Synthesis and Antibacterial Activity of Bis[2-amino-4-phenyl-5-thiazolyl] Disulfides

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Different dimeric disulfides, having the basic skeleton of bis[2-amino-4-phenyl-5-thiazolyl] disulfides were synthesized in a straightforward manner from acetophenones. 2-Amino-4-phenyl-1,3-thiazoles were prepared by the reaction of thiourea with substituted acetophenones in the presence of iodine which were then converted to the title compounds. All the compounds were subjected to preliminary evaluation for their biological activity against Gram positive and Gram negative bacteria. Some of the assayed compounds showed marked activity against *Bacillus cereus* and *Pseudomonas aeruginosa*.

Key words dimeric disulfide; aminothiazole; acetophenone; *Bacillus cereus*; *Pseudomonas aeruginosa*

Pharmacologically, 2-aminothiazoles are among the most important classes of organic compounds. These compounds possess versatile type of biological activities; some of these are well known for their anti-inflammatory activities such as Fentiazac[1] and Meloxicam,[2] while compounds like Nizatidine possess anti-ulcer activity.[3] Some of 2-aminothiazoline derivatives are known for their inhibition of kinurenine-3-hydroxylase[4] and cyclin-dependent kinase enzymes.[5]

Similarly, compounds having disulfide bonds play a vital role in living organisms. The inter-conversion of disulfides and thiols is a fundamental transformation in organosulfur chemistry and such switching plays important role in biological systems due to the presence of thiol groups in some of amino acids.[6,7] A large number of compounds having disulfide linkage have been isolated from different plants and animals. Among these, polycarpine dimeric disulfides were the first to be isolated as unusual bioactive secondary metabolites from marine ascidians (urochordates),[8,9] having 2-aminoimidazole rings linked by disulfide bridges[10] (Fig. 1). This class of compounds got a great deal of attention due to their higher sulphur contents[11] and diverse biological activities such as anti-tumor,[12] anti-cancer, raussarcoma and avian myeloblastoma viruses reverse transcriptase inhibition activity and rat brain Na^+, K^+-ATPase activities.[13] Some of these have been found active in inducing apoptosis in JB_6 cells through P53- and caspase 3-dependant pathways[14] and in inhibiting inosine monophosphate dehydrogenase (IMPDH).[15,16]

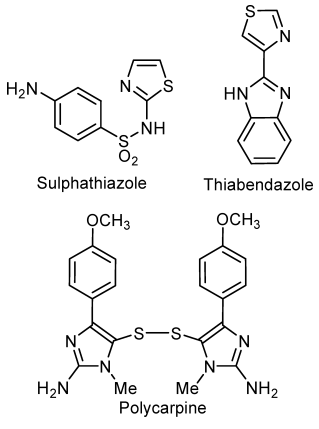

Fig. 1

Keeping in view the antimicrobial properties of the compounds having aminothiazole moiety such as Sulphathiazole® and Thiabendazole®[1], it was planned to synthesize different polycarpine analogues (having aminothiazole group) and investigate their anti-bacterial activities. In this quest, various [2-amino-4-phenyl-5-thiazolyl] disulfides were synthesized and subjected to antibacterial activity.

Chemistry Here, for the synthesis of [2-amino-4-phenyl-5-thiazolyl] disulfides, different aryl aminothiazoles were prepared from substituted acetophenones (Table 1). These acetophenones can be converted to the respective 2-aminothiazoles by their reaction with thiourea in the presence of an oxidizing agent such as sulfuryl chloride, thionyl chloride, sulfur monochloride and iodine[17] (Fig. 1).

Literature reveals the availability of a variety of techniques for preparing both symmetric and unsymmertric disulfides, many of which are based upon the reaction of a thiol with a sulfenylating agent such as sulfenyl halides,[18] sulfenamides,[19] sulfinimides,[20] sulfenylhydrazides[21] and disulfides.[22] In the present case, sulfur monochloride in glacial acetic acid was proved to be excellent to synthesize the disulfide linkage as carbon of thiazole ring is very susceptible to S_2Cl_2 thus avoiding the formation of the thiols first (Table 2). Summary of the reactions involved in the synthesis is given in Chart 1.

