Abstract

Bis 2-thioxo-4-thiazolidinones (5a,b) were achieved by cyclocondensation of bis-isothiocyanates (3a,b) with sulfanylacetic acid at reflux temperature. Compounds (5a-c) were exploited to synthesize the versatile hitherto unknown bis(2-thioxo-4-thiazolidinone) derivatives (8, 9, 11, 12 & 16) via its reaction with some electrophiles. Reaction of bis ammonium dithiocarbamate derivatives [2b, (2a,c)] with chloroacetone, 4-nitrophenacyl bromide and 3-(2-bromoacetyl)-2H-chromene-2-one gave the corresponding bis thiazoles [18, (23a,b), 24], respectively, whereas, reaction of 2a,b with chloroacetonitrile gives bis (4-aminothiazoles) 21a,b. The synthesized compounds were characterized by IR, 1HNMR and mass spectral studies.

Keywords: Bis-isothiocyanates, bis 4-thiazolidinones, bis thiazoles, bis 4-aminothiazole derivatives.

Introduction

Over the years, thiazolidine-4-ones have enjoyed a prominent place in heterocyclic chemistry largely due to the wide-ranging biological activity demonstrated by this class of compounds. Thiazolidine-4-ones are well known for their pharmacological activities. Thus, 4-thiazolidinone derivatives have been demonstrated to act as antibacterial, antiviral, antifungal, anticonvulsant, anticancer, antituberculosis, antitumor and antiparasitic, herbicidal agents, anti-inflammatory, analgesic, and antipsychotic agents.

A literature survey revealed that many different protocols have been developed in a way that allows the synthesis of 4-thiazolidinone skeletons. Based on these facts and in continuation of our studies on the synthesis of biologically active heterocycles, a simple and one-pot route to the synthesis of hitherto unknown bis 2-thioxo-4-thiazolidinone derivatives via the reaction of bis-isothiocyanates with sulfanylacetic acid is reported.

Results and discussion

Isothiocyanates are useful, widely-used building blocks in the synthesis of nitrogen, sulfur and oxygen heterocycles and organometallic compounds of academic, pharmaceutical and industrial interests. Bis isothiocyanates (3a,b) was
prepared according to the method of Garin via treatment of \( p \)-phenylenediamine & benzidine with \( \text{CS}_2/\text{NH}_4\text{OH} \) to produce bisdithiocarbamates (2a,b) and desulfurization (-NH\(_3\), H\(_2\)S). Reaction of di-o-toluidine with \( \text{CS}_2/\text{NH}_4 \) under similar reaction conditions gave bis dithiocarbamate (2c) as the only isolable product (Scheme 1).

Scheme 1:

Cyclocondensation of isothiocyanates 3a,b with sulfanylacetic acid in dioxane in the presence of triethylamine yielded bis 2-thioxo-4-thiazolidinone derivatives 5a,b. Alternative route was the reaction of the ammonium dithiocarbamates 2a-c with ethyl chloroacetate in dimethylformamide containing a catalytic amount of triethylamine at reflux conditions gave 5a-c (Scheme 2). The molecular structures of compounds 5a-c were confirmed on the basis of their elemental analyses and spectral data. The infrared spectra of 5a-c showed absorption bands at 2910, 2974, 2922 (CH-aliph.) and 1736, 1728, 1740 cm\(^{-1}\) corresponding to C=O functional group (4-thiazolidinone), in addition the presence of absorption bands at 1232, 1224, 1230 cm\(^{-1}\) corresponding to the C=S, respectively. The \(^1\)H-NMR spectrum of compound 5a (DMSO-\( \text{d}_6 \)) revealed signals at \( \delta = 4.40 \) ppm corresponding to two methylene moiety of thiazolidinone, in addition to aromatic protons. \(^1\)H-NMR spectrum of compound 5b revealed signals at \( \delta = 4.10, 7.35-7.76 \) ppm corresponding to methylene and aromatic protons. Moreover, \(^1\)H-NMR spectrum of compound 5c revealed the presence of a two singlets at \( \delta = 2.08 \) and 4.43 ppm attributed to two
methyl groups and two methylene moiety of 4-thiazolidinone, respectively in addition to the presence of a multiplet at \( \delta = 7.31-7.71 \) ppm corresponding to aromatic protons. Mass spectrum of 5a displayed a molecular ion peak at m/z 340 (100\%) which also was the base peak, mass spectrum of 5b showed a molecular ion peak at m/z 416. The formation of 5 may be assumed to proceed through nucleophilic attack of mercapto functional group of sulfanylacetic acid to the thiocarbonyl moiety of isothiocyanate followed by intramolecular cyclization through dehydration of the non-isolable intermediate 4 as depicted in Scheme 2.\textsuperscript{28}

**Scheme 2:**

The methylene moiety in compound 5 was exploited to synthesize hitherto unknown bisthiazolidinone derivatives through its reaction with some electrophiles.

