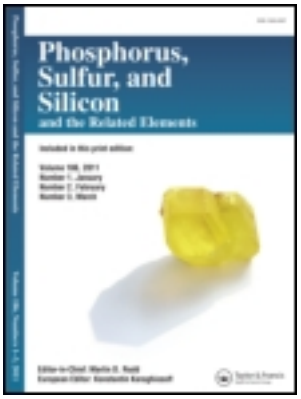

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis of 1,2,4,5-Tetrakis(1,2,4-Triazolyl) Benzene and 1,2,4,5-Tetrakis(1,3,4-Oxadiazolyl) Benzene Derivatives

Abbas Nikoo [a] & Karim Akbari Dilmaghani [a]

[a] Department of Chemistry, Faculty of Science, Urmia University, Urmia, Iran

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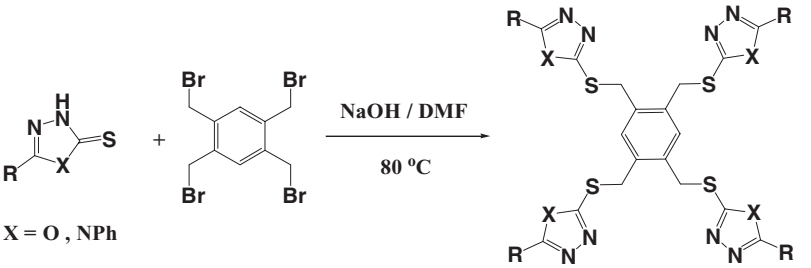
SYNTHESIS OF 1,2,4,5-TETRAKIS(1,2,4-TRIAZOLYL) BENZENE AND 1,2,4,5-TETRAKIS(1,3,4-OXADIAZOLYL) BENZENE DERIVATIVES

Abbas Nikoo and Karim Akbari Dilmaghani
Department of Chemistry, Faculty of Science, Urmia University, Urmia, Iran

GRAPHICAL ABSTRACT



Abstract *A series of 1,2,4,5-tetrakis(1,2,4-triazolyl)benzenes and 1,2,4,5-tetrakis(1,3,4-oxadiazolyl)benzenes was synthesized by nucleophilic addition of sodium salts of 4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thiones and 1,3,4-oxadiazole-2(3H)-thiones to 1,2,4,5-tetrakis(bromomethyl)benzene. The structure of the newly synthesized compounds was confirmed by elemental analysis, IR and ^{1}H and ^{13}C NMR spectra.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource: 1H and 13C NMR spectra of products (Figures S1-S24).*

Keywords 1,3,4-Oxadiazole; 1,2,4,5-tetrakis(bromomethyl)benzene; 1,2,4-triazole

INTRODUCTION

Heterocycles containing sulfur atoms represent an important group of sulfur compounds that are promising for use in practical applications. Moreover, these heterocycles are of great utility in preparative organic chemistry. Among these, the mercapto-1,2,4-triazoles and mercapto-1,3,4-oxadiazoles have been well studied and a large number of derivatives have been used. It was reported that by alkylation of 1,2,4-triazolethiones and 1,3,4-oxadiazolethiones with alkyl halides in an alkali solution, *S*-alkylated derivatives could

