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ORIGINAL ARTICLE

Synthesis of some alkoxy based bisthiadiazolines

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Abstract The bisthiadiazolines **3a–3h** built around the alkyl chains of varying lengths have been synthesized in good yields by refluxing bisthiosemicarbazones **2a–2h** in acetic anhydride. The reactions of bisaldehydes **1a–1h** with thiosemicarbazide in alcoholic medium provided **2a–2h** and the former were obtained by using the reported methods. The formation and stereochemical features of the bisthiadiazolines **3a–3h** are found to be independent of the internal spacer length. The intermediates **2a–2h** and bisheterocyclic compounds **3a–3h** have been characterized by means of IR, ^{1}H NMR, ^{13}C NMR, Mass (ESI) and elemental analysis.

1. Introduction

The synthesis of macrocyclic compounds have been studied in the past decades on the compounds containing heterocyclic subunits, because of their unique chemical and biological properties. Several five-membered systems having three hetero atoms have been investigated because of their interesting physiological properties (Montegomery, 1981; Hetzhein and Mockel, 1996; Sandstorm, 1968). It is well established that various derivatives of trizole, thiadiazole and oxadiazole exhibit broad spectrum of pharmacological properties such as anti-inflammatory, (Boschelli et al., 1993; Unangst et al., 1992) antiviral (Shrivastava et al., 1984) and antibacterial (Hosam, 1996; Hui et al., 2002). Thiadiazoline and their derivatives (Gursoy et al., 1997; Joshi et al., 2000; Yamamoto et al., 1989; Brousse et al., 2002; Abdelhamid et al., 2004; H-Zaki et al., 2006; Wolkoff and Hammerum, 1976; Hu et al., 2005; Nagao et al., 1998; Araki et al., 1988; Gupta et al., 2008; Kumar et al., 2009; Gannon et al., 1980; Hagiwara et al., 1992; Eroglu, 2008; Hagiwara et al., 1993; Polvonov et al., 2003; Abbas and Rateb, 2005; Alho et al., 2000; Er et al., 2008; Aridoss et al., 2009) represent a group of compounds possessing a wide spectrum of biological activities. They exhibit hypoglycemic, antitubercular, antifungal and antibacterial properties (Leafe, 1966; Bhat et al., 1967; Zsolnai, 1962a,b; Thakar and Bhawal, 1977; Holmberg, 1954). In view of the above mentioned facts and in continuation of our work on the synthesis of biologically important heterocyclic compounds (Khan and Yusuf, 2009), the present investigations focus upon the synthesis of some bisthiadiazolines **3a–3h** built around the carbon chains of varying lengths. The major interest behind this study was to investigate the effect of internal spacer length upon the stereochemical features and biological activity of the resultant bisthiadiazolines.

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2. Results and discussion

The bisthiadiazolines **3a–3h** required for the present study were obtained starting from 4-hydroxybenzaldehyde which was reacted with suitable 1,ω-dibromoalkane in the presence of KOH in dry EtOH and DMF to yield bisaldehydes **1a–1h** (Abdelhamid and El-Shaity, 1988; Ibrahim et al., 1994). The latter were treated with thiosemicarbazide in dry EtOH and catalytic amounts of HCl to furnish bisthiosemicarbazones **2a–2h** which were further refluxed in Ac_2O to furnish bisthiadiazolines **3a–3h** in good yields (Scheme 1).

The structures of compounds **2a–2h** and **3a–3h** were based upon their spectroscopic data (IR, ^1H and ^{13}C NMR and Mass) and elemental analysis.

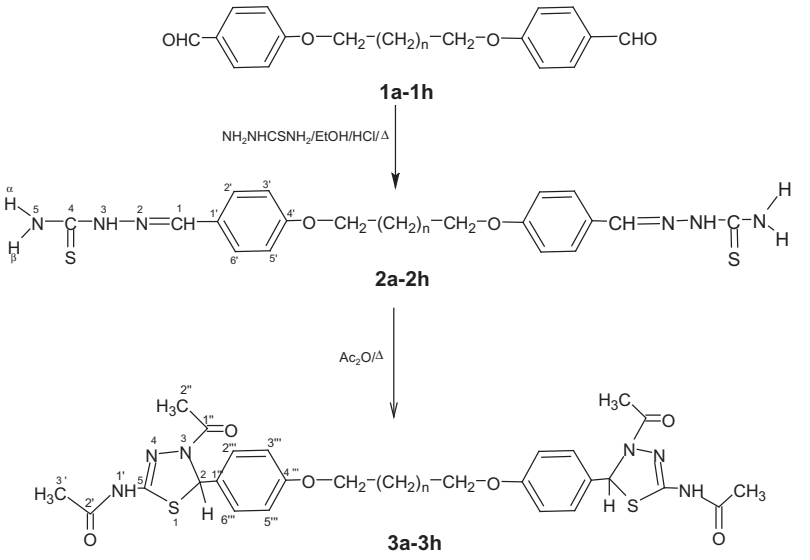
In compounds **2a–2h**, 5-NH_2 and 3-NH protons appeared as two broad singlets at δ 7.74–7.30 and a sharp singlet at δ 11.33–11.20, respectively, which were exchangeable with D_2O and their IR spectra also exhibited the NH stretching at 3364–3160 cm^{-1} and did not reveal any absorption in the carbonyl group region. Other major features of their ^1H NMR spectra were the appearance of sharp singlet at δ 8.03–7.99 which could be very well ascribed to azomethyne proton (H-1) and the two doublets in the aromatic region at δ 7.63–7.58 (J_o = 8.8 Hz) and δ 6.92–6.88 (J_o = 8.8 Hz) integrating for four hydrogens each that could be denoted by H-2′, 6′ and H-3′, 5′, respectively. In the ^{13}C NMR spectra of **2a–2h**, C-4 and C-1 were found placed at δ 176–173 and 149–147, respectively, and the resonances present at δ 133–130 and 118–115 could be resulted by aromatic carbons C-6′, 2′ and 5′, 3′, respectively.