Treatment of compound 5a,b with 1,1,2,2-ethenetetra-carbonitrile (TCNE) led to the formation of bis 5-dicyanomethylene-2-thioxo-4-thiazolidinone derivatives 8a,b and the other possible structures bispyranothiazoles 7a,b were excluded on the basis of analytical and spectral data (Scheme 3). The infrared spectrum of compound 8a,b showed the strong and sharp absorption band at 2204 cm\(^{-1}\) corresponding to the C≡N functional group. The mass spectrum of 8a revealed a molecular ion peak at m/z 464 (12.07\%). Also, the mass spectrum of 8b revealed a molecular ion peak at
m/z 540 (2.16%). Compound 8 may be assumed to be formed via Michael addition of the active methine carbanion formed from 5a to the activated double bond in TCNE to form 6 followed by elimination of malononitrile\(^{29}\) to furnish 8, (Scheme 4). Condensation of compound 5a-c with dimethylformamide–dimethylacetal (DMF–DMA) in refluxing xylene yielded 5-dimethylaminomethylene derivatives 9a-c. The infrared spectrum of compounds 9a-c exhibited characteristic absorption bands at 1684, 1678 and 1680 cm\(^{-1}\) respectively for the C=O functional group. \(^1\)H-NMR spectrum of compound 9a displayed signals at δ 3.08, 3.19 corresponding to two N-dimethyl protons, in addition to the presence of signals at 7.40-7.67 and 7.96 ppm attributable to aromatic and methine protons, respectively. \(^1\)H-NMR spectrum of compound 9b revealed signals at δ 3.12, 3.23, 7.32-7.73, and 7.89 ppm attributed to N(CH\(_3\))\(_2\), aromatic, and methine protons, respectively. \(^1\)H-NMR spectrum of compound 9c displayed signals at δ 2.26, 3.06, 3.24, 7.12-7.77, 8.42 ppm which may be attributed to aliphatic, aromatic and methine protons, respectively. The mass spectrum of compound 9a showed a molecular ion peak at m/z 450 (1.82%) and the base peak in the spectrum was found at m/z 340 (bis 4-thiazolidinone). The molecular ion peak of compound 9b was at m/z 526 (29.78%) corresponding to the molecular formula C\(_{24}\)H\(_{22}\)N\(_4\)O\(_2\)S\(_4\) and the base peak was found at m/z 121. The mass spectrum of compound 9c displayed the molecular ion peak at m/z 554 (1.00%) and the base peak was found at m/z 91. Bis (hydrazone) derivative 11 was achieved by diazotization of 4-ethoxyaniline followed by coupling with active methylene group of compound 5a in pyridine at room temperature. The corresponding coupling product was assigned as 3,3’-(1,4-phenylene)bis(5-(2-(4-ethoxyphenyl)hydrazono)-2-thioxo-thiazolidin-4-one) 11. The latter compound was preferred rather than the azo structure 10 based on the spectral data studies. The \(^1\)H-NMR spectrum of compound 11 revealed signals as triplet at δ = 1.29 ppm for two CH\(_3\) groups, quartet at δ = 4.15 ppm for the two CH\(_2\) groups, multiplet at δ = 7.35-7.77 ppm corresponding to aromatic protons, and at δ = 9.84 ppm for two hydrazone NH.
The reaction of compound 5b with 5-fluoroindoline-2,3-dione in dioxane in the presence of piperidine at reflux temperature led to the formation of 3,3’-(biphenyl-4,4’-diyl)-bis(5-(5-fluoro-2-oxoindolin-3-ylidene)-2-thioxothiazolidin-4-one) (Scheme 4). The infrared spectrum showed NH stretching bands at 3196 cm$^{-1}$, in addition to stretching band at 1698 cm$^{-1}$ attributed to the C=O functional group (4-thiazolidinone). Mass spectrum of this compound revealed a molecular ion peak at m/z 708 (M$^+$-2; 20%) with a base peak at m/z 193.
Treatment of compound 5a and/or 5b with α-cinnamionitriles in refluxing dioxane containing a catalytic amount of piperidine furnished bis(5-substituted-benzylidene-2-thioxo-1,3-thiazolidin-4-one) derivatives 16a-c and the other possible pyranothiazole derivatives 15a-c was ruled out on the basis of analytical and spectral data. Mass spectrum of compound 16a revealed a molecular ion peak at m/z 602 (11.08%). The mass spectrum of compound 16b displayed a molecular ion peak at m/z 652 (6.59%) in consistent with its molecular formula C_{34}H_{24}N_{2}O_{4}S_{4}. The mass spectrum of 16c revealed a molecular ion peak at m/z 678 (27.53%). Another synthetic route of compounds 16a-c was achieved via Knoevenagel condensation of compounds 5a,b with the corresponding aromatic aldehydes (Scheme 4).

