J. Chem. Sci. Vol. 124, No. 3, May 2012, pp. 703–715.

Synthesis and antimicrobial studies of new N,N′-[5,5′-{2,2′-(*bis*-alkoxy) *bis*(2,1-phenylene)]*bis*(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5, 2-diyl)]diacetamide

MOHAMAD YUSUF*, INDU SOLANKI and PAYAL JAIN
Department of Chemistry, Punjabi University, Patiala 147 002, India
e-mail: yusuf_sah04@yahoo.co.in

MS received 23 September 2011; revised 25 November 2011; accepted 14 December 2011

Abstract. The bisthiadiazolines **4a(a′-f′)** and **4b(a′-f′)** built around the various rigid chains have been synthesized in good yields by refluxing bisthiosemicarbazones **3a(a′-f′)** and **3b(a′-f′)** in acetic anhydride medium. The reaction of bisaldehydes **2a(a′-f′)** and **2b(a′-f′)** with thiosemicarbazide under alcoholic medium yielded **3a(a′-f′)** and **3b(a′-f′)** and the former were obtained from the reaction of 2/4-hydroxybenzaldehyde with suitable alkylating agent in the presence of anhydrous K_2CO_3/dry acetone and $Bu_4N^+I^-$ (PTC). The intermediates and final compounds have been characterized from the rigorous analysis of their IR, ^{1}H-NMR, ^{13}C-NMR, ESI-Mass and elemental analysis. The antibacterial and antifungal activities of the prepared compounds were also evaluated against the *Klubsellia pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Bacillius subtilis* and *Aspergillius janus* and *Pencillium glabrum* strains, respectively. The formation and antimicrobial behaviour of the bisthiadiazolines **4a(a′-f′)** and **4b(a′-f′)** are found to be independent of nature of the internal spacer unit.

Keywords. Cyclization; bisaldehydes; bisthiosemicarbazones; bisthiadiazolines and antimicrobial activity.

1. Introduction

The heterocyclic compounds bearing nitrogen and sulphur atoms constitute the core structure of a number of biologically significant derivatives. 1,3,4-Thiadiazolines are the heterocyclic substrates containing three heteroatoms (N, N and S) in a five-membered ring and these compounds have been the subject of major attraction in the past due to their significant biological activities.[1,2] These substrates have also been used in dyes, optically active liquid crystals and photographic materials and many of their derivatives have also been reported as herbicides, insecticides, fungicides, bactericides and anthelmintics.[3,4] These heterocycles are also found to possess antihypertensive,[5] anticonvulsive[6] and many related activities.[7] Thiadiazolines are usually synthesized from the cyclization reaction of thiosemicarbazones and the later derivatives are also associated with variety of biological and industrial applications.[8–20] By keeping this aspect in view and in continuation of our researches on the synthesis of heterocyclic compounds, present investigations have been focused on the synthesis of bisthiadiazolines built around the intermediate chains of rigid geometry. The major interest behind this study was to investigate the effect of the internal unit (olefinic/alkynic/aromatic) upon the formation and the antimicrobial behaviour of the final bisheterocyclic compounds.

2. Experimental

Melting points reported are uncorrected. IR spectra were scanned in KBr pellets on a Perkin Elmer RXIFT Infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a 400 MHz Bruker spectrometer using TMS as the internal standard. The mass spectra have been scanned on the Waters Micromass Q-T of Micro (ESI) spectrometer. TLC plates were coated with silica gel suspended in MeOH-$CHCl_3$ and iodine vapours were used as visualizing agent.

2.1 *Synthesis of 2,2′-[but-2-ene-1,4-diylbis(oxy)] benzaldehyde* **2aa′**

A suspension of 2-hydroxybenzaldehyde (1.22 g, 0.01 mol), *trans*-1,4-dibromo-2-butene (1.06 g, 0.005 mol) and tetrabutylammonium iodide (1.0 g) in

*For correspondence

dry acetone (25 ml) was refluxed for 6 h with continuous stirring. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture turned to a colourless mass which was poured into iced-HCl to obtain a crude product that was crystallized with MeOH to yield a pure bisaldehyde **2aa**′.

2*aa*′: Brown solid, Yield 81%; m.p.: 228–230°C. IR (KBr) cm^{-1} 3091 (aromatic C-H), 2921 (methylene C-H), 2868, 2741 (aldehydic C-H), 1675 (C=O); ^{1}H-NMR ($CDCl_3$): δ 10.48 (2H, s, 1, 1′-C***H***O), 7.75 (2H, d, J_o = 7.6 Hz, H-6, 6′), 7.57 (2H, t, J = 7.3 Hz, H-4, 4′), 7.08 (2H, d, J_o = 8.9 Hz, H-5, 5′), 7.04 (2H, d, J_o = 7.4 Hz, H-3, 3′), 6.20 (2H, brs, $OCH_2C\boldsymbol{H}$=), 4.77 $OC\boldsymbol{H}_2CH$=); ^{13}C-NMR ($CDCl_3$): δ 189.00 (1, 1′-***C***HO), 160.67 (C-2, 1′-***C***HO), 160.67 (C-2, 2′), 135.90 (C-5, 5′), 128.72 (C-1, 1′), 127.87 ($OCH_2\boldsymbol{C}H$=), 125.12 (C-6, 6′), 121.11 (C-4, 4′), 112.77 (C-3, 3′), 68.62 ($O\boldsymbol{C}H_2CH$=), MS(ESI): m/z $(M+Na)^+$ = 319; Anal. Calc. for $C_{18}H_{16}O_4$: Calc. C, 72.97%; H, 5.40%; Found C, 72.90%; H, 5.47%.

2.2 *Synthesis of 2,2′-[but-2-yne-1,4-diylbis(oxy)] benzaldehyde* **2ab**′

The bisaldehyde **2ab**′ was obtained from the reaction of 2-hydroxybenzaldehyde (1.22 g, 0.01 mol) with 1,4-dichloro-2-butyne (0.64 g, 0.005 mol) under the similar conditions as described above for **2aa**′.

2*ab*′: Black solid, Yield 61%; m.p.: 238–240°C. IR (KBr) cm^{-1} 3065 (aromatic C-H), 2940 (methylene C-H), 2860, 2740 (aldehydic C-H), 1670 (C=O); ^{1}H-NMR (DMSO-d_6): δ 10.48 (2H, s, 1, 1′-C***H***O), 7.75 (2H, d, J_o = 7.6 Hz, H-6, 6′), 7.55 (2H, t, J = 7.3 Hz, H-4, 4′), 7.07 (2H, d, J_o = 8.4 Hz, H-5, 5′), 7.04 (2H, d, J_o = 7.4 Hz, H-3, 3′), 5.12 (4H, brs, $OC\boldsymbol{H}_2CH$=); ^{13}C-NMR (DMSO-d_6): δ 190.01 (1, 1′-***C***HO), 160.65 (C-2, 2′), 135.28 (C-5, 5′), 128.24 (C-1, 1′), 125.01 (C-6, 6′), 121.11 (C-4, 4′), 113.12 (C-3, 3′), 82.05 (C-1‴, 2‴), 55.04 ($O\boldsymbol{C}H_2$), 82.05 (C-1‴, 2‴); MS(ESI): m/z $(M+Na)^+$ = 317; Anal. Calc. for $C_{18}H_{14}O_4$: Calc. C, 73.47%; H, 4.76%; Found C, 73.43%; H, 4.72%.

2.3 *Synthesis of 2,2′-[1,2-phenylenebis(methylene)] bis(oxy)dibenzaldehyde* **2ac**′

The bisaldehyde **2ac**′ was synthesized from the reaction of 2-hydroxybenzaldehyde (1.22 g, 0.01 mol) with α, α′-dibromo-*o*-xylene (1.32 g, 0.005 mol) under the similar conditions as described above for **2aa**′.

2*ac*′: Cream solid, Yield 69%; m.p.: 98–100°C. IR (KBr) cm^{-1} 3070 (aromatic C-H), 2934 (methylene C-H), 2849, 2761 (aldehydic C-H), 1684 (C=O); ^{1}H-NMR ($CDCl_3$): δ 10.43 (2H, s, 1, 1′-C***H***O), 7.79 (2H, d, J_o = 7.6 Hz, H-6, 6′), 7.51 (4H, m, H-4, 4′, 5, 5′), 7.32 (2H, m, H-4‴, 5‴), 7.02 (4H, m, H-3, 3′, 3‴, 6‴), 5.28 (4H, s, $OC\boldsymbol{H}_2$); ^{13}C-NMR ($CDCl_3$): δ 189.36 (1, 1′-***C***HO), 160.67 (C-2, 2′), 136.04 (C-5, 5′), 134.26 (C-1‴, 2‴), 129.27 (C-3‴, 6‴), 129.00 (C-4‴, 5‴), 128.96 (C-1, 1′), 125.10 (C-6, 6′), 121.30 (C-4, 4′), 112.79 (C-3, 3′), 68.62 ($O\boldsymbol{C}H_2$); MS(ESI): $(M+1)^+$ = 347; Anal. Calc. for $C_{22}H_{18}O_4$: Calc. C, 76.30%; H, 5.20%; Found C, 76.24%; H, 5.15%.

2.4 *Synthesis of 2,2′-[1,4-phenylenebis(methylene)] bis(oxy)dibenzaldehyde* **2ad**′

The bisaldehyde **2ad**′ was prepared from the reaction of 2-hydroxybenzaldehyde (1.22 g, 0.01 mol) with α,α′-dibromo-*p*-xylene (1.32 g, 0.005 mol) under the similar conditions as described above for **2aa**′.

2*ad*′: Off white solid, Yield 75%; m.p.: 178–180°C. IR (KBr) cm^{-1} 3070 (aromatic C-H str), 2934 (methylene C-H), 2849, 2761 (aldehydic C-H), 1680 (C=O); ^{1}H-NMR ($CDCl_3$): δ 10.52 (2H, s, 1, 1′-C***H***O), 7.80 (2H, d, J_o = 7.4 Hz, H-6, 6′), 7.57 (2H, t, J = 7.3 Hz, H-4, 4′), 7.52 (4H, s, H-2‴, 3‴, 5‴, 6‴), 7.13 (2H, d, 7.13 (2H, d, J = 8.3 Hz, H-5, 5′), 7.06 (2H, t, J_o = 7.3 Hz, H-3, 3′), 5.25 (4H, s, $OC\boldsymbol{H}_2$); ^{13}C-NMR ($CDCl_3$): δ 189.36 (1, 1′-***C***HO), 160.67 (C-2, 2′), 136.04 2′), 136.04 (C-5, 5′), 134.78 (C-1‴, 4‴),129.27 (C-2‴, 3‴, 5‴, 6‴), 128.96 (C-1, 1′), 125.10 (C-6, 6′), 121.30 (C-4, 4′), 112.79 (C-3, 3′), 68.62 ($O\boldsymbol{C}H_2$); MS(ESI): m/z $(M+Na)^+$ = 369; Anal. Calc. for $C_{22}H_{18}O_4$: Calc. C, 76.30%; H, 5.20%; Found C, 76.34%; H, 5.26%.

