

## Synthesis of novel substituted 4,4'-(1,4-phenylene)bis(1,3-thiazole)s

Sreedharan L. Manju,<sup>\*a</sup> Sarojini Asha,<sup>b</sup> Thankappan F. A. F. Reji,<sup>c</sup> and Kallikat N. Rajasekharan<sup>b</sup>

<sup>a</sup>Chemistry Division, Vellore Institute of Technology, Katpadi, Vellore 632014, Tamilnadu, India

<sup>b</sup> Department of Chemistry, University of Kerala, Kariavattom, Trivandrum 695581, Kerala, India

<sup>c</sup>Department of Chemistry, Nesamony Memorial Christian College, Marthandam, Tamilnadu

E-mail: [girishmanju@gmail.com](mailto:girishmanju@gmail.com)

---

### Abstract

A series of novel substituted 4,4'-(1,4-phenylene)bis(1,3-thiazole)s were synthesized by the reaction of new substituted *N,N'*-Bis(aminocarbonothioyl)terephthalamides with phenacyl bromides. The reaction has been completed within 3-5 min and afforded the title compounds in good yields. The required thioureas, hitherto unreported, were successfully accessed by reacting terephthaloyl diisothiocyanate, prepared in a phase transfer catalyzed reaction with secondary amines *in situ*. All the synthesized compounds have been characterized by spectral analysis.

**Keywords:** *N,N'*-Bis(aminocarbonothioyl)terephthalamides, aminothiazole, 4,4'-(1,4-phenylene)bis(1,3-thiazole), thiazole

---

### Introduction

A comparatively new trend in drug design is the exploitation of the ability of drug molecules so designed as to bind in more than one docking site to its biological target in which the presence of multiple binding sites allows simultaneous binding of a multivalent ligand. This phenomenon has been termed as the chelate effect, which arises either from the entropy driven additional stability in comparison with two individual monovalent binding or from probability factors that promote the second binding event subsequent to the first, or both. Molecules with such bi- or multivalent binding ability exhibit enhanced bioactivity and the recent literature reveals several examples of such multivalent ligand design aimed at a variety of drug targets.<sup>1-4</sup> This concept of simultaneous, multivalent binding in drug design has also been reviewed.<sup>5</sup> Aminothiazoles, as a class, have served well as a useful pharmacophore unit and several examples of such drugs are clinically prescribed. Molecules that incorporate a bithiazole moiety in which two thiazole rings are joined directly as in bleomycin or a bithiazole unit in which the two thiazole rings are

connected through a few intervening bonds also exhibit useful biological activities. Though, the synthesis of 5,5'-bis-1,3-thiazoles<sup>6</sup> and 2,2'-bis-1,3-thiazoles<sup>7</sup> have been reported, the synthesis of two aminothiazole units linked through a phenylene unit has not been reported. With our interest in cytotoxic aminothiazoles<sup>8</sup> and in the synthesis of 2-aminothiazoles<sup>9</sup> we now report the synthesis of novel substituted 4,4'-(1,4-phenylene)bis(1,3-thiazole)s.

