Synthesis and Antimicrobial Evaluations of 1,3,4-Thiadiazoline-based Bisheterocyclics

Mohamad Yusuf,* Manpreet Kaur, and Payal Jain

Department of Chemistry, Punjabi University, Patiala 147002, Punjab, India
*E-mail:yusuf_sah04@yahoo.co.in

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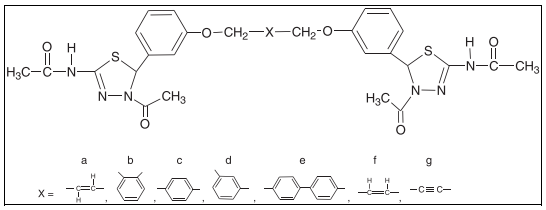

The bisthiadiazolines **4**(**a–g**) were synthesized from the cyclization of bisthiosemicarbazones **3**(**a–g**) by refluxing under Ac_2O medium. The intermediates were obtained from the reactions of dibenzaldehydes **2** (**a–g**) with thiosemicarbazide by refluxing in the presence of dry EtOH/HCl. The latter were prepared in good yields from the O-alkylation of 3-hydroxybenzaldehyde with suitable dibromo derivatives under the alkaline conditions. The structures of prepared compounds were determined from rigorous analysis of their spectral parameters (UV–vis, IR, ^{1}H NMR, ^{13}C NMR and ESI-MS). The newly prepared compounds were screened for their antimicrobial activity against seven bacterial and five fungi strains using serial tube dilution method.

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INTRODUCTION

Heterocyclic chemistry is an integral part of the chemical sciences and constitutes a considerable part of the modern researches that are occurring presently throughout the world. A wide range of heterocyclic compounds have been synthesized in order to develop physiologically and pharmacologically active molecules [1–4]. Five-membered heterocyclic systems having three heteroatoms at the symmetrical positions are known as thiadiazolines, and these compounds have been studied because of their interesting physiological properties [5]. These heterocyclics are found to exhibit various biological applications like antitubercular [6], antimicrobial [7–9], anti-inflammatory [10–12], antiviral, anticonvulsant [13,14], hypertensive [15,16], anesthetic [17], anticancer [18,19], hypoglycemic [20] and cytotoxic activities [21–27]. Bisthiadiazolines are the molecules, which are formed by joining two thiadiazoline moieties together through the rigid linkers. In continuation of our researches upon the bisheterocyclic compounds [28], the present investigations have been focused upon the synthesis of new bisthiadiazolines built around seven rigid spacers.

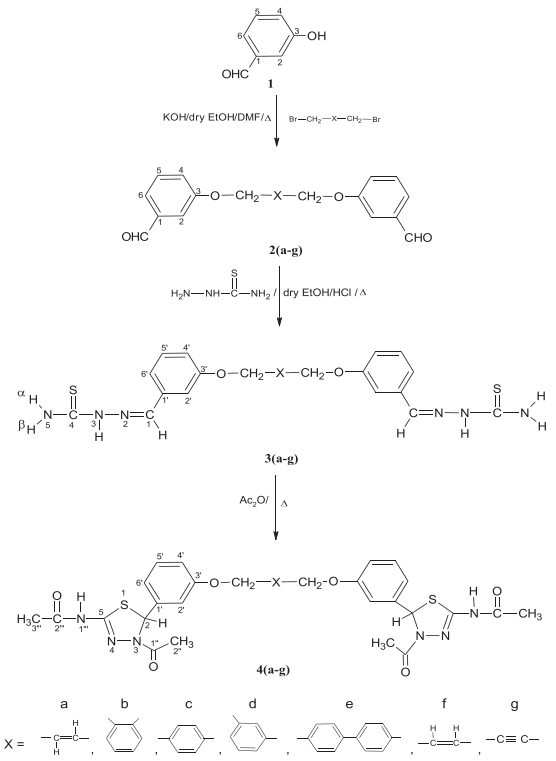
RESULTS AND DISCUSSION

The bisthiadiazolines **4**(**a–g**) required for the present study were synthesized from the reactions of bisthiosemicarbazones **3**(**a–g**) with Ac_2O under refluxing conditions (Scheme 1). The latter were prepared in good yields from the condensation reactions of dibenzaldehydes **2**(**a–g**) with thiosemicarbazide by refluxing in the presence of dry EtOH and catalytic amount of HCl. The dibenaldehydes in turns were obtained successfully from the reaction of 3-hydroxybenzaldehyde with suitable dibromo reagents (*trans*-1,4-dibromo-2-butene, α,α′-dibromo-*o*-xylene, α,α′-dibromo-*p*-xylene, α,α′-dibromo-*m*-xylene, 4,4′-bischlorome thylbiphenyl, *cis*-1,4-dibromo-2-butene and 1,4-dichloro-2-butyne) in the presence of KOH in dry EtOH/DMF. The structures of the intermediates **2**(**a–g**) and **3** (**a–g**) and final compounds **4**(**a–g**) were determined with the help of their spectroscopic parameters (UV–vis, IR, ^{1}H NMR, ^{13}C NMR and ESI-MS). The purity of these products has also been confirmed with the help of their elemental analysis results.

The IR spectra of **2**(**a–g**) exhibited the strong absorptions at 1694–1682 cm^{-1} because of the conjugated C═O group, while the C–H stretching band appeared at 2879–2832 and 2759–2726 cm^{-1}. In their ^{1}H NMR (400 MHz, $CDCl_3$) spectra, the most downfield resonance placed at δ 9.97–9.95 may be occurring because of the C***H***O group proton. The signals resonating at δ 7.74–7.45 (2H, d, J = 3.7–1.2 Hz), 7.49–7.40 (2H, dd, J = 7.4–1.3 Hz), 7.48–7.26 (2H, t, J = 7.3–1.9 Hz) and 7.28–7.20 (2H, dt, J = 3.6–1.6, 7.1–2.7 Hz) were easily assignable to phenyl ring protons H-2, 6, 5 and 4, respectively. Further, in the upfield region, the signal of suitable multiplicity was observed for four protons of OC***H***$_2$ group at δ 5.23–4.65 (vide experimental).

In the ^{13}C NMR (100 MHz, $CDCl_3$) spectra of **2**(**a–g**), the presence of aldehyde group (***C***HO) was confirmed by the appearance of signal at δ 192.13–191.15. The resonances

Scheme 1



placed at δ 159.92–159.01, 137.87–136.86, 134.64–129.87, 123.92–122.91, 122.76–121.42 and 113.19–112.80 could be furnished by the aromatic ring carbon atoms C-3, 1, 2, 6, 5 and 4, respectively. The internal rigid chain O*C*H_2 group also provided suitable signals in the aliphatic region at δ 69.99–64.38 (vide experimental). The UV–vis spectra of **2**(**a–g**) had two maxima at 332–320 and 272–261 nm, which were assignable to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions, respectively.

The IR spectra of bisthiosemicarbazones **3**(**a–g**) had major absorptions at 3449–3400, 3269–3240, 3160–3102 (N–H), 1600–1589 (C═N) and 1180–1162 cm^{-1} (C═S) and did not reveal any absorption in the carbonyl group region, which confirms that C═O group has undergone transformation during the reaction. The $n \rightarrow \pi^*$ transition in the UV–vis spectra of **3**(**a–g**) was found to be placed at 328–320 nm.

The ^{1}H NMR (400 MHz, DMSO-d_6) spectra of **3**(**a–g**) showed a singlet at δ 11.43–11.39, which was assignable to 3-N***H*** proton, and two singlets resonating at δ 8.12–8.01 and 7.89–7.70 may be resulted by N***H***-β and N***H***-α protons, respectively. Another sharp singlet at δ 8.04–7.94 (2H) was easily given by azomethyne hydrogen (H-1). The aromatic ring protons were found to be placed at their expected positions (vide experimental).

In the ^{13}C NMR (100 MHz, DMSO-d_6) spectra of **3** (**a–g**), the presence of C═S group was confirmed by the appearance of a signal at δ 178.01–176.70. The

Table 1

In vitro MIC (μg/ml) of bisthiosemicarbazones **3**(**a–g**).