2.5 *Synthesis of 2,2′-[biphenyl-4,4′-diylbis(methylene)] bis(oxy)benzaldehyde* **2ae**′

The bisaldehyde **2ae**′ was synthesized from the reaction of 2-hydroxybenzaldehyde (1.22 g, 0.01 mol) with 4,4′-bischloromethyl-di-phenyl (1.25 g, 0.005 mol) under the similar conditions as described above for **2aa**′.

2*ae*′: Cream solid, Yield 65%; m.p.: 180–182°C. IR (KBr) cm^{-1} 3071 (aromatic C-H), 2940 (methylene C-H), 2891, 2721 (aldehydic C-H), 1688 (C=O); ^{1}H-NMR ($CDCl_3$): δ 10.61 (2H, s, 1, 1′-C***H***O), 7.90 (2H,

d, J = 6.9 Hz, H-6, 6′), 7.67 (4H, d, J = 8.1 Hz, H-3′′′′, 3′′′′′, 5′′′′, 5′′′′′), 7.58 (2H, td, J = 4.6, 6.7 Hz, H-4, 4′), 7.55 (4H, d, J = 5.2 Hz, H-2′′′′, 2′′′′′′, 6′′′′, 6′′′′′), 7.10 (2H, dd, J = 3.6, 7.5 Hz, H-5, 5′), 7.08 (2H, d, J_o = 8.1 Hz, H-3, 3′), 5.27 (4H, s, OC***H***$_2$); ^{13}C-NMR ($CDCl_3$): δ 188.70 (1, 1′-***C***HO), 160.49 (C-2, 2′), 139.64 (C-4′′′′, 4′′′′′), 135.78 (C-1′′′′, 1′′′′′), 135.70 (C-5, 5′), 127.68 (C-3′′′′, 3′′′′′, 5′′′′, 5′′′′′), 127.73 (C-1, 1′), 124.48 (C-6, 6′), 120.58 (C-4, 4′), 113.22 (C-3, 3′), 69.59 (O***C***H$_2$); MS(ESI): m/z $(M+Na)^+$ = 445; Anal. Calc. for $C_{28}H_{22}O_4$: Calc. C, 79.62%; H, 5.21%; Found C, 79.56%; H, 5.28%.

2.6 *Synthesis of 4,4′-[but-2-ene-1,4-diylbis(oxy)] benzaldehyde* **2ba**′

The bisaldehyde **2ba**′ was obtained from the reaction of 4-hydroxybenzaldehyde (1.22 g, 0.01 mol) with *trans*-1,4-dibromo-2-butene (1.06 g, 0.005 mol) under the similar conditions as described above for **2aa**′.

2ba′: Brown solid, Yield 79%; m.p.: 126–128°C. IR (KBr) cm^{-1} 3071 (aromatic C-H), 2921 (methylene C-H), 2863, 2745 (aldehydic C-H), 1681 (C=O); ^{1}H-NMR($CDCl_3$): δ 9.79 (2H, s, 1, 1′-C***H***O), 7.76 (4H, dt, J = 2.6, 9.5 Hz, H-2, 2′, 6, 6′), 6.99 (4H, d, J_o = 8.7 Hz, H-3, 3′, 5, 5′), 6.05 (2H, t, J_{vic} = 2.4 Hz, OCH$_2$C***H***=), 4.65 (4H, q, J_{vic} = 2.4 Hz, OC***H***$_2$CH=); ^{13}C-NMR ($CDCl_3$): δ 190.79 (1, 1′-***C***HO), 163.36 (C-4, 4′), 132.02 (C-1, 1′), 130.20 (C-2, 2′, 6, 6′), 127.98 (OCH$_2$***C***H=), 114.96 (C-3, 3′, 5, 5′), 67.74 (O***C***H$_2$CH=); MS(ESI): m/z $(M+1)^+$ = 297; Anal. Calc. for $C_{18}H_{16}O_4$: 5.40%; Found C, 72.91%; H, 5.46%.

2.7 *Synthesis of 4,4′-[but-2-yne-1,4-diylbis(oxy)] benzaldehyde* **2bb**′

The bisaldehyde **2bb**′ was synthesized from the reaction of 4-hydroxybenzaldehyde (1.22 g, 0.01 mol) with 1,4-dichloro-2-butyne (0.64 g, 0.005 mol) under the similar conditions as described above for **2aa**′.

2bb′: Dark brown solid, Yield 61%; m.p.: 140–142°C. IR (KBr) cm^{-1} 3070 (aromatic C-H), 2929 (methylene C-H), 2810, 2746 (aldehydic C-H), 1678 (C=O); ^{1}H-NMR(DMSO-d_6): δ 9.88 (2H, s, 1, 1′-C***H***O), 7.82 (4H, dt, J = 2.6, 4.7 Hz, H-2, 2′, 6, 6′), 7.01 (4H, dt, J = 2.6, 4.7 Hz, H-3, 3′, 5, 5′), 4.80 (4H, s, OC***H***$_2$); ^{13}C-NMR (DMSO-d_6): δ 190.07 (1, 1′-***C***HO), 135.67 (C-1, 1′), 128.46 (C-2, 2′, 6, 6′), 114.72 (C-3, 3′, 5, 5′), 82.05 (C-1′′′′, 2′′′′), 55.1 (O***C***H$_2$); MS(ESI): m/z $(M+Na)^+$ = 319; Anal. Calc. for $C_{18}H_{14}O_4$: Calc. C, 73.47%; H, 4.76%; Found C, 73.42%; H, 4.70%.

2.8 *Synthesis of 4,4′-[1,2-phenylenebis(methylene)] bis(oxy)dibenzaldehyde* **2bc**′

The bisaldehyde **2bc**′ was prepared from the reaction of 4-hydroxybenzaldehyde (1.22 g, 0.01 mol) with α, α'-dibromo-*o*-xylene (1.32 g, 0.005 mol) under the similar conditions as described above for **2aa**′.

2bc′: Off white solid, Yield 81%; m.p.: 146–148°C. IR (KBr) cm^{-1} 3071 (aromatic C-H), 2940 (methylene C-H), 2891, 2721 (aldehydic C-H), 1688 (C=O); ^{1}H-NMR ($CDCl_3$): δ 9.78 (2H, s, 1, 1′-C***H***O), 7.74 (4H, d, J_o = 8.6 Hz, H-2, 2′, 6, 6′), 7.47 (2H, dd, J = 3.3, 5.2 Hz, H-4′′′′, 5′′′′), 7.33 (2H, dd, J = 3.6, 5.4 Hz, H-3′′′′, 6′′′′), 7.02 (4H, d, J_o = 8.6 Hz, H-3, 3′, 5, 5′), 5.23 (4H, s, OC (4H, s, OC***H***$_2$); ^{13}C-NMR ($CDCl_3$): δ 190.74 (1, 1′-***C***HO), 163.41 (C-4, 4′), 134.25 (C-1, 1′), 132.06 (C-1′′′′, 2′′′′), 130.35 (C-2, 2′, 6, 6′), 129.37 (C-3′′′′, 6′′′′), 129.02 (C-4′′′′, 5′′′′), 115.03 (C-3, 3′, 5, 5′), 68.34 (O***C***H$_2$); MS(ESI): m/z $(M+Na)^+$ = 369; Anal. Calc. for $C_{22}H_{18}O_4$: Calc. C, 76.30%; H, 5.20%; Found C, 76.35%; H, 5.25%.

2.9 *Synthesis of 4,4′-[1,4-phenylenebis(methylene)] bis(oxy)dibenzaldehyde* **2bd**′

The bisaldehyde **2bd**′ was prepared from the reaction of 4-hydroxybenzaldehyde (1.22 g, 0.01 mol) with α, α'-dibromo-*p*-xylene (1.32 g, 0.005 mol) under the similar conditions as described above for **2aa**′.

2bd′: Cream colour solid, Yield 58%; m.p.:152–154°C. IR (KBr) cm^{-1} 3071 (aromatic C-H), 2940 (methylene C-H), 2891, 2721 (aldehydic C-H), 1688 (C=O); ^{1}H-NMR ($CDCl_3$): δ 9.80 (2H, s, 1, 1′-C***H***O), 7.78 (4H, d, J_o = 8.7 Hz, H-2, 2′, 6, 6′), 7.40 (4H, s, H-2′′′′, 3′′′′, 5′′′′, 6′′′′), 7.01 (4H, d, J_o = 8.7 Hz, H-3, 3′, 5, 5′), 5.25 (4H, s, OC***H***$_2$); ^{13}C-NMR ($CDCl_3$): δ 190.24 (1, 1′-***C***HO), 163.09 (C-4, 4′), 135.78 (C-1, 1′), 131.48 (C-1′′′′, 4′′′′), 129.62 (C-2, 2′, 6, 6′), 127.51 (C-2′′′′, 3′′′′, 5′′′′, 6′′′′), 114.84 (C-3, 3′, 5, 5′), 69.32 (O***C***H$_2$); MS(ESI): m/z $(M+Na)^+$ = 369; Anal. Calc. for $C_{22}H_{18}O_4$: Calc. C, 76.30%; H, 5.20%; Found C, 76.26%; H, 5.16%.

2.10 *Synthesis of 4,4′-[biphenyl-4,4′-diylbis(methylene)] bis(oxy)benzaldehyde* **2be**′

The bisaldehyde **2be**′ was synthesized from the reaction of 4-hydroxybenzaldehyde (1.22 g, 0.01 mol) with 4,4′-bischloromethyl-di-phenyl (1.25 g, 0.005 mol) under the similar conditions as described above for **2aa**′.

2*be*′: Cream solid, Yield 85%; m.p.: 225–227°C. IR (KBr) cm^{-1} 3031 (aromatic C-H), 2933 (methylene C-H), 2874, 2739 (aldehydic C-H), 1691 (C=O); ^{1}H-NMR ($CDCl_3$): δ 9.80 (2H, s, 1, 1′-C***H***O), 7.78 (4H, d, J_o = 7.8 Hz, H-2, 2′, 6, 6′), 7.58 (4H, d, J_o = 8.1 Hz, H-3‴, 3⁗, 5‴, 5⁗), 7.47 (4H, d, J_o = 8.1 Hz, H-2‴, 2⁗, 6‴, 6⁗), 7.07 (4H, d, J_o = 8.2 Hz, H-3, 3′, 5, 5′), 5.17 (4H, s, OC***H***$_2$); ^{13}C-NMR ($CDCl_3$): δ 190.47 (1, 1′-1′-***C***HO), 163.17 (C-4, 4′), 136.05 (C-4‴, 4⁗), 135.78 (C-1, 1′), 131.57 (C-1‴, 1⁗), 129.02 (C-2, 2′, 6, 6′), 126.71 (C-3‴, 3⁗, 5‴, 5⁗), 126.54 (C-2‴, 2⁗, 6‴, 6⁗), 115.00 (C-3, 3′, 5, 5′), 69.02 (O***C***H$_2$); MS(ESI): m/z $(M+1)^+$ = 423; Anal. Calc. for $C_{28}H_{22}O_4$: Calc. C, 79.62%; H, 5.21%; Found C, 79.53%; H, 5.26%.

