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SCHIFF BASES DERIVED FROM 4-AMINO-N-SUBSTITUTED BENZENESULFONAMIDE: SYNTHESIS, SPECTRAL CHARACTERISATION AND MIC EVALUATION

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ABSTRACT. The present study is aimed to synthesise Schiff bases from sulfathiazole/ sulfamethoxazole/ sulfadimidine with 2-hydroxybenzaldehyde. The synthesized Schiff bases were characterized by analytical data, IR, ^{1}H-NMR, ^{13}C-NMR, UV-Vis spectra, mass spectra and screened for antibacterial activity against gram positive bacteria *Staphylococcus aureus* and gram negative bacteria *Salmonella typhi*and antifungal activity against *Candida albicans* and *Mucor* by disc diffusion method. Zone of inhibition indicated that the Schiff base possessed highly potent antimicrobial activity when compared to sulpha drugs.

KEY WORDS: 4-Amino-N-(1,3-thiazol-2-yl)benzenesulfonamide, 4-amino-N-(5-methylisoxazol-3-yl)-benzenesulfonamide,4-amino-N-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide, 2-hydroxybenzaldehyde, antimicrobial activity

INTRODUCTION

Schiff bases are condensation products of primary amine and carbonyl compounds and they were discovered by a German chemist, Noble prize wined Hugo Schiff in 1864 [1]. Schiff base ligands are essential in the field of coordination chemistry, especially in the development of complexes of Schiff bases because these compounds are potentially capable of stable complexes with metal ions [2].

A large number of Schiff base complexes are characterized by an excellent catalytic activity in a variety of reactions at high temperature (>100 ^{o}C) and in the presence of moisture [3]. In recent years, there have been numerous reports of their use in homogeneous and heterogeneous catalysis [4]. They are increasingly being used as catalysts in various biological systems, polymers and dyes [5]. A large number of different Schiff bases ligands have been used as cation carriers in potentiometric sensors [6]. So much interest in imines can be explained by the fact that they are widely distributed in many biological systems and they are used in organic synthesis and chemical catalysis, medicine, pharmacy and chemical analysis, as well as new technologies [7].

Sulfonamides, also known as sulfa drugs were the first effective chemotherapeutics agents employed systematically for the prevention and cure of bacterial infections in humans. Many different families of organic and inorganic compounds are currently investigated today because of their applications. Sulfonamides and their N-derivatives are one of the outstanding groups. Sulfonamides represent are important compounds which are extensively used antibacterial agent. It interferes with *p*-aminobenzoic acid (PABA) in biosynthesis of tetrahydro folic acid which is a basic growth factor essential for the metabolic process of bacteria [8-10].

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EXPERIMENTAL

All chemicals and reagents used were of AR grade except ethanol which was purified prior to use. Solvents were purified and dried according to the standard procedures. Elemental analysis of the ligand and complexes were obtained using ElementarVario EL CHN rapid analyzer. IR spectra of the complexes were recorded as KBr pellets on a SHIMADZU 8000 - FTIR spectrophotometer. The ^{13}C-NMR and ^{1}H-NMR spectra of the ligand was recorded with a Bruker Spectrospin Advance (DPX-400) using TMS as internal standard and DMSO-d^{6} as solvent. Melting points were determined by open capillary method (silicon bath electric melting point apparatus) and uncorrected.

Synthesis of Schiff base ligand

Synthesis of (E)-4-((2-hydroxybenzylidene)amine)-N-(thiazol-2-yl)benzene sulfonamide. To a hot stirred ethanolic solution of sulphathiazole (0.001 mol) an ethanolic solution of 2-hydroxybenzaldehyde (0.6 mL) was added. The reaction mixture was refluxed for 5 h. The yellow coloured solid mass formed during refluxing was cooled, filtered, washed thoroughly with ethanol and dried in a desiccator. The compound was purified by recrystallisation from ethanol (yield: 85%, m.p. 220 ^{o}C).

Synthesis of 4-((2-hydroxy-benzylidine)-amine)-N-(methyl-1,2-oxazol-3-yl)-benzene sulphonamide. To a hot stirred ethanolic solution of 2-hydroxybenzaldehyde (0.6 mL) an ethanolic solution of sulphamethaoxazole (0.001 mol) was added. The reaction mixture was refluxed for 5 h. The yellow coloured solid mass formed during refluxing was cooled, filtered, washed thoroughly with ethanol and dried in a desiccator. The compound was purified by recrystallisation from ethanol (yield: 85%, m.p. 271 ^{o}C).