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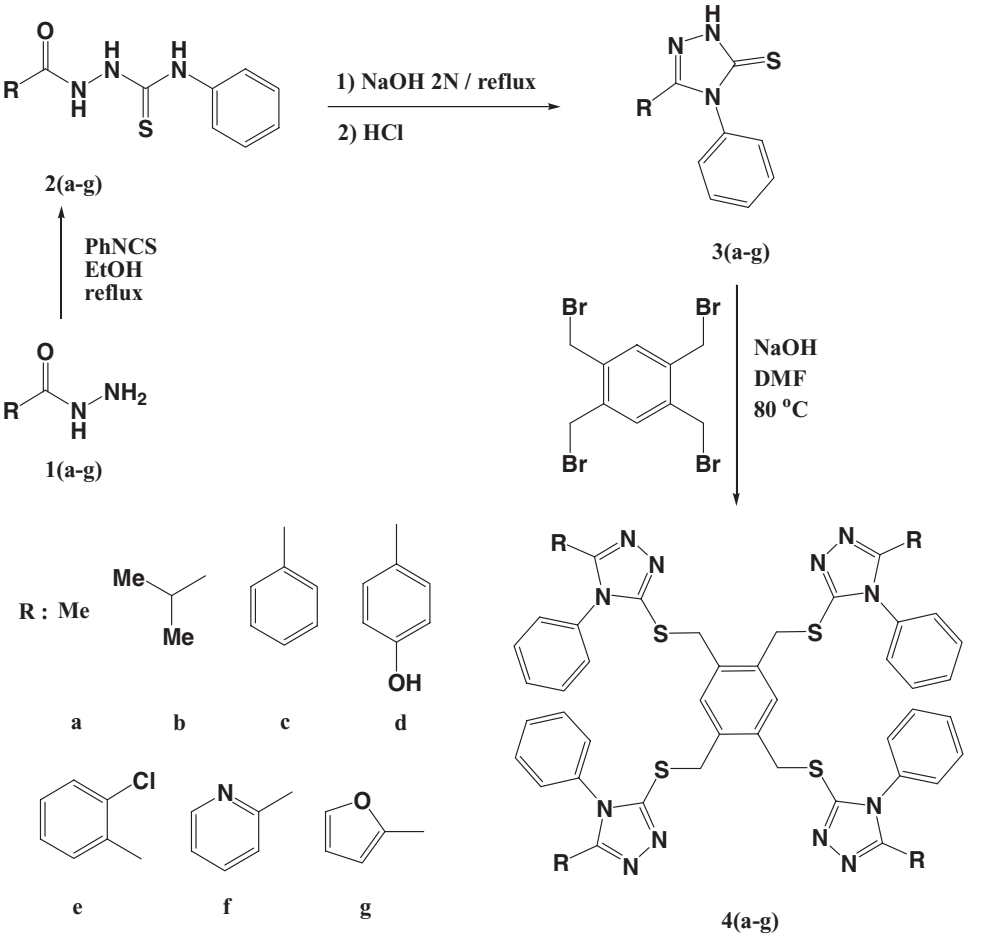
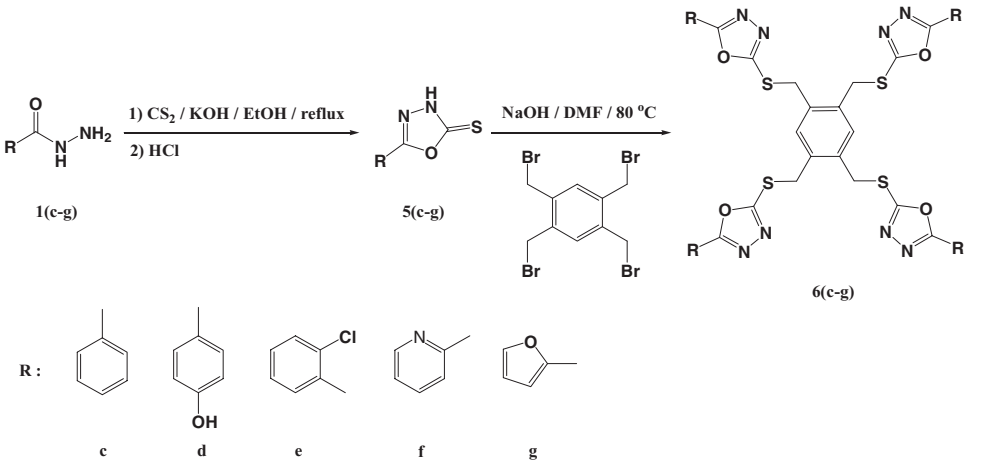
Address correspondence to Karim Akbari Dilmaghani, Department of Chemistry, Faculty of Science, Urmia University, 57159 Urmia, Iran. E-mail: kadilmaghani@yahoo.com

be prepared successfully.[1–3] In this context, the biological activity of *S*-alkylated of 1,2,4-triazolethiones and 1,3,4-oxadiazolethiones is well known and it was found out that the bacteriostatic and diuretic activity of *S*-alkylated-1,2,4-triazolethiones correlates with the size of the alkyl groups.[4] Several *S*-alkylated-1,2,4-triazolethiones were synthesized with anti-inflammatory,[5,6] antibacterial, and antifungal activities.[7] The *S*-alkylated-1,3,4-oxadiazoles showed in vitro activity against *Mycobacterium tuberculosis*.[8] The antihepatitis-B virus activity,[10] bactericidal,[11] antifungal,[12,13] genotoxic activity,[14] antituberculosis,[15] antimicrobial, and anti-HIV-1 activity[9] have been also reported for 2-substituted thio-1,3,4-oxadiazoles.