2.11 *Synthesis of 2,2′-[2,2′-{but-2-ene-1,4-diylbis(oxy)} bis(4,1-phenylene)]bis(methan-1-yl-1-ylidene) bis(hydrazinecarbothioamide)* **3aa**′

A mixture of bisaldehyde **2aa**′ (1.0 g, 0.0034 mol) and thiosemicarbazide (0.61 g, 0.0068 mol) in dry EtOH (20 ml) and HCl (1.0 ml) was refluxed for 4 h. After cooling of the reaction mixture in an ice bath, a solid was separated out. The resulting product was filtered under suction and crystallised from MeOH to yield pure bisthiosemicarbazone **3aa**′.

3*aa*′: Light brown solid, Yield 78%; m.p.: 228–230°C. IR (KBr) cm^{-1} 3402, 3225, 3145 (NH), 3016 (aromatic C-H), 2890 (methylene C-H) 1599 (C=N), 1250, 1089 (C-O), 1160 (C=S); ^{1}H-NMR(DMSO-d_6): δ 11.40 (2H, s, NH-3″, 3‴), 8.52 (2H, s, H-1″, 1‴), 7.90 (2H, d, J_o = 7.8 Hz, H-6, 6′), 7.80 (2H, brs, NH-β, β′), 7.26 (2H, dd, $J_{m,o}$ = 1.5, 7.4 Hz, H-4, 4′), 7.48 (2H, s, NH-α, α′), 6.90 (4H, t, J_o = 8.0 Hz, H-3, 3′, 5, 5′), 6.16 (2H, s, OCH$_2$C***H***=), 4.61 (4H, s, OC***H***$_2$CH=); ^{13}C-NMR (DMSO-d_6): δ 177.80 (C-4″, 4‴), 156.64 (C-2, 2′), 138.18 (C-1″, 1‴), 130.99 (C-4, 4′), 127.11 (OCH$_2$***C***H=), 125.98 (C-6, 6′), 122.43 (C-5, 5′), 120.62 (C-1, 1′), 112.42 (C-3, 3′), 67.56 (O***C***H$_2$CH=); MS(ESI): m/z $(M+Na)^+$ = 465; Anal. Calc. for $C_{20}H_{22}N_6S_2O_2$: Calc. C, 52.30%; H, 4.98%; N, 19.00%, S, 14.48%; Found C, 52.37%; H, 4.90%; N, 19.06%, S, 14.554%.

2.12 *Synthesis of 2,2′-[2,2′-{but-2-yne-1,4-diylbis(oxy)} bis(4,1-phenylene)]bis(methan-1-yl-1-ylidene) bis(hydrazinecarbothioamide)* **3ab**′

The bisthiosemicarbazone **3ab**′ was obtained from the reaction of bisaldehyde **2aa**′ (1.0 g, 0.0034 mol) with thiosemicarbazide (0.61 g, 0.0068 mol) under the similar conditions as described above for **3aa**′.

3*ab*′: Light black solid, Yield 68%; m.p.: 248–250°C. IR (KBr) cm^{-1} 3430, 3220, 3145 (NH), 3017 (aromatic C-H), 2891 (methylene C-H), 1590 (C=N), 1248, 1087 (C-O), 1162 (C=S); ^{1}H-NMR(DMSO-d_6): δ 11.40 (2H, s, NH-3″, 3‴), 8.60 (2H, s, H-1″, 1‴), 7.92 (2H, d, J_o = 7.8 Hz, H-6, 6′), 7.72 (2H, brs, NH-β, β′), 7.24 (2H, dd, $J_{m,o}$ = 1.5, 7.4 Hz, H-4, 4′), 7.46 (2H, s, NH-α, α′), 6.92 (4H, t, J = 8.0 Hz, H-3, 3′, 5, 5′), 5.25 (2H, s, OC***H***$_2$); ^{13}C-NMR (DMSO-d_6): δ 177.84 (C-4″, 4‴), 157.64 (C-2, 2′), 138.30 (C-1″, 1‴), 130.19 (C-4, 4′), 4′), 125.98 (C-6, 6′), 122.43 (C-5, 5′), 120.21 (C-1, 1′), 112.32 (C-3, 3′), 82.50 (C-1⁗, 2⁗), 62.61 (O***C***H$_2$CH=); MS(ESI): m/z $(M+1)^+$ = 441; Anal. Calc. for $C_{20}H_{20}N_6S_2O_2$: Calc. C, 54.54%; H, 4.54%; N, 19.09%, S, 14.54%; Found C, 54.50%; H, 4.49%; N, 19.02%, S, 14.59%.

2.13 *Synthesis of 2,2′-[2,2′-{1,2-phenylenebis (methylene)}bis(oxy)bis(2,1-phenylene)]bis(methan-1-yl-1-ylidene) bis(hydrazinecarbothioamide)* **3ac**′

The bisthiosemicarbazone **3ac**′ was synthesised from the reaction of bisaldehyde **2ac**′ (1.0 g, 0.0029 mol) with thiosemicarbazide (0.52 g, 0.0058 mol) under the similar conditions as described above for **3aa**′.

3*ac*′: Yellow solid, Yield 78%; m.p.: 219–221°C. IR (KBr) cm^{-1} 3363, 3247, 3154 (N-H), 3020 (aromatic C-H), 2865 (methylene C-H), 1597 (C=N), 1254, 1086 (C–O), 1160 (C=S); ^{1}H-NMR (DMSO-d_6): δ 11.46 (2H, s, NH-3″, 3‴), 8.54 (2H, s, H-1″, 1‴), 8.02 (2H, dd, $J_{p,o}$ = 0.9, 7.6 Hz, H-6, 6′), 7.97 (2H, brs, NH-β, β′), 7.65 (2H, brs, NH-α, α′), 7.63 (2H, td, 7.63 (2H, td, J = 3.6, 5.2 Hz, H-3⁗, 6⁗), 7.40 (2H, td, J = 3.3, 5.5 Hz, H-4⁗, 5⁗), 7.30 (2H, td, $J_{m,o}$ = 1.4, 8.5 Hz, H-4, 4′), 7.06 (2H, d, J_o = 8.4 Hz, H-5, 5′), 6.92 (2H, t, J_o = 7.5 Hz, H-3, 3′), 5.27 (4H, s, OC***H***$_2$); ^{13}C-NMR (DMSO-d_6): δ 177.84 (C-4″, 4‴), 159.55 (C-2, 2′), 143.00 (C-1″, 1‴), 132.11 (C-1⁗, 2⁗), 130.96 (C-4, 4′), 127.90 (C-3⁗, 6⁗), 127.41 (C-2⁗, 4⁗), 125.72 (C-6, 6′), 121.20 (C-5, 5′), 116.90 (C-1, 1′), 114.47 (C-3, 3′), 65.20 (O***C***H$_2$); MS(ESI): m/z $(M+Na)^+$ = 515; Anal. Calc. for $C_{20}H_{22}N_6S_2O_2$: Calc. C, 58.54%; H,

4.88%; N, 17.07%, S, 13.00%; Found C, 58.49%; H, 4.94%; N, 17.12%, S, 13.08%.

2.14 *Synthesis of 2,2′-[2,2′-{1,4-phenylenebis (methylene)bis(oxy)bis(2,1-phenylene) bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide)* **3ad′**

The bisthiosemicarbazone **3ad′** was prepared from the reaction of bisaldehyde **2ad′** (1.0 g, 0.0029 mol) with thiosemicarbazide (0.52 g, 0.0058 mol) under the similar conditions as described above for **3aa′**.

3ad′: Yellow solid, Yield 78%; m.p.: 226–228°C. IR (KBr) cm^{-1} 3363, 3247, 3154 (N-H), 3020 (aromatic C-H), 2865 (methylene C-H), 1597 (C=N), 1237, 1107 (C-O), 1160 (C=S); ^{1}H-NMR(DMSO-d_6): δ 11.49 (2H, s, NH- 3″, 3‴), 8.60 (2H, s, H-1″, 1‴), 7.92 (2H, d, J = 7.6 Hz, H-6, 6′), 7.67 (2H, s, NH-β, β'), 7.54 (4H, s, H-2⁗, 3⁗, 5⁗, 6⁗), 7.47 (2H, s, NH-α, α'), 7.35 (2H, t, J_o = 8.1 Hz, H-4, 4′), 7.02 (2H, d, J = 8.3 Hz, H-5, 5′), 6.97 (2H, t, J = 7.5 Hz, H-3, 3′), 5.16 (4H, s, OC***H***$_2$); ^{13}C-NMR (DMSO-d_6): δ 177.82 (C-4″, 4‴), 157.65 (C-2, 2′), 140.65 (C-1″, 1‴), 138.23 (C-1⁗, 4⁗), 130.96 (C-4, 4′), 129.82 (C-6, 6′), 127.40 (C-2⁗, 3⁗, 5⁗, 6⁗), 122.40 (C-5, 5′), 112.73 (C-3, 3′), 69.31 (O***C***H$_2$); MS(ESI): m/z (M+Na)$^+$ = 515; Anal. Calc. for $C_{20}H_{22}N_6S_2O_2$: Calc. C, 58.54%; H, 4.88%; N, 17.07%, S, 13.00%; Found C, 58.59%; H, 4.82%; N, 17.00%, S, 13.10%.

2.15 *Synthesis of 2,2′-[2,2′-{biphenyl-4,4′-diylbbis (methylene)}bis(oxy)bis(4,1-phenylene)bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide)* **3ae′**

The bisthiosemicarbazone **3ae′** was prepared from the reaction of bisaldehyde **2ae′** (1.0 g, 0.0023 mol) with thiosemicarbazide (0.43 g, 0.0047 mol) under the similar conditions as described above for **3aa′**.

3ae′: Yellow solid, Yield 74%; m.p.: 236–238°C. IR (KBr) cm^{-1} 3420, 3291, 3153 (NH), 3060 (aromatic C-H), 2980 (methylene C-H), 1598 (C=N), 1253, 1082 (C-O), 1162 (C=S); ^{1}H-NMR (DMSO-d_6): δ 11.50 (2H, s, NH-3″, 3‴), 8.60 (2H, s, H-1″, 1‴), 8.18 (2H, s, NH-β, β'), 8.08 (2H, dd, J = 1.6, 7.8 Hz, H-6, 6′), 7.78 (2H, s, NH-α, α'), 7.70 (4H, d, J_o = 8.3 Hz, H-3⁗, 3⁗, 5⁗, 5⁗), 7.61 (4H, d, J_o = 8.3 Hz, H-2⁗, 6⁗, 6⁗), 7.36 (2H, td, $J_{m,o}$ = 1.7, 8.6 Hz, H-4, 4′), 7.15 (2H, d, J_o = 8.3 Hz, H-5, 5′), 6.97 (2H, t, J = 7.5 Hz, H-3, 3′), 5.21 (4H, s, OC***H***$_2$); ^{13}C-NMR (DMSO-d_6): 177.82 (C-4″, 4‴), 156.79 (C-2, 2′), 139.42 (C-1″, 1‴), 138.28 (C-4⁗, 4⁗), 135.88 (C-1⁗, 1⁗), 130.96 (C-4, 4′), 127.86 (C-3, 3′), 126.69 (C-6, 6′), 126.73 (C-3⁗, 3⁗, 5⁗, 5⁗), 126.54 (C-2⁗, 2⁗, 6⁗, 6⁗), 122.43 (C-5, 5′) 120.75 (C-1, 1′), 112.73 (C-3, 3′), 69.31 (O***C***H$_2$); MS(ESI): m/z (M+1)$^+$ = 569; Anal. Calc. for $C_{30}H_{28}N_6S_2O_2$: Calc. C, 63.38%; H, 4.93%; N, 14.79%, S, 11.27%; Found C, 63.30%; H, 4.98%; N, 14.84%, S, 11.20%.

