Synthesis and Biological Evaluation of Novel Methylene-bis-thiazolidinone Derivatives as Potential Nematicidal Agents

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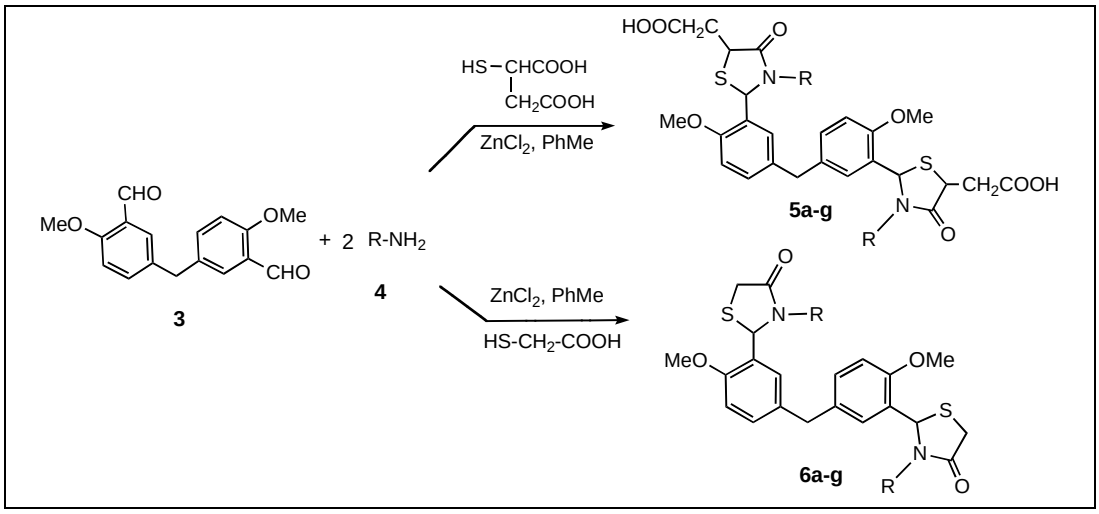

In a one pot procedure, a series of novel methylene-bis-thiazolidinone derivatives **5** and **6** was prepared by condensation of 5-(3-formyl-4-methoxybenzyl)-2-methoxybenzaldehyde **3** with mercapto acids and primary aromatic amines **4** in presence of $ZnCl_2$ under both microwave irradiation and conventional heating conditions. High yields are achieved even on a gram scale, while reaction times are considerably shortened under microwave irradiation compared to conventional heating conditions. Characterization of new compounds has been done by means of IR, NMR, MS and elemental analysis. The nematicidal and antibacterial activity of the compounds has also been evaluated.

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INTRODUCTION

Thiazolidinone and its derivatives are known to possess significant pharmacological [1] and biological activities [2] like sedative [3], anti-inflammatory [4], antitubercular [5], anticancer [6], antitumor [7], anti-HIV [8], antibacterial [9], antifungal [10], analgesis, hypotermic [11], anestetic [12] nematicidal [13] and CNS stimulant [14]. Furthermore, thiazolidinones have been used for the treatment of cardiac diseases [15], diabetic complications like cataract, nephropathy, neuropathy [16] and selective anti-platelet activating factor [17]. Moreover, the thiazolidinone derivatives are also employed in the synthesis of cyanine dyes, which are used in the photographic film industry [18].

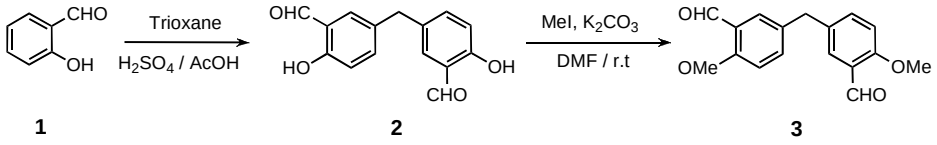
Led by the above facts, we report here the microwave-assisted synthetic route for the synthesis of some new heterocycles incorporating two thiazolidinone moieties in order to prepare molecules having enhanced biological activity and to have them evaluated for their nematicidal and antibacterial activity.