IR spectra of bisthiadiazolines **3a–3h** displayed intense absorptions at 3220–3180, 1690–1638 and 1610–1600 cm^{-1} due to NH, C=O and C=N stretchings, respectively. ^1H NMR (400 MHz, DMSO) spectra of **3a–3h** had D_2O exchangeable singlet at δ 11.46–11.24 generated by the 1′-NH proton. The hydrogen (H-2) belonging to thiadiazoline ring appeared as a singlet at δ 6.75–6.70; the downfield resonance of this hydrogen could be ascribed to its benzylic nature and its placement between two heteroatoms (N and S). The singlets present at δ 2.26–2.22 and 2.15–2.11 could be very well represented by 2″ and 3′ methyl groups, respectively, and these groups have also been confirmed by the two resonances at δ 28–22 in ^{13}C NMR spectra. Additionally, the internal methylene protons were resonating at δ 4.11–3.90 (OCH_2) and 2.21–1.20 {$(CH_2)_n$}. The downfield resonance of the former could be attributed to their direct linkage to the electronegative oxygen atom. These methylene groups also furnished suitable signals in the ^{13}C NMR (DMSO) spectra at δ 68–66 (OCH_2) and 28–22{$(CH_2)_n$}. The presence of two carbonyl groups in **3a–3h** were confirmed by the appearance of two resonances at δ 169–164 and the signals resonating at δ 158–154 and 146–143 could be allotted to C-4‴ and C-5, respectively.

3. Biological activity

All the synthesized compounds were evaluated for antibacterial activity by disc-diffusion method. The compounds **2a–2h** and **3a–3h** were examined for their antibacterial activity against bacteria strains, namely, *Escherichia coli* (MTCC 390), *Staphylococcus aureus* (MTCC 435), *Klebsiella* pneumoniae (MTCC 3384) and *Pseudomonas* (MTCC 130). Norfloxin (MIC-2 μg/ml) and Amoxicillin (MIC-20 μg/ml) were taken as the standard drugs and DMSO was used as a blank.

The bisthiosemicarbazones **2c** (MIC-100 μg/ml), **2d** (MIC-250 μg/ml) and **2f** (MIC-250 μg/ml) showed low activity against gram-positive bacteria, *Staphylococcus aureus* and **2c** (MIC-100 μg/ml) also exhibited low activity against gram-negative bacteria, *Escherichia coli* as compared to the reference drugs. Unfortunately, bisthiadiazolines **3a–3h** did not exhibit any significant activity against the above said bacteria.



a(n=0), b(n=1), c(n=2), d(n=3), e(n=4), f(n=6), g(n=8), h(n=10)

Scheme 1

4. Conclusion

It may be concluded that the present study describes the general and efficient method for the synthesis of some bisthiadiazolines built around the alkyl chains of varying length under the normal conditions. The length of the intermediate spacer did not have any significant effect upon the stereochemistry and biological behaviour of bisthiadiazolines.

5. 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 vapors were used as visualizing agent. Bisaldehydes **1a–1h** were synthesized according to the reported methods (Abdelhamid and El-Shaity, 1988; Ibrahim et al., 1994).

5.1. Synthesis of 1,2-bis[2-benzylidene-hydrazinecarbothioamide-4′-oxy]ethane ***2a***

A mixture of bisaldehyde **1a** (1.0 g, 0.0038 mol) and thiosemicarbazide (0.678 g, 0.0076 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 crystallized from MeOH to yield pure bisthiosemicarbazone **2a**.

2a: Yellow solid; Yield 70%; m.p.: 220–222 °C. IR (KBr) cm^{-1} 3363 and 3288 (NH_2), 3178 (NH), 2951, 2882 (methylene C—H), 1601 (C═N), 1251, 1038 (C—O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.25 (2H, s, 3-NH), 8.00 (2H, s, H-1), 7.60 (4H, d, J_o = 8.7 Hz, H-2′, 6′), 7.52 (2H, brs, NH-α), 7.35 (2H, brs, NH-β), 6.92 (4H, d, J_o = 8.7 Hz, H-3′, 5′), 4.20 (4H, s, OCH_2); ^{13}C NMR (DMSO-d_6): δ 175.30 (C-4), 157.77 (C-4′), 148.82 (C-1), 138.67 (C-1′), 133.41 (C-2′, 6′), 118.44 (C-3′, 5′), 66.10 (OCH_2); MS(ESI): m/z $(M+1)^+$ 417. Anal. Calc. for $C_{18}O_2N_6S_2H_{20}$: Calc. C, 51.92%; H, 4.80%; N, 20.19%; Found: C, 51.89%; H, 4.78%; N, 20.17%.