Synthesis of N-(4,6-dimethylpyrimidin-2-yl)-4-((2-hydroxybenzylidine) amino)benzene sulfonamide. To a hot stirred ethanolic solution of sulphadimidine (0.001 mol) anethanolic solution of 2-hydroxybenzaldehyde (0.6 mL) was added. The reaction mixture was refluxed for 5 h. The yellow coloured solid mass formed during refluxing was cooled, filtered, washed thoroughly with ethanol and dried in a desiccator. The compound was purified by recrystallisation from ethanol (yield: 80%, m.p. 264 ^{o}C).

RESULTS AND DISCUSSION

In the present work, the Schiff bases 4-((2-hydroxybenzylidene)amino-N-(1,3-thiazol-2-yl)benzenesulfonamide) (L_1), 4-((2-hydroxy-benzylidine)-amino)-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide) (L_2), 4-((2-hydroxybenzylidene)amino)-N-(4,6-dimethylpyrimidin-2-yl)-benzene sulfonamide (L_3) have been synthesized. The stoichiometry of the compounds has been determined by standard procedures.

Analytical data

The Schiff base ligand L_1 was synthesized by condensing 2-hydroxy benzaldehyde and 4-amino-N-(1,3-thiazol-2-yl)benzenesulfonamide. It is an orange colored solid with melting point =270 ^{o}C. The Schiff base ligand L_2 was synthesized by condensing 2-hydroxy benzaldehyde and 4-amino-N-(5-methylisoxazol-3-yl)benzenesulfonamide. It is a yellow colored solid with melting point = 271 ^{o}C. The Schiff base ligand L_3 was synthesized by condensing 2-hydroxy benzaldehyde and 4-amino-N-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide. It is an orange colored solid with melting point = 264 ^{o}C. The analytical data and physical characteristics of the Schiff base are (Table 1) indicates that the molecular formula as, L_1: $C_{16}H_{13}N_3O_3S_2$; L_2: $C_{17}H_{15}N_3O_4S$; L_3: $C_{20}H_{19}N_3O_3S$.

Table 1. Physical characteristics and analytical data of Schiff bases.

S. No.	Schiff base	Molecular formula	Colour	Yield %	m.p. °C	Elemental analysis% found (calculated)			
						C	H	N	S
1	L_1	$C_{16}H_{13}N_3O_3S_2$	Yellow	85	270	52.93 (53.48)	3.30 (3.62)	10.81 (11.69)	17.45 (17.82)
2	L_2	$C_{18}H_{16}N_3O_4S$	Orange	85	271	57.79 (58.37)	4.21 (4.32)	10.92 (11.31)	8.52 (8.64)
3	L_3	$C_{20}H_{19}N_3O_3S$	Yellow	80	264	61.89 (62.99)	4.62 (4.98)	10.98 (11.02)	7.88 (8.39)

FT-IR spectrum

The ligands used in the present investigation contain five donor sites: (i) phenolic oxygen, (ii) azomethine nitrogen, (iii) sulfonamide oxygen, (iv) sulfonamide nitrogen and (v) ring nitrogen. The vibrational spectra of the ligands shows a band in the region of 1616–1659 cm^{-1} corresponds to ν(>C=N-) group [11] and another broad band between 3456–3471 cm^{-1} which is the characteristic frequency of hydrogen bonded phenolic ν(O-H) stretching vibration [12, 13]. Schiff base L_1 IR (solid state, cm^{-1}): 1616 ν(>C=N-); 3462 ν(O-H); 1417 $\nu_{as}(SO_2)$; 2919 $\nu_s(SO_2)$; 2924 ν(N-H). Schiff base L_2 IR (solid state, cm^{-1}): 1616 ν(>C=N-); 3471 ν(O-H); 1406 $\nu_{as}(SO_2)$; 2934 $\nu_s(SO_2)$; 2963 ν(N-H). Schiff base L_2 IR (solid state, cm^{-1}): 1659 ν(>C=N-); 3456 ν(O-H); 1437 $\nu_{as}(SO_2)$; 2927 $\nu_s(SO_2)$; 2938 ν(N-H).