RESULTS AND DISCUSSION

The 5-(3-formyl-4-hydroxybenzyl)-2-hydroxybenzaldehyde **2** was prepared by the reaction of salicylaldehyde **1** with trioxane in the presence of a mixture of acetic acid and conc. sulphuric acid [18]. Treatment of **2** with MeI in presence of K_2CO_3 in DMF at room temperature gave the desired intermediate 5-(3-formyl-4-methoxybenzyl)-2-methoxybenzaldehyde **3** (Scheme 1).

The one-pot synthesis of methylene-bis-thiazolidinone derivatives **5a-g** and **6a-g** was carried out by the condensation-cyclization reaction between 5-(3-formyl-4-methoxybenzyl)-2-methoxybenzaldehyde **3,** primary aromatic amine **4** and a suitable mercapto acid in the presence of $ZnCl_2$ under microwave irradiation/ conventional heating (Scheme 2). In the "classical" method, the reactions were performed in dry toluene at reflux for a long time (2-4 h), often leading to degradation processes and consequent low yields of isolated products, whereas with the application of microwave-assisted technology, the reaction is completed in only 5-7 minutes and the compounds, isolated by conventional work-up, are obtained in satisfactory yields, often higher than those achieved by the traditional methods (Table 1). The structures of synthesized compounds were confirmed by IR, NMR, MS and elemental analyses. Further the compounds were subject to nematicidal and antibacterial testing.