5.2. Synthesis of 1,3-bis[2-benzylidene-hydrazinecarbothioamide-4′-oxy]propane ***2b***

The bisthiosemicarbazone **2b** was obtained from the reaction of bisaldehyde **1b** (1.0 g, 0.0036 mol) with thiosemicarbazide (0.640 g, 0.0072 mol) under the similar conditions as described above for **2a**.

2b: Yellow solid; Yield 82%; m.p.: 180–182 °C. IR (KBr) cm^{-1} 3360 and 3290 (NH_2), 3180 (NH), 2950, 2880 (methylene C—H), 1600 (C═N), 1252, 1035 (C—O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.28 (2H, s, 3-NH), 8.01 (2H, s, H-1), 7.61 (4H, d, J_o = 8.8 Hz, H-2′, 6′), 7.51 (2H, brs, NH-α), 7.37 (2H, brs, NH-β), 6.91 (4H, d, J_o = 8.8 Hz, H-3′, 5′), 4.19 (4H, t, J_{vic} = 6.1 Hz, O$CH_2$$CH_2$), 2.28 (2H, quintet, J_{vic} = 6.1 Hz, O$CH_2$$CH_2$); ^{13}C NMR (DMSO-$d_6$): δ 175.28 (C-4), 157.80 (C-4′), 148.84 (C-1), 138.69 (C-1′), 133.40 (C-2′, 6′), 118.42 (C-3′, 5′), 68.82 (O$CH_2$$CH_2$), 28.21 (O$CH_2$$CH_2$); MS(ESI): m/z $(M+1)^+$ 431. Anal. Calc. for $C_{19}O_2N_6S_2H_{22}$: Calc. C, 53.02%; H, 5.11%; N, 19.53%; Found: C, 53.23%; H, 5.13%; N, 19.45%.

5.3. Synthesis of 1,4-bis-[2-benzylidene-hydrazinecarbothioamide-4′-oxy]butane ***2c***

The bisthiosemicarbazone **2c** was synthesized from the reaction of bisaldehyde **1c** (1.0 g, 0.0034 mol) with thiosemicarbazide (0.618 g, 0.0068 mol) under the similar conditions as described above for **2a**.

2c: Yellow solid; Yield 80%; m.p.: 175–177 °C. IR (KBr) cm^{-1} 3350 and 3282 (NH_2), 3171 (NH), 2953, 2882 (methylene C—H), 1603 (C═N), 1246, 1044 (C—O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.33 (2H, s, 3-NH), 8.02 (2H, s, H-1), 7.74 (2H, brs, NH-α), 7.62 (4H, d, J_o = 8.8 Hz, H-2′, 6′), 7.47 (2H, brs, NH-β), 6.89 (4H, d, J_o = 8.8 Hz, H-3′, 5′), 4.08 (4H, t, J_{vic} = 6.3 Hz, O$CH_2$$CH_2$), 1.98 (4H, quintet, J_{vic} = 6.3 Hz, O$CH_2$$CH_2$); ^{13}C NMR (DMSO-$d_6$): δ 174.14 (C-4), 156.59 (C-4′), 147.93 (C-1), 138.91 (C-1′), 132.54 (C-2′, 6′), 117.34 (C-3′, 5′), 67.70 (O$CH_2$$CH_2$), 27.92 (O$CH_2$$CH_2$); MS(ESI): m/z $(M+Na)^+$ 467. Anal. Calc. for $C_{20}O_2N_6S_2H_{24}$: Calc. C, 50.05%; H, 5.40%; N, 18.90%; Found: C, 49.85%; H, 5.42%; N, 18.83%.

5.4. Synthesis of 1,5-bis-[2-benzylidene-hydrazinecarbothioamide-4′-oxy]pentane ***2d***

The bisthiosemicarbazone **2d** was prepared from the reaction of bisaldehyde **1d** (1.0 g, 0.0032 mol) with thiosemicarbazide (0.582 g, 0.0064 mol) under the similar conditions as described above for **2a**.

2d: Orange yellow solid; Yield 82%; m.p.: 170–172 °C. IR (KBr) cm^{-1} 3345 and 3280 (NH_2), 3175 (NH), 2940, 2890 (methylene C—H), 1610 (C═N), 1235, 1045 (C—O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.28 (2H, s, 3-NH), 8.01 (2H, s, H-1), 7.63 (4H, d, J_o = 8.8 Hz, H-2′, 6′), 7.60 (2H, brs, NH-α), 7.41 (2H, brs, NH-β), 6.89 (4H, J_o = 8.8 Hz, H-3′, 5′), 4.01 (4H, t, J_{vic} = 6.3 Hz, O$CH_2$$CH_2$$CH_2$), 1.87 (4H, quintet, J_{vic} = 6.3 Hz, O$CH_2$$CH_2$$CH_2$), 1.67 (2H, quintet, J_{vic} = 6.3 Hz, O$CH_2$$CH_2$$CH_2$); ^{13}C NMR (DMSO-$d_6$): δ 175.89 (C-4), 157.13 (C-4′), 147.98 (C-1), 139.40 (C-1′), 133.69 (C-2′, 6′), 116.20 (C-3′, 5′), 66.93 (O$CH_2$$CH_2$$CH_2$), 27.23 (O$CH_2$$CH_2$$CH_2$), 21.69 (O$CH_2$$CH_2$$CH_2$); MS(ESI): m/z 458 (M^+). Anal. Calc. for $C_{21}O_2N_6S_2H_{26}$: Calc. C, 55.02%; H, 5.67%; N, 18.34%; Found: C, 54.80%; H, 5.69%; N, 18.41%.

