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Synthesis, Characterization and Biological Activity of Schiff Bases of 2, 5-Dimercapto-1,3,4-thiadiazole

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Abstract: The synthesis and characterization of Schiff bases derived from 2,5-dimercapto-1,3,4-thiadiazole are described. The structures of the titled Schiff bases were elucidated by elemental analysis, electronic absorption, infrared, ^{1}H- and ^{13}C-NMR spectral measurements. All prepared compounds were screened for their biological activity. The results indicated that the Schiff bases have good biological activity.

Key words: Synthesis, characterization, Schiff bases, antibacterial activity, 1,3,4-thiadiazole

INTRODUCTION

Heterocyclic moieties can be found in a large number of compounds which display biological activity. The biological activity of the compounds is mainly dependent on their molecular structures (Elzahany *et. al.* 2008). 1, 3, 4-thiadiazoles are very interesting compounds due to their important applications in many pharmaceutical, biological and analytical field (Hadizadeh *et. al.* 2008 and Lu *et. al.* 2000). Schiff bases-bimolecular condensation products of primary amines with aldehydes- represent valuable intermediates in organic synthesis and, at the same time, compounds with various applications (Ugras *et. al.* 2006). Schiff bases resulted from aromatic aldehydes *ortho*-substituted with a hydroxyl group have initially arouse the researches interest because of their ability to act as bidentate ligands for transition metal ions (Wadher *et. al.* 2009). Schiff bases are important class of compounds due to their flexibility, structural similarities with natural biological substances and also due to presence of imine (-N=CH-) which imports in elucidating the mechanism of transformation and rasemination reaction in biological system (Rajavel *et. al.* 2008). These novel compounds could also act as valuable ligands whose biological activity has been shown to increase on complexation (Mohamed *et. al.* 2006). Derivatives of 1,3,4-thiadiazoles have been recognized as molecules with potential antimicrobial utility most of the molecules studied contain substutituents on the 2 and 5 position of the thiadiazole ring. In this study we attempt to investigate the influence of 2, 5-di aryl hydrazone on the antimicrobial activity.

This paper presents a series of new Schiff bases with a potential biological activity resulted from condensation of 2,5-dihydrazinyl-1,3,4-thiadiazole with aromatic aldehydes.

MATERIALS AND METHODS

Instrumentation:

The percentage compositions of the elements (CHNS) for the compounds were determined using an elemental analyzer CHNS Model Fison EA 1108. The infrared spectra were recorded as potassium bromide discs using a Perkin-Elmer spectrophotometer GX. The ^{1}H (400 MHz) and ^{13}C (100 MHz) nuclear magnetic resonance spectra were recorded using the JEOL JNM-ECP 400 spectrometer. Ultraviolet spectra were recorded using Shimadsu UV-Vis spectrophotometer UV -2450, and EtOH was used as solvent. All reactions were monitored by TLC (aluminium foil-backed, 0.25mm silica gel 60 F_{254}; Merck).

Synthesis of 2,5-dimercapto-1,3,4-thiadiazole (1):

A mixture of (99%) hydrazine hydrate (5 mL, 0.02 mol) and carbon disulfide (15 mL, 0.02 mol) with dry pyridine (50 mL) was refluxed for (5 h). Then the excess solvent was then distilled off, and the resulting solid

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was separated out by adding (25 mL) of water and (5 mL) of hydrochloric acid. The mixture was then filtered and the solid was recrystalized from ethanol.

Synthesis of 2,5-dihydrazino-1,3,4-thiadiazole (2):

To 2,5-dimercapto-1,3,4-thiadiazole (1) (1.5 g,0.01 mol) dissolved in ethanol, hydrazine hydrate (5 mL,0.02 mol) was added dropwise with stirring and the mixture was then refluxed for (6 h), then the excess solvent was distilled off. Filtered the resulting solid which was separated out on cooling and recrystalized from ethanol to give the desired product.