Scheme 1



1 **2** **3**

Scheme 2

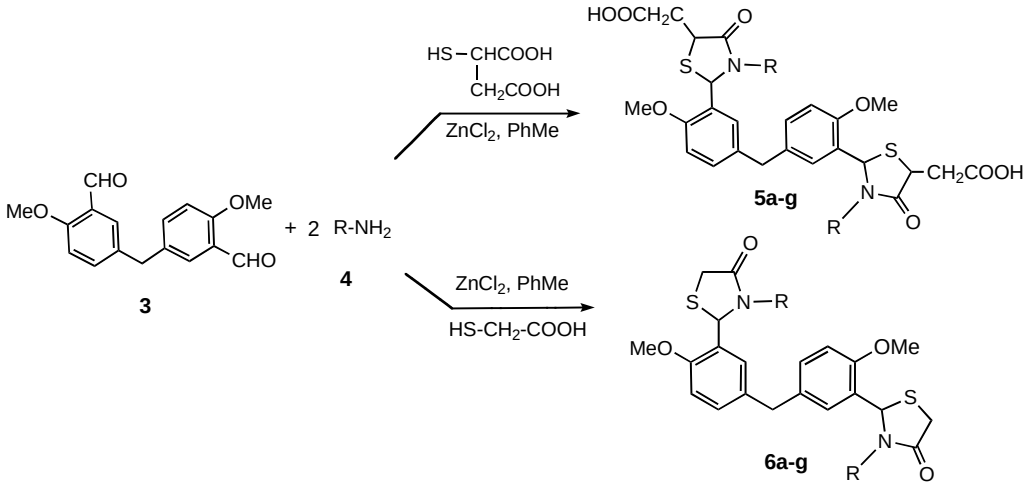


Table 1

Synthesis of Compounds **5(a-g)** and **6(a-g)**

Compd.	R	Mol. formula	Reaction time		Yield %	
			A (h)	B (min)	A	B
5a	C_6H_5	$C_{37}H_{34}N_2O_8S_2$	3.5	5	62	80
5b	4-Cl-C_6H_4	$C_{37}H_{32}Cl_2N_2O_8S_2$	2.5	6	71	89
5c	4-NO_2-C_6H_4	$C_{37}H_{32}N_4O_{12}S_2$	3.0	6	69	82
5d	2-CH_3-C_6H_4	$C_{39}H_{38}N_2O_8S_2$	2.0	5	63	86
5e	4-CH_3-C_6H_4	$C_{39}H_{38}N_2O_8S_2$	2.5	5	68	88
5f	3-OH-C_6H_4	$C_{37}H_{34}N_2O_{10}S_2$	3.0	5	79	86
5g	4-OH-C_6H_4	$C_{37}H_{34}N_2O_{10}S_2$	2.0	3	80	91
6a	C_6H_5	$C_{33}H_{30}N_2O_4S_2$	3.5	5	63	79
6b	4-Cl-C_6H_4	$C_{33}H_{28}Cl_2N_2O_4S_2$	2.5	6	65	82
6c	4-NO_2-C_6H_4	$C_{33}H_{28}N_4O_8S_2$	3.0	7	61	79
6d	2-CH_3-C_6H_4	$C_{35}H_{34}N_2O_4S_2$	2.5	5	70	81
6e	4-CH_3-C_6H_4	$C_{39}H_{38}N_2O_8S_2$	2.0	5	67	82
6f	3-OH-C_6H_4	$C_{33}H_{30}N_2O_6S_2$	3.0	5	77	87
6g	4-OH-C_6H_4	$C_{33}H_{30}N_2O_6S_2$	2.5	4	79	90

A: conventional heating. B: microwave irradiation.

Antibacterial Activity. Compounds **5a-g** and **6a-g** were screened for their antibacterial activity using the tube dilution method [19] by measuring the minimum inhibitory concentration (MIC) in μg/mL against four representative organisms *viz Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Staphylococcus pyogenes*. Standard antibacterial agents, such as Streptomycin and Neomycin, were also screened under identical conditions for comparison. The minimum inhibitory concentrations are given in Table 2. It has been observed that the test compounds however exhibited an interesting biological activity however, with a degree of variation.

Compounds in series **5** and **6**, which contain 4-Cl / 3-OH, displayed good antibacterial activity against all the organisms. Compounds **5b** and **6f** were highly active against *B. subtilis*, *S. aureus* and *S. pyogenes*, compound **5f** was highly active against *B. subtilis*, *S. aureus*, *E. coli*, compound **6b** was highly active against *B. subtilis*, *E. coli*, *S. pyogenes* and the compound **5c** was highly active against *E. coli* and *S. pyogenes*. Compounds **6a** and **6d** did not exhibit any activity against *E. coli* even at 100 μg/mL

Table 2

Antibacterial and Nematicidal Activity of **5a-g** and **6a-g**

Compd	Antibacterial Activity				Nematicidal Activity	
	Minimum inhibition concentration (MIC, μg/mL)				LD_{50} value (ppm)	
	B. subtilis	*S. aureus*	*E. coli*	*S. pyogenes*	*D.myceliophagus*	*C.elegans*
5a	50	25	50	50	940	960
5b	12.5	12.5	25	12.5	360	400
5c	25	25	12.5	12.5	440	390
5d	25	50	25	25	610	650
5e	100	50	50	50	1070	1010
5f	12.5	12.5	12.5	25	210	320
5g	50	50	100	25	420	670
6a	50	50	--	25	710	650
6b	12.5	25	12.5	12.5	400	350
6c	25	25	25	12.5	490	510
6d	50	100	--	50	1030	1050
6e	50	50	50	50	910	970
6f	12.5	12.5	25	12.5	360	240
6g	50	25	50	50	660	540
Streptomycin	10	10	10	10	--	--
Neomycin	30	30	30	30	--	--

concentration. The alkyl substituted derivatives displayed moderate levels of antibacterial activity (Table 2).

Nematicidal Activity. The compounds **5a-g** and **6a-g** were also screened for their nematicidal activity against *Ditylenchus myceliophagus* and *Caenorhabditis elegans* by aqueous *in vitro* screening technique [20] at various concentrations. The results have been expressed in terms of LD_{50} *i.e.* median lethal dose at which 50% nematodes became immobile (dead). The screened data reveal that compound **5f** and **6f** are the most effective against *D. myceliophagus* and *C. elegans* with LD_{50} value of 210 and 240 ppm, respectively (Table 2).