Therefore, in the light of these interesting biological activities, we decided to synthesize some new 1,2,4,5-Tetrakis(1,2,4-triazolyl)benzenes **4a**–**g** and 1,2,4,5-Tetrakis(1,3,4-oxadiazolyl) benzenes **6c–g** by nucleophilic substitution of 1,2,4,5-tetrakis(bromomethyl)benzene with the corresponding 4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thiones **3a**–**g** and 1,3,4-oxadiazole-2(3H)-thiones **5c–g** in an alkali solution of dimethylformamide (DMF) at 80 °C (Schemes 1 and 2).



Scheme 1



Scheme 2

RESULTS AND DISCUSSION

The synthesis of 1,2,4,5-tetrakis(1,2,4-triazolyl)benzenes **4a**–**g** is outlined in Scheme 1. Reaction of carboxylic acid hydrazides **1a**–**g** with phenylisothiocyanate in ethanol gave 1-substituted-4-phenylthiosemicarbazides **2a**–**g**. Cyclization of compounds **2a**–**g** was accomplished in an aqueous alkaline media to give 4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **3a**–**g** according to the literature.[16] In addition, it was reported that the crystalline form of 1,2,4-triazolethiones existed as the thione tautomer. They showed, however, thiol-thione tautomerism in solution.[17,18] The reaction of 4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **3a**–**g** with 1,2,4,5-tetrakis(bromomethyl)benzene in the presence of NaOH in DMF gave 1,2,4,5-tetrakis(1,2,4-triazolyl)benzenes **4a**–**g**. The IR spectra of compounds **4a**–**g** clearly showed the stretching vibration band between at 1590 and 1600 cm^{-1} which was attributed to the C=N double bond of 1,2,4-triazole. In the ^1H NMR spectra, the protons signals due to methylene groups ($ArCH_2S$) were recorded between at 4.03 and 4.56 ppm with integrals of eight protons. The ^{13}C signals of these groups ($ArCH_2S$) appeared between at 33.75 and 34.30 ppm. In the ^{13}C NMR spectra of compounds **4a**–**g**, two signals belong to the N—C=N group of 1,2,4-triazole which appeared between at 145.55 and 160.82 ppm.

The synthetic pathway leading to 1,2,4,5-tetrakis(1,3,4-oxadiazolyl)benzenes **6c**–**g** is shown in Scheme 2. 1,3,4-Oxadiazole-2(3*H*)-thiones **5c**–**g** were synthesized by the reaction of carboxylic acid hydrazides **1c**–**g** with carbon disulfide in the presence of potassium hydroxide followed by a condensation reaction according to the literature.[19] In 1956, Ainsworth found that 1,3,4-oxadiazolethiones exist in the thione form.[20] Later studies by spectroscopic methods gave the same result.[21] The reaction of 1,3,4-oxadiazole-2(3*H*)-thiones **5c**–**g** with 1,2,4,5-tetrakis(bromomethyl)benzene under the same condition as **4a**–**g** gave 1,2,4,5-tetrakis(1,3,4-oxadiazolyl)benzenes **6c**–**g**. In the IR spectra of compounds **6c**–**g**, the observed absorption band at 1588–1670 cm^{-1} is duo to C=N of 1,3,4-oxadiazole. The ^1H NMR spectra of compounds **6c**–**g** shows a multiplet at 4.63–4.69 ppm with an integral of eight protons of the methylene groups ($ArCH_2S$). The peak belonging to the same groups was observed between at 33.41 and 33.54 ppm in the ^{13}C NMR spectra. In the ^1H NMR spectra of compounds **6c–g**, the signal observed at 7.63–7.74 ppm with an

integral of two protons was assigned to ArH of benzene ring. The ^{13}C NMR spectra of 1,3,4-oxadiazole shows two signals belonging to O—C=N between 145.55 and 160.82 ppm.