	Gram negative bacteria				Gram positive bacteria				Fungi				
Compound	*Escherichia coli*	*Klubsellia pneumoniae*	*Pseudomonas aeruginosa*	*Pseudomonas fluorescens*	*Staphylococcus aureus*	*Bacillus subtilis*	*Streptoccus pyrogens*	*Aspergillius janus*	*Pencillium glabrum*	*Aspergillius niger*	*Fusarium oxysporum*	*Aspergillus sclerotiorum*
3(a)	16	**8**	**8**	**8**	16	**8**	16	16	**8**	16	16	16
3(b)	16	16	16	16	16	**8**	16	**8**	**8**	**8**	**8**	16
3(c)	**8**	**8**	**8**	**8**	64	**4**	16	16	16	16	16	16
3(d)	32	16	**8**	32	**8**	**8**	32	16	**8**	16	32	**8**
3(e)	16	**8**	**8**	**8**	16	**8**	16	16	**8**	**8**	16	16
3(f)	16	16	16	32	**8**	**8**	32	32	16	**8**	32	**8**
3(g)	32	16	64	16	32	16	32	16	16	32	32	32
Amoxicillin	2	2	2	2	2	2	2	–	–	–	–	–
Fluconazole	–	–	–	–	–	–	–	1	1	1	1	1

The bold emphasis indicates the significant activity of the corresponding compounds.

downfield signals placed at δ 158.62–158.27 and 143.01–142.05 may be assigned to C-3′ and C=N, respectively, because of their direct linkage to the electronegative oxygen and nitrogen atom, respectively. The rest of the carbons C-1′, C-6′, C-5′, C-2′, C-4′ and O***C***H_2 were found to be resonating at δ 137.39–134.97, 129.81–128.91, 122.82–120.52, 119.08–116.51, 111.86–111.46 and 69.12–67.18, respectively.

The comparison of the ^{1}H NMR spectra (400 MHz, DMSO-d_6) of **3**(**a–g**) and **4**(**a–g**) revealed that signals present at δ 8.12–8.01 (N***H***-β) and 7.89–7.70 (N***H***-α) in the former were found to be missing in **4**(**a–g**), which clearly describes that these protons have undergone transformation during the cyclization reaction. Here, signal of the 1‴–N***H*** proton was present at δ 11.70–11.05 (2H) as a sharp singlet. The protons H-2′, 6′, 5′ and 4′ were very well resonating in the aromatic region at δ 7.38–7.25 (2H, J = 2.6–2.1 Hz), 7.35–7.04 (2H, t, J = 8.0–4.7 Hz), 7.26–6.69 (2H, d, J_o = 7.8–0.7 Hz) and 6.90–6.68 (2H, d, J_o = 7.7–1.2 Hz), respectively. A singlet integrating for two hydrogens at δ 6.80–6.68 may be allotted to thiadiazoline ring proton H-2, and two methyl groups (3‴ and 2″) also appeared as two sharp singlets at δ 2.28–2.20 and 2.09–2.01, respectively, which were integrating for six protons each.

The UV–vis spectra of **4**(**a–g**) had n → π* and π → π* transitions at 327–322 and 279–269 nm, respectively. IR spectra exhibited strong absorptions at 3161–3154 (N–H), 2951–2928, 2873–2849 (methylene C–H), 1688–1682, 1640–1636 (C=O) and 1610–1606 cm^{-1} (C=N).

In the ^{13}C NMR (100 MHz, DMSO-d_6) spectra of **4** (**a–g**), the downfield signals corresponding to 2‴–C=O and 1″–C=O were found to be present at δ 169.90–169.02 and 169.30–167.01, respectively. The signal placed at δ 147.87–145.89 could be attributed to C=N group. The aromatic carbon atoms were found to be resonating at expected positions (vide experimental). The remaining signals were observed in the aliphatic region at δ 69.23–67.69 (O***C***H_2), 22.75–22.31 (3‴–***C***H_3) and 22.64–20.46 (2″–***C***H_3).

ANTIMICROBIAL EVALUATIONS

Antibacterial activity. The cultures required for the biological studies of **3**(**a–g**) and **4**(**a–g**) were obtained from MTCC (Microbial Type Culture Collection and Gene Bank, Chandigarh, India). The newly prepared compounds were screened for their antimicrobial activities against seven bacterial strains namely *Klubsellia pneumoniae* (MTCC 3384), *Pseudomonas aeruginosa* (MTCC 424), *Escherichia coli* (MTCC 443), *Staphylococcus aureus* (MTCC 96), *Bacillius subtilis* (MTCC 441), *Pseudomonas fluorescens* (MTCC 103) and *Streptoccus pyrogens* (MTCC 442) using serial tube dilution method at various concentrations of 128, 64, 32, 16, 8, 4, 2 and 1 µg/ml. In this protocol, weighed amounts of compounds were dissolved in DMSO to prepare a stock solution. After that, they were diluted to the final concentration of 128 µg/ml in nutrient broth medium. Amoxicillin was used as a reference drug for comparison and DMSO as a negative control. All the bacterial strains were grown in nutrient broth media at 37 °C, then 100 µl of the broth containing bacteria were inoculated to the test compounds in the different dilutions. The inoculated tubes were incubated for 24 h at 37 °C. The growth of bacteria cultures was monitored visually after 24 h. The susceptibility of studied compounds on the bacteria growth was determined by the appearance of turbidity after 24 h of incubation at 37 °C. The results of antibacterial activity have been presented in Table 1 (**3**(**a–g**)), Figure 1, and Table 2 (**4**(**a–g**)), Figure 2.

Antifungal activity. The antifungal activity of synthesized compounds **3**(**a–g**) and **4**(**a–g**) was also determined *in vitro* by using the serial tube dilution method against five fungi strains, namely, *Aspergillius*

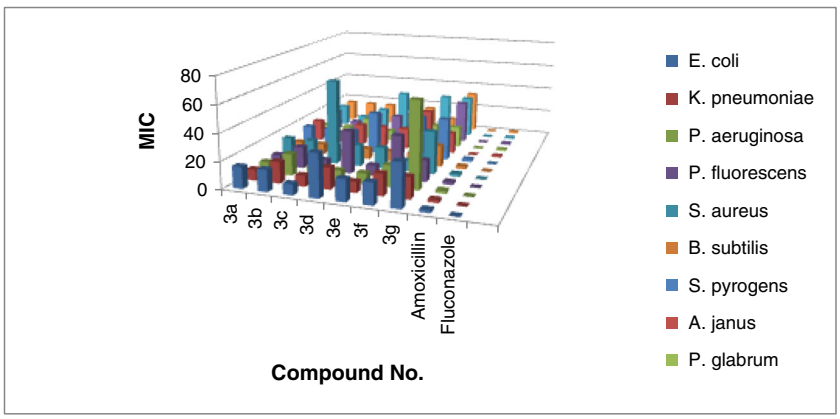


Figure 1. *In vitro* MIC (µg/ml) of bisthiosemicarbazones **3**(**a–g**).

Table 2
In vitro MIC (μg/ml) of bisthiadiazolines **4(a–g)**.

	Gram negative bacteria				Gram positive bacteria				Fungi				
Compound	*Escherichia coli*	*Klubsellia pneumoniae*	*Pseudomonas aeruginosa*	*Pseudomonas fluorescens*	*Staphylococcus aureus*	*Bacillius subtilis*	*Streptoccus pyrogens*	*Aspergillius janus*	*Pencillium glabrum*	*Aspergillius niger*	*Fusarium oxysporum*	*Aspergillus sclerotiorum*
4(a)	**8**	16	16	**8**	16	16	**8**	**4**	**8**	16	**8**	**8**
4(b)	16	16	16	**4**	16	**8**	16	**4**	**8**	16	**8**	**8**
4(c)	**8**	16	16	**8**	**8**	16	**8**	**4**	**4**	**8**	16	**8**
4(d)	16	**8**	**8**	16	**8**	16	16	**8**	**8**	16	**8**	16
4(e)	**8**	16	16	**8**	16	**8**	**4**	**4**	**8**	16	16	**4**
4(f)	16	**8**	16	16	32	32	**8**	16	32	32	32	16
4(g)	16	**8**	**4**	**8**	**8**	16	16	16	**8**	16	**8**	**8**
Amoxicillin	2	2	2	2	2	2	2	–	–	–	–	–
Fluconazole	–	–	–	–	–	–	–	1	1	1	1	1

The bold emphasis indicates the significant activity of the corresponding compounds.

janus (MTCC 2751), *Aspergillius niger* (MTCC 281), *Fusarium oxysporum* (MTCC 2480), *Aspergillus sclerotiorum* (MTCC 1008) and *Pencillium glabrum* (MTCC 4951). Similar method was used for analysis of antifungal activity as described earlier for the antibacterial activity. Fluconazole was used as a reference drug for comparison and DMSO as a negative control. The fungi strains were grown in the Malt extract for 3 days, and 100 μl of the strains were inoculated to different dilutions of the test compounds and incubated for 72 h at 28 °C. The reference drug was also sustained at similar conditions for comparison. The susceptibility of the fungal strain on the studied compounds was determined by the appearance of turbidity after 72 h of incubation at 28 °C. The observed antifungal activity values are given in Table 1 (**3(a–g)**), Figure 1, and Table 2 (**4(a–g)**), Figure 2.