EXPERIMENTAL

All chemicals and solvents were of analytical grade and used as purchased. Evaporations were performed at reduced pressure below 40°C. The reactions and purifications were monitored by tlc on aluminium sheets coated with silica gel 60 F_{254} (Merck), column chromatography on silica gel 60 (Merck). Melting points were taken using a Fisher-Johns melting point instrument and are uncorrected. IR spectra were obtained on a Perkin-Elmer FTIR 5000 spectrophotometer, using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were obtained with Varian Gemini (^{1}H: 300 MHz, ^{13}C: 75 MHz) spectrometer and the chemical shifts were reported as parts per million (δ ppm) down field from internal tetramethylsilane and coupling constants (J) in Hz. Mass spectra were obtained on a VG Micromass 7070H spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer.

5-(3-Formyl-4-methoxybenzyl)-2-methoxybenzaldhyde (3). To a solution of **2** (2.56 g, 0.01 mol) and K_2CO_3 (5.60 g, 0.04 mol) in DMF (16 mL), MeI (4.25 g, 1.9 mL, 0.03 mol) was added. The mixture was stirred at room temperature for 12 h (tlc, EtOAc: Pet-ether, 2:1) then the mixture was poured in water (30 mL), and extracted with Et_2O (3x20 mL). The organic phase was washed with 2 *N* NaOH solution, dried over Na_2SO_4. Evaporation of the solvent gave compound **3**. The structure of compound **3** was confirmed by its spectral data and compared with the data reported in the literature [21].

General procedure for the synthesis of methylene-bis-thiazolidinones (5a-g). To a stirred mixture of **3** (1.42 g, 0.005 mol), appropriate aromatic amine **4** (0.015 mol) and thiomalic acid (4.5 g, 0.03 mol) in dry toluene (5 mL), $ZnCl_2$ (1.36 g, 0.01 mol) was added after 2 min and irradiated in a microwave oven at 280 W for 4-7 minutes at 110 °C. After cooling, the filtrate was concentrated to dryness under reduced pressure, the residue was taken up in ethyl acetate, and the resulting solution was washed with brine solution. The organic phase was dried over Na_2SO_4, filtered, the filtrate was concentrated under reduced pressure to dryness, and the crude product was purified by column chromatography on silica gel using methanol/ dichloromethane as eluent. The purity of the products was checked by TLC using methanol/dichloromethane (1:9) as solvent. Under conventional method the same reaction mixture in toluene (30 mL) was refluxed at 110 °C for the appropriate time (Table 1).

2-[2-(5-3-[5-(Carboxymethyl)-4-oxo-3-phenyl-1,3-thiazolan-2-yl]-4-methoxybenzyl-2-methoxyphenyl)-4-oxo-3-phenyl-1,3-thiazolan-5-yl]acetic acid (5a). mp 201-203 °C; IR (KBr): ν 3130-2890, 3021, 2980, 1724, 1716, 1610, 1480, 1410, 1224, 688 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.37 (4H, d, CH_2), 3.36 (2H, s, CH_2), 4.12 (6H, s, OCH_3), 4.67 (2H, t, CH), 6.16 (2H, s, CH-S). 6.70-7.32 (16H, m, ArH), 11.41 (2H, s, COOH); ^{13}C NMR (DMSO-d_6): δ 36.4, 41.0, 45.3, 54.2, 61.7, 107.8, 121.3, 123.6, 127.1, 128.4, 130.3, 134.7, 135.9, 138.5, 152.7, 166.9, 170.9; MS: m/z 698 (M^+). *Anal.* calcd for $C_{37}H_{34}N_2O_8S_2$: C, 63.60; H, 4.90; N, 4.01. Found: C, 63.42; H, 4.77; N, 4.00.

2-[2-(5-3-[5-(Carboxymethyl)-3-(4-chlorophenyl)-4-oxo-1,3-thiazolan-2-yl]-4-methoxybenzyl-2-methoxyphenyl)-3-(4-chlorophenyl)-4-oxo-1,3-thiazolan-5-yl]acetic acid (5b). mp 249-251 °C; IR (KBr): ν 3140-2900, 3010, 2980, 1720, 1700, 1605, 1479, 1410, 1220, 746, 688 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.37 (4H, d, CH_2), 3.36 (2H, s, CH_2). 4.12 (6H, s, OCH_3), 4.67