5.5. Synthesis of 1,6-bis-[2-benzylidene-hydrazinecarbothioamide-4′-oxy]hexane ***2e***

The bisthiosemicarbazone **2e** was obtained from the reaction of bisaldehyde **1e** (1.0 g, 0.0030 mol) with thiosemicarbazide (0.558 g, 0.0062 mol) under the similar conditions as used for **2a**.

2e: Yellow solid; Yield 75%, m.p.: 166–168 °C. IR (KBr) cm^{-1} 3353 and 3282 (NH_2), 3160 (NH), 2940, 2870 (methylene C—H), 1600 (C═N), 1242, 1040 (C—O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.20 (2H, s, 3-NH), 7.99 (2H, s, H-1), 7.58 (4H, d, J_o = 8.8 Hz, H-2′, 6′), 7.56 (2H, brs, NH-α), 7.30 (2H, brs, NH-β), 6.88 (4H, d, J_o = 8.8 Hz, H-3′, 5′), 4.01 (4H, t, J_{vic} = 6.3 Hz, O$CH_2$$CH_2$$CH_2$), 1.82 (4H, quintet, J_{vic} = 6.3 Hz, O$CH_2$$CH_2$$CH_2$), 1.55 (4H, quintet, J_{vic} = 6.3 Hz,

$OCH_2CH_2CH_2$); ^{13}C NMR (DMSO-d_6): δ 173.75 (C-4), 156.10 (C-4′), 148.08 (C-1), 140.10 (C-1′), 131.23 (C-2′, 6′), 116.98 (C-3′, 5′), 67.42 ($OCH_2CH_2CH_2$), 28.85 ($OCH_2CH_2CH_2CH_2$), 24.89 ($OCH_2CH_2CH_2CH_2$); MS(ESI): m/z $(M+Na)^+$ 495. Anal. Calc. for $C_{22}O_2N_6S_2H_{28}$: Calc. C, 55.93%; H, 5.93%; N, 17.79%; Found: C, 55.70%; H, 5.91%; N, 17.72%.

5.6. Synthesis of 1,8-bis-[2-benzylidene-hydrazinecarbothioamide-4′-oxy]octane **2f**

The bisthiosemicarbazone **2f** was prepared from the reaction of bisaldehyde **1f** (1.0 g, 0.0028 mol) with thiosemicarbazide (0.514 g, 0.0056 mol) under the similar conditions as described earlier for **2a**.

2f: Yellow solid; Yield 70%; m.p.: 163–165 °C. IR (KBr) cm^{-1} 3350 and 3275 (NH_2), 3165 (NH), 2951, 2883 (methylene C—H), 1605 (C=N), 1250, 1036 (C—O); ^1H NMR (400 MHz, DMSO-d_6): δ 11.26 (2H, s, 3-NH), 8.01 (2H, s, H-1), 7.59 (4H, d, J_o = 8.8 Hz, H-2′, 6′), 7.56 (2H, brs, NH-α), 7.33 (2H, brs, NH-β), 6.88 (4H, d, J_o = 8.9 Hz, H-3′, 5′), 3.97 (4H, t, J_{vic} = 6.4 Hz, $OCH_2CH_2CH_2CH_2$), 1.79 (4H, quintet, J_{vic} = 6.3 Hz, $OCH_2CH_2CH_2CH_2$), 1.47 (4H, m, $OCH_2CH_2CH_2CH_2$), 1.40 (4H, m, $OCH_2CH_2CH_2CH_2$); ^{13}C NMR (DMSO-d_6) δ 174.09 (C-4), 155.42 (C-4′), 148.56 (C-1), 140.12 (C-1′), 132.49 (C-2′, 6′), 117.02 (C-3′, 5′), 68.48 ($OCH_2CH_2CH_2CH_2$), 28.42 ($OCH_2CH_2CH_2CH_2$), 28.02 ($OCH_2CH_2CH_2CH_2$), 25.03 ($OCH_2CH_2CH_2CH_2$); MS(ESI): m/z $(M+K)^+$ 539. Anal. Calc. for $C_{24}O_2N_6S_2H_{32}$: Calc. C, 57.60%; H, 6.40%; N, 16.80%; Found: C, 57.83%; H, 6.38%; N, 16.74%.

5.7. Synthesis of 1,10-bis-[2-benzylidene-hydrazinecarbothioamide-4′-oxy]decane **2g**

The bisthiosemicarbazone **2g** was synthesized from the reaction of bisaldehyde **1g** (1.0 g, 0.0027 mol) with thiosemicarbazide (0.494 g, 0.0052 mol) under the similar conditions as used above for **2a**.