It is evident from Table 1 that compound **3(a)** exhibited significant MIC (8 μg/ml) against the bacterial strains *Klubsellia pneumonia*, *P. aeruginosa*, *P. fluorescens*, *B. subtilis* and fungi strain *P. glabrum*. But the compound **3(b)** was found to be active at the same MIC against strains *B. subtilis*, *A. janus*, *P. glabrum*, *A. niger* and *Fusarium oxysporum*. The compound **3(c)** inhibited the growth of strains *Escherichia coli*, *Klubsellia pneumonia*, *P. aeruginosa* and *P. fluorescens* at the MIC of 8 μg/ml. The compound **3(c)** was found to be the most active against *B. subtilis* (MIC – 4 μg/ml). The compounds **3(d** and **e)** showed activity against *P. aeruginosa*, *B. subtilis* and *P. glabrum* at MIC of 8 μg/ml. Compound **3(e)** also inhibited the growth of *Klubsellia pneumoniae*, *Pseudomonas fluoresencens* and *A. niger*, while the compound **3(f)** was active against *Staphylococcus aureus*, *B. subtilis*, *A. niger* and *A. sclerotiorum* at MIC of 8 μg/ml.

Table 2 describes that compounds **4(a–e)** displayed significant activity (MIC – 4 μg/ml) against the strain *A. janus*, whereas compounds **4(b** and **c)** also inhibited the growth of strain *Pseudomonas flurescens* and *P. glabrum*, respectively, at the same MIC. The compound **4(e)** was found to be active at MIC of 4 μg/ml against *Streptoccus pyrogens* and *A. sclerotiorum*. The compound **4(g)** was significantly active against the strain *P. aeruginosa* (MIC – 4 μg/ml). Most of the compounds exhibited good activity at MIC of 8 μg/ml against the tested microorganisms.

It was also observed from Tables 1 and 2 that bisthiadiazolines **4(a–g)** were found to be biologically more active than their corresponding bisthiosemicarbazones **3(a–g)**. The geometry of internal spacer had significant effect upon the antimicrobial behavior of the bisthiadiazoline, and the bisheterocyclics linked through the aromatic moiety (*o*-xylene **4(b)**, *p*-xylene **4(c)** and biphenyl **4(e)**) exhibited better activity as compared to the compounds involving olefinic and alkynic chain.

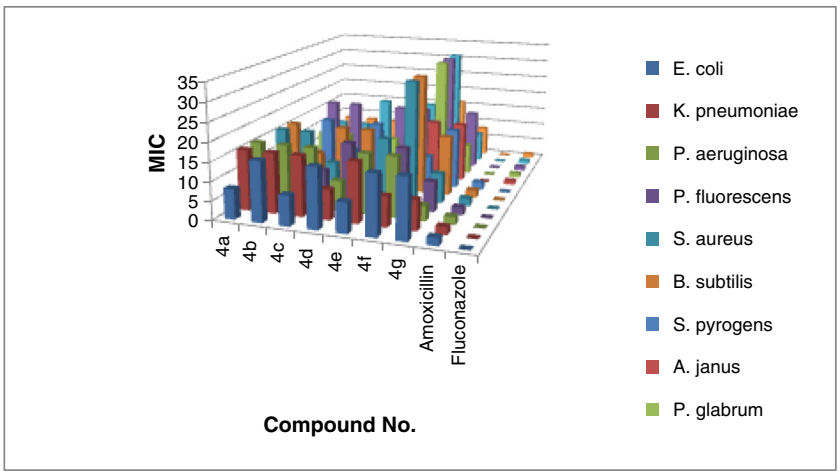


Figure 2. *In vitro* MIC (μg/ml) of bisthidiazolines **4**(**a–g**).

CONCLUSION

It may be concluded that this study describes a general and efficient method for the synthesis of new thiadiazoline-based symmetrical bisheterocyclic compounds built around the seven rigid spacers. It was also observed that the bisthidiazolines **4** (**a–g**) seem to be significant antifungal agents.

EXPERIMENTAL

Melting points reported are uncorrected. IR spectra were scanned in KBr pellets on a Perkin Elmer (Buckinghamshire, England) RXIFT Infrared spectrophotometer. ^{1}H NMR spectra (Fallanden, Switzerland) were recorded on a 400 MHz Bruker spectrometer using TMS as the internal standard. The mass spectra (Vernon Hills, USA) 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.

Synthesis of 3,3′-[but-2-ene-1,4-diylbis(oxy)]dibenzaldehyde 2a. 3-ydroxybenzaldehyde (1.22 g, 0.01 mol) and KOH (0.55 g, 0.01 mol) were dissolved in alcohol (100 ml), and then solvent was removed under vacuum. The residue was dissolved in DMF (25 ml), and *trans*-1,4-dibromo-2-butene (1.07 g, 0.005 mol) was added slowly. The reaction mixture was refluxed for 4 h, during which KBr was separated out. The solvent was removed under vacuum, and the remaining mixture was poured into iced HCl to give a solid substance, which was filtered under suction and thoroughly washed with water. The crude product thus obtained was crystallized from MeOH to yield pure compound **2**(**a**).

2(**a**): light brown solid; yield 71%; m.p.: 70–72 °C; IR (KBr): ν_{max} (cm^{-1}): 3070 (aromatic C–H), 2910, 2832 (methylene C–H), 2864, 2751 (aldehyde C–H), 1686 (C═O), 1258, 1025 (C–O); UV–vis (MeOH): λ_{max} (nm): 324, 261; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (2H, s, C***H***O), 7.48 (2H, d, J = 1.2 Hz, H-2), 7.46 (2H, dd, J = 2.3, 4.9 Hz, H-6), 7.39 (2H, t, J = 7.3 Hz, H-5), 7.20 (2H, dt, J = 2.3, 4.9 Hz, H-4), 6.12 (2H, t, J_{vic} = 1.6 Hz, C***H***═), 4.65 (4H, dd, J = 1.2, 2.3 Hz, OC$\boldsymbol{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.13 (***C***═O), 159.09 (C-3), 137.87 (C-1), 130.22 (C-2), 128.17 (***C***H═), 123.90 (C-6), 122.18 (C-5), 112.97 (C-4), 67.83 (O***C***H_2); ESI-MS: m/z 319 (M + Na, 50%), 281 (4%), 181 (3%), 173 (29%), 159 (13%), 154 (5%), 131 (8%). *Anal*. Calc. for $C_{18}H_{16}O_4$: Calc. C, 73.00%; H, 5.40%. Found: C, 72.70%; H, 5.12%.

Synthesis of 3,3′-[benzene-1,2-diylbis(methanediyloxy)]dibenzaldehyde 2b. The compound **2**(**b**) was obtained by reacting 3-hydroxybenzaldehyde (1.22 g, 0.01 mol) with α,α′-dibromo-*o*-xylene (1.32 g, 0.005 mol) under similar conditions as used earlier for **2**(**a**).

2(**b**): Light brown solid; Yield 74%; m.p.: 57–59 °C; IR (KBr): ν_{max} (cm^{-1}): 3064 (aromatic C–H), 2920, 2826 (methylene C–H), 2877, 2758 (aldehyde C–H), 1684 (C═O), 1261, 1038 (C–O); UV–vis (MeOH): λ_{max} (nm): 328, 264; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (2H, s, C***H***O), 7.53 (2H, dd, J = 3.5, 6.9 Hz, H-4′, 5′), 7.45 (2H, d, J_m = 2.2 Hz, H-2), 7.43 (2H, d, J = 4.0 Hz, H-6), 7.41 (2H, d, J = 4.0 Hz, H-3′, 6′), 7.38 (2H, t, J = 3.4 Hz, H-5), 7.23 (2H, td, J = 1.6, 2.7 Hz, H-4), 5.23 (4H, s, OC$\boldsymbol{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.98 (***C***═O), 159.14 (C-3), 137.86 (C-1), 134.64 (C-2), 130.22 (C-1′, 2′), 129.32 (C-4′, 5′), 128.83 (C-3′, 6′), 123.92 (C-6), 122.07 (C-5), 113.19 (C-4), 68.31 (O***C***H_2); ESI-MS: m/z 369 (M + Na, 53%), 347 (M + 1, 100%), 302 (3%), 301 (4%), 225 (12%), 210 (8%), 209 (40%), 181 (11%). *Anal*. Calc. for $C_{22}H_{18}O_4$: Calc. C, 76.30%; H, 5.40%. Found: C, 76.60%; H, 5.42%.

