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NOTE

Synthesis, characterization and antimicrobial study of substituted bis-[1,3,4]-oxadiazole, bis-[1,3,4]-thiadiazole and bis-[1,2,4]-triazole derivatives

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Abstract : Series of compounds 1,4-bis-(2-aryl/alkyl-amino-[1,3,4]-oxadiazol-5-yl)-benzenes, 1,4-bis-(2-aryl/alkyl-amino-[1,3,4]-thiadiazol-5-yl)-benzenes and 1,4-bis-(3-mercapto-4-aryl/alkyl-[1,2,4]-triazol-5-yl)-benzenes have been synthesized by the oxidative cyclization of di-(*N*-aryl/alkyl thiocarbamido) terephthalamides using alkaline ethanolic solution of iodine containing potassium iodide, *ortho*-phosphoric acid and aqueous potassium hydroxide solution respectively. These compounds on acetylation afforded bis-acetyl derivatives, on benzoylation afforded bis-benzoyl derivatives and on reaction with ethyl iodide afforded bis-ethylmercapto derivatives respectively. These compounds have been assayed for their antimicrobial activity against gram-positive as well as gram-negative microorganisms.

Keywords : Bis-oxadiazole, bis-thiadiazole, bis-triazole, synthesis, antimicrobial activity.

Introduction

The synthesis of [1,3,4]-oxadiazoles is of considerable interest due to their biological activities. Reported among these activities were nervous system depressing[1], analgesic[2], herbicidal[3], muscle relaxant[4] and tranquilizing[5] activities. Also the synthesis of compounds incorporating [1,3,4]-thiadiazole and [1,2,4]-triazole rings has been attracting widespread attention due to their diverse pharmacological properties such as antimicrobial, anti-inflammatory, analgesic and antitumoral activities[6]. The therapeutic effects of [1,2,4]-triazole containing compounds, have been well studied for a number of pathological conditions including inflammation, cancer, pain, tuberculosis or hypertension[7]. Although there are numbers of antibiotics which are commercially used in medicine, the synthesis of new compounds is of vital importance due to increasing drug resistance. Moreover it is important to obtain therapeutical compounds having less toxic effects.

There seems to be scanty work on the synthesis of substituted bis-[1,3,4]-oxadiazoles, bis-[1,3,4]-thiadiazoles and bis-[1,2,4]-triazoles. Their biological[8] as well as antitumoral[9] activities were reported earlier in few communications. In view of the utility of these tri-heterocyclic compounds in various fields and as a part of wider programme to provide alternative routes for the synthesis of 5 and 6 membered heterocyclic compounds[10], now the synthesis of bis tri-heterocyclic compounds viz. bis-[1,3,4]-oxadiazoles, bis-[1,3,4]-thiadiazoles and bis-[1,2,4]-triazoles by oxidative cyclization method is reported.

