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Synthesis, Characterization and Antimicrobial Studies of Some Novel 1,3,4-Thiadiazolium-2-thiolate Derivatives

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ABSTRACT

In this study, ten new 5-substituted-3-[4,6-di(morpholine-4-yl)-1,3,5-triazine-2-yl]-1,3,5-thiadiazolium-2-thiolate 6(a–j) were prepared *via* a five step procedure from the starting material 1,3,5-triazine (1). Structures of all synthesized compounds were confirmed by spectral data and elemental analyses. Newly synthesized compounds were tested for their antibacterial and antifungal activities against some important bacterial and fungal species. Some of the compounds were found to be moderately active against the tested organisms.

KEYWORDS

Thiadiazol, *s*-triazine, mesoionic, NMR spectroscopy, IR spectroscopy.

1. Introduction

Mesoionic compounds are one of the essential classes of heterocycles because of their synthetic utilities and various biological and synthetically applications.[1,2] They have received much attention and have been extensively studied because of their unique structures, reaction behaviour and pharmaceutical activities.[3–5] 1,3,4-Thiadiazolium mesoionics have been found to possess potential applications in various fields of chemistry like pharmaceutical, polymer, industrial, agriculture, coordination chemistry, etc.[6–10] 1,3,4-Thiadiazolium-2-thiolates are one of the important mesoionic compounds having good biological activities.[11–13] *s*-Triazine is a six membered heterocycle consisting of three nitrogen atoms and three carbon atoms alternately located in the ring system. Several derivatives of *s*-triazine have exhibited antibacterialactivities.[14–18] In addition, they are also found application as pharmaceutical products and herbicides.[19,20] *s*-Triazine derivatives have also been applied as anti-HIV[21,22], anti-malarial [23,24] and anti-cancer[25,26] agents. Jogul and Badami[27] have synthesized various 4-[4-(2-sulphido-1,3,4- thiadiazolium)benzoyl]-1,3,4-thiadiazolium-2-thiolate derivatives and some of these compounds were found to possess anti-tuberculosis activity and anti-bacterial activity, notably higher than the activity of the reference drug used.

2. Results and Discussion

Synthesis of the compounds **6(a–j)** has been carried out as depicted in Fig. 1. 2-(4,6-Dimorpholin-4-yl-1,3,5-triazin-2-yl) hydrazinecarbodithioic acid (**5**) was prepared from *s*-triazine **(1)** in four steps. The two chlorine atoms of *s*-triazine ring were replaced by morpholine group to give compound **3** which on treatment with hydrazine hydrate, followed by reaction with carbondisulfide in the presence of potassium hydroxide resulted in the formation of compound **5**. Cyclization of 2-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)hydrazinecarbodithioic acid (**5**) with various acid chlorides then gave 5-substituted-3-[4,6-di(morpholine-4-yl)-1,3,5-triazine-2-yl]-1,3,5-thiadiazolium-2-thiolates **6(a–j)**. All the synthesized compounds were characterized by their spectral data. The structure of compounds **6(a–j)** were established on the basis of elemental analysis and spectral data. The IR spectra of compounds **6(a–j)** showed a strong band between 1150–1097 cm^{-1} for the C-O-C stretching of morpholine.[28] The C=N stretching of the *s*-triazine ring was observed around ~1530, ~1350 (weak) and ~760 cm^{-1};[29–31] furthermore, the bands at 1310–1328 cm^{-1} are attributed to C-S stretching of thiadiazolium.[27] Finally, the bands observed around 3485–3228 cm^{-1} and 3200 cm^{-1} due to NH_3 stretching and NH stretching of hydrazine group.[27] The ^{1}H-NMR spectra of compounds **6(a–j)** showed chemical shifts for the N-CH_2 groups of morpholine at *ca.* δ 2.56 and the O-CH_2 groups at *ca.* δ 3.80. The chemical shifts of the NH protons of the hydrazine group of compound **4** were found upfield ($\delta \approx$6.00 ppm) in comparison with those of the chemical shift of hydrazinocarbonyl group ($\delta \approx$10.31 ppm), as reported in the literature,[27] due to the effect of electron withdrawing characteristics of carbonyl group. Finally, the ^{13}C-NMR spectra for compounds **6(a–j)** showed signals nearly *ca.* δ 164.5 for C-2 of the thiadiazole ring which was found in good agreement with literature data.[27]