Synthesis of 2,5-di(arylhydrazone)-1,3,4-thiadaizoles (3-12):

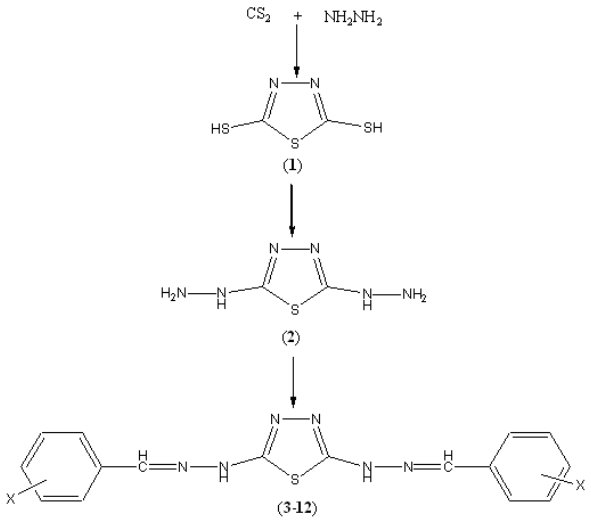
A mixture of (2) (1.46 g, 0.01 mol) in absolute ethanol (20 mL) and appropriate aldehyde (0.02 mol) was refluxed on water bath at (80 ˚C) for (8 h). The crude product was isolated and recrystalized from ethanol.

Biology:

All the newly synthesized compounds were evaluated for their in vitro antibacterial activity against Klebsiella pneumoniae ATCC 10031, Staphyloccus aureus ATCC 6538, Bacillus subtilis PTCC 1023, Pseudomonas aeruginosa and Escherichia coli ATCC 8739. Disk diffusion method (Reeves and White 1983) was used for determination of the preliminary antibacterial activity. Disks measuring 6.25 mm in diameter were punched from Whatman no. 1 filter paper. Batches of 100 disks were dispensed to each screw-capped bottle and sterilized by dry heat at 140 C for an hour. The test compounds were prepared with different concentration using DMSO. 1 mL containing 100 times the amount of chemical in each disk was added to each bottle, which contained 100 discs. Disks of each concentration were place in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37 C for 24 h. The results are given in Table 5.

RESULTS AND DISCUSSION

The Schiff bases under investigation were synthesized in the usual way for the preparation of anils (Gaber *et. al.* 2001) by condensation of 2,5-dihydrazino-1,3,4-thiadiazole (2) with different aromatic aldehydes in 1:1 molar proportion in ethanol. The reaction mixture was heated under reflux for about 8 h, then filtered off and washed with ethanol. The compounds were purified by repeated recrystalization from ethanol and then dried. The purity of the compounds was checked by elemental analysis and constancy of melting points (Table 1).



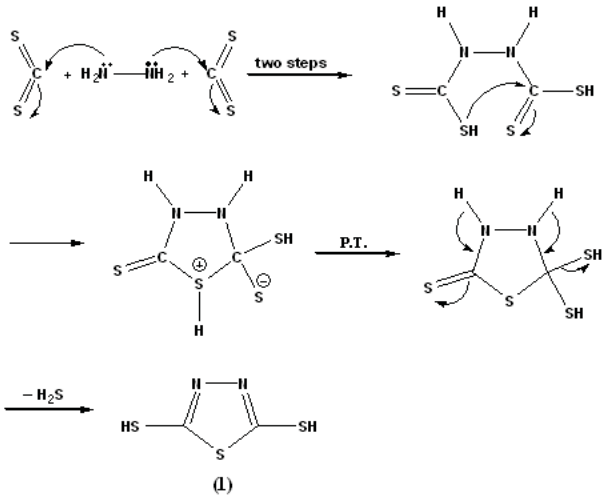
3 X= *m*-NO_2 **4** X= *p*-NO_2 **5** X= *p*-OH
6 X= *p*-CH_3 **7** X= *o*-OH **8** X= *p*-$N(CH_3)_2$
9 X= 3,4-OH **10** X= *m*-CH_3 **11** X= *p*-Cl
12 X= *m*=OH