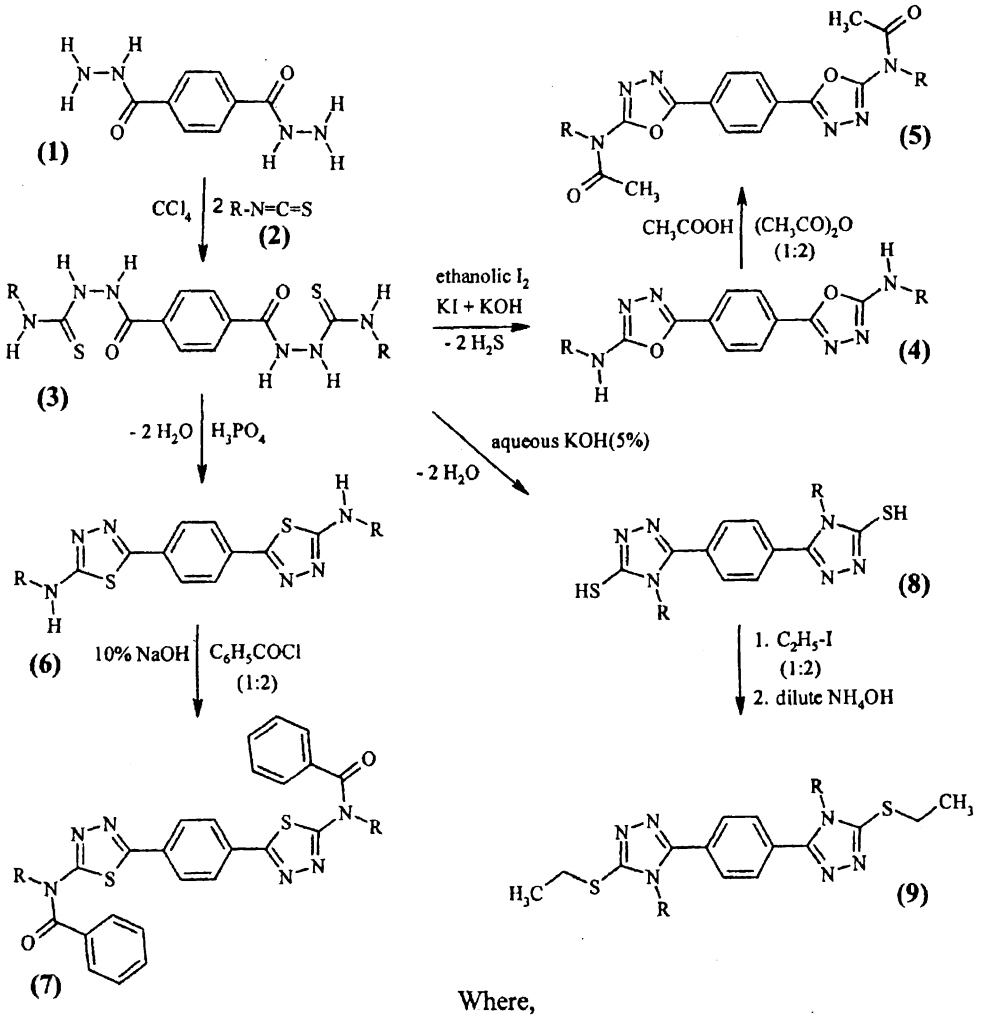
Results and discussion

The parent compound terephthalic acid dihydrazide (**1**) was prepared by refluxing the mixture of terephthalic acid (0.01 mol) and thionyl chloride (0.02 mol) for 30 min, followed by the addition of hydrazine hydrate (0.02 mol). It was transformed into di-(*N*-aryl/alkyl thiocarbamido) terephthalamides (**3a-h**) by condensing with *N*-aryl/alkyl isothiocyanates (**2a-h**) (0.02 mol) in refluxing carbon tetrachloride medium for 2 h by known method[11]. Compounds (**3a-h**) were then transformed into 1,4-bis-(2-aryl/alkyl-amino-[1,3,4]-oxadiazol-5-yl)-benzenes (**4a-h**) by oxidative cyclization using alkaline ethanolic solution of iodine containing potassium iodide with evolution of hydrogen sulphide gas[12]. Compounds (**4a-h**) on acylation with acetic anhydride and glacial ace-

tic acid in 1 : 2 ratio afforded bis-acetyl derivatives (**5a-h**). Compounds (**3a-h**) were also reacted separately with *ortho*-phosphoric acid and aqueous potassium hydroxide solution by constant stirring for 30 min and allowing to stand at room temperature for 3 h to yield 1,4-bis-(2-aryl/alkyl-amino-[1,3,4]-thiadiazol-5-yl)-benzenes (**6a-h**) and 1,4-bis-(3-mercapto-4-aryl/alkyl-[1,2,4]-triazol-5-yl)-benzenes (**8a-h**) respectively by oxidative cyclization. Compounds (**6a-h**) were benzoylated using benzoyl chloride and 10% sodium hydroxide solution to yield bis-benzoyl derivatives (**7a-h**). Compounds (**8a-h**) were reacted with ethyl iodide to afford bis-ethylmercapto derivatives (**9a-h**) (Scheme 1).