## Result and Discussion

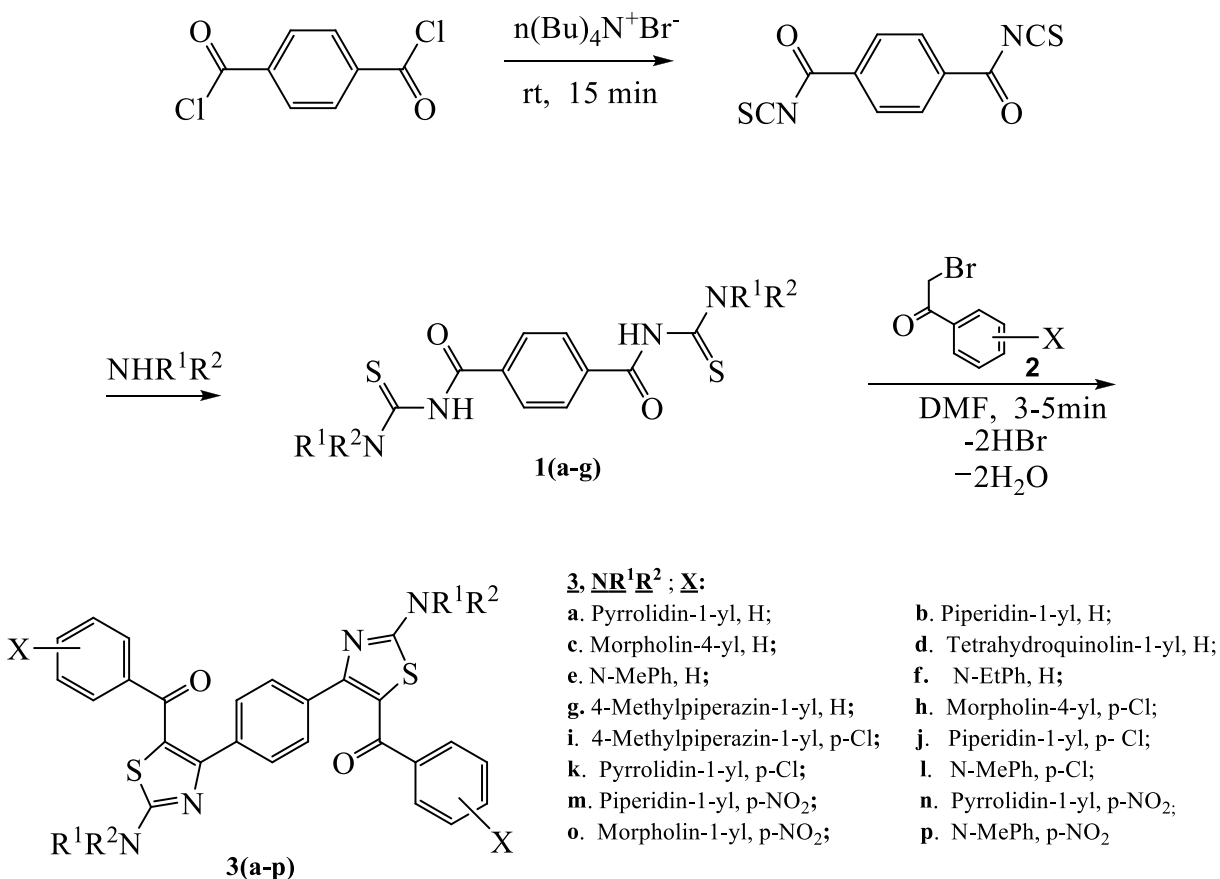
The synthesis of 5-ketothiazoles can be envisaged through three general methods, all starting from an appropriate thiourea derivative. In the first, and the classic, the Hantzsch route, a 2-halo-1,3-diketone is reacted with a substituted thiourea in a [C-C + N-C-S] cyclization strategy. In the second, the Liebscher and Hartmann method,<sup>10</sup> acylthioureas are reacted with  $\alpha$ -haloketones. In the third, Rajappa's approach,<sup>11</sup> imidoylthioureas are treated with  $\alpha$ -haloketones. The latter two reactions are examples of a [C-N-C-S + C] cyclization method. To access the bis-5-ketothiazoles connected at 4,4'-position, we decided to explore the acylthiourea [4+1] heterocyclization strategy. Accordingly, based on a retrosynthetic analysis, the substituted *N,N'*-Bis(aminocarbonothioyl)terephthalamides **1(a-g)** and phenacyl bromides were identified as the starting materials.

The hitherto unreported thioureas **1(a-g)** were successfully synthesized by reacting terephthaloyl diisothiocyanate, prepared in a phase transfer catalyzed reaction with secondary amines *in situ*. The secondary amines used for the preparation of thioureas were pyrrolidine, piperidine, morpholine and *N*-methylpiperazine. The products **1(a-g)** were recrystallized from ethanol and characterized by IR, <sup>1</sup>H NMR and mass spectral analysis. As a typical example, synthesis and characterization of *N,N'*-bis(pyrrolidin-1-ylcarbonothioyl)terephthalamide **1a** is described here. The product **1a** formed from terephthaloyl diisothiocyanate and pyrrolidine had a molecular formula C<sub>18</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> and showed a [M+H<sup>+</sup>] ion at m/z 391 in its FAB mass spectrum. The IR spectrum of the compound showed a peak at 1670 cm<sup>-1</sup> indicative of a carbonyl group. The <sup>1</sup>H NMR spectrum of the compound **1a** showed a multiplet at  $\delta$  1.96 due to eight hydrogens characteristic of C3 and C4 of two pyrrolidine rings. Two triplets at  $\delta$  3.59 and  $\delta$  3.72 (J, 6.3 and 6 Hz respectively) could be attributed to the hydrogens attached to the C2 and C5 of the pyrrolidine rings. The appearance of the two triplets pointed to some restriction in the rotation for the C-N bond, a phenomenon often seen in amides. A singlet seen at  $\delta$  8.01 was due to the four hydrogen atoms of the phenyl ring flanked by two carbonyl groups. A broad singlet at  $\delta$  10.98 could be assigned to NH group.

The reaction of *N,N'*-bis(morpholin-4-ylcarbonothioyl)terephthalamide **1c** with phenacyl bromide (1:2 mole ratio) in DMF rapidly yielded a single product, as a free base, which showed M<sup>+</sup> at m/z 622. In the <sup>1</sup>H NMR spectrum, compound showed two triplets at  $\delta$  3.62 and at  $\delta$  3.84. The former could be assigned to methylene groups adjacent to nitrogen and the latter to methylene groups adjacent to oxygen of a morpholine ring. In the aromatic region, three sets of

multiplets were observed at  $\delta$  7.14-7.22 (partially overlapped by solvent peak), at  $\delta$  7.29-7.34 and at  $\delta$  7.50-7.56 arising apparently from eight, two and four hydrogens attached to aromatic ring. This triplet-triplet-doublet pattern is characteristic for a Ph-CO structural unit. The  $^{13}\text{C}$  NMR spectrum revealed the presence of morpholine ring due to the appearance of the peaks at  $\delta$  48.1 and  $\delta$  66.1. The peaks at  $\delta$  138.4,  $\delta$  157.7 and  $\delta$  171.4 were characteristics of C5, C4 and C2 of a substituted thiazole ring and the peak at  $\delta$  188.4 was assigned to a carbonyl group. The correlations between C and H were further confirmed by a HETCOR 2D NMR spectrum.