Scheme 4:
The bis-dithiocarbamates 2a-c were exploited to synthesize new bis-thiazolidine derivatives. Cyclocondensation of the intermediate 2b with chloroacetone in refluxing DMF containing a catalytic amount of triethylamine afforded bis(4-methylthiazole) derivative 18 through initial alkylation followed by intramolecular cyclization and elimination of water. The mass spectrum of compound 18 exhibited a molecular ion peak at m/z 412 (15.6%) and the base peak at m/z 269. On the other hand, cyclocondensation of bis-dithiocarbamates 2a,b with chloroacetonitrile in dimethylformamide afforded bis(4-aminothiazole) derivatives 21a,b. The structure of the isolated products was confirmed based on elemental analysis and spectral data. The infrared spectrum of compound 21b displayed absorption bands at 3308, 3198 cm\(^{-1}\) (NH\(_2\)). The structure of 21a was supported by its mass spectrum which revealed a molecular ion peak at m/z 338 (3.32%) and a base peak at m/z 107. In addition, the mass spectrum of compound 21b showed a molecular ion peak at m/z 414 (5.95%). The formation of compounds 21a,b was assumed to proceed via the initial alkylation by loss of ammonium chloride followed by heterocyclization through nucleophilic addition of the secondary amino group to the cyano group, (Scheme 5).

**Scheme 5:**

The reaction of 2a,c with 4-nitrophenacyl bromide afforded the thioester derivative 22 as intermediate followed by intramolecular cyclization to give the bisthiazole derivatives 23a,b, via Thorpe-Ziegler reaction\textsuperscript{30}. Finally, the reaction of 2c with 3-(2-bromoacetyl)-2H-chromen-2-one gave bisthiazole derivative 24. The formation of 24 is assumed to proceed via initial alkylation via loss of ammonium bromide and elimination of water (Scheme 6). The mass spectrum of compound 23a showed a molecular ion peak at m/z 550 (9.75%) and the base peak was found in the spectrum at m/z 150. The mass spectrum of compound 23b showed a molecular ion peak at m/z 654 (4.31%) and the base peak was found in the spectrum at m/z 149. The \textsuperscript{1}H-NMR spectrum of compound 24 showed that the numbers of protons are consistent with the proposed structure.

\textbf{Scheme 6:}

\textbf{Experimental}

All melting points are uncorrected and were determined on a digital Gallenkamp MFB-595 instrument. IR spectra (KBr) were measured on a Shimadzu 440 spectrometer. \textsuperscript{1}H-NMR spectra were recorded in dimethylsulfoxide on a Varian Gemini 200 (200 MHz) spectrometer using TMS as an internal standard; chemical shifts are reported as δ units. Mass spectra were obtained on GS MS-QP 1000 Ex
mass spectrometer at 70eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. The starting materials 3a,b was prepared according to the method of Garin [27].

**General procedure for the reaction of bis-isothiocyanates with sulfanylacetic acid.**

**Method A:** A mixture of sulfanylacetic acid (0.02 mole), the requisite 3a,b (0.01 mole) and triethylamine (0.5 ml) in dioxane (20 ml) was refluxed for 6 hours. The reaction mixture was left to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from an appropriate solvent to give 5a,b respectively.

**Method B:** A mixture of the requisite bis(diammoniumdithiocarbamate) 2a-c (0.01 mole) and ethyl chloroacetate (0.02 mole) in dimethylformamide (20 ml) containing triethylamine (0.5 ml) was refluxed for 8 hours. The reaction mixture was left to cool at room temperature, then was poured onto ice water and acidified with dilute HCl. The solid formed was collected, filtered off, and recrystallized from the proper solvent to give 5a-c.