(2H, t, CH), 6.16 (2H, s, CH-S). 6.70-7.10 (6H, m, ArH), 7.20 (4H, d, J = 8.71 Hz, ArH), 7.51 (4H, d, J = 8.71 Hz, ArH), 11.39 (2H, s, COOH); ^{13}C NMR (DMSO-d_6): δ 36.4, 41.1, 45.2, 54.2, 61.3, 107.8, 121.3, 123.1, 127.9, 128.7, 130.7, 134.6, 135.3, 138.9, 153.4, 167.2, 170.9; MS: m/z 728 (M^+). *Anal.* calcd for $C_{37}H_{32}Cl_2N_2O_8S_2$: C, 57.89; H, 4.20; N, 3.65. Found: C, 57.70; H, 4.17; N, 3.61.

2-[2-(5-3-[5-(Carboxymethyl)-3-(4-nitrophenyl)-4-oxo-1,3-thiazolan-2-yl]-4-methoxybenzyl-2-methoxyphenyl)-3-(4-nitrophenyl)-4-oxo-1,3-thiazolan-5-yl]acetic acid (5c). mp 249-251 °C; IR (KBr): ν 3140-2900, 3010, 2980, 1720, 1700, 1605, 1479, 1410, 1220, 746, 688 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.37 (4H, d, CH_2), 3.36 (2H, s, CH_2), 4.11 (6H, s, OCH_3), 4.67 (2H, t, CH), 6.16 (2H, s, CH-S). 6.70-7.10 (6H, m, ArH), 7.81 (4H, d, J = 9.08 Hz, ArH), 8.11 (4H, d, J = 9.08 Hz, ArH), 11.39 (2H, s, COOH); ^{13}C NMR (DMSO-d_6): δ 36.6, 41.1, 45.7, 54.6, 61.7, 108.4, 122.3, 123.6, 127.9, 128.3, 131.9, 134.9, 139.2, 143.2, 154.1, 167.3, 170.7; MS: m/z 788 (M^+). *Anal.* calcd for $C_{37}H_{32}N_4O_{12}S_2$: C, 56.34; H, 4.09; N, 7.10. Found: C, 56.27; H, 4.00; N, 7.05.

2-[2-(5-3-[5-(Carboxymethyl)-3-(2-methylphenyl)-4-oxo-1,3-thiazolan-2-yl]-4-methoxybenzyl-2-methoxyphen-yl)-3-(2-methylphenyl)-4-oxo-1,3-thiazolan-5-yl]acetic acid (5d). mp 245-247 °C; IR (KBr): ν 3140-2950, 3010, 2995, 1715, 1700, 1610, 1480, 1410, 1224, 686 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.10 (6H, s, CH_3), 2.36 (4H, d, CH_2), 3.36 (2H, s, CH_2). 4.11 (6H, s, OCH_3), 4.67 (2H, t, CH), 6.16 (2H, s, CH-S). 6.70-7.50 (14H, m, ArH), 11.40 (2H, s, COOH); ^{13}C NMR (DMSO-d_6): δ 18.3, 36.6, 41.1, 45.4, 54.9, 62.3, 108.3, 122.3, 123.6, 127.8, 128.2, 129.1, 130.1, 132.7, 135.9, 136.4, 139.2, 154.1, 167.3, 170.2; MS: m/z 726 (M^+). *Anal.* calcd for $C_{39}H_{38}N_2O_8S_2$: C, 64.45; H, 5.27; N, 3.85. Found: C, 64.39; H, 5.12; N, 3.82.

2-[2-(5-3-[5-(Carboxymethyl)-3-(4-methylphenyl)-4-oxo-1,3-thiazolan-2-yl]-4-methoxybenzyl-2-methoxyphenyl)-3-(4-methylphenyl)-4-oxo-1,3-thiazolan-5-yl]acetic acid (5e). mp 182-184 °C; IR (KBr): ν 3140-2950, 3011, 2990, 1715, 1698, 1610, 1475, 1412, 1224, 684 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.05 (6H, s, CH_3), 2.36 (4H, d, CH_2), 3.36 (2H, s, CH_2). 4.10 (6H, s, OCH_3), 4.66 (2H, s, CH), 6.19 (2H, s, CH-S). 6.70-7.10 (6H, m, ArH), 7.16 (4H, d, J = 8.33 Hz, ArH), 8.23 (4H, d, J = 8.33 Hz, ArH), 11.40 (2H, s, COOH); ^{13}C NMR (DMSO-d_6): δ 19.4, 36.6, 41.1, 45.3, 54.9, 62.5, 108.9, 117.7, 123.3, 124.8, 129.7, 133.2, 135.7, 136.1, 138.7, 153.2, 167.3, 170.1; MS: m/z 726 (M^+). *Anal.* calcd for $C_{39}H_{38}N_2O_8S_2$: C, 64.45; H, 5.27; N, 3.85. Found: C, 64.36; H, 5.19; N, 3.78.