On the basis of these and elemental analysis data, the product was formulated as [1,4-phenylenebis(2-morpholin-4-yl-1,3-thiazole-4,5-diyl)]bis(phenylmethanone) (**3c**). The reaction conceivably involved the formation of an S-alkyl intermediate first which then underwent heterocyclization followed by the elimination of one molecule of water to afford the bithiazole. The reaction (Scheme 1) was found to be general and additional analogues (**3a,b,d-p**) were thus obtained in 65-85 % yield.



Scheme 1

## Conclusions

We have designed and synthesized the new bistioureas **1(a-g)** and using these, we have further demonstrated the preparation of hitherto unreported 4,4'(1,4-phenylene)bis(1,3-thiazole)s in good yield. The generality of this methodology has been confirmed by the synthesis of sixteen bistiiazole derivatives.

## Experimental Section

**General Procedures.** Melting points are uncorrected. The IR spectra were recorded in Potassium bromide pellets on an AVATAR 330 FTIR spectrometer, the  $^1\text{H}$ ,  $^{13}\text{C}$  spectra, on a AMX-400/DRX-500 NMR spectrometer and the FAB-MS spectra, on a JEOL SX 102/DA-6000 mass spectrometer using argon/Xenon as the FAB gas and NBA matrix.. The 2D NMR experiment was carried out using DRX 500 NMR spectrometer. The elemental analysis has been carried out with Elementar Vario EL III apparatus. The compounds were purified by column chromatography using silica gel (60-120 mesh, E. Merck). All the chemicals were purchased from E. Merck and Aldrich.

### General procedure for the preparation of substituted *N,N'*-bis(amino-carbonothioyl)terephthalamides **1(a-g)**

To a mixture of benzene (10 mL) and aqueous solution of potassium thiocyanate (33 %, 11 mL), tetrabutylammonium bromide (0.2 g) was added and stirred at room temperature for 30 minutes. To this, a solution of terephthaloyl dichloride (2.9 g, 0.015 mol) in benzene (10 mL) was added and stirring continued for another 10-15 minutes. The benzene layer was transferred to another flask and aqueous layer was then extracted with benzene (4 mL). To this combined benzene layer, after drying, *N,N*-dialkylamines (0.03 mol) were added and stirred for 2 hours (monitored by TLC using hexane: ethyl acetate 1:1v/v as eluent). The precipitated solid was filtered and washed with ethanol. The compounds were crystallized from ethanol.

***N,N'*-Bis(pyrrolidin-1-ylcarbonothioyl)terephthalamide (1a).** Colorless solid, yield 77 %, m. p. 188-189 °C; IR (KBr)  $\nu$  3443, 3263, 2963, 2871, 1670, 1537, 1458, 1438, 1252, 1217, 863, 723, 691;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  1.96 (quintet, 8H,  $J=6.4\text{Hz}$ ,  $-\text{CH}_2$ ), 3.59 (t, 4H,  $N-\text{CH}_2$ ,  $J=6.3\text{Hz}$ ), 3.72 (t, 4H,  $N-\text{CH}_2$ ,  $J=6.0\text{Hz}$ ), 8.01 (s, 4H, Ar-H), 10.98 (s, 2H, NH); FABMS  $\text{MH}^+$   $m/z$  391. Anal. calcd. for  $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_2\text{S}_2$  (390.52): C, 55.36; H, 5.68; N, 14.35 %. Found: C, 55.19; H, 5.51; N, 14.46 %.

***N,N'*-Bis(piperidin-1-ylcarbonothioyl)terephthalamide (1b).** Colorless solid, yield 78 %, m. p. 171-173 °C; IR (KBr)  $\nu$  3289, 2940, 2921, 2855, 1673, 1534, 1452, 1246, 1170, 1153, 1017, 863, 724;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  1.50-1.78 (m, 12H,  $-\text{CH}_2$ ), 3.48-3.70 (m, 4H,  $-\text{CH}_2$ ), 4.05-4.26 (m, 4H,  $N-\text{CH}_2$ ), 8.02 (s, 4H, Ar-H), 10.74 (s, 2H, NH). Anal. calcd. for

$C_{20}H_{26}N_4O_2S_2$  (418.57): C, 57.39 %; H, 6.26 %; N, 13.39 %. Found: C, 57.22 %; H, 6.36; N, 13.45 %.

***N,N'*-Bis(morpholin-4-ylcarbonothioyl)terephthalamide (1c)**. Colorless solid, yield 80 %, m.p. 180-182 °C; IR (KBr)  $\nu$  3442, 3267, 2972, 2928, 2861, 1664, 1522, 1461, 1272, 1246, 1107, 1031, 874, 711, 644, 511;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.53-3.82 (m, 8H, N-CH<sub>2</sub>), 4.10-4.23 (m, 8H, O-CH<sub>2</sub>), 8.05 (s, 4H, Ar-H), 10.95 (s, 2H, NH). Anal. calcd. for  $C_{18}H_{22}N_4O_4S_2$  (422.53): C, 51.16; H, 5.25; N, 13.26 %. Found: C, 50.96; H, 5.32; N, 13.17 %.