Antimicrobial activity :

The synthesized compounds (**4a-h**), (**6a-h**) and (**8a-h**) were screened for their antibacterial activity using cup plate diffusion method[13]. The bacterial organisms used included both gram-positive as well as gram-negative strains like *E. coli*, *S. aureus*, *S. typhi*, *B. subtilis* and *A. aerogenes*. Sensitivity plates were seeded with a bacterial innoculum of 1×10^6 CIU ml^{-1} and each well (diameter 10 mm) was loaded with 0.1 ml of test compound solution (1000 μg ml^{-1}) in dimethylformamide, so that concentration of each test compound was 100 μg ml^{-1}. The zones of inhibition were recorded after incubation for 24 h



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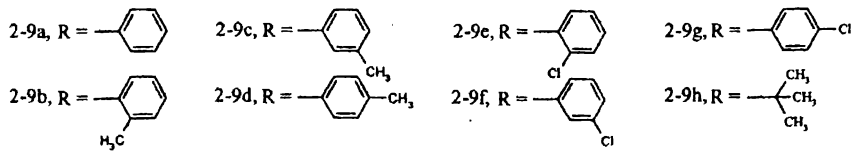

Scheme 1

at 37 °C, using Vernier caliper. Inhibition zone record of the compounds clearly indicated that (**4d**), (**4g**), (**6c**), (**6f**) and (**8c**), (**8g**) were highly active against *S. aureus*, *B. subtilis* and moderately active against *S. typhi*. Majority of the compounds were found inactive against *E. coli* and *A. aerogenes*.

To determine minimum inhibitory concentration (MIC), the serial dilution technique[14] was followed using nutrient broth medium. The MIC values of compounds (**4d**), (**6c**) and (**8c**) were determined against *S. aureus*, *B. subtilis* and *S. typhi*, which were found to be 85, 70 and 85 μg ml^{-1} respectively.

Screening of these compounds (**4a-h**), (**6a-h**) and (**8a-h**) having the concentration 1% and 2%, for antifungal activity using paper disc method[15] showed that (**4c**), (**4f**), (**6c**), (**6g**) and (**8b**), (**8d**) were highly active against *A. niger*, whereas other compounds showed low to moderate activity. The zones of inhibition were recorded after incubation for 48 h at 37 °C.

Experimental

The melting points of all synthesized compounds were recorded using hot paraffin-bath and are uncorrected. Chemicals used were of A.R. grade. ^1H NMR spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvents. IR spectra were recorded on Perkin-Elmer spectrophotometer in the range 4000-400 cm^{-1} in nujol mull and as KBr pellet. Purity of the compounds was checked on silica gel-G plates by TLC.

Parent compound terephthalic acid dihydrazide (**1**) was prepared by refluxing the mixture of terephthalic acid (0.01 mol) and thionyl chloride (0.02 mol) for 30 min, followed by the addition of hydrazine hydrate (0.02 mol) by reported method.

Synthesis of di-(N-phenyl thiocarbamido) terephthalamide (**3a**) :

The compound di-(*N*-phenyl thiocarbamido) terephthalamide (**3a**) was prepared by refluxing the mixture of terephthalic acid dihydrazide (**1**) (0.01 mol) and *N*-phenylisothiocyanate (**2a**) (0.02 mol) in carbon tetrachloride (20 ml) for 2 h. The reaction mixture was cooled and the solid residue obtained was crystallised from ethanol, **3a** (78%), m.p. 198 °C (Found : C, 56.80; H, 4.31; N, 18.01; S, 13.67. Calcd. for $C_{22}H_{20}N_6O_2S_2$: C, 56.88; H, 4.34; N, 18.09; S, 13.80%); ν_{max} 3334, 3328, 3318 (NH), 1708 (C=O), 1289 (C-N), 1236 (C=S), 1210 cm^{-1} (N-N)[16]; δ ($CDCl_3$ + DMSO-d_6) 8.11 (4H, s, Ar-H), 8.01 (2H, s, CO-NH-N), 6.64-7.40 (10H, m, Ar-H), 4.03 (2H, s, CS-NH-Ar), 2.07 (2H, s, CS-NH-N). This reaction was extended to synthesize other compounds, **3b-h** using different *N*-aryl/alkyl isothiocyanates, **2b-h** : **3b** (80%), m.p. 206 °C; **c** (68%), m.p. 156 °C; **d** (76%), m.p. 188 °C; **e** (82%), m.p. 224 °C; **f** (75%), m.p. 210 °C; **g** (85%), m.p. 165 °C; **h** (79%), m.p. 240 °C.