**3,3’-(1,4-Phenylene)bis(2-thioxothiazolidin-4-one) (5a):** Yellow crystals (EtOH/dioxane), Yield: 75%, m.p.: 234-236°C; IR (KBr) \( \nu = 3005 \text{ (CH-arom.)}, 2910 \text{ (CH-aliph.)}, 1736 \text{ (C=O)}, 1232 \text{ cm}^{-1} \text{ (C=S)}; ^1 \text{H NMR (DMSO-}d_6, 200 MHz, \delta \text{ ppm): 4.40 (s, 4H, 2CH}_2, 7.45 \text{ ppm (s, 4H, Ar-H); MS: m/z (%): 344 (M}^+ + 4, 3.13), 343 (M}^+ + 3, 6.76), 342 (M}^+ + 2, 16.70), 341 (M}^+ + 1, 26.97), 340 (M}^+, 100), 311 (2.92), 298 (4.96), 280 (8.87), 266 (23.72), 264 (7.41), 239 (21.09), 192 (55.23), 188 (2.56), 160 (69.16), 134 (32.43), 118 (26.34), 102 (50.95), 90 (39.57), 76 (57.93), 64 (78.25). Anal. Calcd. for C_{12}H_{8}N_{2}O_{2}S_{4} (340.46): C, 42.33; H, 2.37; N, 8.23. Found: C, 42.18; H, 2.21; N, 8.11%.

**3,3’-(1,1’-Biphenyl)-4,4’-diyl)bis(2-thioxothiazolidin-4-one) (5b):** Yellow crystals (EtOH/dioxane), Yield: 72%, m.p.: 241-243°C; IR (KBr) \( \nu = 3040 \text{ (CH-arom.)}, 2978 \text{ (CH-aliph.), 1708 \text{ (C=O)}, 1224 \text{ cm}^{-1} \text{ (C=S)}; ^1 \text{H NMR (DMSO-}d_6, 200 MHz, \delta \text{ ppm): 4.40 (s, 4H, 2CH}_2, 6.78-7.47 \text{ (m, 8H, Ar-H); MS: m/z (%) = 416 (M}^+ + 26.45), 415 (M}^+ + 15.6), 339 (11.3), 326 (14.2), 284 (12.5), 268 (64.04), 264 (12.56), 236 (9.45), 208 (7.55), 183 (100), 167 (40.41), 149 (94.62), 132 (4.93), 118 (6.15), 90 (29.85), 76 (96.28), 70 (100), 56 (79.89). Anal. Calcd. for C_{18}H_{12}N_{2}O_{2}S_{4} (416.56): C, 51.90; H, 2.90; N, 6.72. Found: C, 51.74; H, 2.67; N, 6.53%.
3,3’-(3,3’-Dimethyl-[1,1’-biphenyl]-4,4’-diyl)bis(2-thioxothiazolidin-4-one) (5c).

Yellow crystals (EtOH/dioxane), Yield: 77%, m.p.: 253-255°C; IR (KBr) ν = 2922 (CH-aliph.), 1740 (C=O), 1230 cm⁻¹ (C=S); ¹H NMR (DMSO-d₆, 200 MHz, δ ppm): 2.12 (s, 6H, 2CH₃), 4.47 (s, 4H, 2CH₂), 7.31 (s, 2H, Ar-H), 7.71 ppm (s, 4H, Ar); Anal. Calcd. for C₂₀H₁₆N₂O₂S₄ (444.61): C, 54.03; H, 3.63; N, 6.30. Found: C, 53.83; H, 3.66; N, 6.17%.

General procedure for the reaction of bis-isothiocyanates with tetracyanoethylene (TCNE).

A mixture of 5a or 5b (0.01 mole), tetracyanoethylene (0.02 mole) and triethylamine (0.5 ml) in dioxane (20 ml) was refluxed for 3hr. After cooling, the resulting solid product which obtained was collected by filtration, washed with little amount of dioxane, and was recrystallized from the proper solvent to give 8a,b.

2,2’-(3,3’-(1,4-Phenylene)bis(4-oxo-2-thioxothiazolidin-3-yl-5-ylidene))dimalononitrile (8a): This compound was obtained in 65% yield as brown crystals (dioxane/DMF), m.p.: 281-283°C. IR (KBr) ν = 3020 (CH-arom.), 2926 (CH-aliph.), 2204 (C≡N), 1730 (C=O), 1114 cm⁻¹ (C=S); MS: m/z (%) = 464 (M⁺, 12.07), 352 (13.43), 340 (18.64), 309 (14.15), 284 (13.97), 272 (11.62), 224 (32.55), 192 (49.05), 120 (29.18), 58 (100). Anal. Calcd. For C₁₈H₄N₆O₂S₄ (464.52): C, 46.54; H, 0.87; N, 18.09. Found: C, 46.33; H, 0.64; N, 17.92%.