***N,N'*-Bis(3,4-dihydroquinolin-1(2H)-ylcarbonothioyl)terephthalamide (1d)**. Colourless solid, yield 88 %, m.p. 178-80 °C; IR (KBr)  $\nu$  3398, 3138, 2945, 1665, 1520, 1461, 1390, 1274, 1240, 1172, 1160, 1016, 771;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.01 (q, 4H, CH<sub>2</sub>, J=6.2 Hz), 2.75 (t, 4H, CH<sub>2</sub>), 3.98 (t, 4H, CH<sub>2</sub>, J= 6Hz), 7.02-7.10(m, 2H, Ar-H ), 7.29-7.32 ( m, 4H, Ar-H), 7.98-8.04(d, 2H, Ar-H), 8.07 (s, 4H, Ar-H), 10.74 (s, 2H, NH). Anal. calcd. for  $C_{28}H_{26}N_4O_2S_2$  (514.65): C, 65.34; H, 5.09; N 10.89, %. Found: C, 65.27; H, 5.19; N, 10.81 %.

***N,N'*-Bis[[methyl(phenyl)amino]carbonothioyl]terephthalamide (1e)**. Colorless solid, yield 65 %, m. p. 152-154 °C; IR (KBr)  $\nu$  3390, 3145, 3033, 1663, 1525, 1491, 1432, 1373, 1271, 1113, 1075, 912, 771, 697;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.61 (s, 6H, N-CH<sub>3</sub>), 7.09-7.18 (m, 6H, Ar-H), 7.42-7.50 (m, 4H, Ar-H), 8.01 (s, 4H, Ar-H), 10.28-11.20 (b, 2H, NH). Anal. calcd. for  $C_{24}H_{22}N_4O_2S_2$  (462.58): C, 62.31; H, 4.79; N 12.11 %. Found: C, 62.49; H, 4.62; N, 12.03 %.

***N,N'*-Bis[[ethyl(phenyl)amino]carbonothioyl]terephthalamide (1f)**. Colorless solid, yield 75 %, m. p. 138-140 °C; IR (KBr)  $\nu$  3387, 3148, 2969, 2931, 1666, 1522, 1491, 1456, 1407, 1285, 1245, 1169, 1123, 1083, 768, 695;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  1.29 (t, 6H, -CH<sub>3</sub>), 3.98 (q, 4H, -CH<sub>2</sub>), 7.10-7.18 (m, 6H, Ar-H), 7.42-7.48 (m, 4H, Ar-H), 8.01 (s, 4H, Ar-H), 10.30-11.18 (b, 2H, NH). Anal. calcd. for  $C_{26}H_{26}N_4O_2S_2$  (490.63): C, 63.65; H, 5.34; N 11.42 %. Found: C, 63.79; H, 5.43; N, 11.38 %.

***N,N'*-Bis[(methylpiperidin-1-yl)carbonothioyl]terephthalamide (1g)**. Colorless solid, yield 81 %, m. p. 150-152 °C; IR (KBr)  $\nu$  3444, 2976, 2810, 1684, 1541, 1465, 1435, 1435, 1250, 1186, 997, 858, 725;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.21-3.45 (m, 6H, N-CH<sub>3</sub>), 3.50-3.72 (m, 8H, N-CH<sub>2</sub>), 4.09-4.25 (m, 8H, N-CH<sub>2</sub>), 8.03 (s, 4H, Ar-H), 10.30-11.20 (b, 2H, NH). Anal. calcd. for  $C_{20}H_{28}N_6O_2S_2$  (448.60): C, 53.54; H, 6.29; N 18.74 %. Found: C, 53.32; H, 6.43; N, 18.83 %.

### General procedure for the synthesis of 4,4'-(1,4-phenylene)bis(1,3-thiazole)s

A solution of *N,N'*-bis[(alkyl/arylamino)carbonothioyl]terephthalamides (1 mmol) in *N,N*-dimethylformamide (5 mL) was reacted with phenacyl bromides (2 mmol) dissolved in the same solvent. The mixture was then heated in a water bath for 3-5 minutes (monitored by TLC using chloroform as eluent) and was added to water. The yellow solid obtained was chromatographed on silica gel and the compound was eluted using chloroform (5 x 50 mL). In the case of compounds **3e**, **3f**, **3g**, **3i**, **3l** and **3p**, the reaction mixture was added to water and the solution upon neutralization afforded yellow solids. The compounds **3d** and **3i** were eluted using methanol and compound **3l** using chloroform: ethyl acetate (2:1, 5 x 50 mL). Subsequent crystallization of the compounds from chloroform provided yellow needles.