2g: Yellow solid; Yield 65%; m.p.: 160–162 °C. IR (KBr) cm^{-1} 3364 and 3270 (NH_2), 3162 (NH), 2955, 2890 (methylene C—H), 1608 (C=N), 1226, 1025 (C—O); ^1H NMR (400 MHz, DMSO-d_6): δ 11.25 (2H, s, 3-NH), 8.03 (2H, s, H-1), 7.60 (4H, d, J_o = 8.8 Hz, H-2′, 6′), 7.59 (2H, brs, NH-α), 7.42 (2H, brs, NH-β), 6.92 (4H, d, J_o = 8.9 Hz, H-3′, 5′), 3.92 (4H, t, J_{vic} = 6.4 Hz, $OCH_2CH_2CH_2CH_2$), 1.73 (4H, quintet, J_{vic} = 6.4 Hz, $OCH_2CH_2CH_2CH_2$), 1.38 (4H, m, $OCH_2CH_2CH_2CH_2$), 1.31 (4H, m, $OCH_2CH_2CH_2CH_2$), 1.26 (4H, m, $OCH_2CH_2CH_2CH_2CH_2$); ^{13}C NMR (DMSO-d_6): δ 175.34 (C-4), 154.94 (C-4′), 149.12 (C-1), 139.82 (C-1′), 130.48 (C-2′, 6′), 115.14 (C-3′, 5′), 67.94 ($OCH_2CH_2CH_2CH_2CH_2$), 28.68 ($OCH_2CH_2CH_2CH_2CH_2$), 28.30 ($OCH_2CH_2CH_2CH_2CH_2$), 28.08 ($OCH_2CH_2CH_2CH_2CH_2$), 25.10 ($OCH_2CH_2CH_2CH_2CH_2$); MS(ESI): m/z $(M+Na)^+$ 551. Anal. Calc. for $C_{26}O_2N_6S_2H_{36}$: Calc. C, 59.09%; H, 6.80%; N, 15.90%; Found: C, 59.32%; H, 6.82%; N, 15.96%.

5.8. Synthesis of 1,12-bis-[2-benzylidene-hydrazinecarbothioamide-4′-oxy] dodecane **2h**

The bisthiosemicarbazone **2h** was synthesized from the reaction of bisaldehyde **1h** (1.0 g, 0.0025 mol) with thiosemicarbazide (0.462 g, 0.0048 mol) under the similar conditions as used above for **2a**.

2h: Yellow solid; Yield 58%; m.p.: 188–190 °C. IR (KBr) cm^{-1} 3362 and 3272 (NH_2), 3163 (NH), 2958, 2891 (methylene C—H), 1606 (C=N), 1225, 1027 (C—O); ^1H NMR (400 MHz, DMSO-d_6): δ 11.23 (2H, s, 3-NH), 8.01 (2H, s, H-1), 7.62 (4H, d, J_o = 8.8 Hz, H-2′, 6′), 7.58 (2H, brs, NH-α), 7.43 (2H, brs, NH-β), 6.90 (4H, d, J_o = 8.9 Hz, H-3′, 5′), 3.95 (4H, t, J_{vic} = 6.4 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.71 (4H, quintet, J_{vic} = 6.4 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.40 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.30 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.24 (8H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$); ^{13}C NMR (DMSO-d_6): δ 175.32 (C-4), 154.96 (C-4′), 149.11 (C-1), 139.80 (C-1′), 130.49 (C-2′, 6′), 115.15 (C-3′, 5′), 67.89 ($OCH_2CH_2CH_2CH_2CH_2CH_2$), 28.68 $OCH_2CH_2CH_2CH_2CH_2CH_2$), 28.43 ($OCH_2CH_2CH_2CH_2CH_2CH_2$), 28.09 ($OCH_2CH_2CH_2CH_2CH_2CH_2$), 27.90 ($OCH_2CH_2CH_2CH_2CH_2CH_2$), 25.31 ($OCH_2CH_2CH_2CH_2CH_2CH_2$); MS(ESI): m/z $(M+Na)^+$ 551. Anal. Calc. for $C_{28}O_2N_6S_2H_{40}$: Calc. C, 60.43%; H, 7.19%; N, 15.10%; Found: C, 60.48%; H, 7.14%; N, 15.07%.

5.9. Synthesis of 1,2-bis[5-acetamido-3-N-acetyl-2-phenyl-thiadiazol-2-yl-4′-oxy] ethane **3a**

A mixture of bisthiosemicarbazone **2a** (1.0 g, 0.0026 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 **3a**.

3a: Brown solid; Yield 53%; m.p.:132–134 °C. IR (KBr) cm^{-1} 3208 (NH), 2950, 2905 (methylene C—H), 1688, 1642 (C=O), 1601 (C=N), 1238, 1041 (C—O); ^1H NMR (400 MHz, DMSO-d_6): δ 11.32 (2H, s, 1′-NH), 7.21 (4H, d, J_o = 8.7 Hz, H-2‴, 6‴), 6.85 (4H, d, J_o = 8.7 Hz, H-3‴, 5‴), 6.70 (2H, s, H-2), 4.10 (4H, s, OCH_2), 2.26 (6H, s, 2″-CH_3), 2.15 (6H, s, 3′-CH_3); ^{13}C NMR (DMSO-d_6): δ 169.68 (1″-C=O), 168.25 (2′-C=O), 158.12 (C-4‴), 146.92 (C-5), 132.35 (C-1‴), 127.27 (C-2‴, 6‴), 114.50 (C-3‴, 5‴), 67.43 (C-2), 67.12 (OCH_2), 25.90 (2″-CH_3), 22.95 (3′-CH_3); MS(E-SI): m/z $(M+Na)^+$ 607. Anal. Calc. for $C_{26}O_6N_6S_2H_{28}$: Calc. C, 53.42%; H, 4.79%; N, 14.38%; Found: C, 53.47%; H, 4.82%; N, 14.35%.