CONCLUSION

In this study, we describe the synthesis of some new *S*-alkylated tetrakis-1,2,4-triazoles and tetrakis-1,3,4-oxadiazoles by a nucleophilic substitution of 1,2,4,5-tetrakis(bromomethyl)benzene with 4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones and 1,3,4-oxadiazole-2(3*H*)-thiones. Characterization and check for purity of all compounds were carried out by elemental analysis, IR, ^1H, and ^{13}C NMR spectroscopy.

EXPERIMENTAL

Melting points were determined on a Buchi 530 instrument and are uncorrected. IR spectra were recorded by use of the FT-IR Thermo Nicolet Nexus 670 spectrometer (cm^{-1}, KBr pellets). ^1H NMR (300 MHz) ^{13}C NMR (75 MHz) spectra were measured on a Bruker 300 MHz Ultra shield spectrometer using $CDCl_3$ and DMSO-d_6 as solvents. Elemental analyses (C, H, N, and S) were performed on a Leco CHNS 932 analyzer.

Preparation of 1-Substituted-4-Phenylthiosemicarbazides 2a–g. General Procedure

A mixture of compounds **1a**–**g** (0.01 mol) and phenylisothiocyanate (2 g, 0.015 mol) was stirred in refluxing ethanol (100 mL) for 4 h to give a white precipitate. The mixture was cooled to room temperature. The crude solid was then filtered and crystallized from ethanol to yield the compounds **2(a–g)**.

Preparation of 4-Phenyl-2,4-Dihydro-3H-1,2,4-Triazole-3-Thiones 3(a–g). General Procedure

An aqueous solution of NaOH (2*N*, 50 mL) and compounds **2a–g** (0.01 mol) was stirred under reflux conditions for 6h. After completion of the reaction, the mixture was filtered and the filtrate was neutralized with conc. HCl up to pH 7. The mixture was kept aside for few minutes to precipitate. The precipitated solid was filtered and washed with water. Crystallization from ethanol afforded the compounds **3a–g**.

Preparation of 1,3,4-Oxadiazole-2(3H)-Thiones 5(c–g). General Procedure

Compounds **1c–g** (0.01 mol) was dissolved in a hot solution of KOH (0.56 g, 0.01 mol) in 96% ethanol (50 mL). CS_2 (0.96 mL, 0.015 mol) was then added and the reaction mixture was heated under reflux conditions for 6 h until the evolution of H_2S ceased. The reaction mixture was cooled to room temperature and diluted with water. Acidifying the mixture with conc. HCl gave an oxadiazole precipitate. The solid was filtered, dried and crystallized from ethanol to afford the compounds **5c–g**.

Synthesis of 1,2,4,5-Tetrakis(1,2,4-Triazolyl)Benzenes 4a–g and 1,2,4,5-Tetrakis(1,3,4-Oxadiazolyl)Benzenes 6c–g. General Procedure

To a solution of 4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **3a–g** or 1,3,4-oxadiazole-2(3H)-thiones **5c–g** (1 mmol) in DMF (20 mL), NaOH (1 mmol, 40 mg) was added and the mixture was stirred for 30 min at room temperature. After consumption of NaOH 1,2,4,5-tetrakis(bromomethyl), benzene (0.2 mmol, 0.09 g) was added and the mixture was heated at 75 °C–80 °C for 8–12 h. The mixture was then cooled to the room temperature and distilled water (100 mL) was added to the resulting mixture. The precipitate was filtered and recrystallized in an appropriate solvent to give 1,2,4,5-tetrakis (1,2,4-triazolyl)benzenes **4a–g** or 1,2,4,5-tetrakis(1,3,4-oxadiazolyl)benzenes **6c–g**. Sample spectra are presented in the Supplemental Materials (Figures S1–S24).

1,2,4,5-Tetrakis(5-Methyl-4-Phenyl-1,2,4-Triazol-3-yl-Thiomethyl) Benzene (4a)

Yield: 70%, crystallized from EtOH, mp 208.5 °C–210.5 °C; IR: 3047, 3008, 2971, 2933, 1597, 1535, 1500, 1428, 772, 725, 694, 556; ^{1}H NMR ($CDCl_3$) δ: 2.21 (12H, s, CH_3), 4.22 (8H, s, $ArCH_2S$), 6.98 (2H, s, ArH), 7.08 (8H, bs, ArH), 7.43 (12H, bs, ArH); ^{13}C NMR ($CDCl_3$) δ: 11.28, 34.17, 126.96, 129.88, 133.11, 135.16, 150.14, 152.92; Anal. Calcd. for $C_{46}H_{42}N_{12}S_4$: 62.00 C, 4.75 H, 18.86 N, 14.39 S. Found: 62.08 C, 4.81 H, 18.82 N, 14.29 S.