Table 1. Synthesis of Substituted Aryl Aminothiazoles

Entry	Reactant	Product	Yield (%)[a)]
1	2-Bromoacetophenone	**2a**	87
2	3-Bromoacetophenone	**2b**	98
3	4-Bromoacetophenone	**2c**	98
4	2-Chloroacetophenone	**2d**	71
5	3-Chloroacetophenone	**2e**	83
6	4-Chloroacetophenone	**2f**	88
7	3,4-Dichloroacetophenone	**2g**	97
8	2,5-Dichloroacetophenone	**2h**	89
9	3,4-Dimethoxyacetophenone	**2i**	77

a) Isolated yield based on corresponding acetophenone.

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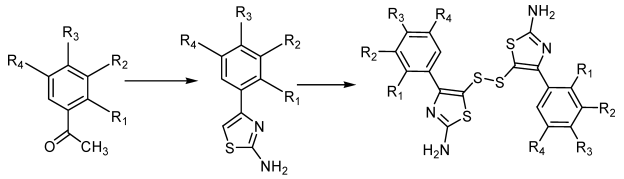
Table 2. Synthesis of [2-Amino-4-phenyl-5-thiazolyl] Disulfides

Entry	Reactant	Product	Reaction time (h)	Yield (%)[a]
1	**2a**	**3a**	7	86
2	**2b**	**3b**	6	77
3	**2c**	**3c**	5	82
4	**2d**	**3d**	7	74
5	**2e**	**3e**	6	76
6	**2f**	**3f**	5	79
7	**2g**	**3g**	6	87
8	**2h**	**3h**	7	90
9	**2i**	**3i**	7	80

a) Isolated yield based on corresponding 2-amino-4-phenyl-1,3-thiazole.



1,2,3	a	b	c	d	e	f	g	h	i
R_1	Br	H	H	Cl	H	H	H	Cl	H
R_2	H	Br	H	H	Cl	H	Cl	H	OMe
R_3	H	H	Br	H	H	Cl	Cl	H	OMe
R_4	H	H	H	H	H	H	H	Cl	H

Chart 1. Synthesis of [2-Amino-4-phenyl-5-thiazolyl] Disulfides from Acetophenones

Antimicrobial Testing All the newly synthesized compounds (dissolved in dimethylsulfoxide) were subjected to antimicrobial screening by determining the minimum inhibitory concentration (MIC) using the agar dilution technique.[23,24]

The *in vitro* antimicrobial activity of the prepared compounds (**2**, **3a**—**i**) against the Gram positive bacterium, *Bacillus cereus* and a Gram negative bacterium, *Pseudomonas aeruginosa* was determined by preparing suspensions of each microorganism to contain approximately 10^5—10^6 CFU (colony forming units)/well. The test compounds were applied to the wells at concentrations ranging from 200 to about 0.1 $\mu g\,ml^{-1}$ in dimethyl sulfoxide solution, in addition to the 0 (control), and the standard tetracycline. The plates were incubated for 24 h at 37 °C and growth assessed by visual inspection. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of inhibitor at which microbial growth was not apparent disregarding a single colony or a faint haze caused by the inoculums.

Results

The MICs of the active compounds against the susceptible pathogenic organisms are presented in Table 3. It was found that all the synthesized dimeric disulfide compounds (**3a**—**i**) have greater inhibitory activities against *Bacillus cereus* and *Pseudomonas aeruginosa* than the corresponding thiazoles (**2a**—**i**). However, among the aminothiazoles, only **2e** and **h** were found active against *Bacillus cereus* while **2a**, **e** and **h** exhibited anti-bacterial activity against *Pseudomonas aeruginosa*. Compounds **2b**, **c**, **d**, **f**, **g** and **i** were found inactive or presented a MIC more than 200 $\mu g\,ml^{-1}$ against both the species.

It is obvious from the results that aminothiazoles are more active against *Pseudomonas aeruginosa* than *Bacillus cereus* while reverse is true for their dimeric disulfides. An insight in to the structures of the synthesized compounds reveals that the *para* substituted compounds are more active than those having halogens substituted at *meta* or *ortho* positions. Also, incorporation of two halogen atoms (**3g**, **h**) resulted in decrease of activity against both the strains indicates the probable steric hindrance to the disulfide bond towards target sites.

In conclusion, the present study revealed that dimerism of substituted aminothiazoles resulted in to more active dimeric disulfides which could be useful as a template for future development through further derivatization to design more potent biologically active compounds.