2.16 *Synthesis of 2,2′-[4,4′-{but-2-ene-1,4-diylbis (oxy)}bis(4,1-phenylene)]bis(methan-1-yl-1-ylidene) bis(hydrazinecarbothioamide)* **3ba′**

The bisthiosemicarbazone **3ba′** was prepared from the reaction of bisaldehyde **2ba′** (1.0 g, 0.0033 mol) with thiosemicarbazide (0.61 g, 0.0067 mol) under the similar conditions as described above for **3aa′**.

3ba′: Light brown solid, Yield 82%; m.p.: 222–224°C. IR (KBr) cm^{-1} 3342, 3264, 3159 (NH), 3071 (aromatic C-H), 2921, 2863 (methylene C-H), 1602 (C=N), 1246, 1080 (C–O), 1167 (C=S); ^{1}H-NMR (DMSO-d_6): δ 11.26 (2H, s, NH-3″, 3‴), 7.95 (2H, s, H-1″, 1‴), 7.62 (2H, brs, NH-β, β'), 7.56 (4H, d, J_o = 8.6 Hz, H-2, 2′, 6, 6′), 7.47 (4H, s, NH-α, α'), 6.85 (4H, d, J_o = 8.5 Hz, H-3, 3′, 5, 5′), 6.02 (4H, t, OCH$_2$C***H***=), 4.57 (4H, d, OC***H***$_2$CH=); ^{13}C-NMR (DMSO-d_6): δ 177.62 (C-4″, 4‴), 159.47 (C-4, 4′), 142.37 (C-1″, 1‴), 128.54 (C-1, 1′), 127.76 (OCH$_2$***C***H=), 126.69 (C-2, 2′, 6, 6′), 114.52 (C-3, 3′, 5, 5′), 67.15 (O***C***H$_2$CH=); MS(ESI): m/z (M+Na)$^+$ = 465; Anal. Calc. for $C_{20}H_{22}N_6S_2O_2$: Calc. C, 52.30%; H, 4.98%; N, 19.00%, 14.48%; Found C, 52.35%; H, 4.93%; N, 19.06%, 14.40%.

2.17 *Synthesis of 2,2′-[4,4′-{but-2-yne-1,4-diylbis(oxy)} bis(4,1-phenylene)]bis(methan-1-yl-1-ylidene) bis(hydrazinecarbothioamide)* **3bb′**

The bisthiosemicarbazone **3bb′** was prepared from the reaction of bisaldehyde **2bb′** (1.0 g, 0.0032 mol) with thiosemicarbazide (0.61 g, 0.0068 mol) under the similar conditions as described above for **3aa′**.

3bb′: Brown solid, Yield 80%; m.p.: 238–240°C. IR (KBr) cm^{-1} 3499, 3381, 3152 (NH), 1602 (C=N), 1232, 1089 (C-O), 1168 (C=S); ^{1}H-NMR(DMSO-d_6): δ 11.32 (2H, s, 3, 3′-NH), 8.01 (2H, brs, NH-β, β'), 7.96 (2H, s, H-1″, 1‴), 7.66 (4H, d, J = 8.4 Hz, H-2, 2′, 6, 6′), 7.64 (2H, s, NH-α, α'), 6.94 (4H, d, J = 8.8 Hz, H-3, 3′, 5, 5′), 4.82 (4H, s, OC***H***$_2$); ^{13}C-NMR (DMSO-d_6): δ 177.67 (C-4″, 4‴), 158.44 (C-4, 4′), 142.17 (C-1″, 1‴), 128.46 (C-2, 2′, 6, 6′), 127.26 (C-1, 1′), 114.72 (C-3, 3′, 5, 5′), 82.05 (C-1⁗, 2⁗), 55.51 (O***C***H$_2$); MS(ESI): m/z

$(M+Na)^+ = 463$; Anal. Calc. for $C_{20}H_{20}N_6S_2O_2$: Calc. C, 54.54%; H, 4.54%; N, 19.09%, S, 14.54%; Found C, 54.50%; H, 4.48%; N, 19.02%, S, 14.60%.

2.18 *Synthesis of 2,2′-[4,4′-{1,2-phenylenebis (methylene)}bis(oxy)bis(4,1-phenylene)]bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide)* **3bc′**

The bisthiosemicarbazone **3bc′** was obtained from the reaction of bisaldehyde **2bc′** (1.0 g, 0.0029 mol) with thiosemicarbazide (0.52 g, 0.0058 mol) under the similar conditions as described above for **3aa′**.

3bc′: Yellow solid, Yield 79%; m.p.: 219–221°C. IR (KBr) cm^{-1} 3410, 3254, 3150 (NH), 3013 (aromatic C-H), 2915, 2854 (methylene C-H), 1602 (C=N), 1248, 1097 (C-O), 1167 (C=S); ^{1}H-NMR(DMSO-d_6): δ 11.26 (2H, s, NH-3″, 3‴), 7.93 (2H, s, H-1″, 1‴), 7.72 (2H, brs, NH-β, β'), 7.55 (4H, d, J_o = 8.4 Hz, H-2, 2′, 6, 6′), 7.43 (4H, brs, H-3⁗, 4⁗, 5⁗, 6⁗), 7.29 (2H, brs, NH-α, α'), 6.89 (4H, d, J_o = 8.4 Hz, H-3, 3′, 5, 5′), 5.13 (4H, s, OC***H***$_2$); ^{13}C-NMR (DMSO-d_6): δ 177.62 (C-4″, 4‴), 159.47 (C-4, 4′) 142.47 (C-1″, 1‴), 132.04 (C-1⁗, 2⁗), 131.48 (C-1, 1′), 128.54 (C-2, 2′, 6, 6′), 127.76 (C-3⁗, 6⁗), 127.27 (C-4⁗, 5⁗), 114.52 (C-3, 3′, 5, 5′), 67.15 (O***C***H$_2$); MS(ESI): m/z $(M+1)^+$ = 493; Anal. Calc. for $C_{20}H_{22}N_6S_2O_2$: Calc. C, 58.54%; H, 4.88%; N, 17.07%, S, 13.00%; Found C, 58.60%; H, 4.94%; N, 17.12%, S, 13.06%.

2.19 *Synthesis of 2,2′-[4,4′-{1,4-phenylenebis (methylene)bis(oxy)bis(4,1-phenylene) bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide)* **3bd′**

The bisthiosemicarbazone **3bd′** was prepared from the reaction of bisaldehyde **2bd′** (1.0 g, 0.0028 mol) with thiosemicarbazide (0.52 g, 0.0057 mol) under the similar conditions as described above for **3aa′**.

3bd′: Yellow solid, 84%; m.p.: 250–252°C. IR (KBr) cm^{-1} 3346, 3280, 3154 (NH), 3013 (aromatic C-H), 2913, 2855 (methylene C-H), 1602 (C=N), 1235 and 1079 (C-O), 1170 (C=S); ^{1}H-NMR (DMSO-d_6): δ 11.26 (2H, s, NH-3″, 3‴), 7.94 (2H, s, H-1″, 1‴), 7.62 (2H, brs, NH-β, β'), 7.56 (4H, d, J_o = 8.6 Hz, H-2, 2′, 6, 6′), 7.39 (4H, s, H-2⁗, 3⁗, 5⁗, 6⁗), 7.36 (2H, brs, NH-α, α'), 6.90 (4H, d, J_o = 8.4 Hz, H-3, 3′, 5, 5′), 5.12 (4H, s, OC***H***$_2$); ^{13}C-NMR (DMSO-d_6): δ 177.64 (C-4, 4′), 159.63 (C-4″, 4‴), 142.47 (C-1″, 1‴), 131.48 (C-1, 1′), 128.49 (C-1⁗, 4⁗), 127.41 (C-2, 2′, 6, 6′), 126.71 (C-2⁗, 3⁗, 5⁗, 6⁗), 114.64 (C-3, 3′, 5, 5′), 69.08 (O***C***H$_2$); MS(ESI): m/z $(M+Na)^+$ = 515; Anal. Calc. for $C_{20}H_{22}N_6S_2O_2$: Calc. C, 58.54%; H, 4.88%; N, 17.07%, S, 13.00%; Found C, 58.61%; H, 4.82%; N, 17.00%, S, 12.93%.

2.20 *Synthesis of 2,2′-[4,4′-{biphenyl-4,4′-diylbbis (methylene)}bis(oxy)bis(4,1-phenylene)bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide)* **3be′**

The bisthiosemicarbazone **3be′** was prepared from the reaction of bisaldehyde **2be′** (1.0 g, 0.0023 mol) with thiosemicarbazide (0.43 g, 0.0047 mol) under the similar conditions as described above for **3aa′**.

3be′: Yellow solid, Yield 74%; m.p.: 285–287°C. IR (KBr) cm^{-1} 3410, 3250, 3150 (NH), 3061 (aromatic C-H), 2933, 2874 (methylene C-H), 1601 (C=N), 1239 and 1081 (C-O), 1168 (C=S); ^{1}H-NMR(DMSO-d_6): δ 11.30 (2H, s, NH), 8.06 (2H, s, H-1″, 1‴), 7.97 (2H, brs, NH-β, β'), 7.66 (4H, d, J_o = 8.4 Hz, H-2, 2′, 6, 6′), 7.64 (2H, s, NH-α, α'), 7.60 (4H, d, J_o = 8.6 Hz, H-3⁗, 5⁗, 3⁗⁗, 5⁗⁗), 7.48 (4H, d, J_o = 8.0 Hz, H-2⁗, 2⁗⁗, 6⁗, 6⁗⁗), 6.97 (4H, d, J_o = 8.6 Hz, H-3, 3′, 5, 5′), 5.12 (4H, s, ***OCH***$_2$); ^{13}C-NMR (DMSO-d_6): δ 177.62 (C-4″, 4‴), 159.66 (C-4, 4′), 142.19 (C-1″, 1‴), 139.45 (C-4⁗, 4⁗⁗), 135.80 (C-1⁗, 1⁗⁗), 128.68 (C-1, 1′), 127.82 (C-3⁗, 3⁗⁗, 5⁗, 5⁗⁗), 126.89 (C-2⁗, 2⁗⁗, 6⁗, 6⁗⁗), 126.63 (C-2, 2′, 6, 6′), 114.73 (C-3, 3′, 5, 5′), 69.03 (O***C***H$_2$); MS(ESI): m/z $(M+Na)^+$ = 591; Anal. Calc. for $C_{30}H_{28}N_6S_2O_2$: Calc. C, 63.38%; H, 4.93%; N, 14.79%, S, 11.27%; Found C, 63.44%; H, 4.98%; N, 14.72%, S, 11.34%.