Scheme 1: Synthetic protocol for the preparation of compounds 1-12

Table 1: Elemental analysis and physical properties of prepared compounds

No.	Color	Formula	% Yield	m. p (°C)	Elemental analysis calc. (found)			
					%C	%H	%N	%S
1	Yellow	$C_2H_2N_2S_3$	62	164-166	15.99 (15.98)	1.34 (1.35)	18.65 (18.64)	64.03 (64.04)
2	Yellow	$C_2H_6N_6S$	60	198-200	16.43 (16.44)	4.14 (4.15)	57.49 (57.50)	21.94 (21.93)
3	Yellow	$C_{16}H_{12}N_8O_4S$	65	187-189	46.60 (46.61)	2.93 (2.92)	27.17 (27.18)	7.78 (7.79)
4	Orange	$C_{16}H_{12}N_8O_4S$	50	150-152	46.60 (46.59)	2.93 (2.94)	27.17 (27.16)	7.78 (7.77)
5	Yellow	$C_{16}H_{14}N_6O_2S$	40	225-227	54.23 (54.24)	3.98 (3.97)	23.71 (23.70)	9.05 (9.06)
6	Orange	$C_{18}H_{18}N_6S$	55	227-229	61.69 (61.70)	5.18 (3.19)	23.98 (23.97)	9.15 (9.14)
7	Orange	$C_{16}H_{14}N_6O_2S$	45	203-205	54.23 (54.22)	3.98 (3.99)	23.71 (23.70)	9.05 (9.04)
8	Yellow	$C_{20}H_{24}N_8S$	75	199-201	58.80 (58.81)	5.92 (5.91)	27.43 (27.42)	7.85 (7.86)
9	Yellow	$C_{18}H_{18}N_6S$	75	270-272	61.69 (61.70)	5.18 (5.17)	23.98 (23.99)	9.15 (9.14)
10	Yellow	$C_{18}H_{18}N_6S$	50	222-224	61.69 (61.68)	5.18 (5.19)	23.98 (23.97)	9.15 (9.16)
11	Yellow	$C_{16}H_{12}Cl_2N_6S$	45	193-195	49.11 (49.12)	3.09 (3.08)	21.48 (21.47)	8.19 (8.20)
12	Yellow	$C_{16}H_{14}N6O2S$	70	176-178	54.23 (54.22)	3.98 (3.97)	23.71 (23.70)	9.05 (9.04)

The mechanism for the formation of 2,5-dimercapto-1,3,4-thiadiazole (1) is shown in Scheme 2:



Scheme 2: Reaction mechanism for the preparation of compound 1.

Electronic Absorption Spectra:

The electronic spectra of the synthesized diaryl hydrazone compounds (3-12) dissolved in (EtOH) gave the (λmax) absorption bands at about (224-497 nm) for all compounds. The (λmax) are listed in Table 2:

Table 2: Electronic data of compounds (3-12)

No.	Ar group	λmax (nm)/ Ethanol
3	3-nitrophenyl	266
4	4-nitrophenyl	255
5	4-hydroxyphenyl	331
6	4-methylphenyl	262
7	2-hydroxylphenyl	293, 358
8	4-dimethylaminophenyl	497, 389, 241
9	3,4-dihydroxyphenyl	364, 312, 249, 224
10	3-methylphenyl	305, 268
11	4-chlorophenyl	319, 262
12	3-hydroxyphenyl	323, 258

The spectral pattern data (Table 2) is found to be quite similar to other 1,3,4-thiadiazole derivatives reported in earlier literature (Gaber *et. al.* 2001).

FTIR spectra:

The important diagnostic bands in the IR spectra were assigned and the bands positions are compiled in Table 3. The FTIR spectrum of compound (**1**) showed a medium intensity band at 1624 cm^{-1} that could correspond with (C=N) stretching in the vicinity of 1,3,4-thiadiazole ring (Silverstein *et. al.* 1998). In this

spectrum there are two other characteristic bands at 3200 and 2550 cm^{-1} due to (N-H) and (S-H) stretching vibrations, respectively. From this we can say that this compound can exist in the thiol and thion form. On the other hand, the FTIR spectrum of 2,5-dihydrazino-1,3,4-thiadiazole (**2**) showed the disappearance of band at 2550 cm^{-1} for υ(C-S) with a new band at 3396, 3271 and 3200 cm^{-1} which are assigned as υ_{asym} (NH_2), υ_{sym} (NH_2) and υ(NH) group, respectively. These bands proved the conversion of compound (**1**) to (**2**). Moreover, compound (**2**) showed characteristic IR bands at 1284cm^{-1} υ(N-C=C), 1109cm^{-1} υ(C-S-C) thion ether linkage and 1247cm^{-1} υ(N-N). A comparison of the FTIR spectrum of compound (**2**) with the spectra of compounds (**3-12**) revealed in the case of these compounds (υ_{asym} , υ_{sym} NH_2) were absent. Moreover, these di-hydrazones (**3-12**) showed characteristic FTIR band at about 1620 cm^{-1} for Schiff bases (C=N) stretching. The other characteristic bands are listed in Table 3.

