BIS-ISOTHIOCYANATES IN HETEROCYCLIC SYNTHESIS: SYNTHESIS OF BIS 4-THIAZOLIDINONES, BIS THIAZOLES, AND BIS 4-AMINO-THIAZOLE DERIVATIVES

HAMDY KHAMEES THABET

Chemistry Department, Faculty of Science, Al-Azhar University, 11284 Nasr City, Cairo, Egypt.

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, ^{1}HNMR 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[1]. Thiazolidine-4-ones are well known for their pharmacological activities. Thus, 4-thiazolidinone derivatives have been demonstrated to act as antibacterial[2,3], antiviral[4], antifungal[5-8], anticonvulsant[9,10], anticancer[11], antituberculosis[12], antitumor[13] and antiparasitic[14], herbicidal agents[15], anti-inflammatory[16], analgesic[17], and antipsychotic agents[18].

A literature survey revealed that many different protocols have been developed in a way that allows the synthesis of 4-thiazolidinone skeletons[19]. Based on these facts and in continuation of our studies on the synthesis of biologically active heterocycles[20-24], 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[25,26]. Bis isothiocyanates **(3a,b)** was

prepared according to the method of Garin[27] via treatment of *p*-phenylenediamine & benzidine with CS_2/NH_4OH to produce bisdithiocarbamates **(2a,b)** and desulfurization ($-NH_3$, H_2S). Reaction of di-o-toluidine with CS_2/NH_4 under similar reaction of 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-d_6) revealed signals at δ = 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 δ = 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 δ = 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 δ = 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.[28]

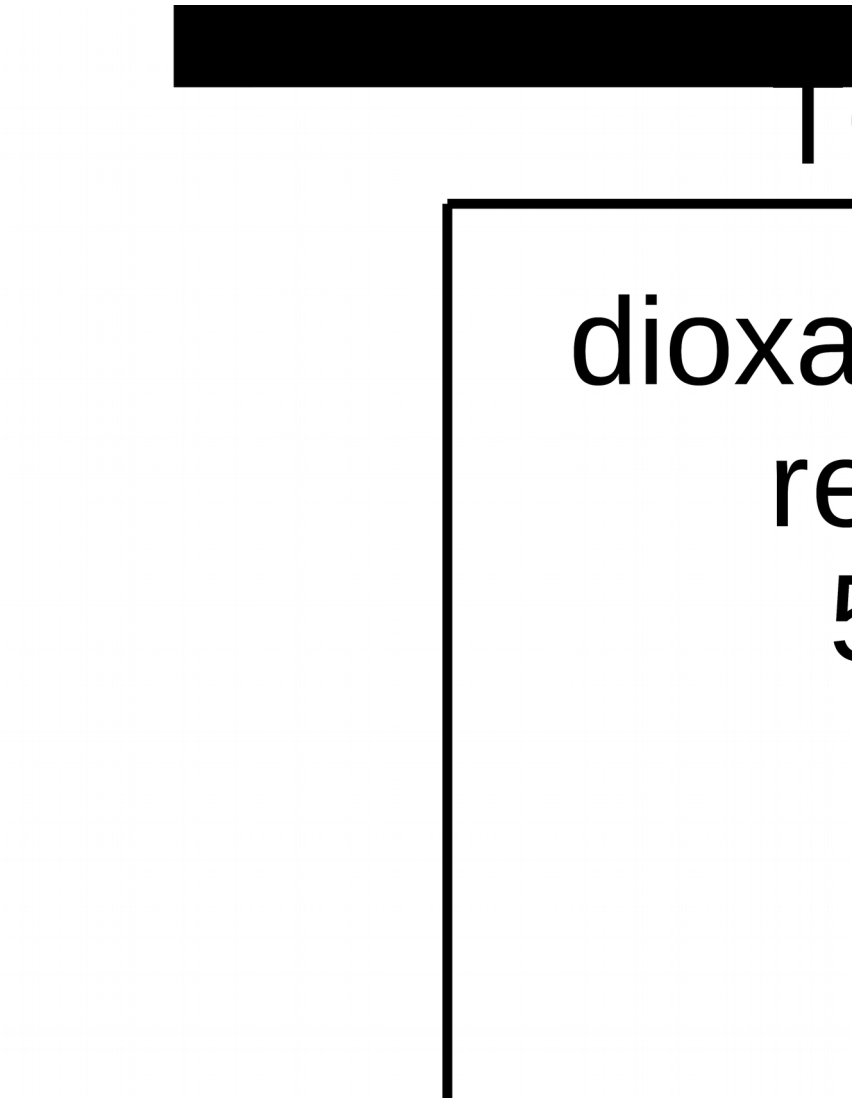
Scheme 2:

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 $C_{24}H_{22}N_4O_2S_4$ 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.

