for C_5-H and/or $C_{5''}$-H (with integration ratio of 50%:50%) and at δ 7.045 and 7.054 ppm for C-H on the phenyl ring (46%:46%) corresponded to the mixture of equal amounts of **3fA** and **3fB** forms. According to Figure 6, 2 rotamers **3fA** (R,S or S,R) and **3fB** (R,R or S,S) are diastereomers.

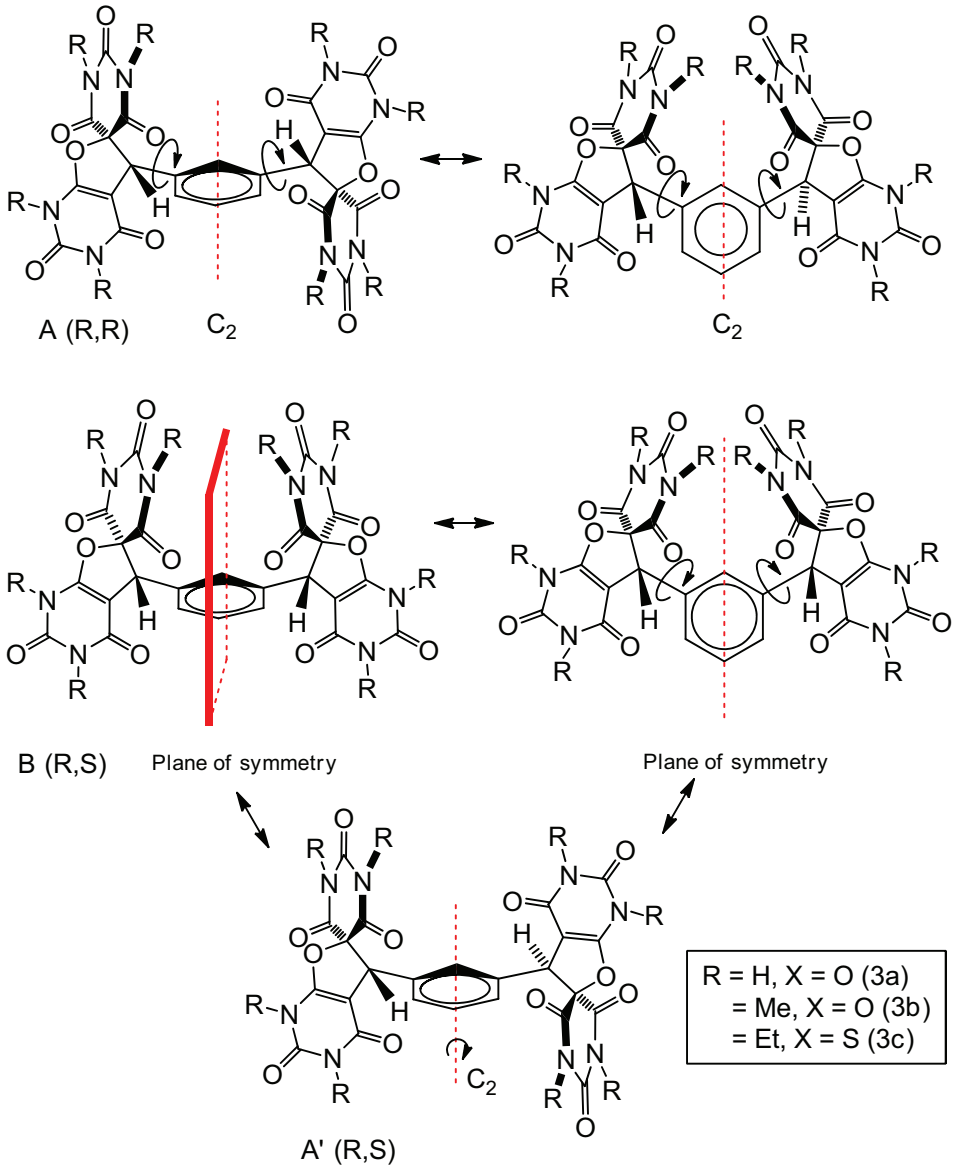


Figure 5. Possible plane of symmetry σ (**B**) and axis of symmetry C_2 (**A** and **A'**) in **3a–c**.

Representatively, the reaction of **1c** with an unsymmetric barbituric acid, **2d**, afforded a diastereomeric mixture of spiro adducts (**3h**) (Figure 7). One of the most interesting situations in these compounds is the

binding of triethylammonium hydrobromide salt to one of the diastereomers among **3h** diastereomers in the ratio of 1:1. First, one can unambiguously think that the salt of triethylammonium hydrobromide is an impurity in the spiro compound. Therefore, it was washed several times with methanol and then with water. The remaining liquid did not show the salt of triethylammonium hydrobromide. These experiments indicated the binding of triethylammonium hydrobromide salt to the molecule (Figure 7).