5.10. Synthesis of 1,3-bis[5-acetamido-3-N-acetyl-2-phenyl-thiadiazol-2-yl-4′-oxy] propane **3b**

The compound **3b** was prepared by refluxing bisthiosemicarbazone **2b** (1.0 g, 0.0025 mol) with acetic anhydride (30 ml) under the similar conditions as described above for **3a**.

3b: Brown solid; Yield 60%; m.p.: 103–105 °C. IR (KBr) cm^{-1} 3204 (NH), 2960, 2900 (methylene C—H), 1685, 1640 (C=O), 1603 (C=N), 1235, 1045 (C—O); ^1H NMR (400 MHz, DMSO-d_6): δ 11.34 (2H, s, 1′-NH), 7.22 (4H, d, J_o = 8.7 Hz, H-2‴, 6‴), 6.83 (4H, d, J_o = 8.7 Hz, H-3‴, 5‴), 6.72 (2H, s, H-2), 4.11 (4H, t, J_{vic} = 6.1 Hz, OCH_2CH_2), 2.25 (6H, s, 2″-CH_3), 2.21 (2H, quintet, J_{vic} = 6.1 Hz, OCH_2CH_2), 2.13 (6H, s, 3′-CH_3); ^{13}C NMR (DMSO-d_6): δ 169.69 (1″-C=O), 168.23 (2′-C=O), 158.15 (C-4‴), 146.93 (C-5), 132.34 (C-1‴), 127.29 (C-2‴, 6‴), 114.55 (C-3‴, 5‴), 67.44 (C-2), 66.83 (OCH_2CH_2), 28.12 (OCH_2CH_2), 25.88 (2″-

CH_3), 22.99 (3′-*CH_3*); MS(ESI): *m*/*z* $(M+Na)^+$ 621. Anal. Calc. for $C_{27}O_6N_6S_2H_{30}$: Calc. C, 54.18%; H, 5.01%; N, 14.04%; Found: C, 53.96%; H, 4.99%; N, 14.09%.

5.11. Synthesis of 1,4 bis[5-acetamido-3-N-acetyl-2-phenyl-thiadiazol-2-yl-4′-oxy] butane ***3c***

The compound **3c** was synthesized by refluxing bisthiosemicarbazone **2c** (1.0 g, 0.0024 mol) with acetic anhydride (30 ml) under the similar conditions as described above for **3a**.

3c: Brown solid; Yield 72%; m.p.: 140–142 °C. IR (KBr) cm^{-1} 3208 (NH), 2955, 2910 (methylene C—H), 1680, 1642 (C═O), 1605 (C═N), 1225, 1040 (C—O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.46 (2H, s, 1′-NH), 7.21 (4H, d, J_o = 8.6 Hz, H-2‴, 6‴), 6.82 (4H, d, J_o = 8.6 Hz, H-3‴, 5‴), 6.72 (2H, s, H-2), 3.99 (4H, t, J_{vic} = 6.4 Hz, O*CH_2*CH_2), 2.24 (6H, s, 2″-*CH_3*), 2.12 (6H, s, 3′-C*H_3*), 1.93 (4H, quintet, J_{vic} = 6.4 Hz, OCH_2*CH_2*); ^{13}C NMR (DMSO-d_6): δ 169.28 (1″-C═O), 168.18 (2′-C═O), 158.95 (C-4‴), 146.91 (C-5), 132.84 (C-1‴), 127.24 (C-2‴, 6‴), 114.53 (C-3‴, 5‴), 67.41 (C-2), 66.23 (O*CH_2*CH_2), 25.92 (OCH_2*CH_2*), 25.83 (2″-*CH_3*), 22.89 (3′-*CH_3*), MS(ESI): *m*/*z* $(M+K)^+$ 651. Anal. Calc. for $C_{28}O_6N_6S_2H_{32}$: Calc. C, 54.90%; H, 5.22%; N, 13.70%; Found: C, 55.12%; H, 5.24%; N, 13.65%.

5.12. Synthesis of 1,5 bis[5-acetamido-3-N-acetyl-2-phenyl-thiadiazol-2-yl-4′-oxy] pentane ***3d***

The compound **3d** was obtained by refluxing bisthiosemicarbazone **2d** (1.0 g, 0.0023 mol) with acetic anhydride (30 ml) under the similar conditions as used earlier for **3a**.

3d: Brown solid; Yield 68%; m.p.: 123–125 °C. IR (KBr) cm^{-1} 3180 (NH), 2965, 2922 (methylene C—H), 1682, 1638 (C═O), 1600 (C═N), 1228, 1044 (C—O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (2H, s, 1′-NH), 7.20 (4H, d, J_o = 8.6 Hz, H-2‴, 6‴), 6.84 (4H, d, J_o = 8.6 Hz, H-3‴, 5‴), 6.70 (2H, s, H-2), 3.96 (4H, t, J_{vic} = 6.4 Hz, O*CH_2*CH_2 CH_2), 2.22 (6H, s, 2″-*CH_3*), 2.15 (6H, s, 3′-*CH_3*), 1.85 (4H, quintet, J_{vic} = 6.4 Hz, OCH_2*CH_2*CH_2), 1.60 (2H, quintet, J_{vic} = 6.4 Hz, OCH_2CH_2*CH_2*); ^{13}C NMR (DMSO-d_6): δ 169.47 (1″-C═O), 168.23 (2′-C═O), 159.02 (C-4‴), 146.80 (C-5), 132.19 (C-1‴), 127.15 (C-2‴, 6‴), 114.56 (C-3‴, 5‴), 67.78 (C-2), 67.49 (O*CH_2*CH_2CH_2), 27.12 (OCH_2*CH_2*CH_2), 25.53 (2‴-*CH_3*), 22.82 (OCH_2CH_2*CH_2*), 22.80 (3′-*CH_3*); MS(ESI): *m*/*z* $(M+Na)^+$ 649. Anal. Calc. for $C_{29}O_6N_6S_2H_{34}$: Calc. C, 55.59%; H, 5.43%; N, 13.41%; Found: C, 55.37%; H, 5.41%; N, 13.46%.