Synthesis of 3,3′-[benzene-1,4-diylbis(methanediyloxy)]dibenzaldehyde 2c. The compound **2**(**c**) was prepared by reacting 3-hydroxybenzaldehyde (1.22 g, 0.01 mol) with α,α′-dibromo-*p*-xylene (1.32 g, 0.005 mol) under similar conditions as discussed for **2**(**a**).

2(**c**): Off white solid; Yield 88%; m.p.: 122–124 °C; IR (KBr): ν_{max} (cm^{-1}): 3065 (aromatic C–H), 2929, 2834 (methylene C–H), 2832, 2742 (aldehyde C–H), 1694 (C═O), 1254, 1037 (C–O); UV–vis (MeOH): λ_{max} (nm): 322, 269; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (2H, s, C***H***O), 7.48 (2H, brs, H-2), 7.47 (4H, s, H-2′, 3′, 5′, 6′), 7.45 (2H, brs, H-6), 7.26 (2H, t, J = 3.1 Hz, H-5), 7.24 (2H, t, J_m = 2.2 Hz, H-4), 5.14 (4H, s, OC$\boldsymbol{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.04 (***C***═O), 159.24 (C-3), 137.86 (C-1), 136.37 (C-1′, 4′), 130.17 (C-2), 127.85 (C-2′, 3′, 5′, 6′), 123.84 (C-6), 122.14 (C-5), 113.18 (C-4), 69.99 (O***C***H_2); ESI-MS: m/z 369 (M + Na, 100%), 347 (M + 1, 41%), 270 (29%), 225 (19%), 211 (16%), 121 (65%), 106 (43%). *Anal*. Calc. for $C_{22}H_{18}O_4$: Calc. C, 76.30%; H, 5.20%. Found: C, 76.00%; H, 5.17%.

Synthesis of 3-(3-(3-formylbenzyloxy)benzyloxy)benzaldehyde 2d. The compound **2**(**d**) was synthesized by reacting 3-hydrox ybenzaldehyde (1.22 g, 0.01 mol) with α,α′-dibromo-*m*-xylene (1.32 g, 0.005 mol) under similar conditions as described earlier for **2**(**a**).

2(**d**): light brown solid; yield 69%; m.p.: 63–65 °C; IR (KBr): ν_{max} (cm^{-1}): 3348 (aromatic C–H), 2927, 2837 (methylene C–H), 2871, 2759 (aldehyde C–H), 1682 (C═O), 1253, 1039 (C–O); UV–vis (MeOH): λ_{max} (nm): 326, 270; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (2H, s, C***H***O), 7.53 (2H, brs, H-2), 7.48 (2H, d, J_m = 1.5 Hz, H-6), 7.44 (2H, brs, H-5), 7.42 (1H, brs, H-6′), 7.36 (1H, d, *J* = 1.1 Hz, H-5′), 7.26 (2H, d, *J* = 4.5 Hz, H-2′, 4′), 7.23 (2H, t, *J* = 2.2 Hz, H-4), 5.13 (4H, s, OC***H***$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.06 (***C***═O), 159.18 (C-3), 137.79 (C-1′), 136.86 (C-1), 130.32 (C-2), 129.16 (C-6′), 128.84 (C-4′), 127.49 (C-3′), 126.72 (C-2′), 126.50 (C-5′), 123.80 (C-6), 122.76 (C-5), 113.19 (C-4), 69.94 (O***C***H$_2$); ESI-MS: m/z 369 (M + Na, 100%), 347 (M + 1, 59%), 268 (12%), 214 (6%), 213 (19%), 109 (24%), 104 (32%). *Anal*. Calc. for $C_{22}H_{18}O_4$: Calc. C, 76.30%; H, 5.40%. Found: C, 76.58%; H, 5.43%.

Synthesis of 3,3′-(biphenyl-4,4′-diylbis(methylene))bis(oxy)dibenzaldehyde 2e. The compound **2**(**e**) was prepared by reacting 3-hydroxybenzaldehyde (1.22 g, 0.01 mol) with 4,4′-bis-chloromethyldiphenyl (1.25 g, 0.005 mol) under similar conditions as given earlier for **2**(**a**).

2(**e**): light brown solid; yield 67%; m.p.: 119–121 °C; IR (KBr): ν_{max} (cm^{-1}): 3063 (aromatic C–H), 2924, 2820 (methylene C–H), 2870, 2726 (aldehyde C–H), 1693 (C═O), 1261, 1027 (C–O); UV–vis (MeOH): λ_{max} (nm): 320, 262; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (2H, s, C***H***O), 7.74 (2H, s, H-2), 7.63 (4H, d, J_o = 8.0 Hz, H-3′, 5′), 7.53 (4H, d, J_o = 8.0 Hz, H-2′, 6′), 7.49 (4H, brs, H-6), 7.48 (2H, brs, H-5), 7.28 (2H, dd, $J_{m,o}$ = 3.6, 7.1 Hz, H-4), 5.18 (4H, s, OC***H***$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.58 (***C***═O), 159.24 (C-3), 139.74 (C-4′), 137.31 (C-1), 135.21 (C-1′), 129.87 (C-2), 127.72 (C-3′, 5′), 126.69 (C-2′, 6′), 122.91 (C-6), 121.42 (C-5), 113.16 (C-4), 69.28 (O***C***H$_2$); ESI-MS: m/z 445 (M + Na, 9%), 423 (M + 1, 2%), 413 (8%), 359 (12%), 302 (23%), 301 (100%), 273 (4%), 219 (26%), 180 (42%), 149 (52%), 104 (8%). *Anal*. Calc. for $C_{28}H_{22}O_4$: Calc. C, 79.62%; H, 5.21%. Found: C, 79.93%; H, 5.23%.

Synthesis of 3,3′-(but-2-ene-1,4-diylbis(oxy))dibenzaldehyde 2f. The compound **2**(**f**) was obtained by reacting 3-hydroxybenza ldehyde (0.01 mol, 1.22 g) with *cis*-1,4-dichloro-2-butene (1.07 g, 0.005 mol) under similar conditions as used earlier for **2**(**a**).

2(**f**): light brown solid; yield 70%; m.p.: 52–54 °C; IR (KBr): ν_{max} (cm^{-1}): 3073 (aromatic C–H), 2909, 2838 (methylene C–H), 2868, 2754 (aldehyde C–H), 1689 (C═O), 1257, 1024 (C–O); UV–vis (MeOH): λ_{max} (nm): 324, 272; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (2H, s, C***H***O), 7.49 (2H, d, *J* = 1.2 Hz, H-2), 7.44 (2H, d, *J* = 1.9 Hz, H-5), 7.40 (2H, t, *J* = 1.3, 7.4 Hz, H-6), 7.22 (2H, m, H-4), 5.98 (2H, t, J_{vic} = 3.4 Hz, C***H***═), 4.76 (4H, d, J_{vic} = 4.0 Hz, OC***H***$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.05 (***C***═O), 158.92 (C-3), 137.83 (C-1), 130.23 (C-2), 128.39 (***C***H═), 123.90 (C-6), 122.11 (C-5), 112.80 (C-4), 64.38 (O***C***H$_2$); ESI-MS: m/z 319 (M + Na, 29%), 297 (M + 1, 100%), 276 (23%), 240 (8%), 194 (43%), 147 (12%), 129 (37%). *Anal*. Calc. for $C_{18}H_{16}O_4$: Calc. C, 73.00%; H, 5.40%. Found: C, 73.29%; H, 5.38%.

Synthesis of 3,3′-[but-2-yne-1,4-diylbis(oxy)]dibenzaldehyde 2g. The compound **2**(**g**) was synthesized by reacting 3-hydroxybenzaldehyde (1.22 g, 0.01 mol) with 1,4-dichloro-2-butyne (1.47 g, 0.005 mol) under similar conditions as used earlier for **2**(**a**).