2.21 *Synthesis of N,N′-[5,5′-{2,2′-(but-2-ene-1,4-diylbis(oxy))bis(2,1-phenylene)]bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)]diacetamide* **4aa′**

A mixture of bisthiosemicarbazone (1.0 g, 0.0023 mol) and acetic anhydride (30 ml) was refluxed for 10 h. The progress of reaction was monitored by TLC. The resulting reaction mixture was poured over ice to obtain a solid product which was filtered under suction and finally crystallized from EtOH to yield pure bisthiadiazoline **4aa′**.

4aa′: White solid, Yield 80%; m.p.: 170–172°C. IR (KBr) cm^{-1} 3221 (C=C), 3064 (N-H), 2950, 2936 (methylene C-H), 1687, 1639 (C=O), 1603 (C=N), 1238 and 1106 (C-O); ^{1}H-NMR(DMSO-d_6): δ 11.53 (2H, s, N***H***COCH$_3$–5″, 5‴), 8.03 (2H, brs, H-6, 6′), 7.27 (2H, m, H-4, 4′), 7.00 (2H, d, J = 8.1 Hz, H-5, 5′), 6.90 (2H, d, J = 6.8 Hz, H-3, 3′), 6.88 (2H, s,

H-2″, 2‴), 6.15 (2H, brs, OCH_2CH=), 4.72 (4H, brs, OCH_2CH=), 2.26 (6H, s, $COCH_3$–3″, 3‴), 2.02 (6H, s, $NHCOCH_3$–5″, 5‴); ^{13}C-NMR (DMSO-d_6): δ 169.00 ($NHCOCH_3$–5″, 5‴), 167.49 ($COCH_3$–3″, 3‴), 153.71 (C-2, 2′), 147.78 (C-5″, 5‴), 128.95 (C-1, 1′), 128.19 (C-5, 5′), 127.54 (OCH_2CH=), 123.90 (C-6, 6′), 120.36 (C-4, 4′), 111.81 (C-3, 3′), 67.50 (OCH_2CH=), 61.79 (C-2″, 2‴), 22.37 ($NHCOCH_3$–5″, 5‴), 21.68 ($COCH_3$–3″, 3‴); MS(ESI): m/z $(M+Na)^+ = 633$; Anal. Calc. for $C_{28}H_{30}O_6N_6S_2$: Calc. C, 55.08%; H, 4.91%, N, 13.77%; S, 10.49%; Found C, 55.00%; H, 4.96%, N, 13.82%; S, 10.54%.

2.22 *Synthesis of N,N′-[5,5′-{2,2′-(but-2-yne-1,4-diylbis(oxy))bis(2,1-phenylene)]bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)]diacetamide* **4ab′**

The compound **4ab′** was synthesized by refluxing bisthiosemicarbazone **3ab′** (1.0 g, 0.0023 mol) with acetic anhydride (30 ml) under the similar conditions as described above for **4aa′**.

4*ab*′: Brown solid, Yield 60%; m.p.: 230–232°C. IR (KBr) cm^{-1} 3062 (N-H), 2934, 2931 (methylene C–H), 1685, 1632 (C=O), 1604 (C=N), 1238 and 1108 (C-O); ^{1}H-NMR(DMSO-d_6): δ 11.43 (2H, s, $NHCOCH_3$-5″, 5‴), 8.04 (2H, brs, H-6, 6′), 7.25 (2H, m, H-4, 4′), 7.02 (2H, d, $J = 8.1$ Hz, H-5, 5′), 6.92 (2H, d, $J = 6.8$ Hz, H-3, 3′), 6.86 (2H, s, H-2″, 2‴), 5.12 (4H, s, OCH_2), 2.26 (6H, s, $COCH_3$–3″, 3‴), 2.12 (6H, s, $NHCOCH_3$–5″, 5‴); ^{13}C-NMR (DMSO-d_6): δ 169.21 ($NHCOCH_3$–5″, 5‴), 167.44 ($COCH_3$–3″, 3‴), 153.24 (C-2, 2′), 146.78 (C-5″, 5‴), 128.92 (C-1, 1′), 128.02 (C-5, 5′), 123.92 (C-6, 6′), 120.11 (C-4, 4′), 112.11 (C-3, 3′), 81.96 (C-1‴, 2‴), 66.50 (OCH_2), 61.79 (C-2″, 2‴), 22.37 ($NHCOCH_3$–5″, 5‴), 21.73 ($COCH_3$–3″, 3‴); MS(ESI): m/z $(M+Na)^+ = 631$; Anal. Calc. for $C_{28}H_{28}N_6O_6S_2$: C, 55.26%; H, 8.33%; N, 13.81%; S, 10.52%; Found C, 55.22%; H, 8.38%; N, 13.77%; S, 10.48%.

2.23 *Synthesis of N,N′-[5,5′-{2,2′-(1,2-phenylenebis(methylene)}bis(oxy)bis(2,1-phenylene)]bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)]diacetamide* **4ac′**

The compound **4ac′** was synthesized by refluxing bisthiosemicarbazone **3ac′** (1.0 g, 0.0020 mol) with acetic anhydride (30 ml) under the similar conditions as described above for **4aa′**.

4*ac*′: White solid, Yield 70%; m.p.: 120–123°C. IR (KBr) cm^{-1} 3064 (N-H), 2950, 2936 (methylene C-H), 1687, 1639 (C=O), 1603 (C=N), 1238, 1106 (C-O); ^{1}H-NMR (DMSO-d_6): δ 11.50 (2H, s, $NHCOCH_3$- 5″, 5‴), 7.96 (2H, brs, H-6, 6′), 7.62 (2H, m, H-2‴′, 6‴′), 7.36 (2H, m, H-3‴′, 5‴′), 7.30 (2H, d, $J_o = 8.0$ Hz, H-4, 4′), 7.06 (4H, d, $J = 8.0$ Hz, H-3, 3′, 5, 5′), 6.92 (2H, d, $J_o = 4.9$ Hz, H-3‴′, 6‴′), 6.89 (2H, s, H-2″, 2‴), 5.30 (4H, s, OCH_2), 2.28 (6H, s, $COCH_3$–3″, 3‴), 2.06 (6H, s, $NHCOCH_3$–5″, 5‴); ^{13}C-NMR (DMSO-d_6): δ 168.85 (5″, 5‴-$NHCOCH_3$), 168.69 (3″, 3‴-$COCH_3$), 153.71 (C-2, 2′), 148.04 (C-5″, 5‴), 130.95 (C-1‴′, 2‴′), 129.63 (C-1, 1′), 128.52 (C-5, 5′), 127.88 (C-3‴′, 6‴′), 127.56 (C-4‴′, 5‴′), 123.70 (C-6, 6′), 120.42 (C-4, 4′), 112.40 (C-3, 3′), 69.79 (OCH_2), 67.09 (C-2″, 2‴), 22.02 ($NHCOCH_3$–5″, 5‴), 20.78 ($COCH_3$—3″, 3‴); MS(ESI): m/z $(M+1)^+ = 661$; Anal. Calc. for $C_{32}H_{32}O_6N_6S_2$: Calc. C, 58.18%; H, 4.85%, N, 12.73; S, 9.69%; Found C, 58.23%; H, 4.89%, N, 12.76; S, 9.74%.

2.24 *Synthesis of N,N′-[5,5′-{2,2′-(1,4-phenylenebis(methylene)}bis(oxy)bis(2,1-phenylene)]bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)]diacetamide* **4ad′**

The compound **4ad′** was prepared by refluxing bisthiosemicarbazone **3ad′** (1.0 g, 0.0020 mol) with acetic anhydride (30 ml) under the similar conditions as described above for **4aa′**.

4*ad*′: White solid, Yield 80%; m.p.: 118–120°C. IR (KBr) cm^{-1} 3066 (N-H), 2950, 2931 (methylene C-H), 1689 and 1663 (C=O), 1601 (C=N), 1238 and 1010 (C-O); ^{1}H-NMR (DMSO-d_6): δ 11.54 (2H, s, $NHCOCH_3$–5″, 5‴), 7.96 (2H, brs, H-6, 6′), 7.47 (4H, brs, H-2‴′, 3‴′, 5‴′, 6‴′), 7.35 (2H, d, $J_o = 7.96$ Hz, H-4, 4′), 6.94 (4H, t, $J = 7.5$ Hz, H-3, 3′, 5, 5′), 6.90 (2H, s, H-2″, 2‴), 5.21 (4H, s, OCH_2), 2.12 (6H, s, $COCH_3$–3″, 3‴), 2.08 (6H, s, $NHCOCH_3$–5″, 5‴); ^{13}C-NMR (DMSO-d_6): δ 170.92 ($NHCOCH_3$–5″, 5‴), 168.97 ($COCH_3$–3″, 3‴), 154.71 (C-2, 2′), 148.07 (C-5″, 5‴), 130.75 (C-1‴′, 4‴′), 128.95 (C-1, 1′) 128.66 (C-2‴′, 3‴′, 5‴′, 6‴′), 128.19 (C-5, 5′), 123.90 (C-6, 6′), 120.36 (C-4, 4′), 112.34 (C-3, 3′), 68.08 (OCH_2), 67.08 (C-2″, 2‴), 21.96 ($NHCOCH_3$–5″, 5‴), 20.68 ($COCH_3$–3″, 3‴); MS(ESI): m/z $(M+1)^+ = 661$; Anal. Calc. for $C_{32}H_{32}O_6N_6S_2$: Calc. C, 58.18%; H, 4.85%, N, 12.73; S, 9.69%; Found C, 58.23%; H, 4.89%, N, 12.70; S, 9.63%.

2.25 *Synthesis of N,N′-[5,5′-{2,2′-(biphenyl-4,4′-diylbis(methylene)}bis(oxy)bis(2,1-phenylene)]bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)]diacetamide* **4ae′**

The compound **4ae′** was obtained by refluxing bisthiosemicarbazone **3ae′** (1.0 g, 0.0017 mol) with acetic

anhydride (30 ml) under the similar conditions as described above for **4aa′**.