2.1 Antimicrobial Activity

All the synthesized compounds were screened for their antibacterial activity against Gram-positive bacteria *Staphylococcus aureus, Streptococcus pyogenes* and Gram-negative bacteria *Escherichia coli* and *Pseudomanas aeruginosa,* as well as antifungal activities against *Candida albicans, Aspergillus niger* and *Aspergillus clavatus* (Table 1). Preliminary antimicrobial testing was carried out by the Microbroth dilution method.[32] The reference drugs used were gentamycin for antibacterial activity and nystatin for antifungal activity. The activity of the samples and the reference drugs was assayed under identical conditions. From the table it can be seen that the 4-nitrophenyl and 2-chloro-5-nitrophenyl at position 5 of the thiadiazole ring showed increasing activity in comparison with the rest of the compounds against *S. aureus* and *S. pyogenes*, respectively. Furthermore, the presence of methyl groups at this position on the thiadiazole ring also increased the activity against *E.coli* and *P. aeruginosa.* All the compounds were found to possess moderate to poor activity against the fungal species in comparison with standard drug nystatin. The numerical values in Table 1

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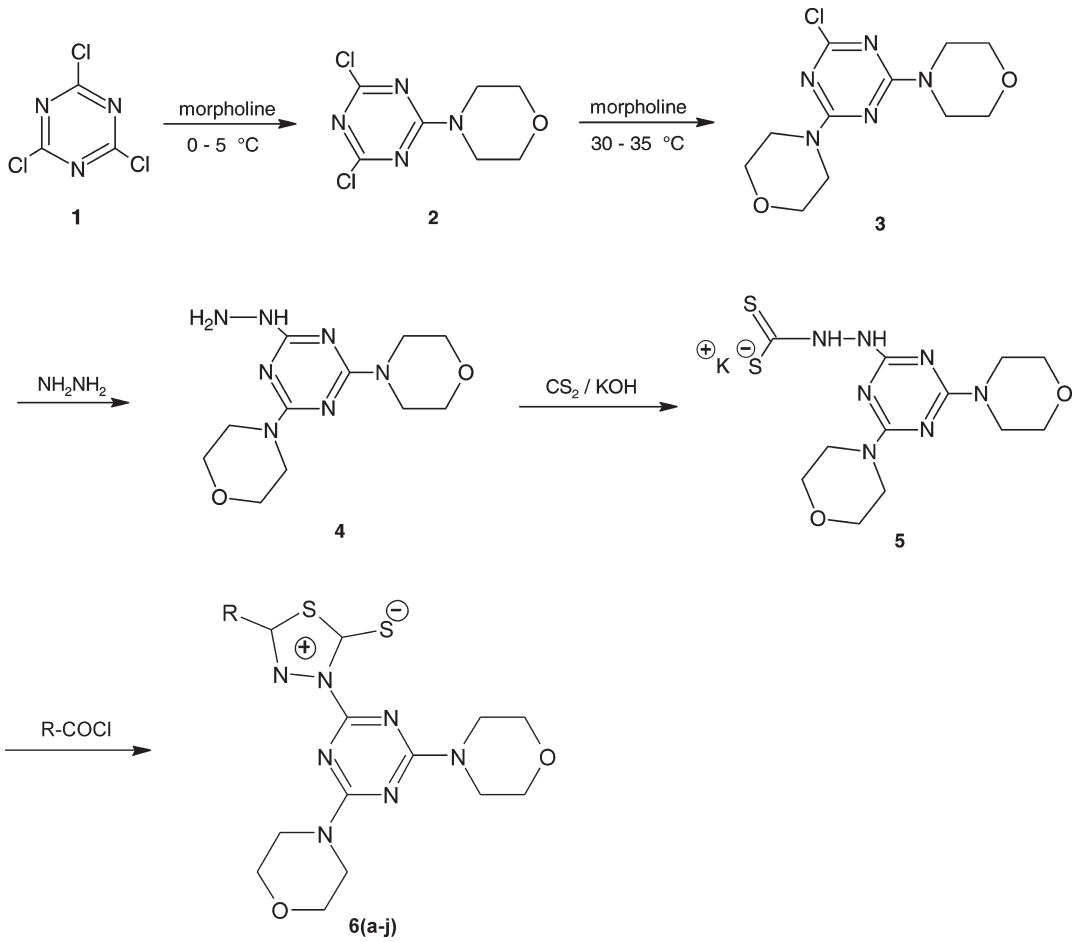