2(**g**): brown solid; yield 64%; m.p.: 184–186 °C; IR (KBr): ν_{max} (cm^{-1}): 3059 (aromatic C–H), 2923, 2832 (methylene C–H), 2879, 2757 (aldehyde C–H), 1682 (C═O), 1260, 1040 (C–O); UV–vis (MeOH): λ_{max} (nm): 332, 269; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (2H, s, C***H***O), 7.56 (2H, d, *J* = 3.7 Hz, H-2), 7.47 (4H, d, *J* = 3.8 Hz, H-6), 7.43 (2H, t, *J* = 3.9 Hz, H-5), 7.25 (2H, td, *J* = 1.6, 2.7 Hz, H-4), 5.15 (4H, s, OC***H***$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.15 (***C***═O), 159.01 (C-3), 137.80 (C-1), 130.36 (C-2), 123.79 (C-6), 122.14 (C-5), 113.19 (C-4), 83.07 (C-2′), 68.31 (O***C***H$_2$); ESI-MS: m/z 317 (M + Na, 32%), 295 (M + 1, 45%), 284 (4%), 262 (100%), 158 (17%), 106 (67%). *Anal*. Calc. for $C_{18}H_{14}O_4$: Calc. C, 73.46%; H, 4.70%. Found: C, 73.24%; H, 4.68%.

Synthesis of 2,2′-(3,3′-(but-2-ene-1,4-diylbis(oxy))bis(3,1-phenylene))bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) 3a. A mixture of **2**(**a**) (1.1 g, 0.005 mol) and thiosemicarbazide (0.91 g, 0.01 mol) in dry EtOH (20 ml) and HCl (1.0 ml) was refluxed for 4 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the resulting mixture was cooled in an ice bath to give a solid substance. The crude product thus obtained was filtered under suction, dried and crystallized from MeOH to yield pure compound **3**(**a**).

3(**a**): off white solid; yield 87%; m.p.: 110–112 °C; IR (KBr): ν_{max} (cm^{-1}) 3447, 3267, 3156 (N–H), 3026 (aromatic C–H), 2984, 2865 (methylene C–H), 1599 (C═N), 1261, 1082 (C–O), 1180 (C═S); UV–vis (MeOH): λ_{max} (nm): 320; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (2H, s, 3-N***H***), 8.01 (2H, s, N***H***-β), 7.99 (2H, s, H-1), 7.70 (2H, brs, N***H***-α), 7.40 (2H, t, *J* = 2.2 Hz, H-2′), 7.27 (2H, t, *J* = 7.8 Hz, H-5′), 7.26 (2H, d, J_o = 7.6 Hz, H-6′), 6.93 (2H, ddd, *J* = 0.8, 2.6, 3.4 Hz, H-4′), 6.11 (2H, t, J_{vic} = 2.4 Hz, C***H***═), 4.65 (4H, d, J_{vic} = 1.1 Hz, OC***H***$_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.97 (***C***═S), 158.27 (C-3′), 142.24 (C═N), 135.33 (C-1′), 129.30 (C-6′), 127.95 (***C***H═), 120.52 (C-5′), 116.51 (C-2′), 111.46 (C-4′), 67.18 (O***C***H$_2$); ESI-MS: m/z 465 (M + Na, 59%), 443 (M + 1, 23%), 426 (4%), 395 (27%), 389 (100%), 369 (6%), 354 (12%), 352 (21%), 324 (22%), 323 (63%), 313 (30%), 308 (23%), 224 (7%), 179 (7%). *Anal*. Calc. for $C_{20}H_{22}N_6O_2S_2$: Calc. C, 54.29%, H, 4.97%; N, 19.00%; S, 14.47%. Found: C, 54.50%; H, 4.99%; N, 18.96%; S, 14.38%.

Synthesis of 2,2′-(3,3′-(1,2-phenylenebis(methylene))bis(oxy)bis(3,1-phenylene)) bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) 3b. The compound **3**(**b**) was obtained by reacting **2**(**b**) (0.5 g, 0.001445 mol) with thiosemicarbazide (0.26 g, 0.00289 mol) under the same conditions as given earlier for **3**(**a**).

3(**b**): off white solid; yield 82%; m.p.: 218–220 °C; IR (KBr): ν_{max} (cm^{-1}) 3425, 3262, 3152 (N–H), 3027 (aromatic C–H), 2974, 2881 (methylene C–H), 1589 (C═N), 1257, 1097 (C–O), 1171 (C═S); UV–vis (MeOH): λ_{max} (nm): 322; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.41 (2H, s, 3-N***H***), 8.09 (2H, brs, N***H***-β), 8.01 (2H, s, H-1), 7.81 (2H, brs, N***H***-α), 7.53 (2H, d, *J* = 3.3 Hz, H-4″, 5″), 7.51 (2H, brs, H-2′), 7.36 (2H, d, *J* = 3.2 Hz, H-3″, 6″), 7.27 (2H, t, *J* = 7.7 Hz, H-5′), 7.22 (2H, d, J_o = 7.3 Hz, H-6′), 6.99 (2H, d, J_o = 7.7 Hz, H-4′), 5.26 (4H, s, OC***H***$_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.01 (***C***═S), 158.46 (C-3′), 142.05 (C-1), 135.45 (C-4″, 5″), 134.97 (C-1′), 129.41 (C-6′), 128.66 (C-1″, 2″), 127.96 (C-3″, 6″), 120.73 (C-5′), 116.55 (C-2′), 111.86 (C-4′), 67.33 (O***C***H$_2$); ESI-MS: m/z 515 (M + Na, 5%), 493 (M + 1, 4%), 491 (6%), 476 (20%), 475 (62%), 453 (100%), 436 (7%), 432 (10%), 417 (6%), 402 (9%), 383 (8%), 374 (11%), 373 (19%), 369 (20%), 359 (13%). *Anal*. Calc. for $C_{24}H_{24}N_6O_2S_2$: Calc. C, 58.53%; H,

4.88%; N, 17.07%; S, 13.00%. Found: C, 58.76%; H, 4.90%; N, 17.13%; S, 13.05%.

Synthesis of 2,2′-(3,3′-(1,4-phenylenebis(methylene))bis(oxy)bis(3,1-phenylene))bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) 3c. The compound **3**(**c**) was prepared by reacting **2**(**c**) (0.5 g, 0.001445 mol) with thiosemicarbazide (0.15 g, 0.00173 mol) under the same conditions as described previously for **3**(**a**).

3(**c**): off white solid; yield 85%; m.p.: 209–211 °C; IR (KBr): υ_{max} (cm^{-1}) 3427, 3240, 3102 (N–H), 3023 (aromatic C–H), 2975, 2883 (methylene C–H), 1589 (C═N), 1262, 1098 (C–O), 1162 (C═S); UV–vis (MeOH): λ_{max} (nm): 323; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (2H, s, 3-N***H***), 8.12 (2H, s, N***H***-β), 8.03 (2H, s, H-1), 7.89 (2H, brs, N***H***-α), 7.53 (2H, brs, H-2′), 7.48 (4H, s, H-2″, 3″, 5″, 6″), 7.30 (2H, t, *J* = 7.8 Hz, H-6′), 7.22 (2H, t, *J* = 7.4 Hz, H-5′), 7.04 (2H, dd, *J* = 1.5, 6.4 Hz, H-4′), 5.14 (4H, s, OC***H***$_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.99 (***C***═S), 158.54 (C-3′), 142.08 (C-1), 136.44 (C-1′), 135.49 (C-1″, 4″), 129.42 (C-6′), 127.65 (C-2″, 3″, 5″, 6″), 120.73 (C-5′), 116.66 (C-2′), 111.67 (C-4′), 69.12 (O***C***H$_2$); ESI-MS: m/z 515 (M + Na, 14%), 493 (M + 1, 54%), 476 (18%), 475 (23%), 445 (27%), 432 (16%), 418 (4%), 417 (11%), 404 (14%), 374 (20%), 373 (53%), 344 (8%), 343 (13%), 300 (7%), 299 (20%), 298 (100%), 179 (14%), 147 (17%), 104 (8%). *Anal*. Calc. for $C_{24}H_{24}N_6O_2S_2$: Calc. C, 58.53%; H, 4.87%; N, 17.07%; S, 13.00%. Found: C, 58.29%; H, 4.85%; N, 17.00%, S, 12.94%.

Synthesis of 2-(3-(3-(3-((2-carbamothioylhydrazono)methyl)benzyloxy)benzylidene) hydrazinecarbothioamide of 3d. The compound **3**(**d**) was synthesized by reacting **2**(**d**) (0.5 g, 0.001445 mol) with thiosemicarbazide (0.26 g, 0.00289 mol) under the same conditions as used in **3**(**a**).