Table 3: FTIR data of compounds (3-12)

No.	Ar group	FTIR bands (cm^{-1})	
		υ (C=N)	Others
3	3-nitrophenyl	1623	Asymmetric ($ArNO_2$)N-O stretching.,1523, Symmetric ($ArNO_2$)N-O stretching., 1350
4	4-nitrophenyl	1621	Asymmetric ($ArNO_2$)N-O stretching.,1521, Symmetric ($ArNO_2$)N-O stretching., 1342
5	4-hydroxyphenyl	1620	Broad, intermolecular hydrogen bonded. O-H stretching.,3336
6	4-methylphenyl	1622	Aliphatic C-H stretching. 2939
7	2-hydroxy phenyl	1624	Broad, intermolecular hydrogen bonded. O-H stretching., 3460
8	4-dimethylaminophenyl	1620	Aliphatic C-H stretching. 2854
9	3,4-dihydroxyphenyl	1621	Broad, intermolecular hydrogen bonded. O-H stretching.,3334
10	3-methylphenyl	1623	Aliphatic C-H stretching. 2922
11	4-chlorophenyl	1622	Ar Cl 1055
12	3-hydroxy phenyl	1620	Broad, intermolecular hydrogen bonded. O-H stretching.,3250

^{1}H and ^{13}C-NMR spectra

The structures of Schiff base under investigation were further supported by the ^{1}H- and ^{13}C-NMR spectral measurement. The ^{1}H- and ^{13}C-NMR spectra data of some Schiff bases are recorded and assigned in Table 4.

Table 4: ^{1}H- and ^{13}C-NMR data of compounds (3-12)