Figure 1 Synthesis of 5-(substituted)-3-[4,6-di(morpholine-4-yl)-1,3,5-triazine-2-yl]-1,3,5-thiadiazolium-2-thiolates **6(a–j)**.

show that the standard drugs were several times more effective than synthesized compounds. In addition, compound **6i** against *S. aureus,* **6d** against *S. pyogenes,* **6c** against *E.coli* and *P. aeruginosa* were found to be the most active in terms of bactericidal activity. The rest of the compounds were found to exhibit moderate to poor activity in comparison with the standard gentamycin. In addition, all the compounds were found to possess moderate to poor activity against the fungal species, in contrast with nystatin. It can thus be concluded that the antibacterial and antifungal activity of the compounds varies with a variation in substitution on thiadiazole ring system.

3. Conclusion

Novel substituted 1,3,4-thiadiazolium-2-thiolates were synthesized from *s*-triazine in good yields and were characterized by spectral data and elemental analysis. This work highlights a simple, interesting synthetic route for 1,3,4-thiadiazolium-2-thiolate derivatives. Some of the compounds were effectively active against tested organisms. This opens the door for further evaluation of this class of compounds, in particular with the aim of generating valuable data pertaining to structure–activity relationships.

Table 1 Antibacterial and antifungal activity of compounds **6(a–j)**.

Compound	Antibacterial				Antifungal		
	Gram-positive		Gram-negative				
	S. aureus	*S. pyogenes*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*	*A. clavatus*
6a	500	500	250	250	1000	1000	1000
6b	500	500	200	250	1000	1000	1000
6c	500	500	100	100	1000	1000	1000
6d	500	200	500	200	500	1000	1000
6e	250	250	250	250	1000	1000	1000
6f	250	500	250	200	500	500	1000
6g	250	500	500	250	1000	500	500
6h	500	250	200	250	500	500	1000
6i	200	250	500	500	1000	1000	500
6j	500	250	500	250	500	500	1000
Gentamycin	0.25	0.5	0.05	1.0	–	–	–
Nystatin	–	–	–	–	100	100	100

4. Experimental

4.1. General Procedures

Melting points were determined by open capillary method and were found uncorrected. The IR spectra were recorded on Shimadzu FTIR instrument using KBr pellets. NMR spectra were recorded on Brucker Avance II NMR at 400 MHz, using TMS as the internal standard and DMSO-d_6 as solvent. TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposure to UV light. Samples were routinely purified by crystallization from ethanol and checked by TLC. 5-(Substituted)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolate **6(a–j)** were synthesized by the synthetic route described in Fig. 1.

4.2. Preparation of 2,4-Dichloro-6-morpholino-4-yl-1,3,5-triazine (2)[33,34]

To a stirred solution of cyanuric chloride (0.01 mol) in acetone (15 mL) at 0–5 °C, the solution of morpholine (0.01 mol) in acetone (5 mL) was added and the pH was maintained neutral by the addition of 10 % sodium carbonate solution. The stirring was continued at 0–5 °C for four hours. After the completion of the reaction the stirring was stopped and the solution was poured into crushed ice. The solid product thus obtained was filtered and dried. The crude product was purified by crystallization from absolute alcohol to get title compound. Yield 72 %. M.p. 137–139 °C.

IR (KBr): 1510, 1350, 1114, 820 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.58–3.93 (m, 8H, CH_2 morpholine); ^{13}C NMR (40 MHz, DMSO-d_6): δ 171.1, 162.4, 47.7, 69.0. Anal (%) for $C_7H_8ON_4Cl_2$. Calcd. C, 35.77; H, 3.43; N, 23.83. Found: C, 35.85; H, 3.38; N, 23.93.