Scheme 3:



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) **12** (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-cinnamonitriles 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 $C_{34}H_{24}N_2O_4S_4$. 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[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 ^{1}H-NMR spectrum of compound **24** showed that the numbers of protons are consistent with the proposed structure.

Scheme 6:

Experimental

All melting points are uncorrected and were determined on a digital Gallen-Kamp MFB-595 instrument. IR spectra (KBr) were measured on a Shimadzu 440 spectrometer. ^{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) ν = 3005 (CH-arom.), 2910 (CH-aliph.), 1736 (C=O), 1232 cm^{-1} (C=S); ^{1}H NMR (DMSO-d_6, 200 MHz, δ ppm): 4.40 (s, 4H, $2CH_2$), 7.45 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 $C_{12}H_8N_2O_2S_4$ (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) ν = 3040 (CH-arom.), 2978 (CH-aliph.), 1708 (C=O), 1224 cm^{-1} (C=S); ^{1}H NMR (DMSO-d_6, 200 MHz, δ ppm): 4.40 (s, 4H, $2CH_2$), 6.78-7.47 (m, 8H, Ar-H); MS: *m*/*z* (%) = 416 (M^+; 26.45), 415 (M-1; 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 $C_{18}H_{12}N_2O_2S_4$ (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); ^{1}H NMR (DMSO-d_6, 200 MHz, δ ppm): 2.12 (s, 6H, $2CH_3$), 4.47 (s, 4H, $2CH_2$), 7.31 (s, 2H, Ar-H), 7.71 ppm (s, 4H, Ar); Anal. Calcd. for $C_{20}H_{16}N_2O_2S_4$ (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 $C_{18}H_4N_6O_2S_4$ (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 $C_{24}H_8N_6O_2S_4$ (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); ^{1}H NMR (DMSO-d_6, 200 MHz, δ ppm): 3.08, 3.19 (2s, 12H, $2N(CH_3)_2$), 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), 267 (22.48), 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 $C_{18}H_{18}N_4O_2S_4$ (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-thioxothiazolidin-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); ^{1}H NMR (DMSO-d_6, 200 MHz, δ ppm): 3.12, 3.23 (2s, 12H, $2N(CH_3)_2$), 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 $C_{24}H_{22}N_4O_2S_4$ (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); ^{1}H NMR (DMSO-d_6, 200 MHz, δ ppm): 2.26 (s, 6H, $2CH_3$), 3.06, 3.24 (2s, 12H, $2N(CH_3)_2$), 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 $C_{26}H_{26}N_4O_2S_4$ (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

was cooled to 0ºC 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 $NaNO_2$ (0.02 mole)]. The reaction mixture was stirred for 6hr, 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); ^{1}H NMR (DMSO-d_6, 200 MHz, δ ppm): 1.29 (t, 6H, $2CH_3$), 4.15 (q, 2H, $2CH_2$), 7.35-7.77 (m, 12H, Ar-H), 9.84 (s, 2H, 2NH; exchangeable with D_2O). Anal. Calcd. for $C_{28}H_{24}N_6O_4S_4$ (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-ylidene))bis(5-fluoroindolin-2-one) (**12**): A mixture of **5b** (0.01 mole), 5-fluoroindoline-2,3-dione (0.02 mole) and pipieridine (0.5 ml) was refluxed in dioxane (30 ml) 2hr. 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 $C_{34}H_{16}F_2N_4O_4S_4$ (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 4hour. 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 2hour. 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 $C_{30}H_{26}N_4O_2S_4$ (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 $C_{34}H_{24}N_2O_4S_4$ (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 $C_{36}H_{30}N_4O_2S_4$ (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 $C_{20}H_{16}N_2S_4$ (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 (20.14), 73 (6.65), 64 (23.03), 52 (52.76). Anal. Calcd. for $C_{12}H_{10}N_4S_4$ (338.49): C, 42.58; H, 2.98; N, 16.55. Found: C, 42.44; H, 2.77; N, 16.37%.

3,3'-([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 $C_{18}H_{14}N_4S_4$ (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 $C_{24}H_{14}N_4O_4S_4$ (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

(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 $C_{32}H_{22}N_4O_4S_4$ (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); ^{1}H NMR (DMSO-d_6, 200 MHz, δ ppm): 2.10 (s, 6H, $2CH_3$), 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 $C_{38}H_{24}N_2O_4S_4$ (700.87): C, 65.12; H, 3.45; N, 4.00. Found: C, 65.22; H, 3.28; N, 3.84%.