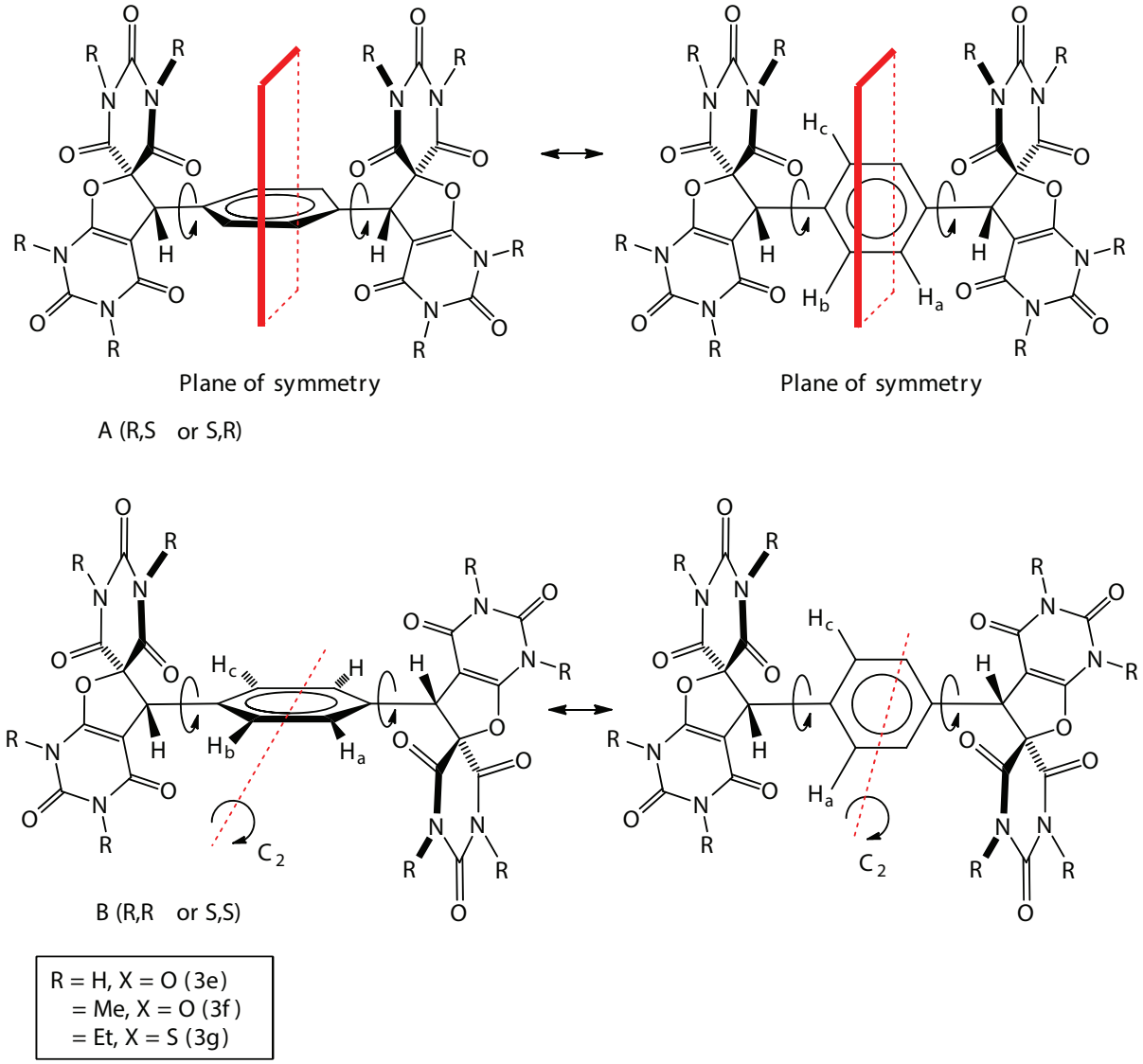


Figure 6. Possible plane of symmetry σ (**A**) and axis of symmetry C_2 (**B**) in **3e–g**.