4.3. Preparation of 2-Chloro-4,6-dimorpholino-4-yl-1,3,5-triazine (3)[33,34]

To a stirred solution of 2,4-dichloro-6-morpholino-4yl-1,3,5-triazine (0.01 mol) in acetone (10 mL) at 30–35 °C, the solution of morpholine (0.01 mol) in acetone (5 mL) was added drop-wise maintaining the temperature at 35°C. The pH was adjusted to neutral by the addition of 10 % sodium carbonate solution. The temperature was gradually raised to 45 °C during two hours. After completion of the reaction, the resultant content was poured into ice-cold water. The solid product obtained was filtered and dried. The crude product was purified by crystallization from absolute alcohol to get the title compound. Yield 68 %. M.p. 164–166 °C.

IR (KBr): 1505, 1356, 1120, 806 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.95 (s, 2H, CH_2), 3.47 (t, 8H, NCH_2 morpholine, J = 4.7 Hz), 4.25 (t, 8H, OCH_2 morpholine, J = 4.6 Hz); ^{13}C NMR (40 MHz, DMSO-d_6): δ 46.8, 68.8, 171.1, 163.2. Anal (%) for $C_{11}H_{16}O_2N_5Cl$. Calcd. C, 46.24; H, 5.64; N, 24.51. Found: C, 46.31; H, 5.56; N, 24.62.

4.4. Preparation of 2-Hydrazino-4,6-dimorpholino-4-yl-1,3,5-triazine (4)[34]

A mixture of 2-chloro-4,6-dimorpholino-4-yl-1,3,5-triazine (0.01 mol) and hydrazine hydrate (0.012 mol) in ethanol (25 mL) was refluxed in a water bath. The temperature was gradually raised to 80–90 °C during three hours. The pH was adjusted neutral by the addition of 10 % aqueous sodium carbonate solution. After the completion of reaction, the refluxed content was added to cold water. The solid product obtained was filtered and dried. The crude product was purified by crystallization from absolute alcohol. Yield 74 %. M.p. 183–185 °C.

IR (KBr): 3485–3228, 1512, 1353, 1110 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.63 (t, 8H, NCH_2 morpholine, J = 4.7 Hz), 4.22 (t, 8H, OCH_2 morpholine, J = 4.6 Hz), 4.79 (s, 2H, NH-*NH*$_2$), 6.00 (s, 2H, *NH*-NH_2); ^{13}C NMR (40 MHz, DMSO-d_6): δ 47.8, 68.9, 170.0, 164.4. Anal (%) for $C_{11}H_{19}O_2N_7$. Calcd. C, 46.96; H, 6.81; N, 34.85. Found: C, 47.07; H, 6.89; N, 34.90.

4.5. Preparation of the Potassium Salt of 2-(4,6-Dimorpholin-4-yl-1,3,5-triazin-2-yl) Hydrazinecarbodithioic Acid (5)[27]

To a stirred mixture of 2-hydrazino-4,6-dimorpholino-4-yl-1,3,5-triazine (0.01 mol) and potassium hydroxide (0.01 mol) in absolute alcohol (15 mL), in which carbon disulphide (0.02 mol) was added drop wise and the mixture was stirred for one hour at room temperature. The yellowish colored precipitate was treated with ether (25 mL). The solid that separated was filtered, washed with ether and dried. M.p. > 300 °C. IR (KBr): 3200, 1518, 1347, 1186, 1103. ^1H NMR (400 MHz, DMSO-d_6): δ 3.63 (t, 8H, NCH_2 morpholine, J = 4.7 Hz), 4.36 (t, 8H, OCH_2 morpholine, J = 4.6 Hz) 10.21 (s, 2H, NH-NH); ^{13}C NMR (40 MHz, DMSO-d_6): δ 46.7, 69.3, 165.9, 173.5, 201.3. Anal (%) for $C_{12}H_{18}O_2N_7S_2K$. Calcd. C, 36.44; H, 4.59; N, 24.79. Found: C, 36.58; H, 4.45 ; N, 24.86 .