2-[2-(5-3-[5-(Carboxymethyl)-3-(3-hydroxyphenyl)-4-oxo-1,3-thiazolan-2-yl]-4-methoxybenzyl-2-methoxyphen-yl)-3-(3-hydroxyphenyl)-4-oxo-1,3-thiazolan-5-yl]acetic acid (5f). mp 209-211 °C; IR (KBr): ν 3540, 3140-2960, 3014, 2985, 1714, 1705, 1605, 1478, 1412, 1220, 680 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.36 (4H, d, CH_2), 3.36 (2H, s, CH_2). 4.11 (6H, s, OCH_3), 4.68 (2H, t, CH), 6.18 (2H, s, CH-S). 6.70-7.10 (14H, m, ArH), 8.24 (2H, s, OH), 9.21 (2H, s, COOH); ^{13}C NMR ($CDCl_3$): δ 36.6, 41.2, 45.7, 54.9, 62.4, 108.2, 109.9, 112.6, 114.3, 123.4, 125.1, 130.1, 132.6, 135.9, 136.1, 153.2, 160.3, 167.3, 170.2; MS: m/z 730 (M^+). *Anal.* calcd for $C_{37}H_{34}N_2O_{10}S_2$: C, 60.81; H, 4.69; N, 3.83. Found: C, 60.76; H, 4.61; N, 3.78.

2-[2-(5-3-[5-(Carboxymethyl)-3-(4-hydroxyphenyl)-4-oxo-1,3-thiazolan-2-yl]-4-methoxybenzyl-2-methoxyphen-yl)-3-(4-hydroxyphenyl)-4-oxo-1,3-thiazolan-5-yl]acetic acid (5g). mp 241-243 °C; IR (KBr): ν 3450, 3140-2960, 3011, 2990, 1720, 1690, 1606, 1470, 1410, 1226, 680 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.37 (4H, d, CH_2), 3.36 (2H, s, CH_2). 4.12 (6H, s, OCH_3), 4.67 (2H, s, CH), 6.20 (2H, s, CH-S). 6.70-7.10 (10H, m, ArH), 7.28 (4H, d, J = 8.87 Hz, ArH), 8.24 (2H, s, OH), 9.21 (2H, s, COOH); ^{13}C NMR ($CDCl_3$): δ 36.6, 41.1, 45.4, 54.7, 62.4, 108.1, 114.7, 123.1, 123.9, 124.7, 133.2, 134.9, 135.2, 154.1, 160.1, 167.2, 170.1; MS: m/z 730 (M^+).. *Anal.* calcd for $C_{37}H_{34}N_2O_{10}S_2$: C, 60.81; H, 4.69; N, 3.83. Found: C, 60.62; H, 4.58; N, 3.71.

General procedure for the synthesis of methylene-bis-thiazolidinones (6a-g). To a stirred mixture of **3** (1.42 g, 0.005 mol), aromatic amine **4** (0.015 mol) and thioglycolic acid (2.76 g, 0.03 mol) in dry toluene (5 mL), $ZnCl_2$ (1.36 g, 0.01 mol) was added after 2 min and irradiated in a microwave oven at 280 W for 4-7 minutes at 110 °C. After cooling, the filtrate was concentrated to dryness under reduced pressure and the residue was taken-up in ethyl acetate. The ethyl acetate layer was washed with brine, 5% sodium bicarbonate solution and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness at reduced pressure. The crude product thus obtained was purified by column chromatography on silica gel with hexane-ethyl acetate as eluent. The purity of the products was checked by TLC using ethyl acetate/hexane (4:6). Under conventional method the same reaction mixture in toluene (30 mL) was refluxed at 110 °C for the appropriate time (Table 1).