4*ae*′: Light brown solid, Yield 60%; m.p.: 160–162°C. 3066 (N-H), 2950, 2931 (methylene C-H), 1689, 1663 (C=O), 1601 (C=N), 1238, 1010 (C-O); ^{1}H-NMR ($CDCl_3$): δ 11.50 (2H, s, N***H***COCH$_3$–5″, 5‴), 7.96 (2H, d, J = 4.5 Hz, H-6, 6′), 7.68 (2H, d, J = 8.2 Hz, H-3⁗, 3⁗′, 5⁗, 5⁗′), 7.57 (4H, d, J = 8.2 Hz, H-2⁗, 2⁗′, 6⁗, 6⁗′), 7.25 (2H, td, J = 6.4, 8.4 Hz, H-4, 4′), 7.05 (2H, d, J_o = 8.2 Hz, H-3, 3′, 5, 5′), 6.96 (2H, s, H-2″, 2‴), 6.93 (2H, 2⁗, 2⁗′, 4⁗, 4⁗′), 5.23 (OC***H***$_2$), 2.28 (6H, s, COC***H***$_3$–3″, 3‴), 2.06 (6H, s, NHCOC***H***$_3$–5″, 5‴); ^{13}C-NMR (DMSO-d$_6$): δ 169.15 (NH***C***OCH$_3$–5″, 5‴), 167.63 (***C***OCH$_3$–3″, 3‴), 153.74 (C-2, 2′), 147.71 (C-5″, 5‴), 139.51 (C-4⁗, 4⁗′), 135.53 (C-1⁗, 1⁗′), 129.00 (C-1, 1′), 128.24 (C-5, 5′), 127.57 (C-3⁗, 3⁗′, 5⁗, 5⁗′), 126.71 (C-2⁗, 2⁗′, 6⁗, 6⁗′), 123.96 (C-6, 6′), 120.46 (C-4, 4′), 111.83 (C-3, 3′), 69.23 (O***C***H$_2$), 61.68 (C-2″, 2‴), 22.39 (NHCO***C***H$_3$–5″, 5‴), 21.64 (CO***C***H$_3$–3″, 3‴); MS(ESI): m/z (M+Na)$^+$ = 759; Anal. Calc. for $C_{38}H_{36}O_6N_6S_2$: Calc. C, 61.96%; H, 4.89%, N, 11.41%; S, 8.69%; Found C, 61.90%; H, 4.82%, N, 11.35%; S, 8.61%.

2.26 *Synthesis of N,N′-[5,5′-{4,4′-(but-2-ene-1,4-diylbis(oxy))bis(4,1-phenylene)]bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)]diacetamide* **4ba′**

The compound **4ba′** was obtained by refluxing bisthiosemicarbazone **3ba′** (1.0 g, 0.0024 mol) with acetic anhydride (30 ml) under the similar conditions as described above for **4aa′**.

4*ba*′: Cream solid, Yield 70%; m.p.:154–156°C. IR (KBr) cm^{-1} 3067 (NH), 2955, 2903 (methylene C-H), 1695, 1637 (C=O), 1609 (C=N), 1239, 1080 (C-O); ^{1}H-NMR (DMSO-d$_6$): δ 11.45 (2H, s, N***H***COCH$_3$–5″, 5‴), 7.68 (2H, s, H-2″, 2‴), 7.22 (2H, d, J_o = 8.2 Hz, H-2, 2′, 6, 6′), 6.85 (2H, d, J_o = 8.5 Hz, H-3, 3′, 5, 5′), 6.72 (2H, brs, OCH$_2$C***H***=), 4.56 (4H, s, OC***H***$_2$CH=), 2.16 (6H, s, COC***H***$_3$–3″, 3‴), 2.11 (6H, s, NHCOC***H***$_3$–5″, 5‴); ^{13}C-NMR (DMSO-d$_6$): δ 169.02 (5″, 5‴-NH***C***OCH$_3$), 167.18 (***C***OCH$_3$–3″, 3‴), 157.89 (C-4, 4′), 146.06 (C-5″, 5‴), 133.35 (C-1, 1′), 127.92 (C-2, 2′, 6, 6′), 126.62 (OCH$_2$***C***H=), 114.44 (C-3, 3′, 5, 5′), 67.13 (C-2″, 2‴), 65.64 (O***C***H$_2$CH=), 22.44 (NHCO***C***H$_3$–5″, 5‴), 21.85 (CO***C***H$_3$–3″, 3‴); MS(ESI): m/z (M+1)$^+$ = 611; Anal. Calc. for $C_{28}H_{30}O_6N_6S_2$: Calc. C, 55.08%; H, 4.91%, N, 13.77%; S, 10.49%; Found C, 55.00%; H, 4.97%, N, 13.70%; S, 10.55%.

2.27 *Synthesis of N,N′-[5,5′-{4,4′-(but-2-yne-1,4-diylbis(oxy))bis(4,1-phenylene)]bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)]diacetamide* **4bb′**

The compound **4bb′** was obtained by refluxing bisthiosemicarbazone **3bb′** (1.0 g, 0.0024 mol) with acetic anhydride (30 ml) under the similar conditions as described above for **4aa′**.

4*bb*′: Black solid, Yield 60%; m.p.:130–132°C. IR (KBr) cm^{-1} 3060 (NH), 2940, 2915 (methylene C-H), 1673, 1630 (C=O), 1605 (C=N), 1238, 1033 (C-O); ^{1}H-NMR (DMSO-d$_6$): δ 11.35 (2H, s, N***H***COCH$_3$–5″, 5‴), 7.66 (2H, s, H-2″, 2‴), 7.32 (2H, d, J_o = 8.2 Hz, H-2, 2′, 6, 6′), 6.94 (2H, d, J_o = 8.5 Hz, H-3, 3′, 5, 5′), 4.80 (4 H, s, OC***H***$_2$), 2.15 (6H, s, COC***H***$_3$–3″, 3‴), 2.11 (6H, s, NHCOC***H***$_3$–5″, 5‴); ^{13}C-NMR (DMSO-d$_6$): δ 169.02 (NH***C***OCH$_3$–5″, 5‴), 167.18 (***C***OCH$_3$–3″, 3‴), 157.89 (C-4, 4′), 146.06 (C-5″, 5‴), 133.35 (C-1, 1′), 127.92 (C-2, 2′, 6, 6′), 114.44 (C-3, 3′, 5, 5′), 67.13 (C-2″, 2‴), 82.05 (C-1⁗, 2⁗′), 55.51 (O***C***H$_2$), 22.34 (NHCO***C***H$_3$–5″, 5‴), 21.65 (CO***C***H$_3$–3″, 3‴); MS(ESI): m/z (M+Na)$^+$ = 631; Anal. Calc. for $C_{28}H_{28}N_6O_6S_2$: C, 55.26%; H, 8.33%; N, 13.81%; S, 10.52%; Found C, 55.28%; H, 8.35%; N, 13.79%; S, 10.54%.

2.28 *Synthesis of N,N′-[5,5′-{4,4′-(1,2-phenylenebis(methylene)}bis(oxy)bis(4,1-phenylene)]bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)]diacetamide* **4bc′**

The compound **4bc′** was synthesized by refluxing bisthiosemicarbazone **3bc′** (1.0 g, 0.0020 mol) with acetic anhydride (30 ml) under the similar conditions as described above for **4aa′**.

4*bc*′: Off white solid, Yield 52%; m.p.: 198–200°C. IR (KBr) cm^{-1} 3065 (NH), 2950, 2935 (methylene C-H), 1683, 1632 (C=O), 1607 (C=N), 1240, 1033 (C-O); ^{1}H-NMR (DMSO-d$_6$): δ 11.51 (2H, s, N***H***COCH$_3$–5″, 5‴), 7.42 (2H, td, J = 3.2, 5.1 Hz, H-4⁗, 5⁗′), 7.28 (2H, td, J = 3.3, 5.4 Hz, H-3⁗, 6⁗′), 7.13 (4H, d, J_o = 8.5 Hz, 2, 2′, 6, 6′), 6.85 (4H, d, J_o = 8.6 Hz, H-3, 3′, 5, 5′), 6.65 (2H, s, H-2″, 2‴), 5.11 (4H, s, OC***H***$_2$), 2.16 (6H, s, COC***H***$_3$–3″, 3‴), 2.01 (6H, s, NHCOC***H***$_3$–5″, 5‴); ^{13}C-NMR (DMSO-d$_6$): δ 169.04 (NH***C***OCH$_3$–5″, 5‴), 167.26 (***C***OCH$_3$–3″, 3‴), 157.96 (C-4, 4′), 146.09 (C-5″, 5‴), 134.70 (C-1⁗, 2⁗′), 133.48 (C-1, 1′), 127.48 (C-2, 2′, 6, 6′), 128.40 (C-3⁗, 6⁗′), 126.66 (C-4⁗, 5⁗′), 114.56 (C-3, 3′, 5, 5′), 67.26 (C-2″, 2‴), 65.68 (O***C***H$_2$), 22.43 (NHCO***C***H$_3$–5″, 5‴), 21.85 (CO***C***H$_3$–3″, 3‴); MS(ESI): m/z (M+Na)$^+$ = 683; Anal. Calc.

for $C_{32}H_{32}O_6N_6S_2$: Calc. C, 58.18%; H, 4.85%, N, 12.73; S, 9.69%; Found C, 58.12%; H, 4.80%, N, 12.78; S, 9.73%.

2.29 *Synthesis of N,N′-[5,5′-{4,4′-(1,4-phenylenebis (methylene)}bis(oxy)bis(4,1-phenylene)]bis(4-acetyl-4, 5-dihydro-1,3,4-thiadiazole-5,2-diyl)]diacetamide* **4bd′**

The compound **4bd′** was prepared by refluxing bisthiosemicarbazone **3bd′** (1.0 g, 0.0020 mol) with acetic anhydride (30 ml) under the similar conditions as described above for **4aa′**.

4*bd′*: Cream solid, Yield 58%; m.p.: 142–144°C. IR (KBr) cm^{-1} 3064 (NH), 2930 (methylene C-H), 1683 (C=O), 1608 (C=N), 1240, 1010 (C-O); ^{1}H-NMR (DMSO-d_6): δ 11.37 (2H, s, N***H***COCH$_3$–5″, 5‴), 7.60 (2H, s, H-2″, 2‴), 7.34 (4H, s, H-2⁗, 3⁗, 5⁗, 6⁗), 7.14 (4H, d, J_o = 8.2 Hz, H-2, 2′, 6, 6′), 6.83 (4H, d, J_o = 8.2 Hz, H-3, 3′, 5, 5′), 4.95 (4H, s, OC***H***$_2$), 2.19 (6H, s, COC***H***$_3$–3″, 3‴), 2.11 (6H, s, NHCOCH$_3$–5″, 5‴); ^{13}C-NMR (DMSO-d_6): δ 169.04 (NH***C***OCH$_3$–5″, 5‴), 167.36 (***C***OCH$_3$–3′, 3‴), 158.04 (C-4, 4′), 146.15 (C-5″, 5‴), 134.70 (C-1⁗, 4⁗), 133.02 (C-1, 1′), 127.27 (C-2, 2′, 6, 6′), 126.67 (C-2⁗, 3⁗, 5⁗, 6⁗), 114.48 (C-3, 3′, 5, 5′), 69.04 (C-2″, 2‴), 65.74 (O***C***H$_2$), 22.40 (NHCO***C***H$_3$–5″, 5‴), 21.82 (CO***C***H$_3$–3″, 3‴); MS(ESI): m/z $(M+1)^+$ = 661; Anal. Calc. for $C_{32}H_{32}O_6N_6S_2$: Calc. C, 58.18%; H, 4.85%, N, 12.73; S, 9.69%; Found C, 58.23%; H, 4.80%, N, 12.78; S, 9.63%.