2,2’-(3,3’-[(1,1’-Biphenyl]-4,4’-diyl)bis(4-oxo-2-thioxothiazolidin-3-yl-5-ylidene))-dimalononitrile (8b): This compound was obtained in 61% yield as brown crystals (dioxane/DMF), m.p.: 272-274°C. IR (KBr) ν = 2934 (CH-aliph.), 2204 (C≡N), 1696 (C=O), 1236 cm⁻¹ (C=S); MS: m/z (%) = 540 (M⁺; 2.16), 455 (2.18), 357 (2.93), 328 (3.48), 298 (4.59), 270 (4.31), 266 (4.80), 236 (4.90), 224 (7.69), 210 (6.53), 207 (12.99), 192 (7.36), 152 (10.74), 127 (9.89), 105 (14.42), 77 (16.46), 76 (40.74), 59 (100). Anal. Calcd. for C₂₄H₁₂N₆O₂S₄ (540.62): C, 53.32; H, 1.49; N, 15.55. Found: C, 53.17; H, 1.31; N, 15.33%.

General procedure for the reaction of bis-isothiocyanate derivatives with dimethylformamide-dimethylacetal.

A mixture of 5 (0.01 mole) and dimethylformamide–dimethylacetal (DMF–DMA) (0.02 mole) was refluxed in dioxane (20 ml) 3hr. After cooling, the resulting
solid product was collected by filtration, washed with water, and the crude product was recrystallized from the proper solvent to give 9a-c.

3,3'-(1,4-Phenylene)bis(5-((dimethylamino)methylene)-2-thioxo-thiazolidin-4-one) (9a): This compound was obtained in 65% yield as red crystals (EtOH/dioxane), m.p.: 285-286°C. IR (KBr) ν = 2912 (CH-aliph.), 1684 (C=O), 1602 (C=N), 1232 cm⁻¹ (C=S); ¹H NMR (DMSO-d₆, 200 MHz, δ ppm): 3.08, 3.19 (2s, 12H, 2N(CH₃)₂), 7.40-7.67 (s, 4H, Ar-H), 7.96 (s, 2H, 2 methine-H); MS: m/z (%) = 450 (M⁺; 1.82), 340 (100; bis 4-thiazolidinone), 298 (5.28), 234 (24.30), 192 (45.59), 160 (60.80), 148 (17.40), 134 (33.04), 129 (16.20), 116 (12.86), 101 (11.46), 90 (33.71), 76 (35.85), 64 (56.13), 50 (11.12). Anal. Calcd. for C₁₈H₁₈N₄O₂S₄ (450.62): C, 47.98; H, 4.03; N, 12.43. Found: C, 47.83; H, 4.16; N, 12.26%.

3,3'-([1,1'-Biphenyl]-4,4'-diyl)bis(5-((dimethylamino)methylene)-2-thioxo-thiazolidin-4-one) (9b): This compound was obtained in 67% yield as red crystals (EtOH/dioxane), m.p.: 277-279°C. IR (KBr) ν = 2904 (CH-aliph.), 1678 (C=O), 1600 (C=N), 1228 cm⁻¹ (C=S); ¹H NMR (DMSO-d₆, 200 MHz, δ ppm): 3.12, 3.23 (2s, 12H, 2N(CH₃)₂), 7.32-7.73 (m, 8H, Ar-H), 7.89 (s, 2H, 2 methine-H); MS: m/z (%) = 526 (M⁺; 29.78), 475 (31.01), 423 (41.38), 328 (48.83), 315 (32.47), 282 (59.32), 253 (49.36), 240 (51.88), 209 (96.13), 184 (64.83), 150 (62.78), 121 (100), 107 (90.01), 77 (82.59), 64 (73.04), 55 (55.86). Anal. Calcd. for C₂₄H₂₂N₄O₂S₄ (526.72): C, 54.73; H, 4.21; N, 10.64. Found: C, 54.56; H, 4.26; N, 10.48%.