2-{2-Methoxy-5-[4-methoxy-3-(4-oxo-3-phenyl-1,3-thiazolan-2-yl)benzyl]phenyl}-3-phenyl-1,3-thiazolan-4-one (6a). mp 129-131 °C; IR (KBr): ν 3015, 2985, 1716, 1610, 1475, 1415, 1224, 686 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.36 (2H, s, CH_2), 3.77 (4H, s, CH_2) 4.11 (6H, s, OCH_3), 6.07 (2H, s, CH-S), 6.70-7.40 (16H, m, ArH); ^{13}C NMR (DMSO-d_6): δ 35.9, 41.1, 54.1, 63.2, 109.1, 123.6, 125.2, 128.4, 129.7, 130.3, 134.3, 135.9, 138.9, 152.0, 171.1; MS: m/z 582 (M^+). *Anal.* Calcd. for $C_{33}H_{30}N_2O_4S_2$: C, 68.02; H, 5.19; N, 4.81. Found: C, 67.93; H, 5.11; N, 4.77.

3-(4-Chlorophenyl)-2-(5-{3-[3-(4-chlorophenyl)-4-oxo-1,3-thiazolan-2-yl]-4-methoxybenzyl}-2-methoxyphenyl)-1,3-thiazolan-4 -one (6b). mp 214-216 °C; IR (KBr): ν 3015, 2987, 1714, 1605, 1481, 1410, 1221, 746, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.36 (2H, s, CH_2), 3.77 (4H, s, CH_2) 4.11 (6H, s, OCH_3), 6.06 (2H, s, CH-S), 6.70-7.10 (6H, m, ArH), 7.21 (4H, d, J = 8.71 Hz, ArH), 7.52 (4H, d, J = 8.71 Hz, ArH); ^{13}C NMR ($CDCl_3$): δ 35.9, 41.1, 54.3, 63.7, 109.3, 121.8, 123.5, 127.6, 128.7, 132.1, 135.3, 136.3, 138.7, 152.9, 171.1; MS: m/z 652 (M^+). *Anal.* calcd for $C_{33}H_{28}Cl_2N_2O_4S_2$: C, 60.83; H, 4.33; N, 4.30. Found: C, 60.71; H, 4.25; N, 4.22.

2-(2-Methoxy-5-{4-methoxy-3-[3-(4-nitrophenyl)-4-oxo-1,3-thiazolan-2-yl]benzyl}phenyl)-3-(4-nitrophenyl)-1,3-thiazolan-4-one (6c). mp 197-199 °C; IR (KBr): ν 3016, 2992, 1695, 1610, 1510, 1318, 1479, 1410, 1224, 682 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.36 (2H, s, CH_2), 3.77 (4H, s, CH_2) 4.12 (6H, s, OCH_3), 6.08 (2H, s, CH-S), 6.70-7.10 (6H, m, ArH), 7.77 (4H, d, J = 9.08 Hz, ArH), 8.11 (4H, d, J = 9.08 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 35.3, 41.1, 54.1, 63.3, 109.2, 123.9, 126.1, 128.3, 133.1, 135.7, 136.1, 138.9, 142.1, 152.5, 171.2; MS: m/z 674 (M^+). *Anal.* calcd for $C_{33}H_{28}N_4O_8S_2$: C, 58.92; H, 4.20; N, 8.33. Found: C, 58.10; H, 4.11; N, 8.20.