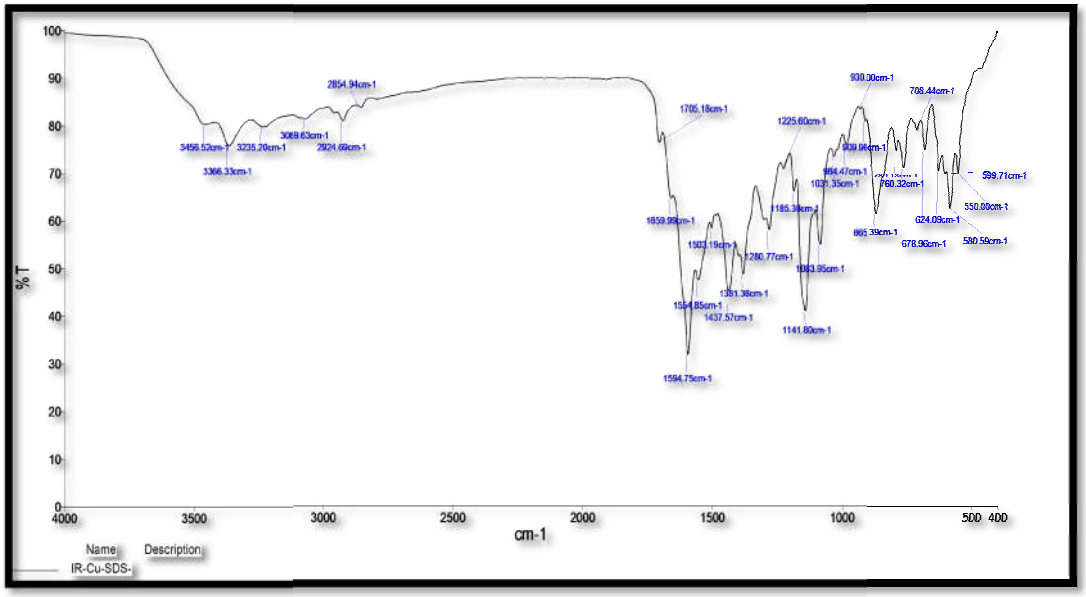


Figure 1. IR spectrum of 4-((2-hydroxybenzylidene)amino)-N-(4,6-dimethylpyrimidin-2-yl) benzenesulfonamide (L_3).

Electronic spectra

The electronic spectra of the ligands show two absorption maxima. L_1 (λ_{max} nm (cm^{-1}): 279 nm (35842 cm^{-1}) π-π* and 345 nm (28985 cm^{-1}) n-π* transition (azomethine linkage) [14, 15]. L_2 (λ_{max} nm (cm^{-1}): 277 nm (36101 cm^{-1}) π-π* (aromatic part of the ligand) [14, 15] and 344 nm (28985 cm^{-1}) n-π* transition. L_3 (λ_{max} nm (cm^{-1}): 276 nm (36231 cm^{-1}) π-π* and 340 nm (29411 cm^{-1}) n→σ^* transition.