Synthesis of 1,4-bis-(2-phenylamino-[1,3,4]-oxadiazol-5-yl)-benzene (**4a**) :

A paste of di-(*N*-phenyl thiocarbamido) terephthalamide (**3a**) (0.01 mol) was prepared in ethanol. To it iodine solution in ethanolic potassium hydroxide containing potassium iodide was added dropwise with constant stirring. The colour of iodine was initially disappeared. The addition was continued till violet colour of the iodine persisted. The reaction mixture was left overnight at room temperature, the granular solid was separated. It was washed with distilled water, crystallised from ethanol and identified as 1,4-bis-(2-phenylamino-[1,3,4]-oxadiazol-5-yl)-benzene (**4a**) (75%), m.p. 186 °C (Found : C, 66.58; H, 3.98; N, 21.16. Calcd. for $C_{22}H_{16}N_6O_2$: C, 66.66; H, 4.04; N, 21.21%); ν_{max} 3310 (NH), 1605 (C=N), 1296 (C-O), 1290 (C-N), 1227 cm^{-1} (N-N) ; δ ($CDCl_3$ + DMSO-d_6) 7.51 (4H, s, Ar-H), 6.32-7.18 (10H, m, Ar-H), 4.06 (2H, s, NH). Similarly, **4b** was prepared from **3b** : **4b** (71%), m.p. 162 °C (Found : C, 61.81; H, 4.67; N, 19.76. Calcd. for $C_{24}H_{20}N_6O_2$: C, 67.92; H, 4.71; N, 19.81%); ν_{max} 3320 (NH), 1598 (C=N), 1310 (C-O), 1288 (C-N), 1224 cm^{-1} (N-N); δ ($CDCl_3$ + DMSO-d_6) 7.51 (4H, s, Ar-H), 6.34-7.12 (8H, m, Ar-H), 4.06 (2H, s, NH), 2.34 (6H, s, Ar-CH_3). This reaction was extended to synthesize other compounds, **4c-h** : **4c** (70%), m.p. 188 °C (Found : C, 61.88; H, 4.64; N, 19.70. Calcd. for $C_{24}H_{20}N_6O_2$: C, 67.92; H, 4.71; N, 19.81%); **d** (65%), m.p. 165 °C (Found : C, 67.90; H, 4.64; N, 19.80. Calcd. for $C_{24}H_{20}N_6O_2$: C, 67.92; H, 4.71; N, 19.81%); **e** (78%), m.p. 212 °C (Found : C, 56.71; H, 2.95; N, 18.02. Calcd. for $C_{22}H_{14}N_6O_2Cl_2$: C, 56.77; H, 3.01; N, 18.06%); **f** (68%), m.p. 191 °C (Found : C, 56.66; H, 2.94; N, 17.98. Calcd. for $C_{22}H_{14}N_6O_2Cl_2$: C, 56.77; H, 3.01; N, 18.06%); **g** (70%), m.p. 164 °C (Found : C, 56.73; H, 3.02; N, 17.95. Calcd. for $C_{22}H_{14}N_6O_2Cl_2$: C, 56.77; H, 3.01; N, 18.06%); **h** (75%), m.p. 206 °C (Found : C, 60.59; H, 6.71; N, 23.54. Calcd. for $C_{18}H_{24}N_6O_2$: C, 60.67; H, 6.74; N, 23.59%).