2.30 *Synthesis of N,N′-[5,5′-{4,4′-(biphenyl-4,4′-diylbis (methylene)}bis(oxy)bis(4,1-phenylene)]bis(4-acetyl-4, 5-dihydro-1,3,4-thiadiazole-5,2-diyl)]diacetamide* **4be′**

The compound **4be′** was synthesized by refluxing bisthiosemicarbazone **3be′** (1.0 g, 0.0017 mol) with acetic anhydride (30 ml) under the similar conditions as described above for **4aa′**:

4*be′*: Off white solid, Yield 63%; m.p.: 158–162°C. IR (KBr) cm^{-1} 3065 (NH), 2943, 2903 (methylene C-H), 1693, 1636 (C=O), 1608 (C=N), 1241, 1036 (C-O); ^{1}H-NMR (DMSO-d_6): δ 11.54 (2H, s, N***H***COCH$_3$–5″, 5‴), 7.56 (4H, d, J_o = 8.1 Hz, H-3⁗, 3⁗, 5⁗, 5⁗⁗), 7.44 (4H, d, J_o = 8.0 Hz, H-2⁗, 2⁗, 6⁗, 6⁗⁗), 7.15 (4H, d, J_o = 8.4 Hz, H-2, 2′, 6, 6′), 6.88 (4H, d, J_o = 8.4 Hz, H-3, 3′, 5, 5′), 6.65 (2H, s, H-2″, 2‴), 5.04 (4H, s, OC***H***$_2$), 2.16 (6H, s, COC***H***$_3$- 3″, 3‴), 2.02 (6H, s, NHCOC***H***$_3$–5″, 5‴); ^{13}C-NMR (DMSO-d_6): δ 169.04 (NH***C***OCH$_3$–5″, 5‴), 167.35 (***C***OCH$_3$–3″, 3‴), 158.12 (C-4, 4′), 146.14 (C-5″, 5‴), 135.70 (C-1, 1′), 133.22 (C-4⁗, 4⁗⁗), 128.11 (C-1⁗, 1⁗⁗), 127.79 (C-2, 2′, 6, 6′), 126.73 (C-3⁗, 3⁗⁗, 5⁗, 5⁗⁗), 126.63 (C-2⁗, 2⁗⁗, 6⁗, 6⁗⁗), 114.51 (C-3, 3′, 5, 5′), 69.04 (C-2″, 2‴), 65.75 (O***C***H$_2$), 22.41 (NHCO***C***H$_3$–5″, 5‴), 21.83 (CO***C***H$_3$–3″, 3‴); MS(ESI): m/z $(M+Na)^+$ = 759; Anal. Calc. for $C_{38}H_{36}O_6N_6S_2$: Calc. C, 61.96%; H, 4.89%; N, 11.41%; S, 8.69%; Found C, 61.90%; H, 4.83%, N, 11.36%; S, 8.62%.

3. Results and discussion

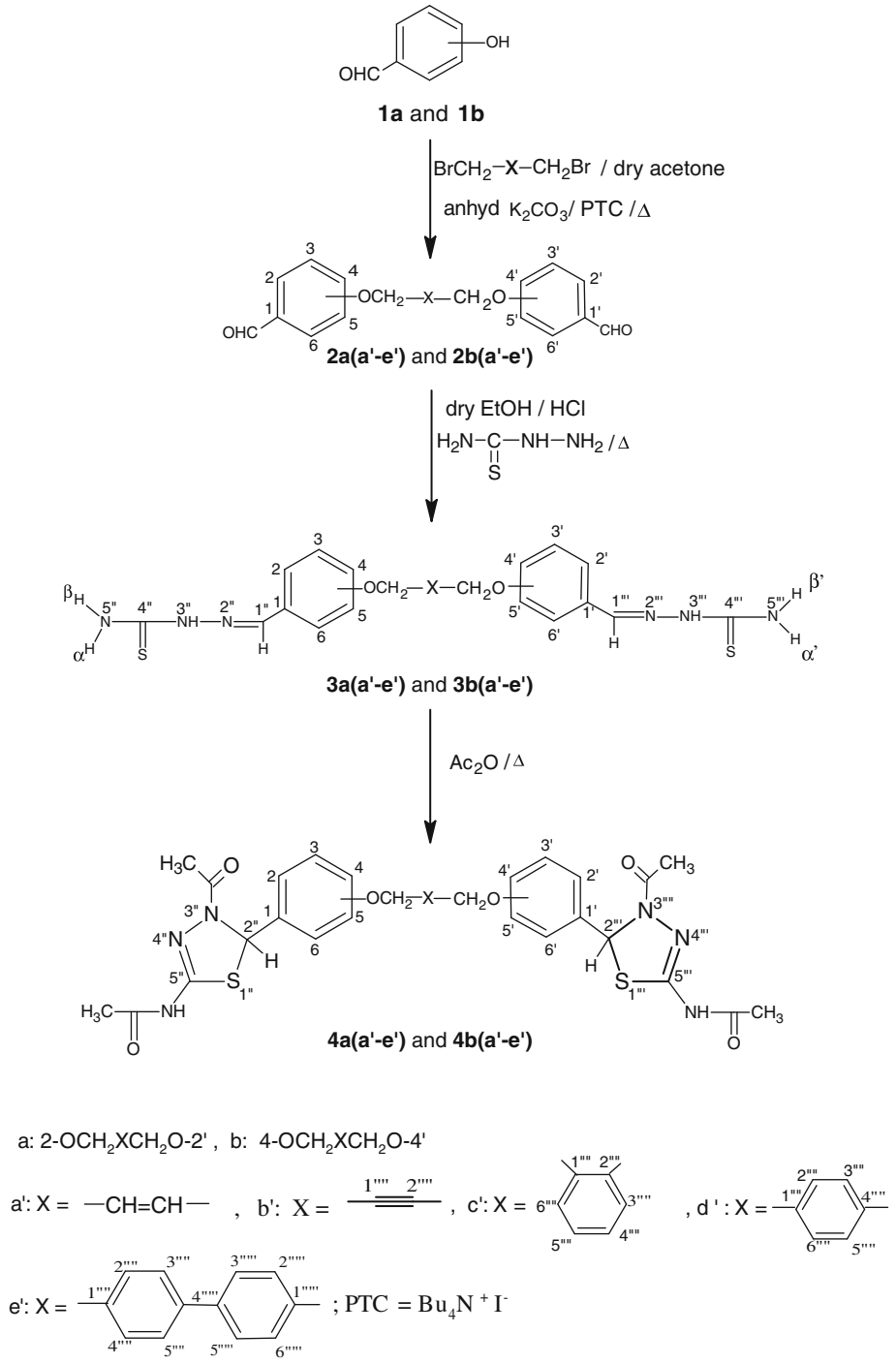
3.1 *Chemistry*

The *bis*(1,3,4-thiadiazolines) **4a(a′-e′)** and **4b(a′-e′)** required for this study were prepared starting from the 2/4-hydroxybenzaldehyde which was reacted with suitable alkylating agent (*trans*-1,4-dibromo-2-butene, 1,4-dichloro-2-butyne, α,α'-dibromo-*o*-xylene, α,α'-dibromo-*p*-xylene and 4,4′-bischloromethyl-diphenyl) in the presence of anhydrous K_2CO_3/dry acetone and $Bu_4N^+I^-$ (PTC) to obtain bisaldehydes **2a(a′-e)** and **2b(a′-e′)**, respectively. The bisaldehydes were reacted with thiosemicarbazide in the presence of dry EtOH under refluxing condition to yield *bis*-thiosemicarbazones **3a(a′-e′)** and **3b(a′-e′)** which were further refluxed under acetic anhydride medium[21–24] to yield the final products **4a(a′-e′)** and **4b(a′-e′)** (scheme 1).

The structures of compounds **2a(a′-e′)**, **2b(a′-e′)**, **3a(a′-e′)**, **3b(a′-e′)**, **4a(a′-e′)** and **4b(a′-e′)** were determined from the analysis of their spectroscopic data (IR, ^{1}H and ^{13}C-NMR and ESI-Mass) and elemental analysis.

The IR spectra of **2a(a′-e′)** and **2b(a′-e′)** exhibited the carbonyl group absorptions at 1688–1675 cm^{-1} and 1691–1678 cm^{-1}, respectively. In their ^{1}H-NMR spectra, signal corresponding to C***H***O group appeared at δ 10.61–10.43 and 9.88–9.78 as sharp singlet and the aromatic ring protons (H-2,2′,3,3′,5,5′,6,6′) were centred at δ 7.90–7.02 and 7.82–6.99 as suitable signals (see experimental). ^{13}C-NMR spectra revealed the most downfield signal at δ 190–188 (C=O) and 191–190 (C=O) and the resonances belonging to the aromatic ring were suitably placed at δ 161–112 and 164–114, respectively (see experimental).

The IR spectra of **3a(a′-e′)** and **3b(a′-e′)** also exhibited the NH stretching at 3360–3145 cm^{-1} and did not reveal any absorption in the carbonyl group region which describes the transformation of C=O group during the reaction. The significant feature of their ^{1}H-NMR spectra was the appearance of sharp singlet at δ 8.60–8.52 and 8.06–7.93 which could be very well ascribed to azomethyne proton (H-1″ and H-1‴) and the



Scheme 1. N,N′-[5,5′-{2,2′-(bis-alkoxy)bis(2,1-phenylene)]bis(4-acetyl-4, 5-dihydro-1,3,4-thiadiazole-5,2-diyl)]diacetamides **4a(a′-e′)** and **4b(a′-e′)**.

four doublets in the aromatic region at δ 8.08–6.90 integrating for four hydrogens each could be denoted by H-3,3′,4,4′,5,5′,6,6′ and the doublets in the range of δ 7.66–7.55 and 6.97–6.85 were assignable to H-2,2′,6,6′ and H-3,3′,5,5′, respectively. 5″,5‴-NH_2 and 3″,3‴-NH protons appeared as two broad singlets at δ 8.18–7.47 and 8.01–7.29 and sharp singlet at δ 11.50–11.40 and 11.32–11.26, respectively and these hydrogens were also exchangeable with D_2O. In the ^{13}C-NMR spectra of **3a(a′-e′)** and **3b(a′-e′)**, C-4″, 4‴ and C-1″, 1‴ were found placed at δ 178–177 and 143–138, respectively and the resonances present at δ 159–156 and 159–158 and 129–125 and 128–126 may be furnished by the aromatic carbons C-2, 2′ and C-6, 6′, respectively.