**[1,4-Phenylenebis(2-pyrrolidin-1-yl-1,3-thiazole-4,5-diyl)]bis(phenylmethanone) (3a).**

Yellow colored solid, yield 77.3 %. m. p 255-257 °C; IR (KBr)  $\nu$  2974, 2925, 2844, 1616, 1595, 1557, 1465, 1331, 1287, 1112, 1044, 882, 723, 700, 658;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.02-2.15 (t, 8H,  $\text{CH}_2$ ), 3.48-3.62 (t, 8H,  $\text{CH}_2$ ), 7.10-7.17 (m, 6H, Ar-H), 7.22-7.30 (m, 4H, Ar-H), 7.44-7.60 (m, 4H, Ar-H);  $^{13}\text{C}$  NMR (100MHz,  $\text{DMSO-d}_6$ )  $\delta$  25.72, 49.68, 122.01, 127.83, 129.09, 129.32, 131.41, 135.26, 138.96, 158.97, 168.13 and 188.28; ESMS  $m/z$ : 591.1. Anal. calcd. for  $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_2\text{S}_2$  (590.74): C, 69.12; H, 5.12; N, 9.49 %. Found: C, 69.22; H, 5.20; N, 9.33 %.

**[1,4-Phenylenebis(2-piperidin-1-yl-1,3-thiazole-4,5-diyl)]bis(phenylmethanone) (3b).**

Yellow colored solid, yield 67.6 %, m. p 264-266 °C; IR (KBr)  $\nu$  2940, 2856, 1612, 1536, 1517, 1474, 1310, 1288, 1256, 1113, 1068, 1021, 866, 716, 633;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.64-1.79 (m, 12H,  $-\text{CH}_2$ ), 3.53-3.68 (m, 8H, N- $\text{CH}_2$ ), 7.1-7.2 (m, 6H, Ar-H), 7.24-7.31 (m, 4H, Ar-H), 7.46-7.55 (m, 4H, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 24.04, 25.22, 49.31, 121.67, 127.86, 129.12, 129.24, 131.51, 135.23, 138.90, 158.48, 171.34 and 188.34; FABMS  $\text{MH}^+$  619. Anal. calcd. for  $\text{C}_{36}\text{H}_{34}\text{N}_4\text{O}_2\text{S}_2$  (618.796): C, 69.87; H, 5.54; N, 9.06 %. Found: C, 69.71; H, 5.61; N, 8.97 %.

**[1,4-Phenylenebis(2-morpholin-4-yl-1,3-thiazole-4,5-diyl)]bis(phenylmethanone) (3c).**

Yellow colored solid, yield 78.3 %, m.p. >300 °C; IR (KBr)  $\nu$  2966, 2924, 2856, 1612, 1537, 1518, 1473, 1314, 1290, 1114, 1070, 878, 718, 690, 644;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.62 (t, 8H, N- $\text{CH}_2$ ,  $J=4.7\text{Hz}$ ), 3.84 (t, 8H, O- $\text{CH}_2$ ,  $J=4.6\text{Hz}$ ), 7.14-7.22 (m, 8H, Ar-H), 7.29-7.34 (m, 2H, Ar-H), 7.50-7.56 (m, 4H, Ar-H);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta$ : 48.05, 66.07, 122.4, 127.92, 129.16, 129.24, 131.84, 134.92, 138.35, 157.69, 171.37 and 188.44; FABMS  $\text{MH}^+$  623. Anal. calcd. for  $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_4\text{S}_2$  (622.76): C, 65.57; H, 4.86; N, 9.00 %. Found: C, 65.70; H, 4.95; N, 8.90 %.

**{1,4-Phenylenebis[2-(3,4-dihydroquinolin-1(2H)-yl)-1,3-thiazole-4,5-diyl]}bis(phenylmethanone) (3d).**

Yellow colored solid, yield 72 %, m. p. >300 °C; IR (KBr)  $\nu$  2917, 2860, 1608, 1497, 1449, 1397, 1331, 1281, 1093, 1049, 861, 760, 698;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.09 (q, 4H,  $\text{CH}_2$ ,  $J=6.2\text{Hz}$ ), 2.83 (t, 4H,  $\text{CH}_2$ ,  $J=6.3\text{Hz}$ ), 4.03 (t, 4H,  $\text{CH}_2$ ,  $J=6.2\text{Hz}$ ), 7.05-7.12 (m, 4H, Ar-H), 7.13-7.28 (m, 8H, Ar-H), 7.30-7.36 (m, 4H, Ar-H), 7.53-7.62 (m, 4H, Ar-H), 7.95-8.04 (d, 2H, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 23.27, 27.46, 49.37, 121.22, 121.87, 124.41, 126.82, 128.00, 129.12, 129.32, 130.49, 131.97, 134.99, 138.52, 139.85, 156.71, 168.73 and 188.68; FABMS  $\text{MH}^+$   $m/z$ : 715. Anal. calcd. for  $\text{C}_{44}\text{H}_{34}\text{N}_4\text{O}_2\text{S}_2$  (714.87): C, 73.92; H, 4.79; N, 7.84 %. Found: C, 73.83; H, 4.91; N, 7.75 %.