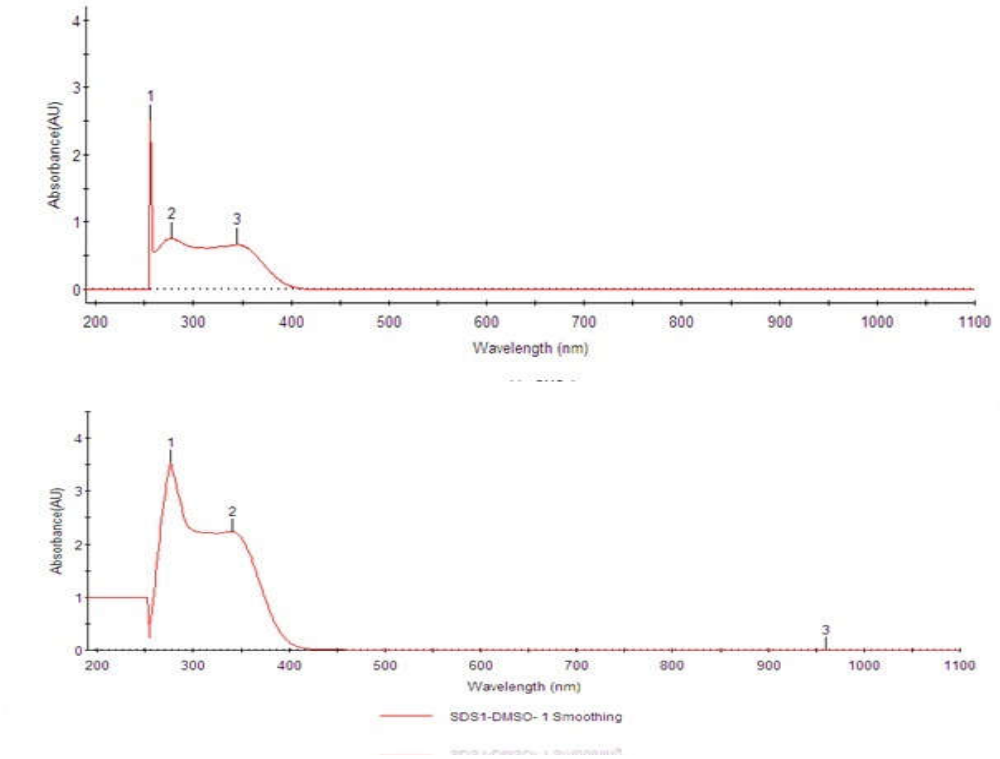


Figure 2. UV spectrum of L_2 and L_3.

^{1}H-NMR spectra

The proton magnetic resonance spectrum of the Schiff base was taken in DMSO-d_6 solvent. The ^{1}H NMR spectrum of ligand (L_1) exhibits peak at δ 8.96 ppm (1H) (Figure 3) suggesting the appearance of –CH = N proton [16]. The peak at δ 12.61 ppm (1H) and peak in the range 6.58–7.88 ppm indicates hydroxyl and aromatic protons. The ^{1}H NMR spectrum of ligand (L_2) exhibits peak at δ 8.94 ppm (1H) suggesting the appearance of –CH=N proton. The peak at δ 12.47 ppm (1H) and peak in the range 6.57-7.91 ppm indicate hydroxyl and aromatic protons [17]. The ^{1}H NMR spectrum of ligand L_3 has a signal at δ 8.97 ppm (Figure 3) suggesting the presence of –CH=N- linkage. The multiplet in the proton NMR spectrum which extends from δ 6.5 to 7.6 ppm corresponds to the ten protons of the aromatic ring. The signal at δ 12.6 ppm

indicates the presence of hydroxyl proton and δ 2.25 to 2.27 ppm corresponds to the presence of $-CH_3$ proton. The presence of NH proton is confirmed by the signal at δ7.7 ppm. Other peaks from ^{1}H-NMR spectra for the ligands are assigned as [DMSO-d_6, δ ppm]: 6.76-7.02 (4H, phenolic ring), 6.74 ppm (1H, pyrimidine) 6.98-7.70 ppm (4H, N-phenyl) [18], 7.47 ppm (d, 2H, oxazole moiety), 7.45 ppm (d, 2H, thiazole moiety).