Synthesis of 1,4-bis-(2-phenylacetamido-[1,3,4]-oxadiazol-5-yl)-benzene (**5a**) :

A mixture of 1,4-bis-(2-phenylamino-[1,3,4]-oxadiazol-5-yl)-benzene (**4a**) (0.01 mol) and acetic anhydride (0.02 mol) in glacial acetic acid (10 ml) was refluxed for 2.5 h. The reaction mixture was cooled and poured in a little crushed ice with water, a whitish yellow solid precipitated was crystallised from aqueous ethanol to give (**5a**) (80%), m.p. 196 °C (Found : C, 64.87; H, 4.14; N, 17.46. Calcd. for $C_{26}H_{20}N_6O_4$: C, 65.00; H, 4.16; N, 17.50%); ν_{max} 1708 (C=O), 1618 (C=N), 1294 (C-O), 1302 (C-N), 1226 cm^{-1} (N-N); δ ($CDCl_3$ + DMSO-d_6) 7.54 (4H, s, Ar-H), 6.26-6.88 (10H, m, Ar-H), 2.05 (6H, s, CO-CH_3). This reaction was extended to synthesize other bis-acetyl derivatives (**5b-h**) : **5b** (70%), m.p. 171 °C; **c** (68%), m.p. 172 °C; **d** (72%), m.p. 204 °C; **e** (75%), m.p. 188 °C; **f** (80%), m.p. 174 °C; **g** (76%), m.p. 207 °C; **h** (75%), m.p. 166 °C.

Synthesis of 1,4-bis-(2-phenylamino-[1,3,4]-thiadiazol-5-yl)-benzene (**6a**) :

To the di-(*N*-phenyl thiocarbamido) terephthalamide (**3a**) (0.01 mol), *ortho*-phosphoric acid (10 ml) was added dropwise with constant stirring. Stirring was continued for 30 min. The reaction mixture was allowed to cool and left at room temperature for 3 h. On cooling the reaction mixture and pouring it in water, a whitish coloured solid was precipitated. It was washed with distilled water, crystallised from aqueous ethanol and identified as 1,4-bis-(2-phenylamino-[1,3,4]-thiadiazol-5-yl)-benzene (**6a**) (75%), m.p. 212 °C (Found : C, 61.62; H, 3.68; N, 19.56; S, 14.88. Calcd. for $C_{22}H_{16}N_6S_2$: C, 61.68; H, 3.73; N, 19.62; S, 14.95%); ν_{max} 3310 (NH), 1594 (C=N), 1312 (C-N), 1232 (N-N), 690 cm^{-1} (C-S); δ ($CDCl_3$ + DMSO-d_6) 7.49 (4H, s, Ar-H), 6.31-6.81 (10H, m, Ar-H), 4.08 (2H, s, NH). Similarly (**6b**) was prepared from (**3b**) : **6b** (70%), m.p. 187 °C (Found : C, 65.10; H, 4.33; N, 18.38; S, 13.97. Calcd. for $C_{24}H_{20}N_6S_2$: C, 63.15; H, 4.38; N, 18.42; S, 14.03%); ν_{max} 3316 (NH), 1589 (C=N), 1305 (C-N), 1216 (N-N), 692 cm^{-1} (C-S); δ ($CDCl_3$ + DMSO-d_6) 7.49 (4H, s, Ar-H), 6.52-7.08 (8H, m, Ar-H), 4.08 (2H, s, NH), 2.36 (6H, s, Ar-CH_3). This reaction was extended to synthesize other compounds (**6c-h**) : **6c** (65%), m.p. 184 °C (Found : C, 63.09; H, 4.37; N, 18.32; S, 13.94. Calcd. for $C_{24}H_{20}N_6S_2$: C, 63.15; H, 4.38; N, 18.42; S, 14.03%); **d** (71%), m.p. 202 °C (Found : C, 63.14; H, 4.32; N, 18.40; S, 13.97. Calcd. for $C_{24}H_{20}N_6S_2$: C, 63.15; H, 4.38; N, 18.42; S, 14.03%); **e** (67%), m.p. 177 °C (Found : C, 53.08; H, 2.76; N, 16.86; S, 12.84. Calcd. for $C_{22}H_{14}N_6S_2Cl_2$: C, 53.11; H, 2.81; N, 16.90; S, 12.87%); **f** (75%), m.p. 165 °C (Found : C, 53.05; H, 2.79; N, 16.81; S, 12.82. Calcd. for $C_{22}H_{14}N_6S_2Cl_2$: C, 53.11; H, 2.81; N, 16.90; S, 12.87%); **g** (65%), m.p. 166 °C (Found : C, 53.10; H, 2.80; N, 16.89; S, 12.78. Calcd. for $C_{22}H_{14}N_6S_2Cl_2$: C, 53.11; H, 2.81; N, 16.90; S, 12.87%); **h** (73%), m.p. 179 °C (Found : C, 55.62; H, 6.16; N, 21.57; S, 16.43. Calcd. for $C_{18}H_{24}N_6S_2$: C, 55.67; H, 6.18; N, 21.64; S, 16.49%).