Table 3. Antibacterial Activity (MIC, $\mu g\,ml^{-1}$)

Compound	Susceptible microorganisms		Compound	Susceptible microorganisms	
	Bacillus cereus	*Pseudomonas aeruginosa*		*Bacillus cereus*	*Pseudomonas aeruginosa*
2a	—	25	**3a**	25.5	31.2
2b	—	—	**3b**	1.4	3.9
2c	—	—	**3c**	1.1	1.9
2d	—	—	**3d**	6.4	10
2e	158	5.62	**3e**	4.5	6.3
2f	—	—	**3f**	3.6	6.3
2g	—	—	**3g**	45.1	55.6
2h	39.8	0.39	**3h**	63	69.9
2i	—	—	**3i**	—	—
Tetracycline	0.20	0.15			

Experimental

All the chemicals were purchased from E. Merck, BDH or Fluka and used without purification. However, solvents were purified through distillation. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DPX-400 instrument at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm referenced to the residual solvent signal. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer. Mass spectra were recorded on a Jeol SX-102 instrument using FAB ionization. Melting points were recorded on a Stuart Scientific-SMP3 apparatus and are uncorrected.

General Procedure of Synthesis of 2-Amino-4-phenyl-1,3-thiazoles Resublimed iodine (0.01 mol) was added to substituted acetophenones (0.01 mol) and thiourea (1.52 g, 0.02 mol), followed by heating of the mixture overnight in an oil bath at 100 °C. After cooling, the reaction mixture was triturated with diethyl ether (*ca.* 50 ml) to remove any unreacted iodine and acetophenone. The solid residue was put in cold distilled water (200 ml) and treated with 25% aqueous ammonium hydroxide (to pH 9—10). The precipitated thiazole was collected and purified by crystallization from hot ethanol.

2-Amino-4-(2-bromophenyl)-1,3-thiazole (**2a**): Light green solid, mp 180 °C; IR (KBr): 3320, 3193, 1510, 1460, 1045 cm^{-1}. ^{1}H-NMR (MeOH-d_4), δ: 4.93 (s, 2H, N<u>H</u>$_2$), (6.87 (s, 1H, thiazole <u>H</u>-5), 7.34 (td, J=11.6, 1.6 Hz, 1H, Ar<u>H</u>), 7.45 (td. J=7.6, 1.6 Hz, 1H, Ar<u>H</u>), 7.58 (dd, J=7.2, 1.2 Hz, 1H, Ar<u>H</u>), 7.72 (dd, J=8.0, 1.2 Hz, 1H, Ar<u>H</u>); ^{13}C-NMR (MeOH-d_4) δ: 107.7, 123.4, 128.8, 130.0, 131.7, 133.1, 134.9, 144.6, 171.2; MS *m*/*z*: 256 [M^++2], 254 [M^+]. *Anal.* Calcd for $C_9H_7BrN_2S$: C, 42.37; H, 2.77; N, 10.98; Found: C, 42.39; H, 2.76; N, 10.96.

2-Amino-4-(3-bromophenyl)-1,3-thiazole (**2b**): Dirty green solid, mp 132 °C; IR (KBr): 3325, 3200, 1513, 1462, 1043 cm^{-1}. ^{1}H-NMR (MeOH-d_4), δ: 4.87 (s, 2H, N<u>H</u>$_2$), 6.92 (s, 1H, thiazole <u>H</u>-5), 7.31—7.62 (m, 4H, Ar<u>H</u>); ^{13}C-NMR (MeOH-d_4) δ: 103.3, 116.9, 117.2, 129.6, 130.1, 134.5, 138.7, 154.2, 170.4; MS *m*/*z*: 256 [M^++2], 254 [M^+]. *Anal.* Calcd for $C_9H_7BrN_2S$: C, 42.37; H, 2.77; N, 10.98; Found: C, 42.34; H, 2.79; N, 11.02.

2-Amino-4-(4-bromophenyl)-1,3-thiazole (**2c**): Light chocolate coloured solid, mp 178 °C; IR (KBr): 3320, 3299, 1515, 1455, 1050 cm^{-1}. ^{1}H-NMR (DMSO-d_6), δ: 3.62 (s, 2H, N<u>H</u>$_2$), 7.07 (s, 1H, thiazole <u>H</u>-5), 7.67 (s, 4H, Ar<u>H</u>); ^{13}C-NMR (DMSO-d_6) δ: 103.5, 115.8, 122.0, 127.8, 129.5, 131.8,

140.7, 155.1, 169.7; MS *m/z*: 256 [M^++2], 254 [M^+]. *Anal.* Calcd for $C_9H_7BrN_2S$: C, 42.37; H, 2.77; N, 10.98; Found: C, 42.35; H, 2.75; N, 10.97.