3,3'-(3,3'-Dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(5-((dimethylamino)-methylene)-2-thioxothiazolidin-4-one) (9c): This compound was obtained in 71% yield as red crystals (EtOH/dioxane), m.p.: >300°C. IR (KBr) ν = 2924 (CH-aliph.), 1692 (C=O), 1606 (C=N), 1238 cm⁻¹ (C=S); ¹H NMR (DMSO-d₆, 200 MHz, δ ppm): 2.26 (s, 6H, 2CH₃), 3.06, 3.24 (2s, 12H, 2N(CH₃)₂), 7.12 (s, 2H, Ar-H), 7.47-7.77 (m, 4H, Ar-H), 8.42 (s, 2H, 2 methine-H); MS: m/z (%) = 554 (M⁺; 1.00), 485 (1.56), 469 (1.03), 437 (1.11), 380 (0.99), 367 (3.99), 360 (1.81), 312 (4.03), 310 (28.18), 296 (0.37), 219 (72.99), 176 (6.98), 91 (100), 77 (9.59), 65 (19.15). Anal. Calcd. for C₂₆H₂₆N₄O₂S₄ (554.77): C, 56.29; H, 4.72; N, 10.10. Found: C, 56.19; H, 4.44; N, 10.21%.

3,3'-(1,4-Phenylene)bis(5-(2-(4-ethoxyphenyl)hydrazono)-2-thioxo-thiazolidin-4-one) (11): A solution of 5a (0.01 mole) was taken in pyridine (15 ml), the solution
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was cooled to 0°C and to this solution was added dropwise during half an hour, 4-ethoxy-benzenediazonium chloride [prepared from 4-ethoxyaniline (0.02 mole) in HCl (8 ml) and NaNO₂ (0.02 mole)]. The reaction mixture was stirred for 6 hr, then poured onto crushed ice and acidified with dil. HCl. The solid product that formed was collected washed with water and filtered off, then recrystallized from dioxane/DMF to give 11.

This compound was obtained in 77% yield, m.p.: 282-284°C.; IR (KBr) ν = 3240 (NH), 2921 (CH-aliph.), 1688 (C=O), 1614 (C=N), 1231 cm⁻¹ (C=S); H NMR (DMSO-d₆, 200 MHz, δ ppm): 1.29 (t, 6H, 2CH₃), 4.15 (q, 2H, 2CH₂), 7.35-7.77 (m, 12H, Ar-H), 9.84 (s, 2H, 2NH; exchangeable with D₂O). Anal. Calcd. for C₂₈H₂₄N₆O₄S₄ (636.79): C, 52.81; H, 3.80; N, 13.20. Found: C, 52.67; H, 3.81; N, 12.96%.

3,3'-((3,3'-(1,1'-Biphenyl)-4,4'-diyl)bis(4-oxo-2-thioxothiazolidin-3-yl-5-ylide-ne))bis(5-fluoroindolin-2-one) (12): A mixture of 5b (0.01 mole), 5-fluoroinodoline-2,3-dione (0.02 mole) and piperidine (0.5 ml) was refluxed in dioxane (30 ml) 2 hr. The resulting solid product was filtered off on hot, washed with ethanol, and recrystallized to give 12.

This compound was obtained in 57% yield as red crystals (EtOH/dioxane), m.p.: >300°C. IR (KBr) ν = 3196 (NH), 2924 (CH-aliph.), 1698 (C=O), 1606 (C=N), 1242 cm⁻¹ (C=S); MS: m/z (%) = 708 (M⁺-2, 0.67), 520 (9.40), 473 (29.01), 432 (0.68), 298 (9.40), 252 (65.14), 225 (12.41), 193 (100), 164 (60.67), 138 (52.12), 121 (14.59), 89 (3.63), 59 (4.00). Anal. Calcd. for C₃₄H₁₆F₂N₄O₄S₄ (710.77): C, 57.45; H, 2.27; N, 7.88. Found: C, 57.27; H, 2.31; N, 7.65%.

**Synthesis of bis-benzylidene derivatives (16a-c): General procedure:**

**Method A:** A mixture of 5a and/or 5b (0.01 mole), requisite α-cinnamonitriles 13a,b (0.02 mole) and piperidine (0.5 ml) in dioxane (20 ml) was refluxed for 4 hour. The solid product obtained was collected by filtration, and recrystallized from an appropriate solvent to give 16a-c.