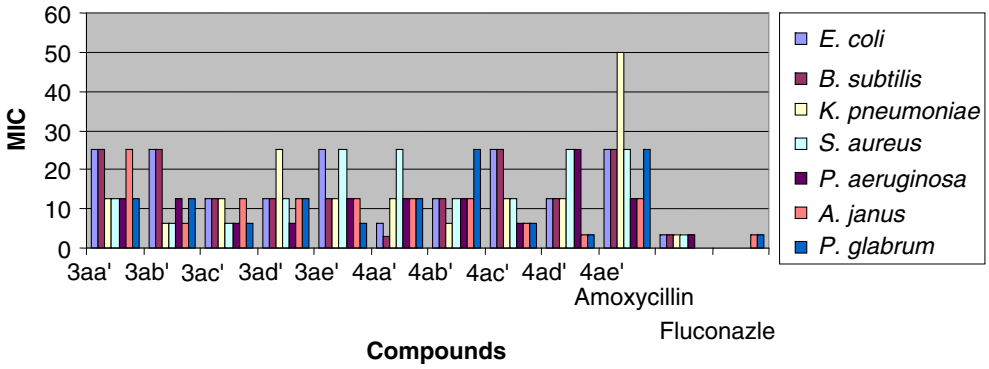


Figure 1. *In vitro* MIC (μg/mL) of compounds **3aa′**-**3ae′** and **4aa′**-**4ae′**.

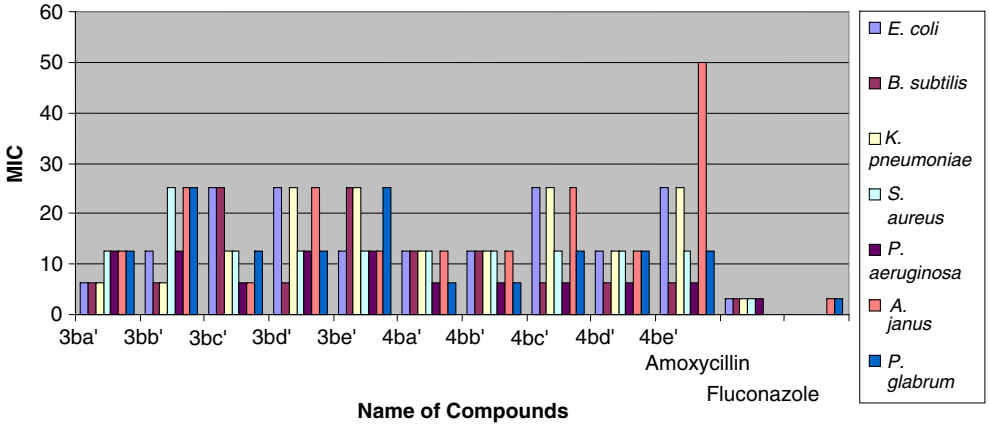


Figure 2. *In vitro* MIC (μg/mL) for compounds **3ba′**-**3be′** and **4ba′**-**4be′**.

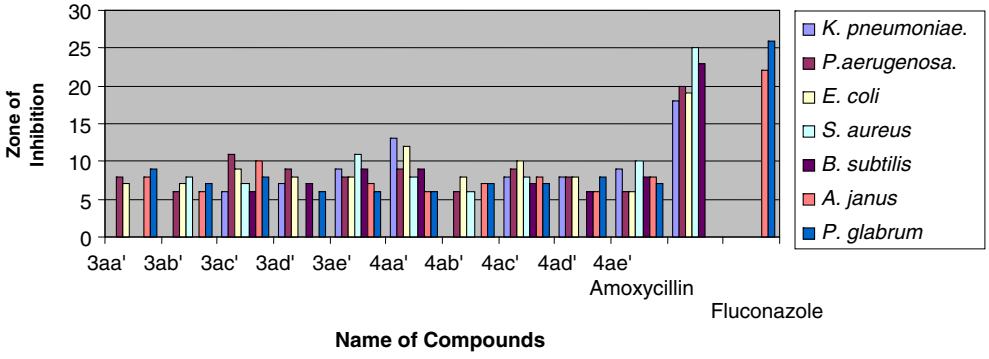


Figure 3. *In vitro* zone of inhibition (*mm*) of compounds **3aa′**-**3ae′** and **4aa′**-**4ae′**.

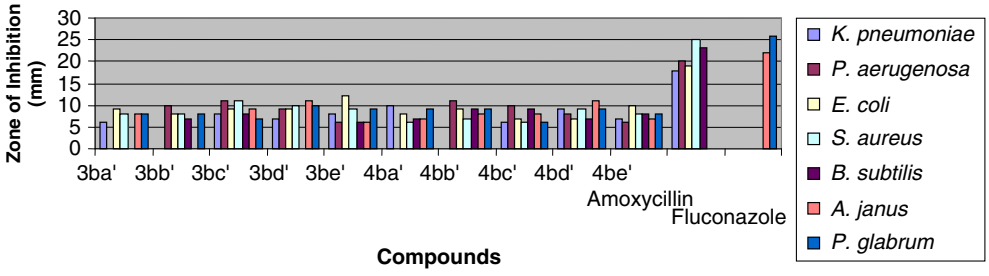


Figure 4. *In vitro* zone of inhibition (*mm*) of compounds **3ba′**-**3be′** and **4ba′**-**4be′**.

Table 1. MIC (μg/mL)of compounds **3aa′**-**3ae′** and **4aa′**-**4ae′**.

Compound no.	Gram-negative bacteria			Gram-positive bacteria		Fungi	
	Klubsellia pneumoniae	*Pseudomonas aeruginosa*	*Escherichia coli*	*Staphylococcus aureus*	*Bacillius subtilis*	*Aspergillus janus*	*Pencilluim glabrum*
3aa′	12.5	12.5	25	12.5	25	25	12.5
3ab′	6.25	12.5	25	6.25	25	6.25	12.5
3ac′	12.5	6.25	12.5	6.25	12.5	12.5	6.25
3ad′	25	6.25	12.5	12.5	12.5	12.5	12.5
3ae′	12.5	12.5	25	25	12.5	12.5	6.25
4aa′	12.5	12.5	6.25	25	3.12	12.5	12.5
4ab′	6.25	12.5	12.5	12.5	12.5	12.5	25
4ac′	12.5	6.25	25	12.5	25	6.25	6.25
4ad′	12.5	25	12.5	25	12.5	6.25	6.25
4ae′	50	25	25	25	25	12.5	25
Amoxicillin	3.12	3.12	3.12	3.12	3.12	–	–
Fluconazole	–	–	–	–	–	3.12	3.12

IR spectra of bisthiadiazolines **4a(a′-e′)** and **4b(a′-e′)** displayed major absorptions at 3066–3062, 1689–1632 and 1604–1601 cm^{-1} which could be ascribed to NH, C=O and C=N stretchings, respectively. ^{1}H-NMR (400 MHz, DMSO) spectra of these compounds had D_2O exchangeable singlet at δ 11.54–11.43 and 11.51–11.31 which may be represented by N***H***$COCH_3$–5″, 5‴ protons. The thiadiazoline ring hydrogen (H-2″, 2‴) produced singlet at δ 7.68–6.65 and the downfield resonance of this hydrogen could be ascribed to its benzylic nature and its placement between two heteroatoms (N and S). The signals present at δ 2.28–2.12 (s) and 2.11–2.02 (s) could be very well given by COC***H***$_3$–3″, 3‴ and NHCOC***H***$_3$–5″, 5‴ methyl groups, respectively and these groups have also been confirmed by the two resonances at δ 22–20 in their ^{13}C-NMR spectra. The presence of two carbonyl groups in **4a(a′-e′)** and **4b(a′-e′)** was confirmed by the availability of two resonances at δ 170–168 and 169–167 and the signals resonating at δ 154–153 and 158–157 could be allotted to C-2, 2′ and C-4, 4′, respectively. The C=N (5″, 5‴) moiety of the thiadiazoline ring resulted suitable signals at δ 148–146 and 147–146 in **4a(a′-e′)** and **4b(a′-e′)**, respectively.

3.2 *Antimicrobial activity*

The antimicrobial activity of synthesized compounds was screened *in vitro* by disc diffusion method[25] against selected pathogens which include *Staphylococcous aureus, Bacillius subtilis, Escherichia coli, Pseudomonas glabrum* and *Klubsellia pneumoniae* and fungus strains

Table 2. MIC (μg/mL) of compounds **3ba′**-**3be′** and **4ba′**-**4be′**.

Compound no.	Gram-negative bacteria			Gram-positive bacteria		Fungi	
	Klubsellia pneumoniae	*Pseudomonas aeruginosa*	*Escherichia coli*	*Staphylococcus aureus*	*Bacillius subtilis*	*Aspergillus janus*	*Pencilluim glabrum*
3ba′	6.25	12.5	6.25	12.5	6.25	12.5	12.5
3bb′	6.25	12.5	12.5	25	6.25	25	25
3bc′	12.5	6.25	25	12.5	25	6.25	12.5
3bd′	25	12.5	25	12.5	6.25	25	12.5
3be′	25	12.5	12.5	12.5	25	12.5	12.5
4ba′	12.5	6.25	12.5	12.5	12.5	12.5	6.25
4bb′	12.5	6.25	12.5	12.5	12.5	12.5	6.25
4bc′	25	6.25	25	12.5	6.25	25	12.5
4bd′	12.5	6.25	12.5	12.5	6.25	12.5	12.5
4be′	25	6.25	25	12.5	6.25	50	12.5
Amoxicillin	3.12	3.12	3.12	3.12	3.12	–	–
Fluconazole	–	–	–	–	–	3.12	3.12

were *Aspergillus janus* and *Pencilluim glabrum*. The bacterial pathogens were subcultured on Muller–Hinton Agar medium whereas fungus pathogens were sub-cultured at malt extract. The newly prepared compounds were screened for their antibacterial and antifungal activity using paper disc method *in vitro* against the above said strains at conc. 100 μg/ml. Amoxicillin was used as reference drug for comparison. All the compounds were also screened for MIC (tables 1 and 2) by using serial tube dilution method[26] at concentration, 3.12, 6.25, 12.5, 25, 50 and 100 μg/mL against the above said microorganisms and observed minimum inhibitory concentration (MIC-μg/ml) values are given in figures 1 and 2. The compounds **3ab**′, **3ba**′, **3bb**′, **4aa**′, **4ab**′, **4ac**′, **4ad**′, **4ba**′, **4bb**′, **4bc**′, **4bd**′ and **4be**′ showed significant MIC (12.50–6.25 μg/ml) against the tested microorganisms. In the disc diffusion method, a standard 5 mm diameter sterilized filter paper disc impregnated with the compound was placed on an agar plate seeded with the test organism. The plates were incubated for 24 h at 37°C for bacteria and 48 h at 28°C for fungi. The zones of inhibition of bacteria and fungi growth around the disc were observed. DMSO was used as a control and it did not show any activity against the strains of micro-organisms used. The zone of inhibition (*mm*) has been recorded as the average diameters which are given in figures 3 and 4.

4. Conclusion

It may be concluded that this study describes the general method for the synthesis of new rigid chain linked new bisthiadiazolines under the normal conditions. The nature of the internal spacer did not have any significant effect on the formation and antimicrobial behaviour of the bisthiadiazolines.

Acknowledgement

Authors are thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi for providing the financial support.

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