3(**d**): light brown solid; yield 88%; m.p.: 63–65 °C; IR (KBr): υ_{max} (cm^{-1}) 3428, 3260, 3154 (N–H), 3025 (aromatic C–H), 2973, 2883 (methylene C–H), 1591 (C═N), 1256, 1095 (C–O), 1175 (C═S); UV–vis (MeOH): λ_{max} (nm): 321; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.39 (2H, s, 3-N***H***), 8.05 (2H, brs, N***H***-β), 8.03 (2H, s, H-1), 7.80 (2H, brs, N***H***-α), 7.55 (2H, d, *J* = 3.1 Hz, H-6″), 7.52 (1H, d, *J* = 2.9 Hz, H-5″), 7.49 (2H, brs, H-2′), 7.37 (2H, d, *J* = 3.0 Hz, H-2″, 4″), 7.26 (2H, t, *J* = 7.5 Hz, H-5′), 7.21 (2H, d, J_o = 7.3 Hz, H-6′), 7.01 (2H, d, J_o = 7.6 Hz, H-4′), 5.13 (4H, s, OC***H***$_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.98 (***C***═S), 158.60 (C-3′), 142.08 (C-1), 136.83 (C-1′), 136.43 (C-1″, 3″), 135.45 (C-4″, 6″), 129.81 (C-6′), 127.96 (C-2″), 121.09 (C-5″), 120.68 (C-5′), 118.01 (C-2′), 111.67 (C-4′), 68.04 (O***C***H$_2$); ESI-MS: m/z 515 (M + Na, 100%), 493 (M + 1, 78%), 478 (12%), 477 (6%), 423 (41%), 421 (9%), 419 (11%), 417 (43%), 399 (60%), 380 (28%), 371 (5%), 370 (9%), 368 (7%), 359 (12%). *Anal*. Calc. for $C_{24}H_{24}N_6O_2S_2$: Calc. C, 58.53%; H, 4.88%; N, 17.07%; S, 13.00%. Found: C, 58.31%; H, 4.85%; N, 17.05%; S, 12.96%.

Synthesis of 2,2′-(3,3′-(1,2-phenylenebis(methylene))bis(oxy)bis(3,1-phenylene)) bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) 3e. The compound **3**(**e**) was synthesized by reacting **2**(**e**) (0.5 g, 0.00118 mol) with thiosemicarbazide (0.214 g, 0.00236 mol) under the similar conditions as described earlier for **3**(**a**).

3(**e**): light brown solid; yield 88%; m.p.: 218–220 °C; IR (KBr): ν_{max} (cm^{-1}): 3400, 3243, 3155 (N–H), 3026 (aromatic C–H), 2982, 2862 (methylene C–H), 1599 (C═N), 1264, 1087 (C–O), 1176 (C═S); UV–vis (MeOH): λ_{max} (nm): 318; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.43 (2H, s, 3-N***H***), 8.10 (2H, s, N***H***-β), 8.04 (2H, s, H-1), 7.82 (2H, brs, N***H***-α), 7.69 (2H, brs, H-2′), 7.67 (4H, d, J_o = 8.1 Hz, H-3″, 5″), 7.55 (4H, d, J_o = 8.0 Hz, H-2″, 6″), 7.30 (2H, t, *J* = 7.7 Hz, H-5′), 7.21 (2H, d, J_o = 6.8 Hz, H-6′), 7.01 (2H, d, J_o = 7.0 Hz, H-4′), 5.18 (4H, s, OC***H***$_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.83 (***C***═S), 158.62 (C-3′), 142.12 (C-1), 139.39 (C-4″), 137.39 (C-1′), 135.71 (C-1″), 129.62 (C-6′), 128.03 (C-3″, 5″), 126.59 (C-2″, 6″), 122.82 (C-5′), 119.08 (C-2′), 114.56 (C-4′), 68.20 (O***C***H$_2$); ESI-MS: m/z 559 (M + Na, 100%), 537 (M + 1, 46%), 455 (39%), 419 (35%), 403 (4%), 375 (27%), 374 (100%), 338 (18%), 298 (31%), 257 (4%), 245 (21%), 197 (6%), 180 (23%), 140 (61%), 105 (4%). *Anal*. Calc. for $C_{30}H_{28}N_6S_2$: Calc. C, 63.38%; H, 4.93%; N, 14.78%. Found: C, 63.63%; H, 4.95%; N, 14.83%.

Synthesis of 2,2′-(3,3′-(but-2-ene-1,4-diylbis(oxy))bis(bis(3,1-phenylene)) bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) 3f. The compound **3**(**f**) was obtained by reacting **2**(**f**) (1.1 g, 0.005 mol) with thiosemicarbazide (0.91 g, 0.01 mol) under the same conditions as described previously for **3**(**a**).

3(**f**): off white solid; yield 87%; m.p.: 168–170 °C; IR (KBr): υ_{max} (cm^{-1}) 3449, 3269, 3154 (N–H), 3027 (aromatic C–H), 2981, 2867 (methylene C–H), 1598 (C═N), 1261, 1082 (C–O), 1178 (C═S); UV–vis (MeOH): λ_{max} (nm): 323; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.39 (2H, s, 3-N***H***), 8.07 (2H, s, N***H***-β), 8.02 (2H, s, H-1), 7.77 (2H, brs, N***H***-α), 7.42 (2H, t, *J* = 2.2 Hz, H-2′), 7.27 (2H, d, J_o = 7.4 Hz, H-6′), 7.25 (2H, t, *J* = 7.6 Hz, H-5′), 6.93 (2H, ddd, *J* = 0.7, 3.2, 2.6 Hz, H-4′), 6.09 (2H, t, J_{vic} = 2.1 Hz, C***H***═), 4.62 (4H, d, J_{vic} = 1.2 Hz, OC***H***$_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.97 (***C***═S), 158.27 (C-3′), 142.42 (C-1), 136.83 (C-1′), 129.30 (C-6′), 127.95 (***C***H═), 120.52 (C-5′), 116.51 (C-2′), 111.46 (C-4′), 67.18 (O***C***H$_2$); ESI-MS: m/z 465 (M + Na, 100%), 443 (M + 1, 100%), 414 (24%), 378 (5%), 377 (8%), 364 (52%), 349 (16%), 348 (76%), 329 (19%), 321 (4%), 300 (6%), 279 (11%), 267 (7%), 248 (27%), 154 (10%). *Anal*. Calc. for $C_{20}H_{22}N_6O_2S_2$: Calc. C, 54.29%, H, 4.97%; N, 19.00%; S, 14.47%. Found: C, 54.50%; H, 5.00%; N, 19.07%; S, 14.53%.

Synthesis of 2,2′-(3,3′-(but-2-yne-1,4-diylbis(oxy))bis(3,1-phenylene))bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) 3g. The compound **3**(**g**) was prepared by reacting **2**(**g**) (0.5 g, 0.00170 mol) with thiosemicarbazide (0.30 g, 0.00340 mol) under the same conditions as used in **3**(**a**).

3(**g**): light brown solid; yield 71%; m.p.: 209–211 °C; IR (KBr): υ_{max} (cm^{-1}) 3429, 3257, 3160 (N–H), 3025 (aromatic C–H), 2982, 2879 (methylene C–H), 1600 (C═N), 1256, 1084 (C–O), 1178 (C═S); UV–vis (MeOH): λ_{max} (nm): 328; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.39 (2H, s, 3-N***H***), 8.07 (2H, s, N***H***-β), 7.94 (2H, s, H-1), 7.79 (2H, brs, N***H***-α), 7.38 (2H, t, *J* = 1.8 Hz, H-2′), 7.29 (2H, t, *J* = 6.7 Hz, H-5′), 7.25 (2H, d, J_o = 7.1 Hz, H-6′), 6.89 (2H, dd, *J* = 0.9, 2.3 Hz, H-4′), 4.72 (4H, s, OC***H***$_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.70 (***C***═S), 158.50 (C-3′), 143.01 (C-1), 136.07 (C-1′), 128.91 (C-6′), 127.89 (C-2″), 121.86 (C-5′), 117.68 (C-2′), 111.86 (C-4′), 67.80 (O***C***H$_2$); ESI-MS: m/z 463 (M + Na, 51%), 441 (M + 1, 12%), 426 (7%), 416 (100%), 412 (43%), 406 (20%), 405 (62%), 381 (17%), 346 (44%), 342 (16%), 310 (3%), 282 (19%), 163 (4%). *Anal*. Calc. for $C_{20}H_{20}N_6O_2S_2$: Calc. C, 54.54%; H, 4.54%; N, 19.09%; S, 14.54%. Found: C, 54.32%; H, 4.52%; N, 19.08%; S, 14.46%.