**(1,4-Phenylenebis{2-[methyl(phenyl)amino]-1,3-thiazole-4,5-diyl})bis(phenylmethanone) (3e).**

Yellow colored solid, yield 62 %, m. p. >280 °C; IR (KBr)  $\text{cm}^{-1}$ : 3052, 2925, 2848, 1604, 1536, 1470, 1331, 1289, 1172, 1121, 858, 721, 696;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.63 (s, 6H,  $-\text{CH}_3$ ), 7.09-7.18 (m, 4H, Ar-H), 7.20(s, 4H, Ar-H), 7.35-7.43 (m, 15H, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  40.73, 122.38, 125.39, 127.86, 128.01, 129.19, 129.42, 130.23, 131.96, 134.48, 138.25, 145.36, 156.37, 170.85 and 188.47; FAB  $\text{MH}^+$  663. Anal. calcd. for  $\text{C}_{40}\text{H}_{30}\text{N}_4\text{O}_2\text{S}_2$  (662.80): C, 72.48; H, 4.56; N, 8.45 %. Found: C, 72.37; H, 4.41; N, 8.59 %.

**(1,4-Phenylenebis{2-[ethyl(phenyl)amino]-1,3-thiazole-4,5-diyl})bis(phenylmethanone) (3f).** Yellow colored solid, yield 70.9 %, m. p. 259-60 °C; IR (KBr)  $\nu$  3062, 2970, 2929, 1633, 1512, 1464, 1319, 1279, 1164, 1111, 1022, 919, 826, 726, 699.7;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.31 (t, 6H,  $\text{CH}_3$ ,  $J=7.1\text{Hz}$ ), 4.10 (q, 4H,  $\text{CH}_2$ ,  $J=7.1\text{Hz}$ ), 7.10-7.18 (m, 4H, Ar-H), 7.20 (s, 4H, Ar-H), 7.26-7.32 (m, 4H, Ar-H), 7.35-7.44 (m, 4H, Ar-H), 7.44-7.55 (m, 8H, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  13.15, 47.72, 122.13, 127.19, 127.88, 128.21, 129.18, 129.27, 130.29, 131.64, 135.14, 138.72, 143.96, 157.79, 170.90 and 188.52. Anal. calcd. for  $\text{C}_{42}\text{H}_{34}\text{N}_4\text{O}_2\text{S}_2$  (690.85): C, 73.01; H, 4.96; N, 8.11 %. Found: C, 73.11; H, 5.09; N, 8.24 %.

**{1,4-Phenylenebis[2-(methylpiperazin-1-yl)-1,3-thiazole-4,5-diyl]}bis(phenylmethanone) (3g).** Yellow colored solid, yield 63.8 %, m. p. >300 °C; IR (KBr)  $\nu$  2936, 2848, 2800, 1610, 1536, 1517, 1471, 1448, 1311, 1287, 1254, 1144, 1073, 1002, 866, 718, 697, 653;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.4 (s, 6H, N- $\text{CH}_3$ ), 2.54 (t, 8H,  $\text{CH}_2$ ,  $J=3.66\text{Hz}$ ), 3.65 (t, 8H,  $\text{CH}_2$ ,  $J=3.66\text{Hz}$ ), 7.1-7.2 (m, 6H, Ar-H), 7.26-7.33 (m, 4H, Ar-H), 7.49-7.55 (m, 4H, Ar-H). FABMS  $\text{MH}^+$  649. Anal. calcd. for  $\text{C}_{36}\text{H}_{36}\text{N}_6\text{O}_2\text{S}_2$  (648.83): C, 66.64; H, 5.59; N, 12.95 %. Found: C, 66.49; H, 5.69; N, 12.81 %.

**[1,4-Phenylenebis(2-morpholin-4-yl-1,3-thiazole-4,5-diyl)]bis[(4-chlorophenyl)methanone] (3h).** Yellow colored solid, yield 85 %, m. p. 296-298 °C; IR (KBr)  $\nu$  2924, 2855, 1602, 1540, 1468, 1310, 1291, 1262, 1113, 1088, 1014, 880, 748;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  3.64 (t, 8H, N- $\text{CH}_2$ ,  $J=4.5\text{Hz}$ ), 3.84 (t, 8H, O- $\text{CH}_2$ ,  $J=4.5\text{Hz}$ ), 7.07-7.22 (m, 8H, Ar-H), 7.38-7.52 (m, 4H, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  48.17, 66.07, 122.24, 128.17, 129.33, 130.48, 135.19, 136.96, 137.88, 158.19, 171.54 and 186.93; FABMS  $\text{MH}^+$   $m/z$ : 691. Anal. calcd. for  $\text{C}_{34}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O}_4\text{S}_2$  (691.64): C, 59.04; H, 4.08; N, 8.10 %. Found: C, 59.15; H, 4.19; N, 8.22 %.