2-Amino-4-(2-chlorophenyl)-1,3-thiazole (**2d**): Light pink crystalline solid, mp 126 °C; IR (KBr): 3328, 3304, 1520, 1461, 1052 cm^{-1}. ^{1}H-NMR (MeOH-d_4), δ: 4.90 (s, 2H, N$\underline{H}_2$), 6.87 (s, 1H, thiazole $\underline{H}$-5), 7.37—7.69 (m, 4H, Ar$\underline{H}$); ^{13}C-NMR (MeOH-d_4) δ: 106.9, 124.0, 128.9, 130.6, 131.8, 132.9, 134.6, 144.1, 171.6; MS *m/z*: 212 [M^++2], 210 [M^+]. *Anal.* Calcd for $C_9H_7ClN_2S$: C, 51.31; H, 3.35; N, 13.30; Found: C, 51.28; H, 3.34; N, 13.33.

2-Amino-4-(3-chlorophenyl)-1,3-thiazole (**2e**): Pale yellow solid, mp 112 °C; IR (KBr): 3323, 3305, 1518, 1459, 1049 cm^{-1}. ^{1}H-NMR (MeOH-d_4), δ: 4.87 (s, 2H, N$\underline{H}_2$), 6.91 (s, 1H, thiazole $\underline{H}$-5), 7.33—7.66 (m, 4H, Ar$\underline{H}$); ^{13}C-NMR (MeOH-d_4) δ: 107.3, 123.8, 130.0, 130.7, 131.6, 133.2, 134.1, 143.8, 172.0; MS *m/z*: 212 [M^++2], 210 [M^+]. *Anal.* Calcd for $C_9H_7ClN_2S$: C, 51.31; H, 3.35; N, 13.30; Found: C, 51.29; H, 3.31; N, 13.28.

2-Amino-4-(4-chlorophenyl)-1,3-thiazole (**2f**): Light yellow crystalline solid, mp 145 °C; IR (KBr): 3330, 3306, 1522, 1463, 1051 cm^{-1}. ^{1}H-NMR (MeOH-d_4), δ: 4.96 (s, 2H, N$\underline{H}_2$), 6.74 (s, 1H, thiazole $\underline{H}$-5), 7.41—7.70 (m, 4H, Ar$\underline{H}$); ^{13}C-NMR (MeOH-d_4) δ: 107.2, 124.4, 128.3, 130.9, 131.7, 133.0, 134.1, 143.7, 171.2; MS *m/z*: 212 [M^++2], 210 [M^+]. *Anal.* Calcd for $C_9H_7ClN_2S$: C, 51.31; H, 3.35; N, 13.30; Found: C, 51.31; H, 3.34; N, 13.28.

2-Amino-4-(3,4-dichlorophenyl)-1,3-thiazole (**2g**): Pale green solid, mp 194 °C; IR (KBr): 3450, 3208, 1644, 1545, 1408, 1036 cm^{-1}. ^{1}H-NMR (acetone-d_6), δ: 2.06 (s, 2H, N$\underline{H}_2$), 7.16 (s, 1H, thiazole ring), 7.58—7.86 (m, 3H, Ar$\underline{H}$); ^{13}C-NMR (acetone-d_6) δ: 108.8, 117.3, 128.5, 130.17, 130.38, 130.9, 137.0, 147.3, 168.1; MS *m/z*: 248 [M^++4], 246 [M^++2], 244 [M^+]. *Anal.* Calcd for $C_9H_6Cl_2N_2S$: C, 44.10; H, 2.47; N, 11.43; Found: C, 44.08; H, 2.48; N, 11.39.

2-Amino-4-(2,5-dichlorophenyl)-1,3-thiazole (**2h**): Chocolate coloured solid, mp 152 °C; IR (KBr): 3445, 3211, 1639, 1542, 1411, 1032 cm^{-1}. ^{1}H-NMR (acetone-d_6), δ: 2.08 (s, 2H, N$\underline{H}_2$), 7.11 (s, 1H, thiazole ring), 7.32—7.56 (m, 3H, Ar$\underline{H}$); ^{13}C-NMR (acetone-d_6) δ: 106.7, 118.2, 129.1, 130.20, 130.41, 131.3, 136.7, 147.7, 169.5; MS *m/z*: 248 [M^++4], 246 [M^++2], 244 [M^+]. *Anal.* Calcd for $C_9H_6Cl_2N_2S$: C, 44.10; H, 2.47; N, 11.43; Found: C, 44.10; H, 2.44; N, 11.48.