**Method B:** A mixture of 5a and/or 5b (0.01 mole), aromatic aldehyde (0.02 mole) in dioxane (20 ml) containing piperidine (0.5 ml) was refluxed for 2 hour. The solid product which obtained was collected by filtration, and recrystallized from an appropriate solvent to give 16a-c.
3,3’-(1,4-Phenylene)bis(5-(4-(dimethylamino)benzylidene)-2-thioxo-thiazolidin-4-one) (16a): This compound was obtained in 60% yield as yellow crystals (DMF), m.p.: >300°C. IR (KBr) ν = 2912 (CH-aliph.), 1740 (C=O), 1238 cm⁻¹ (C=S); MS: m/z (%) = 602 (M⁺, 11.08), 549 (6.51), 478 (10.15), 368 (8.91), 340 (23.29), 313 (6.59), 285 (5.26), 266 (10.85), 234 (7.91), 219 (12.53), 192 (21.31), 160 (39.01), 147 (12.80), 119 (14.54), 90 (41.73), 77 (15.69), 55 (100). Anal. Calcd. for C₃₀H₂₆N₄O₂S₄ (602.81): C, 59.77; H, 4.35; N, 9.29. Found: C, 59.55; H, 4.17; N, 9.07%.

3,3’-([1,1’-Biphenyl]-4,4’-diyl)bis(5-(4-methoxybenzylidene)-2-thioxo-thiazolidin-4-one) (16b): This compound was obtained in 65% yield as orange crystals (DMF), m.p.: >300°C. IR (KBr) ν = 2984 (CH-aliph.), 1710 (C=O), 1242 cm⁻¹ (C=S); MS: m/z (%) = 652 (M⁺, 6.59), 447 (8.40), 431 (10.20), 371 (6.73), 310 (27.06), 268 (6.81), 256 (7.99), 219 (75.38), 161 (15.36), 91 (100), 77 (24.06), 55 (23.09). Anal. Calcd. For C₃₄H₂₄N₂O₄S₄ (652.83): C, 62.55; H, 3.71; N, 4.29. Found: C, 62.39; H, 3.44; N, 4.33%.

3,3’-([1,1’-Biphenyl]-4,4’-diyl)bis(5-(4-(dimethylamino)benzylidene)-2-thioxo-thiazolidin-4-one) (16c): This compound was obtained in 61% yield as orange crystals (DMF), m.p.: >300°C. IR (KBr) ν = 3035 (CH-arom.), 2976 (CH-aliph.), 1688 (C=O), 1246 cm⁻¹ (C=S); MS: m/z (%) = 678 (M⁺), 607 (27.94), 536 (26.82), 400 (42.53), 374 (41.86), 282 (31.63), 256 (46.06), 221 (30.81), 193 (28.15), 162 (61.87), 131 (52.30), 85 (58.90), 84 (73.13), 58 (73.23), 55 (100). Anal. Calcd. for C₃₆H₃₀N₄O₂S₄ (678.91): C, 63.69; H, 4.45; N, 8.25. Found: C, 63.56; H, 4.27; N, 8.11%.

**Reaction of 2a-c with α-halo compounds: General procedure:** A mixture of the requisite bisdithiocarbamates 2 (0.01 mole) and appropriate α-halo compound namely (chloroacetone, chloroacetonitrile, 4-nitrophenacyl bromide, and/or 3-(2-bromoacetyl)-2H-chromen-2-one (0.02 mole) in dimethylformamide (30 ml) was refluxed for 3h. The reaction mixture was left to cool and then poured into ice water. The solid product was collected by filtration, washed with water and recrystallized from an appropriate solvent.

3,3’-([1,1’-Biphenyl]-4,4’-diyl)bis(4-methylthiazole-2(3H)-thione) (18): This compound was obtained from reaction of 2b with chloroacetone. Yield: 61%, brown
crystals (dioxane), m.p.: 251-253°C. IR (KBr) ν = 3068 (CH-arom.), 2926 cm$^{-1}$ (CH-aliph.), 1204 cm$^{-1}$ (C=S); 1H NMR (DMSO-$d_6$, 200 MHz, δ ppm): 1.99 (s, 6H, 2CH$_3$), 7.37-7.94 (m, 10H, Ar-H + 2 thiazole-H); MS: m/z (%) = 412 (M$^+; 15.60)$, 268 (100), 260 (7.12), 210 (51.46), 206 (16.42), 200 (10.65), 183 (72.76), 166 (36.37), 134 (6.75), 130 (15.36), 76 (99.69), 50 (40.05). Anal. Calcd. For C$_{20}$H$_{16}$N$_2$S$_4$ (412.61): C, 58.22; H, 3.91; N, 6.79. Found: C, 57.95; H, 3.69; N, 6.53%.