Synthesis of 1,4-bis-(2-phenylbenzamido-[1,3,4]-thiadiazol-5-yl)-benzene (**7a**) :

To the suspension of 1,4-bis-(2-phenylamino-[1,3,4]-thiadiazol-5-yl)-benzene (**6a**) (0.01 mol) in 10% sodium hydroxide solution (10 ml), benzoyl chloride (0.02 mol) was added within half an hour with vigorous shaking and maintaining the temperature below 5 °C. The reaction mixture was poured in a little crushed ice with water, a cream coloured solid isolated was crystallised from aqueous ethanol to give (**7a**) (70%), m.p. 175 °C (Found : C, 67.87; H, 3.74; N, 13.18; S, 10.01. Calcd. for $C_{36}H_{24}N_6O_2S_2$: C, 67.92; H, 3.77; N, 13.20; S, 10.06%); ν_{max} 1716 (C=O), 1614 (C=N), 1307 (C-N), 1205 (N-N), 691 cm^{-1} (C-S); ($CDCl_3$ + DMSO-d_6) 7.53 (4H, s, Ar-H), 6.35-7.12 (20H, m, Ar-H). This reaction was extended to synthesize other bis-acetyl derivatives (**7b-h**) : **7b** (68%), m.p. 183 °C; **c** (72%), m.p. 192 °C; **d** (80%), m.p. 204 °C; **e** (75%), m.p. 210 °C; **f** (76%), m.p. 198 °C; **g** (75%), m.p. 183 °C; **h** (65%), m.p. 177 °C.

Synthesis of 1,4-bis-(3-mercapto-4-phenyl-[1,2,4]-triazol-5-yl)-benzene (**8a**) :

To the di-(*N*-phenyl thiocarbamido) terephthalamide (**3a**) (0.01 mol) 5% aqueous potassium hydroxide solution (10 ml) was added dropwise with constant stirring. Stirring was continued for 30 min. The reaction mixture was allowed to cool and left at room temperature for 3 h. On cooling the reaction mixture and pouring it in water, a dirty white coloured solid was precipitated. It was washed with distilled water, crystallised from warm water with ethanol and identified as 1,4-bis-(3-mercapto-4-phenyl-[1,2,4]-triazol-5-yl)-benzene (**8a**) (70%), m.p. 207 °C (Found : C, 61.63; H, 3.66; N, 19.57; S, 14.89. Calcd. for $C_{22}H_{16}N_6S_2$: C, 61.68; H, 3.73; N, 19.62; S, 14.95%); ν_{max} 3368 (SH), 1593 (C=N), 1310 (C-N), 1226 (N-N), 688 cm^{-1} (C-S); δ ($CDCl_3$ + DMSO-d_6) 7.50 (4H, s, Ar-H), 6.68-7.24 (10H, m, Ar-H), 3.27 (2H, s, SH). Similarly, (**8b**) was prepared from (**3b**) : **8b** (68%), m.p. 197 °C (Found : C, 63.11; H, 4.30; N,