1,2,4,5-Tetrakis(5-Isopropyl-4-Phenyl-1,2,4-Triazol-3-yl-Thiomethyl) Benzene (4b)

Yield: 60%, crystallized from EtOH, mp 216 °C–218 °C; IR: 3054, 2970, 2930, 2871, 1596, 1518, 1497, 1439, 773, 700, 611; ^{1}H NMR ($CDCl_3$) δ: 1.19 (24H, d, $J = 6.9$Hz, CH_3), 2.75 (4H, sep, $J = 6.9$Hz, CH), 4.18 (8H, s, $ArCH_2S$), 7.00 (10H, bs, ArH), 7.41–7.44 (12H, m, ArH); ^{13}C NMR ($CDCl_3$) δ: 21.01, 25.42, 34.12, 127.37, 129.81, 129.90, 133.17, 133.27, 135.28, 150.03, 160.82; Anal. Calcd. for $C_{54}H_{58}N_{12}S_4$: 64.64 C, 5.83 H, 16.75 N, 12.78 S, Found: 64.71 C, 5.89 H, 16.68 N, 12.72 S.

1,2,4,5-Tetrakis(5-Phenyl-4-Phenyl-1,2,4-Triazol-3-yl-Thiomethyl) Benzene (4c)

Yield: 58%, crystallized from EtOH/DMF, mp 262.5 °C–264.5 °C; IR: 3062, 2936, 2912, 1594, 1497, 1473, 1447, 1424, 1380, 771, 694, 601; ^{1}H NMR ($CDCl_3$) δ: 4.56 (8H, S, $ArCH_2S$), 7.23–7.45 (42H, m, ArH); ^{13}C NMR ($CDCl_3$) δ: 33.94, 125.42, 127.40, 128.44, 128.53, 130.05, 130.18, 133.53, 133.68, 135.20, 152.53, 154.62; Anal. Calcd. for $C_{66}H_{50}N_{12}S_4$: 69.57 C, 4.42 H, 14.75 N, 11.26 S. Found: 69.67 C, 4.53 H, 14.64 N, 11.16 S.

1,2,4,5-Tetrakis[5-(4-Hydroxyphenyl)-4-Phenyl-1,2,4-Triazol-3-yl-Thiomethyl]Benzene (4d)

Yield: 55%, crystallized from EtOH, mp 225 °C–227 °C. IR: 3405, 3238, 3189, 3051, 2855, 1600, 1558, 1496, 1454, 1235, 749, 693; ^{1}H NMR (DMSO-d_6) δ: 4.03 (8H, s, $ArCH_2S$), 6.82 (4H, t, $J = 6.9$ Hz, ArH), 6.91 (2H, s, ArH), 7.17 (15H, s, ArH), 7.41 (17H, m, ArH), 8.30 (4H, s, ArOH); ^{13}C NMR (DMSO-d_6) δ: 34.30, 117.50, 121.00, 128.21, 129.02, 130.11, 132.55, 132.90, 135.35, 141.73, 145.55, 152.63; Anal. Calcd. for

$C_{66}H_{50}N_{12}O_4S_4$: 65.87 C, 4.19 H, 13.96 N, 10.66 S. Found: 65.94 C, 4.23 H, 13.91 N, 10.59 S.