2-Amino-4-(3,4-dimethoxyphenyl)-1,3-thiazole (**2i**): Light yellow coloured solid, mp 200 °C; IR (KBr): 3313, 3276, 1511, 1450, 1045 cm^{-1}. ^{1}H-NMR (DMSO-d_6), δ: 3.01 (s, 2H, N$\underline{H}_2$), 3.64 (s, 6H, OC$\underline{H}_3$), 6.90 (s, 1H, thiazole $\underline{H}$-5), 7.08—7.13 (s, 3H, Ar$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ: 56.3, 56.4, 100.2, 111.9, 116.1, 120.9, 128.2, 149.3, 149.9, 151.0, 170.2; MS *m/z*: 236 [M^+]. *Anal.* Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86; Found: C, 55.93; H, 5.10; N, 11.85.

General Procedure of Synthesis of [2-Amino-4-phenyl-5-thiazolyl] Disulfides Sulfur monochloride (0.01 mol, 1.35 g) was added cautiously to a mixture of 2-amino-4-phenyl-1,3-thiazole (**2a**—**i**) (0.02 mol) and acetic acid (15 ml) followed by stirring of the contents at room temperature (for reaction conditions, see Table 2). Aqueous ammonium hydroxide (25%) was added drop wise till the pH was approximately 10. The precipitated disulfides were collected by filtration, washed with cold water and crystallized from hot ethanol.

[2-Amino-4-(2-bromophenyl)-5-thiazolyl] Disulfide (**3a**): Pale green solid, mp 172 °C; IR (KBr): 3425, 3203, 1638, 1531, 1408, 1019, 522 cm^{-1}. ^{1}H-NMR (MeOH-d_4), δ: 4.97 (s, 4H, N$\underline{H}_2$), 7.03—7.66 (m, 8H, Ar$\underline{H}$); ^{13}C-NMR (MeOH-d_4) δ: 113.0, 124.8, 128.1, 131.4, 132.7, 133.8, 136.5, 157.8, 173.2; MS *m/z*: 574 [M^++4], 572 [M^++2], 570 [M^+]. *Anal.* Calcd for $C_{18}H_{12}Br_2N_4S_4$: C, 37.77; H, 2.11; N, 9.79; Found: C, 37.78; H, 2.10; N, 9.80.

[2-Amino-4-(3-bromophenyl)-5-thiazolyl] Disulfide (**3b**): Dirty brown solid, mp 110—111 °C; IR (KBr): 3430, 3207, 1643, 1532, 1420, 1022, 527 cm^{-1}. ^{1}H-NMR (MeOH-d_4), δ: 4.93 (s, 4H, N$\underline{H}_2$), 7.21—7.71 (m, 8H, Ar$\underline{H}$); ^{13}C-NMR (MeOH-d_4) δ: 111.1, 122.7, 128.9, 130.6, 132.0, 132.9, 137.3, 158.2, 173.5; MS *m/z*: 574 [M^++4], 572 [M^++2], 570 [M^+]. *Anal.* Calcd for $C_{18}H_{12}Br_2N_4S_4$: C, 37.77; H, 2.11; N, 9.79; Found: C, 37.76; H, 2.11; N, 9.80.

[2-Amino-4-(4-bromophenyl)-5-thiazolyl] Disulfide (**3c**): Turmeric solid, mp 238 °C; IR (KBr): 3430, 3207, 1637, 1532, 1410, 1027, 524 cm^{-1}. ^{1}H-NMR (DMSO-d_6), δ: 3.44 (s, 4H, N$\underline{H}_2$), 7.37—7.70 (m, 8H, Ar$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ: 111.8, 127.6, 128.1, 130.1, 132.7, 132.8, 133.4, 151.2, 168.3; MS *m/z*: 574 [M^++4], 572 [M^++2], 570 [M^+]. *Anal.* Calcd for $C_{18}H_{12}Br_2N_4S_4$: C, 37.77; H, 2.11; N, 9.79; Found: C, 37.75; H, 2.12; N, 9.78.

[2-Amino-4-(2-chlorophenyl)-5-thiazolyl] Disulfide (**3d**): Turmeric solid, mp 138 °C; IR (KBr): 3426, 3206, 1641, 1534, 1411, 1023, 529 cm^{-1}. ^{1}H-NMR (DMSO-d_6), δ: 3.51 (s, 4H, N$\underline{H}_2$), 7.03—7.59 (m, 8H, Ar$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ: 110.4, 126.6, 129.4, 129.8, 131.4, 132.2, 133.3, 156.4, 171.2; MS *m/z*: 486 [M^++4], 484 [M^++2], 482 [M^+]. *Anal.* Calcd for $C_{18}H_{12}Cl_2N_4S_4$: C, 44.72; H, 2.50; N, 11.59; Found: C, 44.70; H, 2.51; N, 11.62.