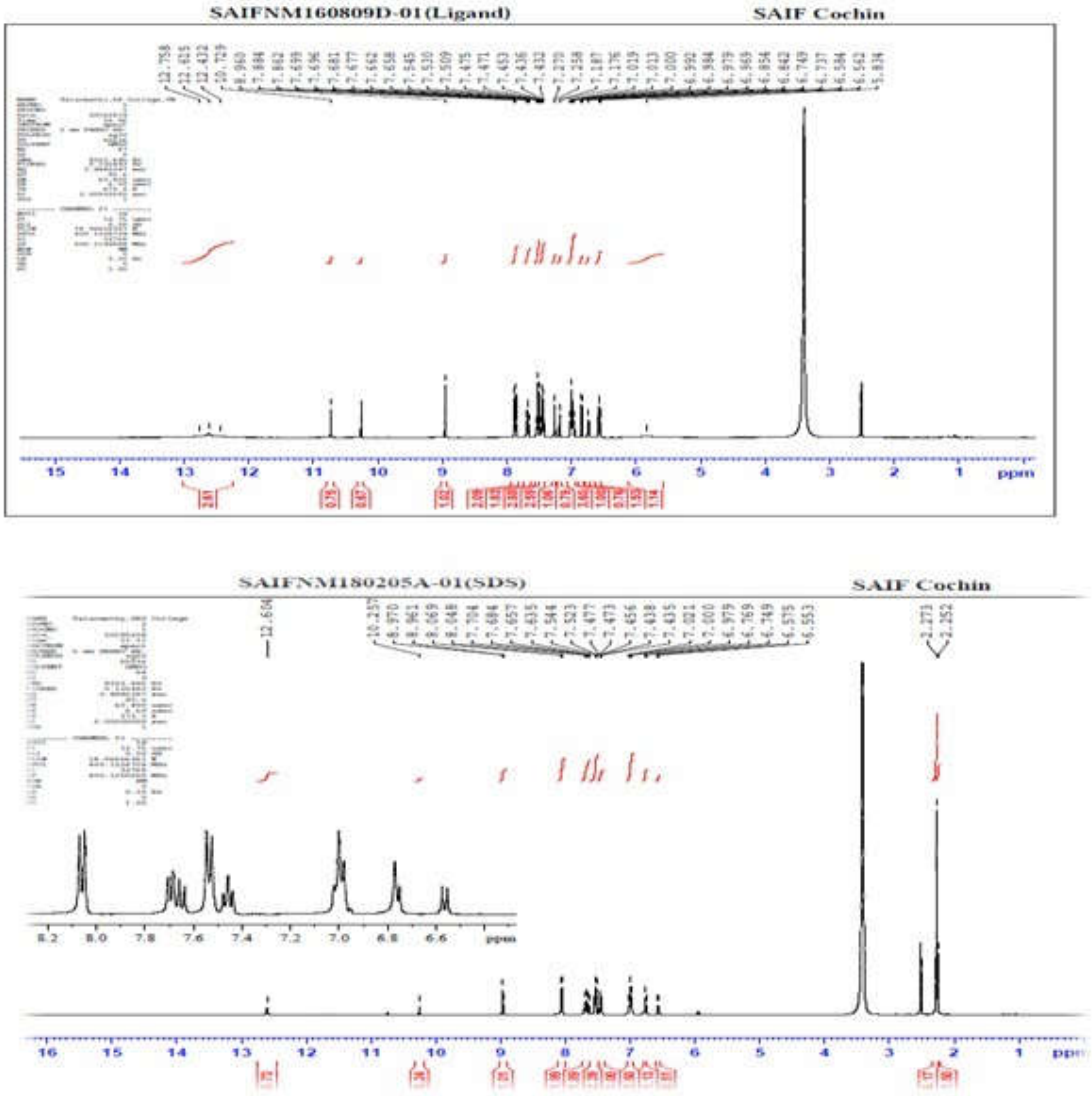


Figure 3. ^{1}H-NMR spectra of L_1 and L_3.

^{13}C NMR spectra

The ^{13}C-NMR spectrum of the Schiff base was taken in DMSO-d_6 solvent (Figure 4). ^{13}C-NMR spectrum of L_1 (DMSO-d_6, δ, ppm): 165.1 ppm (-CH=N-), 150.6 (phenolic C-OH), 168.8, 112.4, 147.9 (C_1, C_3, C_4-thiazole), 122.4, 127.6, 140.1 (C_2 and C_6, C_3 and C_5, C_4, N-phenyl) 119.1, 124.4, 116.0 (C_1, C_2, C_3 and C_4, phenolic) [19]. ^{13}C-NMR spectrum of L_2 (DMSO-d_6, δ, ppm): 165.4 ppm (-CH=N-) 7.47 ppm (d, 2H, oxazole moiety), 160.6 (phenolic C-OH) 128.2, 112.5, 152.6 (C_1, C_2, C_3-N- phenyl) 136.8, 132.5, 122.1, 119.1, 117.1 (C_1, C_2, C_3, C_4, C_5-phenolic ring), 169.8, 157.8, 95.2, 11.9 (C_1, C_2, C_3, C_4, oxazolering. ^{13}C-NMR spectrum of L_3 (DMSO-d_6, δ, ppm): 165.2 ppm (-CH=N-), 150.6 (phenolic C-OH), 167.9, 168.9, 111.8 (C3 and C_5, C_1, C_4, pyrimidine), 122.3, 127.8 (C_2 and C_6, C_3 and C_5, C_4, N-phenyl), 115.8 (C_3 and C_4, phenolic) [20].