1,2,4,5-Tetrakis[5-(2-Chlorophenyl)-4-Phenyl-1,2,4-Triazol-3-yl-Thiomethyl]Benzene (4e)

Yield: 50%, crystallized from EtOH, mp 160 °C–162 °C. IR : 3052, 2969, 2872, 1596, 1530, 1496, 1422, 1383, 765, 728, 695, 605; ^{1}H NMR ($CDCl_3$) δ: 4.54 (8H, s, $ArCH_2S$), 5.30 (2H, s, ArH), 7.01 (8H, d, $J = 7.5$ Hz, ArH), 7.21–7.31 (24H, m, ArH), 7.50 (4H, d, $J = 7.2$ Hz, ArH); ^{13}C NMR ($CDCl_3$) δ: 34.09, 126.28, 126.74, 126.79, 129.41, 129.56, 129.65, 131.62, 132.75, 132.98, 133.74, 134.23, 135.26, 151.52, 153.41; Anal. Calcd. for $C_{66}H_{46}Cl_4N_{12}S_4$: 62.07 C, 3.63 H, 13.16, 10.04 N. Found: 62.16 C, 3.58 H, 13.07 N, 10.11 S.

1,2,4,5-Tetrakis[5-(2-Pyridyl)-4-Phenyl-1,2,4-Triazol-3-yl-Thiomethyl]Benzene (4f)

Yield: 63%, crystallized from EtOH/DMF, mp 156 °C–158 °C. IR: 3053, 3005, 2968, 2940, 1590, 1568, 1499, 1453, 1447, 1417, 1381, 788, 693, 596; ^{1}H NMR ($CDCl_3$) δ: 4.50 (8H, S, $ArCH_2S$), 7.14–7.19 (13H, m, ArH), 7.32–7.38 (13H, m, ArH), 7.69 (4H, t, $J =$ 7.8 Hz, PyH), 8.04 (4H, d, $J = 7.8$ Hz, PyH), 8.25 (4H, d, $J = 3.9$ Hz, PyH); ^{13}C NMR ($CDCl_3$) δ: 33.75, 123.68, 123.89, 127.29, 129.18, 129.27, 133.56, 134.71, 135.23, 136.58, 146.46, 148.87, 153.34, 153.82; Anal. Calcd. for $C_{62}H_{46}N_{16}S_4$: 65.13 C, 4.05 H, 19.60 N, 11.22 S. Found: 65.21 C, 4.11 H, 19.53 N, 11.15 S.

1,2,4,5-Tetrakis[5-(2-Furyl)-4-Phenyl-1,2,4-Triazol-3-yl-Thiomethyl] Benzene (4g)

Yield: 66%, crystallized from EtOH/DMF, mp 255 °C–257 °C. IR: 3148, 3112, 3062, 3013, 2944, 1619, 1595, 1513, 1498, 1445, 1423, 1402, 1371, 1254, 1226, 1017, 1008, 902, 752, 696, 619, 594; ^{1}H NMR ($CDCl_3$) δ: 4.41 (8H, s, $ArCH_2S$), 6.14 (4H, s, furyl), 6.28 (4H, s, furyl), 7.19–7.47 (26H, m, ArH); ^{13}C NMR ($CDCl_3$) δ: 33.99, 111.19, 111.49, 127.50, 129.84, 130.25, 133.43, 135.22, 141.29, 143.94, 147.86, 151.65; Anal. Calcd. for $C_{58}H_{42}N_{12}O_4S_4$: 63.37 C, 3.85 H, 15.29 N, 11.67 S. Found: 63.42 C, 3.94 H, 15.18 N, 11.58 S.

1,2,4,5-Tetrakis(5-Phenyl-1,3,4-Oxadiazol-2-yl-Thiomethyl)Benzene (6c)

Yield: 73%, crystallized from MeOH/$CHCl_3$, mp 162 °C–164 °C; IR: 3059, 2927, 1610, 1555, 1470, 1189, 1066, 773, 698; ^{1}H NMR ($CDCl_3$) δ: 4.68 (8H, S, $ArCH_2S$), 7.46 (12H, bs, ArH), 7.72 (2H, s, ArH), 7.77–7.92 (8H, bs, ArH); ^{13}C NMR ($CDCl_3$) δ: 33.49, 123.41, 126.68, 129.01, 131.71, 133.82, 135.06, 163.13, 166.02; Anal. Calcd. for $C_{42}H_{30}N_8O_4S_4$: 60.13 C, 3.60 H, 13.36 N, 15.29 S. Found: 60.18 C, 3.62 H, 13.31 N, 15.21 S.