No.	^{1}H- and ^{13}C-NMR spectral data
3.	^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.43, 5.87 (2H, 2s, 2 N=CH-), 7.78-8.52 (8H, m, Ar-H), 9.74, 10.06 (2H, 2s, 2-NH, exchangeable with D_2O). ^{13}C-NMR (100MHz, DMSO-d_6): 115.65, 117.32 (2C, thiadiazole carbons), 122.61, 125.42 (2C, 2 N=CH-), 134.11-140.76 (12C, aromatic carbons).
4	^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.78, 6.07 (2H, 2s, 2 N=CH-), 7.69-8.90 (8H, m, Ar-H), 9.14, 10.26 (2H, 2s, 2 NH, exchangeable with D_2O). ^{13}C-NMR (100MHz, DMSO-d_6): 116.04, 118.65 (2C, thiadiazole carbons), 122.31, 125.67 (2C, 2 N=CH-), 134.98-141.36 (12C, aromatic carbons).
5	^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.11, 6.92 (2H, 2s, 2 N=CH-), 7.42-8.91(8H, m, Ar-H), 9.15, 9.26 (2H, 2s, 2 NH, exchangeable with D_2O), 10.87, 10.92 (2H, 2s, 2 OH, exchangeable with D_2O). ^{13}C-NMR (100MHz, DMSO-d_6): 116.04, 118.65 (2C, thiadiazole carbons), 122.31, 125.67 (2C, 2 N=CH-), 134.98-141.36 (12C, aromatic carbons).
6	^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.43, 1.58 (2s, 6H, 2 CH_3), 6.08, 6.11 (2H, 2s, 2 N=CH-), 7.46-8.81 (8H, m, Ar-H), 9.17, 9.88 (2H, 2s, 2-NH, exchangeable with D_2O). ^{13}C-NMR (100MHz, DMSO-d_6): 117.16, 119.21 (2C, thiadiazole carbons), 121.44, 126.89 (2C, 2 N=CH-), 133.52-142.62 (12C, aromatic carbons).
7	^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.23, 6.85 (2H, 2s, 2 N=CH-), 7.50-8.82(8H, m, Ar-H), 9.67, 10.15 (2H, 2s, 2 NH, exchangeable with D_2O), 10.63, 10.87 (2H, 2s, 2 OH, exchangeable with D_2O). ^{13}C-NMR (100MHz, DMSO-d_6): 115.53, 119.21 (2C, thiadiazole carbons), 123.61, 126.05 (2C, 2 N=CH-), 135.91-142.12 (12C, aromatic carbons).
8	^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.04, 2.51 (2s, 12H, 4 CH_3), 6.15, 6.78 (2H, 2s, 2 N=CH-), 7.14-8.75 (8H, m, Ar-H), 9.13, 9.54 (2H, 2s, 2-NH, exchangeable with D_2O). ^{13}C-NMR (100MHz, DMSO-d_6): 118.01, 118.37 (2C, thiadiazole carbons), 118.16, 120.61 (2C, 2 N=CH-), 1323.32-141.71 (12C, aromatic carbons).
9	^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.45, 6.89 (2H, 2s, 2 N=CH-), 7.43-8.89(6H, m, Ar-H), 9.61, 10.14 (2H, 2s, 2 NH, exchangeable with D_2O), 10.13, 10.27, 10.55, 11.02 (4H, 4s, 4 OH, exchangeable with D_2O). ^{13}C-NMR (100MHz, DMSO-d_6): 115.52, 119.63 (2C, thiadiazole carbons), 119.20, 120.25 (2C, 2 N=CH-), 135.11-142.74 (12C, aromatic carbons).
10	^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.24, 1.71 (2s, 6H, 2 CH_3), 6.08, 6.23 (2H, 2s, 2 N=CH-), 7.40-8.94 (8H, m, Ar-H), 9.07, 9.38 (2H, 2s, 2-NH, exchangeable with D_2O). ^{13}C-NMR (100MHz, DMSO-d_6): 118.13, 120.21 (2C, thiadiazole carbons), 120.94, 126.58 (2C, 2 N=CH-), 133.12-142.36 (12C, aromatic carbons).
11	^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.13, 6.25 (2H, 2s, 2 N=CH-), 7.54-8.83(8H, m, Ar-H), 9.13, 10.52 (2H, 2s, 2 NH, exchangeable with D_2O). ^{13}C-NMR (100MHz, DMSO-d_6): 114.63, 116.30 (2C, thiadiazole carbons), 123.50, 126.54 (2C, 2 N=CH-), 134.21-140.29 (12C, aromatic carbons).
12	^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.20, 6.05 (2H, 2s, 2 N=CH-), 7.42-8.75(8H, m, Ar-H), 9.61, 10.35 (2H, 2s, 2 NH, exchangeable with D_2O), 10.23, 10.47 (2H, 2s, 2 OH, exchangeable with D_2O). ^{13}C-NMR (100MHz, DMSO-d_6): 116.33, 118.40 (2C, thiadiazole carbons), 123.46, 126.13 (2C, 2 N=CH-), 135.87-141.30 (12C, aromatic carbons).

Table 5: Antimicrobial activities of compounds (**3**-12)

Compound	Inhibition Zone (mm)				
	K. pneumoniae	*S. aureus*	*B. subitilis*	*P. aeruginosa*	*E. coil*
3	++	+	+	+	+
4	+++	+	++	++	-
5	++	+	+++	++	+
6	+	++	++	++	+
7	++	-	++	++	++
8	+	++	+	+	+
9	++	++	++	+	-
10	++	++	+	+	++
11	++	+++	++	++	+++
12	++	++	+	++	+++

+++ = high activity
++ = moderate activity
+ = low activity
- = no activity

Biology:

The new compounds were tested for their antimicrobial activity, at a concentration of 100μg/cm^3, against five strains of microorganisms, namely *Klebsiella pneumoniae* ATCC 10031, *Staphylococcus aureus* ATCC 6538p, *Bacillus subtilis* PTCC 1023, *Pseudomonas aeruginosa*, and *Escherichia coil* ATCC 8739. From the results in Table 5, we can conclude that compounds (3-12) have moderate to high antibacterial activity. From structure-activity relationships it can be conlude that the antibacterial activity of the synthesized compounds may be due to the presence of the 1,3,4-thiadiazole ring which might increase the lipophilic character of the molecules, which facilitate the crossing through the biological membrane of the microorganisms and thereby inhibit their growth.

Conclusion:

The preparation procedure follow in this work for the synthesis of title compounds offers reduction in the reaction time, opperation simplicity, cleaner reaction and easy work-up. All spectroscopic analysis confirmed the proposed structures for these compounds. Antibacterial data have shown that the synthesized compounds have a significant biological activity against the tested microorganisms.

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