3,3'-(1,4-Phenylene)bis(4-aminothiazole-2(3H)-thione) (21a): This compound was obtained from reaction of 2a with chloroacetonitrile. Yield: 62%, red crystals (dioxane/DMF), m.p.: 289-291°C. IR (KBr) ν = 3230, 3198 (NH$_2$), 2916 (CH-aliph.), 1246 cm$^{-1}$ (C=S); MS: m/z (%) = 338 (M$^+; 3.32)$, 265 (4.30), 254 (3.30), 229 (3.19), 207 (6.80), 192 (6.93), 177 (11.22), 164 (15.97), 150 (46.84), 135 (35.78), 107 (100), 92 (26.16), 80 (40.72), 76 (6.65), 64 (23.03), 52 (52.76). Anal. Calcd. for C$_{12}$H$_{10}$N$_4$S$_4$ (338.49): C, 42.58; H, 2.98; N, 16.55. Found: C, 42.44; H, 2.77; N, 16.37%.

3,3'-(3,3'-Dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(4-aminothiazole-2(3H)-thione) (21b): This compound was obtained from reaction of 2b with chloroacetonitrile. Yield: 66%, red crystals (acetic acid), m.p.: 263-265°C. IR (KBr) ν = 3310, 3242 (NH$_2$), 2958 (CH-aliph.), 1234 cm$^{-1}$ (C=S); MS: m/z (%) = 414 (M$^+; 5.95)$, 317 (9.00), 268 (14.35), 226 (51.24), 207 (13.03), 184 (23.33), 167 (40.00), 152 (36.58), 134 (12.52), 112 (34.29), 91 (27.36), 76 (50.97), 64 (100). Anal. Calcd. for C$_{13}$H$_{10}$N$_4$S$_4$ (414.59): C, 52.15; H, 3.40; N, 13.51. Found: C, 52.04; H, 3.24; N, 13.37%.

3,3'-(1,4-Phenylene)bis(4-(4-nitrophenyl)thiazole-2(3H)-thione) (23a): This compound was obtained from reaction of 2a with 4-nitro-phenacyl bromide. Yield: 66%, brown crystals (dioxane), m.p.: 271-273°C. IR (KBr) ν = 3056 (CH-arom.), 1215 cm$^{-1}$ (C=S); MS: m/z (%) = 550 (M$^+; 9.75$), 446 (10.46), 403 (9.56), 330 (26.97), 329 (22.00), 227 (13.85), 192 (9.89), 177 (27.96), 161 (13.89), 150 (100), 147 (20.53), 134 (16.80), 122 (21.52), 119 (14.97), 107 (49.74), 79 (83.70), 76 (33.63), 64 (94.90). Anal. Calcd. for C$_{20}$H$_{14}$N$_2$O$_4$S$_4$ (550.65): C, 52.35; H, 2.56; N, 10.17. Found: C, 52.19; H, 2.37; N, 9.96%.

3,3'-(3,3'-Dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(4-(4-nitrophenyl)-thiazole-2(3H)-thione) (23b): This compound was obtained from reaction of 2c with 4-nitrophenacyl bromide. Yield: 64%, red crystals (DMF), m.p.: >300°C; IR (KBr) ν = 3104 (CH-arom.), 1220 cm$^{-1}$ (C=S); MS: m/z (%) = 654 (M$^+; 4.31$), 487 (3.07), 459
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(7.50), 443 (2.75), 382 (3.06), 347 (15.87), 328 (3.50), 296 (16.12), 254 (18.24), 185 (6.26), 149 (100), 105 (16.23), 92 (14.07), 76 (27.60), 63 (51.18), 55 (2.07). Anal. Calcd. for C_{32}H_{22}N_{4}O_{4}S_{4} (654.80): C, 58.70; H, 3.39; N, 8.56. Found: C, 58.55; H, 3.17; N, 8.42%.

3,3'-(3,3'-(3,3'-Dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(2-thioxo-2,3-dihydrothiazole-4,3-diyl))bis(2H-chromen-2-one) (24): This compound was obtained from reaction of 1c with 3-(2-bromoacetyl)-2H-chromen-2-one. Yield: 68%, red crystals (dioxane), m.p.: 297-299°C; IR (KBr) ν = 3054 (CH-arom.), 1724 cm⁻¹ (C=O; lactone) 1234 cm⁻¹ (C=S); ¹H NMR (DMSO-d₆, 200 MHz, δ ppm): 2.10 (s, 6H, 2CH₃), 6.70 (s, 2H, Ar-H), 6.89 (s, 2H, thiazole-H), 7.34-7.67 (m, 12H, Ar-H), 8.31 (s, 2H, chromene-H4). Anal. Calcd. For C_{38}H_{24}N_{2}O_{4}S_{4} (700.87): C, 65.12; H, 3.45; N, 4.00. Found: C, 65.22; H, 3.28; N, 3.84%.

References

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