1,2,4,5-Tetrakis[5-(4-Hydroxyphenyl)-1,3,4-Oxadiazol-2-yl-Thiomethyl]Benzene (6d)

Yield: 69%, crystallized from EtOH, mp 237 °C–239 °C. IR: 3153, 2945, 2814, 1609, 1494, 1475, 1441, 1280, 1237, 1193, 1169, 1071, 839; ^{1}H NMR (DMSO-d_6) δ: 4.63 (8H, s, $ArCH_2S$), 6.87 (8H, d, $J = 8.1$ Hz, ArH), 7.63 (2H, s, ArH), 7.68 (8H, d, $J = 8.1$ Hz, ArH), 10.25 (4H, s, ArOH); ^{13}C NMR (DMSO-d_6) δ: 33.54, 114.2, 116.51, 128.82, 133.37,

135.54, 161.21, 162, 165.98; Anal. Calcd. for $C_{42}H_{30}N_8O_8S_4$: 55.86 C, 3.35 H, 12.41 N, 14.20 S. Found: 55.93 C, 3.37 H, 12.39 N, 14.13 S.

1,2,4,5-Tetrakis[5-(2-Chlorophenyl)-1,3,4-Oxadiazol-2-yl-Thiomethyl] Benzene (6e)

Yield: 66%, crystallized from MeOH/$CHCl_3$, mp 141 °C–143 °C. IR: 3068, 2993, 2926, 1670, 1596, 1573, 1469, 1189, 1090, 1034, 764, 727; ^{1}H NMR ($CDCl_3$) δ: 4.68 (8H, s, $ArCH_2S$), 7.31–7.44 (12H, m, ArH), 7.71 (2H, s, ArH), 7.85 (4H, d, $J = 5.7$ Hz, ArH); ^{13}C NMR ($CDCl_3$) δ: 33.50, 122.64, 127.05, 130.89, 131.19, 132.37, 132.91, 133.76, 135.03, 163.75, 164.26; Anal. Calcd. for $C_{42}H_{26}Cl_4N_8O_4S_4$: 51.64 C, 2.68 H, 11.47 N, 13.13 S. Found: 54.74 C, 2.74 H, 11.41 N, 13.07 S.

1,2,4,5-Tetrakis[5-(2-Pyridyl)-1,3,4-Oxadiazol-2-yl-Thiomethyl] Benzene (6f)

Yield: 79%, crystallized from MeOH/$CHCl_3$, mp 216 °C–218 °C. IR: 3055, 2995, 2926, 1588, 1554, 1462, 1197, 1086, 793, 740, 707; ^{1}H NMR ($CDCl_3$) δ: 4.69 (8H, S, $ArCH_2S$), 7.40 (4H, t, $J = 6.9$ Hz, PyH), 7.74 (2H, s, ArH), 7.82 (4H, t, $J = 7.5$ Hz, PyH), 8.13 (4H, d, $J = 7.8$ Hz, PyH), 8.71 (4H, d, $J = 4.2$ Hz, PyH); ^{13}C NMR ($CDCl_3$) δ: 33.41, 122.88, 125.75, 134.09, 134.97, 137.22, 143.10, 150.17, 164.72, 165.01; Anal. Calcd. for $C_{38}H_{26}N_{12}O_4S_4$: 54.14 C, 3.11 H, 19.94 N, 15.22 S. Found: 54.25 C, 3.14 H, 19.87 N, 15.15 S.

1,2,4,5-Tetrakis[5-(2-Furyl)-1,3,4-Oxadiazol-2-yl-Thiomethyl] Benzene (6g)

Yield: 70%, crystallized from MeOH/$CHCl_3$, mp 111 °C–113 °C. IR: 3125, 2929, 1630, 1529, 1471, 1156, 1090, 753; ^{1}H NMR ($CDCl_3$) δ: 4.63 (8H, s, $ArCH_2S$), 6.55 (4H, s, furyl), 7.08 (4H, s, furyl), 7.59 (4H, s, furyl), 7.66 (2H, s, ArH); ^{13}C NMR ($CDCl_3$) δ: 33.50, 112.15, 114.13, 133.86, 134.95, 138.90, 145.75, 158.75, 162.58; Anal. Calcd. for $C_{34}H_{22}N_8O_8S_4$: 51.12 C, 2.78 H, 14.03 N, 16.06 S. Found: 51.19 C, 2.83 H, 13.98 N, 16.01 S.

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