Synthesis of N,N′-(5,5′-(3,3′-(but-2-ene-1,4-diylbis(oxy))bis(3,1-phenylene))bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl))diacetamide 4a. A mixture of **3**(**a**) (0.5 g, 0.00113 mol) and acetic anhydride (25 ml) was refluxed for 10 h, and 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 MeOH to yield pure compound **4**(**a**).

4(**a**): creamish solid; yield 85%; m.p.: 69–71 °C; IR (KBr): ν_{max} (cm^{-1}): 3159 (N–H), 3062 (aromatic C–H), 2934, 2861 (methylene C–H), 1685, 1638 (C═O), 1607 (C═N), 1239, 1015 (C–O); UV–vis (MeOH): λ_{max} (nm): 324, 279; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.62 (2H, s, 1‴–N***H***), 7.27 (2H, brs, H-2′), 7.21 (2H, t, J = 7.2 Hz, H-6′), 6.85 (2H, d, J_o = 7.3 Hz, H-5′), 6.79 (2H, d, J_o = 7.6 Hz, H-4′), 6.76 (2H, s, H-2), 6.04 (2H, t, J_{vic} = 1.8 Hz, C***H***═), 4.57 (4H, d, J_{vic} = 1.4 Hz, OC***H***$_2$), 2.28 (6H, s, 3‴–C***H***$_3$), 2.01 (6H, s, 2″–C***H***$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.67 (2‴–C═O), 169.30 (1″–C═O), 158.88 (C-3′), 147.35 (***C***═N), 141.89 (C-1′), 130.06 (C-6′), 128.30 (OCH$_2$***C***H═), 118.09 (C-5′), 114.26 (C-2′), 112.37 (C-4′), 67.69 (O***C***H$_2$), 67.15 (C-2), 22.75 (3‴–***C***H$_3$), 22.64 (2″–***C***H$_3$); ESI-MS: m/z 633 (M + Na, 100%), 578 (5%), 533 (6%), 532 (11%), 476 (4%), 344 (37%). *Anal*. Calc. for $C_{28}H_{30}N_6O_6S_2$: Calc. C, 55.08%; H, 4.92%; N, 13.77%; S, 10.49%. Found: C, 55.30%; H, 4.94%; N, 13.82%; S, 10.38%.

Synthesis of N,N′-(5,5′-(3,3′-(1,2-phenylenebis(methylene))bis(oxy) bis(3,1-phenylene))bis(4-acetyl-4, 5-dihydro-1,3,4-thiadiazole-5,2-diyl)) diacetamide 4b. The compound **4**(**b**) was prepared by reacting **3**(**b**) (0.5 g, 0.00101 mol) with acetic anhydride (25 ml) under the same conditions as used for earlier for **4**(**a**).

4(**b**): off white solid; yield 66%; m.p.: 108–110 °C; IR (KBr): ν_{max} (cm^{-1}): 3154 (N–H), 3068 (aromatic C–H), 2951, 2862 (methylene C–H), 1682, 1640 (C═O), 1610 (C═N), 1240, 1034 (C–O); UV–vis (MeOH): λ_{max} (nm): 323, 269; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.68 (2H, s, 1‴–N***H***), 7.36 (2H, m, H-2′), 7.30 (2H, brs, H-6′), 7.26 (2H, t, J = 0.7 Hz, H-5′), 7.06 (2H, d, J_p = 0.4 Hz, H-4‴′, 5‴′), 6.93 (2H, d, J_p = 0.3 Hz, H-3′‴, 6‴′), 6.90 (2H, d, J = 1.2 Hz, H-4′), 6.68 (2H, s, H-2), 5.22 (4H, s, OC***H***$_2$), 2.25 (6H, s, 3‴–C***H***$_3$), 2.08 (6H, s, 2″–C***H***$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.04 (2‴–C═O), 167.18 (1″–C═O), 159.01 (C-3′), 145.89 (***C***═N), 143.87 (C-1′), 137.43 (C-1‴′, 2‴′), 136.34 (C-4‴′, 5‴′), 135.02 (C-3‴′, 6‴′), 129.53 (C-6′), 115.65 (C-5′), 113.58 (C-4′), 111.61 (C-2′), 69.20 (O***C***H$_2$), 67.08 (C-2), 22.43 (3‴–***C***H$_3$), 20.46 (2″–***C***H$_3$); ESI-MS: m/z 683 (M + Na, 100%), 661 (M + 1, 71%), 617 (18%), 526 (9%), 491 (4%), 476 (14%), 475 (40%). *Anal*. Calc. for $C_{32}H_{32}N_6O_6S_2$: Calc. C, 58.18%; H, 4.84%; N, 12.72%; S, 9.69%. Found: C, 58.41%; H, 4.86%; N, 12.64%; S, 9.73%.

Synthesis of N,N′-(5,5′-(3,3′-(1,4-phenylenebis(methylene))bis (oxy)bis(3,1-phenylene)) bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl))diacetamide 4c. The compound **4**(**c**) was synthesized by reacting **3**(**c**) (0.5 g, 0.00101 mol) with acetic anhydride (25 ml) under the similar conditions as used for **4**(**a**).

4(**c**): off white solid; yield 80%; m.p.: 96–98 °C; IR(KBr): ν_{max} (cm^{-1}): 3161 (N–H), 3061 (aromatic C–H), 2934, 2852 (methylene C–H), 1687, 1639 (C═O), 1606 (C═N), 1239, 1035 (C–O); UV–vis (MeOH): λ_{max} (nm): 322, 278; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.70 (2H, s, 1‴–N***H***), 7.52 (4H, s, H-2‴′, 3‴′, 5‴′, 6‴′), 7.38 (2H, d, J = 2.6 Hz, H-2′), 7.35 (2H, td, J = 4.9, 8.3 Hz, H-6′), 7.24 (2H, t, J = 7.8 Hz, H-5′), 6.83 (2H, d, J_o = 7.7 Hz, H-4′), 6.75 (2H, brs, H-2), 5.20 (4H, s, OC***H***$_2$), 2.20 (6H, s, 3‴–C***H***$_3$), 2.04 (6H, s, 2″–C***H***$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.09 (2‴–C═O), 167.29 (1″–C═O), 158.48 (C-3′), 146.07 (***C***═N), 142.78 (C-1′), 137.48 (C-1‴′, 4‴′), 135.65 (C-2‴′, 3‴′, 5‴′, 6‴′), 129.50 (C-6′), 115.63 (C-5′), 113.58 (C-4′), 111.62 (C-2′), 69.21 (O***C***H$_2$), 67.08 (C-2), 22.42 (3‴–***C***H$_3$), 20.45 (2″–***C***H$_3$); ESI-MS: m/z 683 (M + Na, 100%), 661 (M + 1, 3%), 629 (4%), 583 (9%), 569 (14%), 527 (8%), 526 (22%), 425 (5%), 386 (4%), 372 (7%), 368 (35%), 344 (92%), 340 (11%), 268 (15%), 238 (11%), 162 (13%). *Anal*. Calc. for $C_{32}H_{32}N_6O_6S_2$: Calc. C, 58.18%; H, 4.84%; N, 12.72%; S, 9.69%. Found: C, 57.95%; H, 4.86%; N, 12.66%; S, 9.75%.

Synthesis of N,N′-(5,5′-(3,3′-(1,3-phenylenebis(methylene))bis (oxy)bis3,1-phenylene))bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5 ,2-diyl))diacetamide 4d. The compound **4**(**d**) was prepared by reacting **3**(**d**) (0.5 g, 0.00101 mol) with acetic anhydride (25 ml) under the same conditions as described for **4**(**a**).