References

1.G. R. Newkome, A. Nayak, *Adv. Heterocycl. Chem.* **25**, 83 (1979).
2.A. H. Bapodra, F. Bharmal, H. Parekh, *Indian J. Pharm. Sci.*, **64**, 501, (2002).
3.A. Kucukguzel, G. Kocatepe, E. De Clercq, F. Sahin, M. Gulluce, *Eur. J. Med. Chem.*, **41**, 353 (2006).
4.S. K. Shukle, S. P. Singh, L. P. Awasthi, D. D. Mukherjee, *Indian J. Pharm. Sci.*, **44**, 153 (1982); *Chem. Abstr.*, **99**, 22365u (1983).
5.S. Giri, A.K. Shukla, J. Nizamuddin, *Indian Pharm. Sci.*, , **52**, 108 (1990).
6.N. Cesur, Z. Cesur, N. Ergenc., M. Uzun, M. Kiraz, O. Kasimoglu, D. Kaya, *Arch. Pharm.*, **327**, 271 (1994).
7.N. Karali, E. Ilhan, A. Gursoy, M. Kiraz, *Farmaco*, **53**, 346 (1998).
8.G. Capan, N. Ulusoy, N. Ergenc, M. Kiraz, *Monatsh. Chem.*, **130**, 1399 (1999).
9.G. Capan, N. Ulusoy, N. Ergenc, A. C. Ekinic, A. Vidin, *Farmaco*, **51**, 729 (1996); *Chem. Abstr.*, **126**, 157436q (1996).
10.N. Ergenc G. Capan, *Farmaco*, **49**, 133 (1994).
11.V. Gududuru, E. Hurh, J. T. Dalton, D. D. Miller, *J. Med. Chem*., **48**, 2584 (2005).
12.K. Babaoglu, M. A. Page, V. C. Jones, M. R. McNeeil, C. Dong, J. H. Naismith, R. E. Lee, *Bioorg. Med. Chem. Lett.*, **13**, 322 (2003).
13.C. J. Anders, J. J. Bronson, S. V. Andrea, M. S. Deshpande, P. J. Falk, K. A. Grant-Young, E. W. Harte, H. T. Ho, P. F. Misco, J. G. Robertson, D. Stock, Y. Sun, A. W. Walsh, *Bioorg. Med. Chem. Lett.*, **10**, 715 (2000).
14.M. A. Mahran, S. M. F. El-Nassy, S. R. Allam, *Pharmazie*, **58**, 527 (2003).
15.M. Suzuki, K. Morita, H. Yukioka, N. Miki, A. Mizutani, *J. Pestic. Sci.*, **28**, 37 (2003).

16.A. K. El-Ansary, A. H. Omar, *Bull. Fac. Pharm. Cairo Univ.*, **39**, 17 (2001); Chem. Abstr., **136**, 216712h (2001).
17.S. Schenone, O. Bruno, A. Ranise, F. Bondavalli, W. Filippeli, G. Falcone, L. Giordano, M. R. Vitelli, *Bioorg. Med. Chem.*, **9**, 2149 (2001).
18.L.M. Barreca, A. Chimirri, L. D. Luca, A. Monforte, P. Monforte, *Bioorg. Med. Chem. Lett.*, **11**, 1793 (2001).
19.S. P. Singh, S. S. Parmar, K. Raman, V. I. Stenberg, *Chem. Rev.*, **81**, 175 (1981).
20.A. M. Sh. El-Sharief; Y. A. Ammar; M. A. Zahran; H. Kh. Sabet, J Chem Res (S), 162 (2003).
21.A. M. Sh. El-Sharief; Y. A. Ammar; M. A. Zahran; H. Kh. Sabet, *Phosphorus, Sulfur and Silicon*, **179**, 267 (2004).
22.Y. A. Ammar; H. Kh. Thabet; M. M. Aly; Y. A. Mohamed; M. A. Ismail; M. A. Salem, *Phosphorus, Sulfur and Silicon*, **185**, 743 (2010).
23.S. F. Mohamed, H. Kh. Thabet, E. E. Mustafa, M. M. Abdalla, S. H. Shafik, *World Journal of Chemistry*, **4**, 100 (2009).
24.A. A. Farrag, H. Kh. Thabet, Y. A. Ammar, *A.* G. El-Sehemi, *J. Chem. Res. (S)*, 163 (2011).
25.A. K. Mukerjee, R. Share, *Chem. Rev.*, **9**, 1 (1991).
26.S. Sharma, *Sulfur Report*, **8**, 327 (1989).
27.J. Garín, E. Meléndez, F. L. Merchán, P. Merino, J. Orduna, T. Tejero, *J. Heterocycl. Chem.*, **27**, 1345 (1990).
28.F. C. Brown, *Chem Rev.*, **61**, 463 (1961).
29.H. Junek, G. Zuschning, R. Thierrichter, G. Gfrerer, H. Sterk, *Monatshefte für Chemie*, **113**, 1045 (1982).
30.S. Gükücükgüzel, S. Rollas, I. Kücükgüzel, and M. Kiraz, *Eur. J. Med. Chem*., **34**, 1093 (1999).