**{1,4-Phenylenebis[2-(4-methylpiperazin-1-yl)-1,3-thiazole-4,5-diyl]}bis[(4-chlorophenyl)methanone] (3i).** Yellow colored solid, yield 79 %, m. p. >300 °C; IR (KBr)  $\nu$  2923, 1608, 1514, 1466, 1323, 1284, 1088, 1013, 974, 878, 751;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  2.86 (s, 6H, N- $\text{CH}_3$ ), 3.52 (bs, 8H, N- $\text{CH}_2$ ), 4.2 (bs, 8H, N- $\text{CH}_2$ ), 7.16 (s, 4H, Ar-H), 7.20-7.35 (m, 4H, Ar-H), 7.35-7.50 (m, 4H, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  42.26, 44.73, 51.41, 127.74, 127.97, 128.13, 128.99, 129.39, 130.39, 131.24, 134.64, 136.67, 137.04, 157.53, 170.32 and 186.06; FABMS  $\text{MH}^+$  718. Anal. calcd. for  $\text{C}_{36}\text{H}_{34}\text{Cl}_2\text{N}_6\text{O}_2\text{S}_2$  (717.73): C, 60.24; H, 4.78; N, 11.71 %. Found: C, 60.09; H, 4.71; N, 11.88 %.

**[1,4-Phenylenebis(2-piperidin-1-yl-1,3-thiazole-4,5-diyl)]bis[(4-chlorophenyl)methanone] (3j).** Yellow colored solid, yield 81 %, m. p. 298-299 °C; IR (KBr)  $\nu$  2935, 2855, 1599, 1536, 1518, 1466, 1340, 1305, 1256, 1111, 1086, 1013, 877, 846, 747, 700;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.63-1.76 (m, 12H,  $\text{CH}_2$ ), 3.53-3.67 (m, 8H,  $\text{CH}_2$ ), 7.05-7.15 (m, 4H, Ar-H), 7.33 (s, 4H, Ar-H), 7.36-7.40 (m, 4H, Ar-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  23.92, 25.19, 49.38, 127.91, 127.95, 128.05, 128.47, 129.27, 129.49, 130.41, 130.50, 131.03, 131.11, 133.52, 141.34, 158.87, 171.73 and 186.78; FABMS  $\text{MH}^+$  688. Anal. calcd. for  $\text{C}_{36}\text{H}_{32}\text{Cl}_2\text{N}_4\text{O}_2\text{S}_2$  (687.69): C, 62.87; H, 4.69; N, 8.15 %. Found: C, 62.76; H, 4.59; N, 8.23 %.

**[1,4-Phenylenebis(2-pyrrolidin-1-yl-1,3-thiazole-4,5-diyl)]bis[(4-chlorophenyl)methanone] (3k).** Yellow colored solid, yield 83 %, m. p. >300 °C; IR (KBr)  $\nu$  2924, 2856, 1597, 1552, 1454,

1327, 1272, 1111, 1083, 1013, 883, 839, 750, 553;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.0-2.18 (bs, 8H,  $-\text{CH}_2$ ), 3.40-3.80 (bs, 8H,  $-\text{CH}_2$ ), 7.0-7.2 (m, 6H, Ar-H), 7.20-7.50 (m, 6H, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  25.70, 49.74, 126.48, 128.05, 128.45, 129.39, 129.58, 130.44, 131.12, 137.44 and 186.71; FABMS  $\text{MH}^+$  660. Anal. calcd. for  $\text{C}_{34}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O}_2\text{S}_2$  (659.64): C, 61.90; H, 4.28; N, 8.49 %. Found: C, 61.71; H, 4.19; N, 8.58 %.

**(1,4-Phenylenebis{2-[methyl(phenyl)amino]-1,3-thiazole-4,5-diyl})bis[(4-chlorophenyl)-methanone] (3l)**. Yellow colored solid, yield 75 %, m. p. 278-280 °C; IR (KBr)  $\nu$  2927, 1608, 1510, 1494, 1469, 1332, 1314, 1291, 1171, 1116, 1087, 1015, 860, 834, 752, 701, 556;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.64 (s, 6H,  $-\text{NCH}_3$ ), 7.1-7.19 (m, 4H, Ar-H), 7.22 (s, 4H, Ar-H), 7.30-7.55 (m, 14H, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  40.25, 122.19, 125.42, 127.72, 128.18, 129.39, 130.15, 130.52, 135.19, 137.06, 137.88, 145.38, 157.82, 171.09 and 187.10; FABMS  $\text{MH}^+$  732. Anal. calcd. for  $\text{C}_{40}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O}_2\text{S}_2$  (731.70): C, 65.66; H, 3.86; N, 7.66 %. Found: C, 65.52; H, 3.98; N, 7.49 %.

**[1,4-Phenylenebis(2-piperidin-1-yl-1,3-thiazole-4,5-diyl)]bis[(4-nitrophenyl)methanone] (3m)**. Yellow colored solid, yield 75 %, m. p. >300 °C; IR (KBr)  $\nu$  3433, 2944, 2856, 1608, 1594, 1550, 1523, 1467, 1345, 1298, 1253, 846, 714;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.70-1.90 (m, 12H,  $\text{CH}_2$ ), 3.50-3.90 (m, 8H,  $\text{N-CH}_2$ ), 6.98 (s, 4H, Ar-H), 7.48 (d, 4H, Ar-H,  $J=8.4\text{Hz}$ ), 7.95 (d, 4H, Ar-H,  $J=8.4\text{Hz}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  23.94, 25.27, 49.52, 122.94, 129.06 and 129.46; FABMS  $\text{MH}^+$ : 709. Anal. calcd. for  $\text{C}_{36}\text{H}_{32}\text{N}_6\text{O}_6\text{S}_2$  (708.796): C, 60.99; H, 4.55; N, 11.86 %. Found: C, 61.10; H, 4.72; N, 11.68 %.