5.13. Synthesis of 1,6 bis[5-acetamido-3-N-acetyl-2-phenyl-thiadiazol-2-yl-4′-oxy] hexane ***3e***

The compound **3e** was obtained by refluxing bisthiosemicarbazone **2e** (1.0 g, 0.0022 mol) with acetic anhydride (30 ml) under the same conditions as used for **3a**.

3e: Brown solid; Yield 65%; m.p.: 148–150 °C. IR (KBr) cm^{-1} 3210 (NH), 2963, 2930 (methylene C—H), 1675, 1641 (C═O), 1605 (C═N), 1222, 1030 (C—O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.24 (2H, s, 1′-NH), 7.21 (4H, d, J_o = 8.7 Hz, H-2‴, 6‴), 6.81 (4H, d, J_o = 8.7 Hz, H-3‴, 5‴), 6.73 (2H, s, H-2), 3.93 (4H, t, J_{vic} = 6.4 Hz, O*CH_2*CH_2CH_2), 2.24 (6H, s, 2″-*CH_3*), 2.13 (6H, s, 3′-*CH_3*), 1.78 (4H, quintet, J_{vic} = 6.4 Hz, OCH_2*CH_2*CH_2), 1.52 (4H, quintet, J_{vic} = 6.4 Hz, OCH_2CH_2*CH_2*); ^{13}C NMR (DMSO-d_6): δ 169.97 (1″-C═O), 168.13 (2′-C═O), 159.05 (C-4‴), 146.88 (C-5), 132.29 (C-1‴), 127.19 (C-2‴, 6‴), 114.53 (C-3‴, 5‴), 67.76 (C-2), 66.48 (O*CH_2*CH_2CH_2), 28.02 (OCH_2*CH_2*CH_2), 25.73 (2″-*CH_3*), 24.16 (OCH_2CH_2*CH_2*), 22.90 (3′-*CH_3*); MS(ESI): *m*/*z* $(M+Na)^+$ 663. Anal. Calc. for $C_{30}O_6N_6S_2H_{36}$: Calc. C, 56.25%; H, 5.62%; N, 13.12%; Found: C, 56.02%; H, 5.64%; N, 13.17%.

5.14. Synthesis of 1,8 bis-[5-acetamido-3-N-acetyl-2-phenyl-thiadiazol-2-yl-4′-oxy] octane ***3f***

The compound **3f** was prepared by refluxing bisthiosemicarbazone **2f** (1.0 g, 0.0021 mol) with acetic anhydride (30 ml) under the similar conditions as described earlier for **3a**.

3f: Brown solid; Yield 70%; m.p.: 153–155 °C. IR (KBr) cm^{-1} 3215 (NH), 2955, 2922 (methylene C—H), 1684, 1648 (C═O), 1608 (C═N), 1255, 1013 (C—O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.45 (2H, s, 1′-NH), 7.20 (2H, d, J_o = 8.7 Hz, H-2‴, 6‴), 6.80 (4H, d, J_o = 8.7 Hz, H-3‴, 5‴), 6.71 (2H, s, H-2), 3.92 (4H, t, J_{vic} = 6.4 Hz, O*CH_2*$CH_2CH_2CH_2$), 2.23 (6H, s, 2″-*CH_3*), 2.11 (6H, s, 3′-*CH_3*), 1.75 (4H, quintet, J_{vic} = 6.4 Hz, OCH_2*CH_2*CH_2CH_2), 1.45 (4H, m, OCH_2CH_2*CH_2*CH_2), 1.38 (4H, m, $OCH_2CH_2CH_2$*CH_2*); ^{13}C NMR (DMSO-d_6): δ 164.82 (1″-C═O), 163.33 (2′-C═O), 154.24 (C-4‴), 143.52 (C-5), 127.77 (C-1‴), 122.30 (C-2‴, 6‴), 109.65 (C-3‴, 5‴), 67.67 (O*CH_2*$CH_2CH_2CH_2$), 63.02 (C-2), 27.21 (OCH_2*CH_2* CH_2CH_2), 27.01 (OCH_2CH_2*CH_2*CH_2), 25.89 (OCH_2CH_2 CH_2*CH_2*), 24.30 (2″-*CH_3*), 23.12 (3′-*CH_3*); MS(ESI): *m*/*z* $(M+K)^+$ 693. Anal. Calc. for $C_{31}O_6N_6S_2H_{38}$: Calc. C, 56.88%; H, 5.81%; N, 12.84%; Found: C, 56.65%; H, 5.79%; N, 12.79%.

5.15. Synthesis of 1,10 bis-[5-acetamido-3-N-acetyl-2-phenyl-thiadiazol-2-yl-4′-oxy] decane ***3g***

The compound **3g** was synthesized by refluxing bisthiosemicarbazone **2g** (1.0 g, 0.0024 mol) with acetic anhydride (30 ml) under the similar conditions as used for **3a**.