4.6. Preparation of 5-(Substituted)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolates 6(a–j)

General procedure: To a stirred solution of potassium salt of 2-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl) hydrazinecarbodithioic acid (0.01 mol) in water was added the appropriate acid chloride (0.012 mol). The reaction mixture was stirred for 2 hours at room temperature. The pale yellow solid that separated was filtered, washed repeatedly with ice-cold water and recrystallized from ethanol.

Spectral data of 5-(substituted)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolates **6(a–j)**:

5-(Phenyl)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolate 6a: Yield: 76 %; m.p. 171–173 °C. IR (KBr): 1560, 1375, 1318, 1110, 760 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.40 (t, 8H, NCH_2 morpholine, J = 4.7 Hz), 4.05 (t, 8H, OCH_2 morpholine, J = 4.6 Hz), 7.52–8.12 (m, 5H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 45.2, 68.0, 127.7, 131.1, 131.9, 137.6, 140.4, 141.5, 165.0, 170.3; Anal. (%) for $C_{19}H_{21}O_2N_7S_2$. Calcd. C, 51.45; H, 4.77; N, 22.11. Found: C, 51.52; H, 4.68; N, 22.23.

5-(Chloromethyl)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolate 6b: Yield: 72 %; m.p. 132–134 °C. IR (KBr): 2950, 2884, 1530, 1370, 1315, 1118, 876, 787 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.00 (s, 2H, CH_2), 3.46 (t, 8H, NCH_2 morpholine, J = 4.7 Hz), 4.14 (t, 8H, OCH_2 morpholine, J = 4.6 Hz); ^{13}C NMR (40 MHz, DMSO-d_6): δ 44.6, 51.7, 67.9, 137.4, 139.4, 164.7, 170.5. Anal. (%) for $C_{14}H_{18}O_2N_7ClS_2$. Calcd. C, 40.43; H, 4.36; N, 23.57. Found: C, 40.56; H, 4.42; N, 23.48.

5-(Methyl)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolate 6c: IR (KBr): Yield: 78 %; m.p. 190–192 °C. 2975, 2886, 1495, 1352, 1325, 1104, 810 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.82 (s, 3H, CH_3), 3.50 (t, 8H, NCH_2 morpholine, J = 4.7 Hz), 4.21 (t, 8H, OCH_2 morpholine, J = 4.6 Hz); ^{13}C NMR (40 MHz, DMSO-d_6): δ 20.7, 45.8, 68.1, 137.6, 140.3, 165.1, 170.5. Anal. (%) for $C_{14}H_{19}O_2N_7S_2$. Calcd. C, 44.08; H, 5.02; N, 25.70. Found C, 44.21; H, 5.18; N, 25.63.

5-(4-Nitrophenyl)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolate 6d: Yield: 70 %; m.p. 137–139 °C. IR (KBr): 1538, 1477, 1380, 1360, 1312,1150, 783 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.42 (t, 8H, NCH_2 morpholine, J =

4.7 Hz), 4.05 (t, 8H, OCH_2 morpholine, J = 4.6 Hz), 8.13–8.32 (m, 4H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 45.3, 68.3, 125.9, 133.4, 137.7, 140.6, 145.5, 148.2, 164.2, 170.6. Anal. (%) for $C_{19}H_{20}O_4N_8S_2$. Calcd. C, 46.71; H, 4.13; N, 22.94. Found: C, 46.60; H, 4.20; N, 22.86.

5-(2-Nitrophenyl)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolate 6e: Yield: 68%; m.p. 148–150 °C. IR (KBr): 1521, 1483, 1367, 1348, 1318, 1134, 768 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.50 (t, 8H, NCH_2 morpholine, J = 4.7 Hz), 4.25 (t, 8H, OCH_2 morpholine, J = 4.6 Hz), 7.84–8.42 (m, 4H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 45.0, 68.3, 127.7, 130.5, 131.1, 137.5, 135.8, 137.8, 140.3, 152.1, 165.5, 170.6. Anal. (%) for $C_{19}H_{20}O_4N_8S_2$. Calcd. C, 46.71; H, 4.13; N, 22.94. Found: C, 46.63; H, 4.02; N, 22.87.