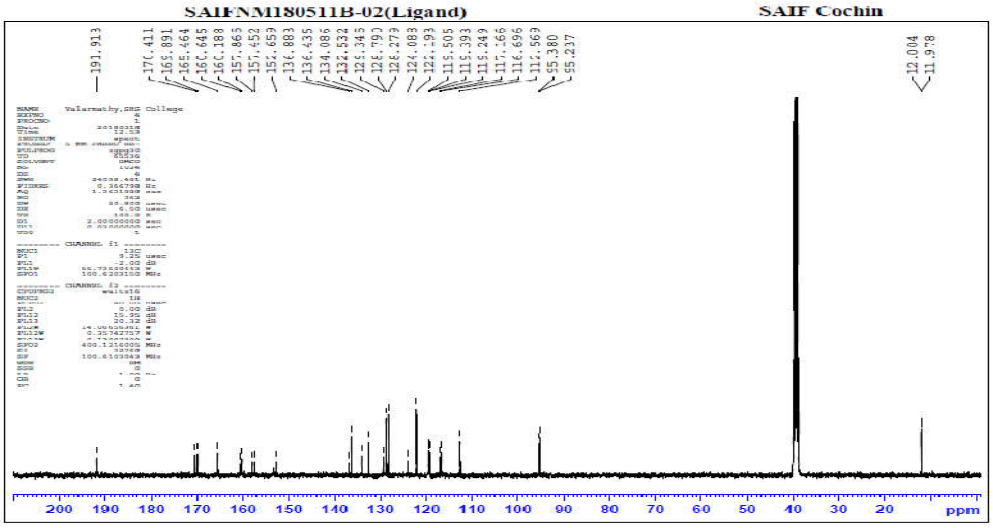


Figure 4. ^{13}C NMR spectrum 4-((2-hydroxybenzylidene)amino)-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide (L_2).

Mass spectra

The mass spectral data of the ligand is consistent with the formulation corresponds to [M+3] and M peaks, respectively, as shown in Figure 5. Ligand-1: $C_{16}H_{13}N_3O_3S_2$: m/z = 363.229 (calcd., 359). Ligand-2: $C_{18}H_{16}N_3O_4S$: m/z = 357 (calcd., 357). Ligand-3: $C_{20}H_{19}N_3O_3S$: m/z = 381 (calcd., 381).

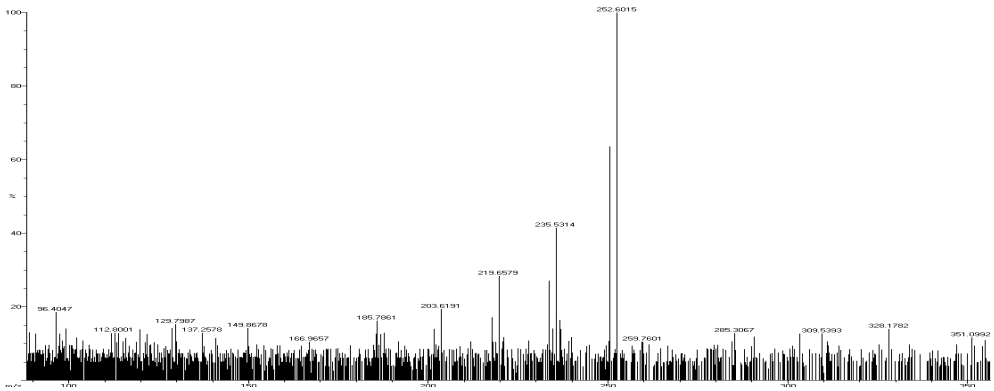
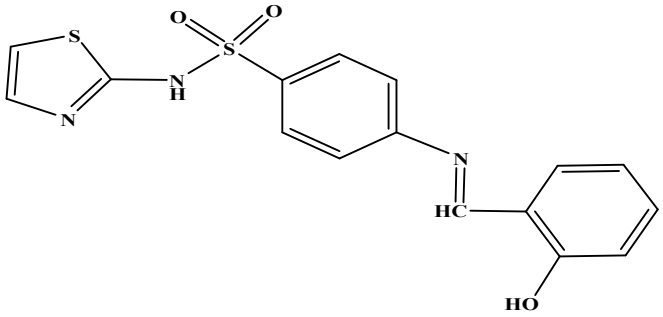
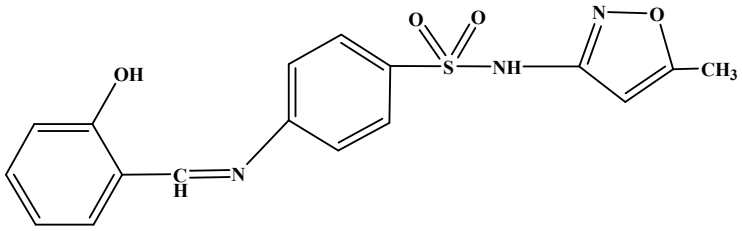


Figure 5. Mass spectrum 4-((2-hydroxybenzylidene)amino-N-(5-methyl-1,2-oxazol-3-yl) benzenesulfonamide) (L_2).