2-(2-Methoxy-5-{4-methoxy-3-[3-(2-methylphenyl)-4-oxo-1,3-thiazolan-2-yl]benzyl}phenyl)-3-(2-methylphenyl)-1,3-thiazolan-4-one (6d). mp 179-181 °C; IR (KBr): ν 3014, 2990, 1705, 1610, 1482, 1410, 1224, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.0 (6H, s, CH_3), 3.36 (2H, s, CH_2), 3.79 (4H, s, CH_2) 4.13 (6H, s, OCH_3), 6.10 (2H, s, CH-S), 6.70-7.60

(14H, m, ArH); ^{13}C NMR (DMSO-d_6): δ 16.4, 35.4, 41.1, 54.3, 64.9, 109.2, 121.7, 124.1, 125.4, 126.9, 127.8, 129.3, 132.1, 133.7, 135.0, 138.9, 152.5, 171.1; MS: m/z 612 (M^+). *Anal*. calcd for $C_{35}H_{34}N_2O_4S_2$: C, 68.83; H, 5.61; N, 4.59. Found: C, 68.71; H, 5.51; N, 4.50.

2-(2-Methoxy-5-{4-methoxy-3-[3-(4-methylphenyl)-4-oxo-1,3-thiazolan-2-yl]benzyl}phenyl)-3-(4-methylphenyl)-1,3-thiazolan-4-one (6e). mp 180-182 °C; IR (KBr): ν 3012, 2988, 1698, 1612, 1475, 1410, 1220, 689 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.02 (6H, s, CH_3), 3.36 (2H, s, CH_2), 3.80 (4H, s, CH_2) 4.13 (6H, s, OCH_3), 6.07 (2H, s, CH-S), 6.70-7.10 (6H, m, ArH), 7.15 (4H, d, J = 8.33 Hz, ArH), 7.39 (4H, d, J = 8.33 Hz, ArH); ^{13}C NMR (DMSO-d_6): δ 19.7, 35.6, 41.1, 54.5, 64.2, 109.2, 113.4, 122.1, 124.3, 128.7, 133.7, 135.1, 136.9, 139.8, 152.3, 171.1; MS: m/z 612 (M^+). *Anal*. calcd for $C_{35}H_{34}N_2O_4S_2$: C, 68.83; H, 5.61; N, 4.59. Found: C, 68.73; H, 5.50; N, 4.52.

3-(3-Hydroxyphenyl)-2-(5-{3-[3-(3-hydroxyphenyl)-4-oxo-1,3-thiazolan-2-yl]-4-methoxybenzyl}-2-methoxyphenyl)-1,3-thiazo lan-4-one (6f). mp 205-207 °C; IR (KBr): ν 3535, 3015, 2982, 1690, 1615, 1478, 1412, 1221, 686 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.36 (2H, s, CH_2), 3.81 (4H, s, CH_2) 4.11 (6H, s, OCH_3), 5.40 (2H, s, OH), 6.07 (2H, s, CH-S), 6.70-7.14 (14H, m, ArH); ^{13}C NMR ($CDCl_3$): δ 35.3, 41.1, 54.1, 64.2, 107.6, 109.7, 113.3, 115.0, 123.8, 124.1, 129.8, 133.9, 135.3, 152.9, 158.3, 171.9; MS: m/z 616 (M^+). *Anal*. calcd for $C_{33}H_{30}N_2O_6S_2$: C, 64.48; H, 4.92; N, 4.56. Found: C, 64.31; H, 4.86; N, 4.50.

3-(4-Hydroxyphenyl)-2-(5-{3-[3-(4-hydroxyphenyl)-4-oxo-1,3-thiazolan-2-yl]-4-methoxybenzyl}-2-methoxyphenyl)-1,3-thiazolan-4-one (6g). mp 259-261 °C; IR (KBr): ν 3541, 3012, 2986, 1710, 1614, 1476, 1412, 1221, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.36 (2H, s, CH_2), 3.80 (4H, s, CH_2) 4.14 (6H, s, OCH_3), 5.15 (2H, s, OH), 6.09 (2H, s, CH-S), 6.70-7.10 (10H, m, ArH), 7.39 (4H, d, J = 8.86 Hz, ArH); ^{13}C NMR ($CDCl_3$): δ 35.9, 41.1, 54.4, 64.3, 109.2, 114.9, 122.1, 123.2, 125.0, 133.8, 134.1, 136.4, 151.1, 155.2, 171.5; MS: m/z 616 (M^+). *Anal*. calcd for $C_{33}H_{30}N_2O_6S_2$: C, 64.48; H, 4.92; N, 4.56. Found: C, 64.40; H, 4.82; N, 4.51.

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