4(**d**): light brown solid; yield 75%; m.p. 86–88 °C; IR(KBr): ν_{max} (cm^{-1}): 3158 (N–H), 3059 (aromatic C–H), 2937, 2849 (methylene C–H), 1684, 1637 (C═O), 1609 (C═N), 1237, 1034 (C–O); UV–vis (MeOH): λ_{max} (nm): 326, 276; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.05 (2H, s, 1‴–N***H***), 7.89 (2H, s, H–6‴′, 4‴′), 7.76 (1H, s, H-2‴′), 7.31 (2H, d, J = 2.3 Hz, H-2′), 7.09 (1H, s, H-5‴′),7.04 (2H, td, J = 4.7, 7.9 Hz, H-6′), 7.02 (2H, t, J = 7.4 Hz, H-5′), 6.90 (2H, d, J_o = 7.3 Hz, H-4′), 6.80 (2H, s, H-2), 5.14 (4H, s, OC***H***$_2$), 2.25 (6H, s, 3‴–C***H***$_3$), 2.09 (6H, s, 2″–C***H***$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.90 (2‴–C═O), 167.01 (1″–C═O), 158.13 (C-3′), 146.80 (***C***═N), 142.09 (C-1′), 137.48 (C-1‴′, 3‴′), 135.45 (C-2‴′), 134.09 (C-4‴′, 6‴′), 131.89 (C-5‴′), 129.05 (C-6′), 115.39 (C-5′), 113.47 (C-4′), 111.58 (C-2′), 69.23 (O***C***H$_2$), 67.21 (C-2), 22.31 (3‴–***C***H$_3$), 21.80 (2″–***C***H$_3$); ESI-MS: m/z 683 (M + Na, 32%), 661 (M + 1, 19%), 627 (23%), 579 (7%), 558 (12%), 519 (10%), 431 (6%), 430 (7%), 376 (4%), 375 (46%), 363 (31%), 344 (81%), 342 (16%), 243 (18%), 169 (28%). *Anal*. Calc. for $C_{32}H_{32}N_6O_6S_2$: C, 58.18%; H, 4.84%; N, 12.72%; S, 9.69%. Found: C, 57.94%; H, 4.86%; N, 12.76%; S, 9.62%.

Synthesis of N,N′-(5,5′-(3,3′-(biphenyl-4,4′-diylbis(methylene))bis (oxy)bis(3,1-phenylene)) bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl))diacetamide 4e. The compound **4**(**e**) was synthesized by reacting **3**(**e**) (0.5 g, 0.0012 mol) with acetic anhydride (25 ml) under the same conditions as used in **4**(**a**).

4(**e**): light brown solid; yield 78%; m.p.: 98–100 °C; IR (KBr): ν_{max} (cm^{-1}): 3160 (N–H), 3057 (aromatic C–H), 2928, 2873 (methylene C–H), 1686, 1639 (C═O), 1606 (C═N), 1237, 1056 (C–O); UV–vis (MeOH): λ_{max} (nm): 327, 278; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.61 (2H, s, 1‴–N***H***), 7.63 (4H, d, J_o = 8.0 Hz, H-3‴′, 5‴′), 7.50 (4H, d, J_o = 7.7 Hz, H-2‴′, 6‴′), 7.25 (2H, t, J = 8.0 Hz, H-6′), 7.21 (2H, d, J = 5.3 Hz, H-5′), 7.32 (2H, d, J = 2.1 Hz, H-2′), 6.86 (2H, t, J = 7.6 Hz, H-4′), 6.73 (2H, s, H-2), 5.11 (4H, d, J = 1.4 Hz, OC***H***$_2$), 2.24 (6H, s, 3‴–C***H***$_3$), 2.06 (6H, s, 2″–C***H***$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.06 (2‴–C═O), 167.38 (1″–C═O), 158.50 (C-3′), 146.12 (***C***═N), 142.58 (C-1′), 139.57 (C-4‴′), 135.70 (C-1‴′), 129.59 (C-6′), 127.97 (C-3‴′, 5‴′), 126.63 (C-2‴′, 6‴′), 117.34 (C-5′), 113.71 (C-2′), 111.63 (C-4′), 69.09 (O***C***H$_2$), 65.83 (C-2), 22.39 (3‴–***C***H$_3$), 21.79 (2″–***C***H$_3$,); ESI-MS: m/z 759 (M + Na, 31%), 737 (M + 1, 19%), 679 (45%), 540 (8%), 475 (32%), 453 (100%), 369 (3%), 344 (18%), 238 (9%), 149 (41%), 102 (4%). *Anal*. Calc. for $C_{38}H_{36}N_6O_6S_2$: Calc. C, 61.95%; H, 4.89%; N, 11.41%; S, 8.69%. Found: C, 61.70%; H, 4.87%; N, 11.46%; S, 8.74%.

Synthesis of N,N′-5,5′-(3,3′-(but-2-ene-1,4-diylbis(oxy))bis(3,1-phenylene))bis(4-acetyl −4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)) diacetamide 4f. The compound **4**(**f**) was obtained by reacting **3**(**f**) (0.5 g, 0.00113 mol) with acetic anhydride (25 ml) under the same conditions as described earlier for **4**(**a**).

4(**f**): off white solid; yield 85%; m.p.: 120–122 °C; IR (KBr): ν_{max} (cm^{-1}): 3157 (N–H), 3061 (aromatic C–H), 2935, 2862 (methylene C–H), 1683, 1638 (C═O), 1607 (C═N), 1237, 1017 (C–O); UV–vis (MeOH): λ_{max} (nm): 323, 279; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (2H, s, 1‴–N***H***), 7.25 (2H, brs, H-2′), 7.19 (2H, t,

J = 7.2 Hz, H-6′), 6.79 (2H, d, J_o = 7.3 Hz, H-5′), 6.69 (2H, s, H-2), 6.68 (2H, d, J_o = 7.5 Hz, H-4′), 6.08 (2H, t, J_{vic} = 1.7 Hz, C***H***═), 5.08 (4H, d, J = 1.4 Hz, OC***H***$_2$), 2.26 (6H, s, 3‴–C***H***$_3$), 2.08 (6H, s, 2″–C***H***$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.81 (2‴–C═O), 169.12 (1″–C═O), 158.79 (C-3′), 147.08 (***C***═N), 141.78 (C-1′), 130.08 (C-6′), 128.27 (***C***H═), 118.23 (C-5′), 114.09 (C-2′), 112.34 (C-4′), 68.01 (O***C***H$_2$), 65.93 (C-2), 22.69 (3‴–***C***H$_3$), 21.68 (2″–***C***H$_3$); ESI-MS: m/z 633 (M + Na, 68%), 611 (M + 1, 100%), 569 (15%), 543 (23%), 502 (16%), 434 (11%), 344 (8%). *Anal*. Calc. for $C_{28}H_{30}N_6O_6S_2$: Calc. C, 55.08%; H, 4.92%; N, 13.77%; S, 10.49%. Found: C, 54.86%; H, 4.86%; N, 13.71%; S, 10.44%.

Synthesis of N,N′-(5,5′-(3,3′-(but-2-yne-1,4-diylbis(oxy))bis(3,1-phenylene))bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl))diacetamide 4g. The compound **4**(**g**) was prepared by reacting **3**(**g**) (0.5 g, 0.00113 mol) with acetic anhydride (25 ml) under the similar conditions as discussed previously for **4**(**a**).

4(**g**): light brown solid; yield 70%; m.p.: 102–104 °C; IR (KBr): ν_{max} (cm^{-1}): 3156 (N–H), 3061 (aromatic C–H), 2931, 2862 (methylene C–H), 1688, 1636 (C═O), 1609 (C═N), 1237, 1014 (C–O); UV–vis (MeOH): λ_{max} (nm): 325, 278; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.59 (2H, s, 1‴–N***H***), 7.25 (2H, brs, H-2′), 7.20 (2H, t, J = 7.4 Hz, H-6′), 6.80 (2H, d, J_o = 7.1 Hz, H-5′), 6.79 (2H, d, J_o = 7.3 Hz, H-4′), 6.73 (2H, s, H-2), 4.49 (4H, d, J = 1.9 Hz, OC***H***$_2$), 2.27 (6H, s, 3‴–C***H***$_3$), 2.07 (6H, s, 2″–C***H***$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.02 (2‴–C═O), 168.00 (1″–C═O), 159.01 (C-3′), 147.87 (C═N), 141.99 (C-1′), 130.86 (C-6′), 128.01 (C-2′′′′), 117.89 (C-5′), 114.67 (C-2′), 112.03 (C-4′), 68.03 (O***C***H$_2$), 65.89 (C-2), 22.68 (3‴–***C***H$_3$), 22.61 (2″–***C***H$_3$); ESI-MS: m/z 631 (M + Na, 100%), 609 (M + 1, 43%), 586 (5%), 582 (5%), 526 (11%), 476 (4%), 344 (3%). *Anal*. Calc. for $C_{28}H_{28}N_6O_6S_2$: Calc. C, 55.26%; H, 4.61%; N, 13.81%; S, 10.52%. Found: C, 55.48%; H, 4.59%; N, 13.78%; S, 10.56%.

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