**[1,4-Phenylenebis(2-pyrrolidin-1-yl-1,3-thiazole-4,5-diyl)]bis[(4-nitrophenyl)methanone] (3n)**. Yellow colored solid, yield 74 %, m. p. >300 °C; IR (KBr)  $\nu$  2950, 2873, 1601, 1552, 1520, 1466, 1348, 1329, 1267, 1106, 844, 715;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  2.06-2.25 (m, 8H,  $\text{CH}_2$ ), 3.48-3.73 (m, 8H,  $\text{CH}_2$ ), 6.98 (s, 4H, Ar-H), 7.54-7.64 (m, 4H, Ar-H), 8.02-8.10 (m, 4H, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  25.72, 49.92, 122.94, 128.28, 129.02, 129.66, 130.63, 130.78, 141.87, 144.61 and 147.70; FABMS  $\text{MH}^+$  681. Anal. calcd. for  $\text{C}_{34}\text{H}_{28}\text{N}_6\text{O}_6\text{S}_2$  (680.74): C, 59.98; H, 4.15; N, 12.35%. Found: C, 60.19; H, 4.26; N, 12.16 %.

**[1,4-Phenylenebis(2-morpholin-4-yl-1,3-thiazole-4,5-diyl)]bis[(4-nitrophenyl)methanone] (3o)**. Yellow colored solid, yield 82.6 %, m. p. >300 °C; IR (KBr)  $\nu$  2922, 2854, 1588, 1539, 1523, 1463, 1347, 1285, 1262, 1116, 1036, 939, 850, 838, 716, 650;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.66 (t, 8H,  $\text{N-CH}_2$ ,  $J=4.5\text{Hz}$ ), 3.87 (t, 8H,  $\text{O-CH}_2$ ,  $J=4.8\text{Hz}$ ), 7.43 (s, 4H, Ar-H), 7.57-7.63 (m, 4H, Ar-H), 8.01-8.08 (m, 4H, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  48.24, 66.09, 123.02 and 129.52; FABMS  $\text{MH}^+$  713. Anal. calcd. for  $\text{C}_{34}\text{H}_{28}\text{N}_6\text{O}_8\text{S}_2$  (712.74): C, 57.29; H, 3.96; N, 11.79 %. Found: C, 57.40; H, 4.08; N, 11.88 %.

**(1,4-Phenylenebis{2-[methyl(phenyl)amino]-1,3-thiazole-4,5-diyl})bis[(4-nitrophenyl)-methanone] (3p)**. Yellow colored solid, yield 71 %, m.p. >300 °C; IR (KBr)  $\nu$  2925, 1612, 1596, 1522, 1467, 1338, 1283, 1175, 838, 714, 693.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  3.63 (s, 6H,  $\text{N-CH}_3$ ), 7.1 (s, 4H, Ar-H), 7.3-7.62 (m, 14H, Ar-H), 7.89-8.1 (m, 4H, Ar-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  123.08, 125.63, 129.63 and 130.61; FABMS  $\text{MH}^+$  753. Anal. calcd. for  $\text{C}_{40}\text{H}_{28}\text{N}_6\text{O}_6\text{S}_2$  (752.80): C, 63.82; H, 3.75; N, 11.16 %. Found: C, 63.93; H, 3.86; N, 11.08 %.



## References

1. Haviv, H.; Wong, D. M.; Silman, I.; Sussman, J. L. *Curr. Top. Med. Chem.* **2007**, *7*, 375.
2. Long, Y. Q.; Jiang, X. H.; Dayam, R.; Sanchez, T.; Shoemaker, R.; Sei, S.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 2561.
3. Lalchandani, S. G.; Lei, L.; Zheng, W.; Suni, M. M.; Moore, B. M.; Liggett, S. B.; Miller, D. D.; Feller, D. R.; *J. Pharm. Exp. Therap.* **2002**, *303*, 979.
4. Lee, G. F.; Lazarus, R. A.; Kelley, R. F. *Biochemistry* **1997**, *36*, 5607.
5. Wright, D. ; Usher, L., *Curr. Org. Chem.* **2001**, *5*, 1107.
6. Noack, A.; Schroder, A.; Hartmann, H. *Dyes Pigments* **2002**, *57*, 131.
7. Martin-Cantalejo, Y.; Saez, B.; Soto, J.; Villa, M. J.; Brana, M. F. *Synthesis* **2003**, *15*, 2211.
8. Devi, S. K. C.; Rajasekharan, K. N. *Synth. Commun.* **2001**, *9*, 2303.
9. Jenardanan, G. C.; Francis, M.; Deepa, S.; Rajasekharan K. N.; *Synth. Commun.* **1997**, *27*, 3457.
10. Liebscher, J.; Hartmann, H. *Z. Chem.* **1974**, *14*, 470.
11. Rajappa, S.; Nair, M. D.; Advani, B. G.; Sreenivasan, R.; Desai, J. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1762.