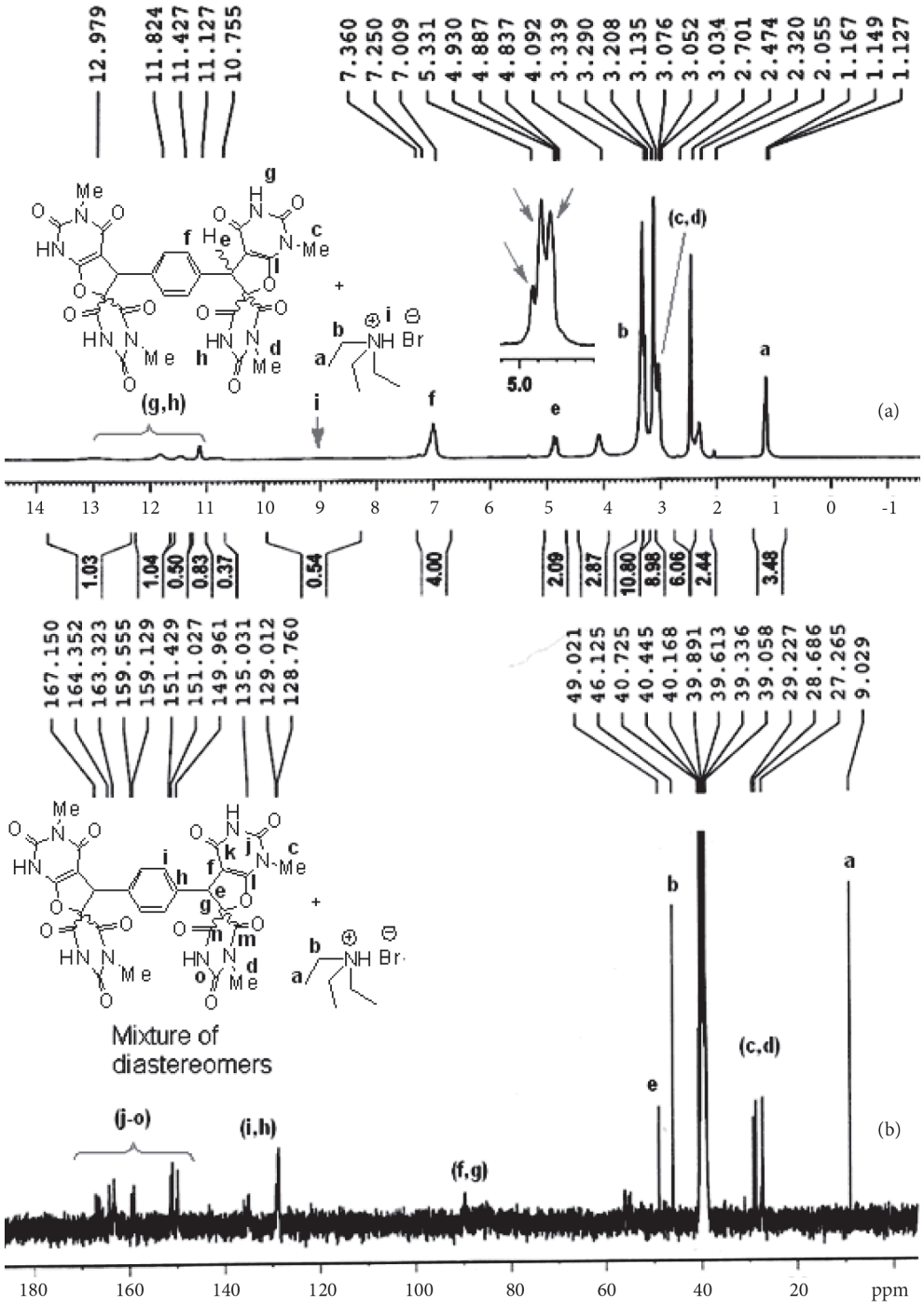


Figure 7. [1]H-NMR (a) and [13]C-NMR spectra of diastereomeric mixture of **3h** (b) and the binding of Et_3NHBr salt (in DMSO-d_6).

Conclusion

In summary, the reaction of symmetrical (thio)barbituric acids (BA, DMBA, TBA, and DETBA) with cyanogen bromide and phthalaldehyde afforded mono-functionalized spiro compound derivatives. This reaction with isophthalaldehyde or terphthalaldehyde afforded bifunctionalized spiro compound derivatives and their sulfur analogues as major products and mono-functionalized spiro compound as minor product. In the reaction of 1,3-diethylthiobarbituric acid with isophthalaldehyde and terphthalaldehyde the Michael product as major and spiro adduct as minor products were obtained. The later Michael product showed an 8-membered intramolecular H-bond.

Supporting information

Full characterization data for compounds **3a**, **3b**, **3c**, **3e**, **3f**, **3h, 4a**, **4b**, **4c**, **5a**, **11c**, and **11g** are available.

Acknowledgements

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