5-(3-Nitrophenyl)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolate 6f: Yield: 73 %; m.p. 159–161 °C. IR (KBr): 1538, 1443, 1354, 1328, 1110, 811 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.64 (t, 8H, NCH_2 morpholin, J = 4.7 Hz), 4.12 (t, 8H, OCH_2 morpholin, J = 4.6 Hz), 7.86–8.38 (m, 4H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 45.3, 68.3, 122.7, 127.3, 132.1, 137.5, 138.00, 140.6, 141.3, 151.3, 165.8, 170.5. Anal. (%) for $C_{19}H_{20}O_4N_8S_2$. Calcd. C, 46.71; H, 4.13; N, 22.94. Found: C, 46.60; H, 4.25; N, 22.83.

5-(4-Methoxy-3-nitrophenyl)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolate 6g: Yield: 66 %; m.p. 145–147 °C. IR (KBr): 2920, 2863, 1567, 1483, 1348, 1310, 1323, 1278, 1134, 1097, 768 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.48 (t, 8H, NCH_2 morpholine, J = 4.7 Hz), 4.26 (s, 3H, OCH_3), 4.30 (t, 8H, OCH_2 morpholine, J = 4.6 Hz), 7.26 (d, 1H, Ar-H), 8.35 (d, 1H, Ar-H), 8.96 (d, 1H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 45.6, 58.3, 68.3, 115.4, 127.6, 135.9, 136.8, 137.2, 140.7, 141.7, 152.6, 164.8, 170.7. Anal. (%) for $C_{20}H_{22}O_5N_8S_2$. Calcd. C, 46.32; H, 4.28; N, 21.61. Found: C, 46.39; H, 4.38; N, 21.55.

5-(4-Chlorophenyl)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolate 6h: Yield: 65 %; m.p. 152–154 °C. IR (KBr): 1436, 1353, 1313, 1109, 874, 805 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.52 (t, 8H, NCH_2 morpholine, J = 4.7 Hz), 4.21 (t, 8H, OCH_2 morpholine, J = 4.6 Hz), 7.53–7.71 (m, 4H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 45.9, 68.1, 131.1, 132.7, 133.8, 137.9, 139.6, 140.7, 165.1, 170.6. Anal. (%) $C_{19}H_{20}O_2N_7S_2Cl$. for Calcd. C, 47.74; H, 4.22; N, 20.51. Found: C, 47.66; H, 4.34; N, 20.64.

5-(2-Chloro-5-nitrophenyl)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolate 6i: Yield: 72 %; m.p. 140–142 °C. IR (KBr): 1552, 1406, 1342, 1104, 1374, 1319, 883, 820 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.60 (t, 8H, NCH_2 morpholine, J = 4.7 Hz), 4.00 (t, 8H, OCH_2 morpholine, J = 4.6 Hz), 7.93 (d, 1H, Ar-H), 8.54 (d, 1H, Ar-H), 8.76 (d, 1H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 45.4, 68.5, 126.5, 127.4, 135.9, 134.3, 137.7, 140.6, 141.5, 150.4, 165.4, 170.6. Anal. (%) for $C_{19}H_{19}O_4N_8S_2Cl$. Calcd. C, 43.63; H, 3.66; N, 21.43. Found: C, 43.59; H, 3.72; N, 21.29.

5-(4-Chloro-3-nitrophenyl)-3-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-1,3,4-thiadiazolium-2-thiolate 6j: Yield: 76 %; m.p. 136–138 °C. IR (KBr): 1545, 1415, 1369, 1343, 1310, 1117, 1054, 828 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.53 (t, 8H, NCH_2 morpholine, J = 4.7 Hz), 4.12 (t, 8H, OCH_2 morpholine, J = 4.6 Hz), 7.95 (d, 1H, Ar-H, J = 7.9 Hz), 8.32 (d, 1H, Ar-H, J = 7.9 Hz), 8.83 (d, 1H, Ar-H, J= 7.9 Hz); ^{13}C NMR (40 MHz, DMSO-d_6): δ 45.8, 68.4, 126.6, 128.5, 135.9, 137.3, 137.7, 140.3, 141.0, 150.4, 164.4, 170.6. Anal. (%) for $C_{19}H_{19}O_4N_8S_2Cl$.Calcd. C, 43.63; H, 3.66; N, 21.43. Found: C, 43.59; H, 3.72; N, 21.29.

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