[2-Amino-4-(3-chlorophenyl)-5-thiazolyl] Disulfide (**3e**): Light yellow solid, mp 112 °C; IR (KBr): 3428, 3210, 1645, 1537, 1417, 1026, 532 cm^{-1}. ^{1}H-NMR (DMSO-d_6), δ: 3.38 (s, 4H, N$\underline{H}_2$), 7.34—7.84 (m, 8H, Ar$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ: 110.5, 127.0, 127.8, 128.2, 129.8, 132.4, 135.8, 150.7, 170.9; MS *m/z*: 486 [M^++4], 484 [M^++2], 482 [M^+]. *Anal.* Calcd for $C_{18}H_{12}Cl_2N_4S_4$: C, 44.72; H, 2.50; N, 11.59; Found: C, 44.72; H, 2.49; N, 11.61.

[2-Amino-4-(4-chlorophenyl)-5-thiazolyl] Disulfide (**3f**): Chocolate coloured solid, mp 220 °C; IR (KBr): 3432, 3205, 1639, 1534, 1413, 1031, 527 cm^{-1}. ^{1}H-NMR (DMSO-d_6), δ: 3.46 (s, 4H, N$\underline{H}_2$), 7.35—7.74 (m, 8H, Ar$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ: 109.8, 128.0, 130.2, 132.6, 132.7, 151.3, 168.6; MS *m/z*: 486 [M^++4], 484 [M^++2], 482 [M^+]. *Anal.* Calcd for $C_{18}H_{12}Cl_2N_4S_4$: C, 44.72; H, 2.50; N, 11.59; Found: C, 44.73; H, 2.51; N, 11.57.

[2-Amino-4-(3,4-dichlorophenyl)-5-thiazolyl] Disulfide (**3g**): Turmeric solid, mp 203—204 °C; IR (KBr): 3433, 3216, 1646, 1536, 1423, 1024, 531 cm^{-1}. ^{1}H-NMR (DMSO-d_6), δ: 3.38 (s, 4H, N$\underline{H}_2$), 7.57—7.92 (m, 6H, Ar$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ: 110.7, 128.4, 130.0, 130.2, 130.5, 130.7, 134.3, 150.1, 168.7; MS *m/z*: 558 [M^++8], 554 [M^++4], 552 [M^++2], 550 [M^+]. *Anal.* Calcd for $C_{18}H_{10}Cl_4N_4S_4$: C, 39.14; H, 1.82; N, 10.14; Found: C, 39.16; H, 1.82; N, 10.13.

[2-Amino-4-(2,5-dichlorophenyl)-5-thiazolyl] Disulfide (**3h**): Turmeric solid, mp 143—145 °C; IR (KBr): 3434, 3211, 1644, 1530, 1419, 1020, 535 cm^{-1}. ^{1}H-NMR (DMSO-d_6), δ: 3.50 (s, 4H, N$\underline{H}_2$), 7.46—7.77 (m, 6H, Ar$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ: 111.0, 128.1, 128.9, 129.7, 131.2, 132.1, 135.2, 154.9, 172.0; MS *m/z*: 558 [M^++8], 554 [M^++4], 552 [M^++2], 550 [M^+]. *Anal.* Calcd for $C_{18}H_{10}Cl_4N_4S_4$: C, 39.14; H, 1.82; N, 10.14; Found: C, 39.11; H, 1.82; N, 10.13.

[2-Amino-4-(3,4-dimethoxy phenyl)-5-thiazolyl] Disulfide (**3i**): Light yellow solid, mp 199—200 °C; IR (KBr): 3413, 3206, 1650, 1543, 1417, 1022 cm^{-1}. ^{1}H-NMR (DMSO-d_6), δ: 3.50 (s, 4H, N$\underline{H}_2$), 3.70 (s, 12H, OC$\underline{H}_3$, 6.92—7.07 (m, 6H, Ar$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ: 56.1, 56.2, 102.3, 111.7, 116.1, 120.5, 127.1, 149.7, 150.9, 151.4, 171.7; MS *m/z*: 534 [M^+]. *Anal.* Calcd for $C_{22}H_{22}N_4O_4S_4$: C, 49.42; H, 4.15; N, 10.48; Found: C, 49.41; H, 4.16; N, 10.45.

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