18.36; S, 13.88. Calcd. for $C_{24}H_{20}N_6S_2$: C, 63.15; H, 4.38; N, 18.42; S, 14.03%); ν_{max} 3372 (SH), 1587 (C=N), 1306 (C-N), 1230 (N-N), 690 cm^{-1} (C-S); δ ($CDCl_3$ + DMSO-d_6) 7.50 (4H, s, Ar-H), 6.45-7.27 (8H, m, Ar-H), 3.31 (2H, s, SH), 2.35 (6H, s, Ar-CH_3). This reaction was extended to synthesize other compounds (**8c-h**) : **8c** (70%), m.p. 165 °C (Found : C, 63.06; H, 4.34; N, 18.33; S, 13.99. Calcd. for $C_{24}H_{20}N_6S_2$: C, 63.15; H, 4.38; N, 18.42; S, 14.03%); **d** (68%), m.p. 148 °C (Found : C, 63.13; H, 4.32; N, 18.39; S, 13.96. Calcd. for $C_{24}H_{20}N_6S_2$: C, 63.15; H, 4.38; N, 18.42; S, 14.03%); **e** (72%), m.p. 192 °C (Found : C, 53.10; H, 2.75; N, 16.86; S, 12.76. Calcd. for $C_{22}H_{14}N_6S_2Cl_2$: C, 53.11; H, 2.81; N, 16.90; S, 12.87%); **f** (64%), m.p. 157 °C (Found : C, 53.02; H, 2.82; N, 16.79; S, 12.80. Calcd. for $C_{22}H_{14}N_6S_2Cl_2$: C, 53.11; H, 2.81; N, 16.90; S, 12.87%); **g** (70%), m.p. 166 °C (Found : C, 53.09; H, 2.80; N, 16.86; S, 12.83. Calcd. for $C_{22}H_{14}N_6S_2Cl_2$: C, 53.11; H, 2.81; N, 16.90; S, 12.87%); **h** (75%), m.p. 202 °C (Found : C, 55.60; H, 6.14; N, 21.60; S, 16.42. Calcd. for $C_{18}H_{24}N_6S_2$: C, 55.67; H, 6.18; N, 21.64; S, 16.49%).

Synthesis of 1,4-bis-(3-ethylmercapto-4-phenyl-[1,2,4]-triazol-5-yl)-benzene (**9a**) :

A mixture of 1,4-bis-(3-mercapto-4-phenyl-[1,2,4]-triazol-5-yl)-benzene (**8a**) (0.01 mol) and ethyl iodide (0.02 mol) in ethanol (10 ml) was refluxed for 1.5 h. The reaction mixture was cooled and poured in a little crushed ice with water, a off white solid precipitated was identified as dihydroiodide of 1,4-bis-(3-ethylmercapto-4-phenyl-[1,2,4]-triazol-5-yl)-benzene. It was basified with dilute ammonium hydroxide and crystallised from ethanol to give a free base (**9a**) (80%), m.p. 185 °C (Found : C, 64.37; H, 4.90; N, 17.29; S, 13.18. Calcd. for $C_{26}H_{24}N_6S_2$: C, 64.46; H, 4.95; N, 17.35; S, 13.22%); ν_{max} 1610 (C=N), 1304 (C-N), 1208 (N-N), 688 cm^{-1} (C-S); δ ($CDCl_3$ + DMSO-d_6) 7.52 (4H, s, Ar-H), 6.53-7.21 (10H, m, Ar-H), 2.24 (4H, q, S-CH_2, 1.06 (6H, t, -CH_3). This reaction was extended to synthesize other bis-ethylmercapto derivatives (**9b-h**) : **9b** (75%), m.p. 167 °C; **c** (70%), m.p. 169 °C; **d** (72%), m.p. 186 °C; **e** (67%), m.p. 188 °C; **f** (74%), m.p. 187 °C; **g** (72%), m.p. 203 °C; **h** (65%), m.p. 188 °C.

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