3g: Brown solid; Yield 65%; m.p.: 159–161 °C. IR (KBr) cm^{-1} 3220 (NH), 2964, 2925 (methylene C—H), 1690, 1643 (C═O), 1610 (C═N), 1250, 1038 (C—O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (2H, s, 1′-NH), 7.24 (4H, d, J_o = 8.7 Hz, H-2‴, 6‴), 6.85 (4H, d, J_o = 8.7 Hz, H-3‴, 5‴), 6.74 (2H, s, H-2), 3.90 (4H, t, J_{vic} = 6.4 Hz, O*CH_2*$CH_2CH_2CH_2CH_2$), 2.25 (6H, s, 2″-*CH_3*), 2.14 (6H, s, 3′-*CH_3*), 1.74 (4H, quintet, J_{vic} = 6.4 Hz, OCH_2*CH_2*CH_2 CH_2CH_2), 1.42 (4H, quintet, J_{vic} = 6.4 Hz OCH_2CH_2*CH_2* CH_2CH_2), 1.30 (4H, m, $OCH_2CH_2CH_2$*CH_2*CH_2), 1.24 (4H, m, $OCH_2CH_2CH_2CH_2$*CH_2*); ^{13}C NMR (DMSO-d_6): δ 164.72 (1″-C═O), 163.23 (2′-C═O), 154.14 (C-4‴), 143.41 (C-5), 127.57 (C-1‴), 122.18 (C-2‴, 6‴), 110.48 (C-3‴, 5‴), 67.20 (O*CH_2*$CH_2CH_2CH_2CH_2$), 63.00 (C-2), 28.85 (OCH_2*CH_2*$CH_2CH_2CH_2$), 28.51 (OCH_2CH_2*CH_2*CH_2CH_2), 28.04 ($OCH_2CH_2CH_2$*CH_2*CH_2), 24.89 ($OCH_2CH_2CH_2$ CH_2*CH_2*), 24.18 (2″-*CH_3*), 22.69 (3′-*CH_3*); MS(ESI): *m*/*z* $(M+K)^+$ 707. Anal. Calc. for $C_{32}O_6N_6S_2H_{40}$: Calc. C, 57.48%; H, 5.98%; N, 12.57%; Found: C, 57.71%; H, 5.96%; N, 12.62%.

5.16. Synthesis of 1,12 bis-[5-acetamido-3-N-acetyl-2-phenyl-thiadiazol-2-yl-4′-oxy] dodecane ***3h***

The compound **3h** was synthesized by refluxing bisthiosemicarbazone **2h** (1.0 g, 0.0024 mol) with acetic anhydride (30 ml) under the similar conditions as used for **3a**.

3h: Brown solid; Yield 62%; m.p.:168–170 °C. IR (KBr) cm^{-1} 3218 (NH), 2963, 2926 (methylene C—H), 1689, 1644 (C═O), 1607 (C═N), 1245, 1035 (C—O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (2H, s, 1′-NH), 7.23 (4H, d, J_o = 8.7 Hz, H-2‴, 6‴), 6.83 (4H, d, J_o = 8.7 Hz, H-3‴, 5‴), 6.75 (2H, s, H-2), 3.94 (4H, t, J_{vic} = 6.4 Hz, O*CH*$_2$ $CH_2CH_2CH_2CH_2CH_2$), 2.22 (6H, s, 2″-*CH*$_3$), 2.15 (6H, s, 3′-*CH*$_3$), 1.70 (4H, quintet, J_{vic} = 6.4 Hz, OCH_2*CH*$_2$$CH_2CH_2$ CH_2CH_2), 1.40 (4H, quintet, J_{vic} = 6.4 Hz OCH_2CH_2*CH*$_2$ $CH_2CH_2CH_2$), 1.26 (4H, m, $OCH_2CH_2CH_2$*CH*$_2$$CH_2CH_2$), 1.20 (8H, m, $OCH_2CH_2CH_2CH_2$*CH*$_2$*CH*$_2$); ^{13}C NMR (DMSO-d_6): δ 164.68 (1″-C═O), 163.20 (2′-C═O), 154.11 (C-4‴), 143.43 (C-5), 127.59 (C-1‴), 122.15 (C-2‴, 6‴), 110.45 (C-3‴, 5‴), 68.12 (O*CH*$_2$$CH_2CH_2CH_2CH_2CH_2$), 63.09 (C-2), 28.50 ($OCH_2$*CH*$_2$$CH_2CH_2CH_2CH_2$), 28.22 ($OCH_2CH_2$*CH*$_2$$CH_2CH_2CH_2$), 27.98 ($OCH_2CH_2CH_2$*CH*$_2$ CH_2CH_2), 27.42 ($OCH_2CH_2CH_2CH_2$*CH*$_2$$CH_2$), 24.84 ($OCH_2CH_2CH_2CH_2CH_2$*CH*$_2$), 24.14 (2″-*CH*$_3$), 22.64 (3′-*CH*$_3$); MS(ESI): m/z $(M+K)^+$ 735. Anal. Calc. for $C_{34}O_6N_6S_2H_{44}$: Calc. C, 58.62%; H, 6.32%; N, 12.06%; Found: C, 58.59%; H, 6.29%; N, 12.03%.

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