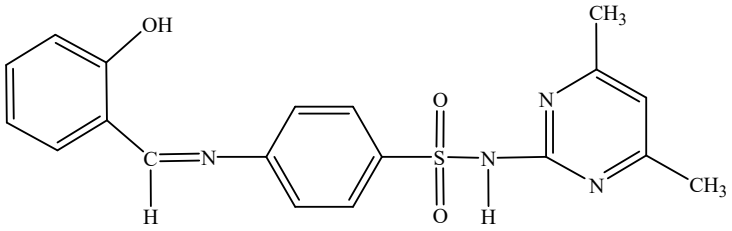
Based on the above spectral studies, the following structure is proposed for the Schiff bases:



Structure of Schiff base 4-((2-hydroxybenzylidene)amino-N-(1,3-thiazol-2-yl) benzenesulfonamide (L_1).



Structure of Schiff base 4-[(2-hydroxybenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl) benzenesulfonamide (L_2).



Structure of the Schiff base 4-((2-hydroxybenzylidene)amino)-N-(4,6-dimethyl pyrimidin-2-yl) benzenesulphonamide (L_3).

Anti microbial studies - minimum inhibitory concentration

Antibacterial, antifungal and MIC activity of sulpha drugs and their Schiff base ligands have been tested by disc diffusion technique [21, 22]. The test was carried out in DMSO solution at a concentration of 50, 75, 100 ppm (Table 2). All the sulpha drugs and their Schiff bases individually exhibit varying degree of inhibitory effects on the growth of tested bacterial and fungal species (Figures 6-8).

Antibacterial bioassay (in-vitro)

Antibacterial activity of sulfa drugs and their Schiff bases were tested against bacterial species like gram positive bacteria *Staphylococcus aureus* and gram negative bacteria *Salmonella typhi*. The activity is enhanced at the concentrations 50, 75, 100 ppm. Results were compared with standard drug ciprofloxacin at the same concentration. According to antibacterial studies, the efficacy against gram negative is higher than gram positive bacteria. The inhibition of growth of bacteria is found to be maximum for the Schiff bases than the corresponding sulpha drugs. However, the Schiff base L_2 is more active against *Staphylococcus aureus* and *Salmonella typhi* at lower concentration.

Table 2. Antimicrobial activity of Schiff bases and compound.

S. No	Compound	*Staphylococcus aureus*			*Salmonella typhi*			*Candida albicans*			*Mucor*		
		50 ppm	75 ppm	100 ppm	50 ppm	75 Ppm	100 ppm	50 ppm	75 ppm	100 ppm	50 ppm	75 ppm	100 ppm
1	STS (L_1)	12	15	20	16	18	22	18	20	24	15	19	21
2	SMS(L_2)	14	19	22	20	22	30	16	18	22	18	20	22
3	SDS(L_3)	15	18	21	12	16	20	16	16	22	13	18	22
4	Sulpha drug ST	12	14	16	15	15	19	12	18	20	10	16	18
5	Sulpha drug SM	14	18	21	16	20	22	12	15	17	12	18	19
6	Sulpha drug SD	14	15	18	12	12	16	10	12	14	14	20	22

Standard = Ciprofloxacin 5 µg/disc for bacteria; Nystatin 100 µg/disc for fungi. Highly active = inhibition zone > 15 mm; Moderately active = inhibition zone > 10 mm; Slightly active = inhibition zone > 5 mm; Inactive = inhibition zone 5 mm.

Antifungal bioassay (in-vitro)

The sulpha drugs and their Schiff bases were carried out against fungi *Candida albicans* and *Mucor*. The activity is greatly enhanced at the concentrations 50, 75, 100 ppm. Compared to the standard drug Nystatin, sulpha drugs show moderate activity against fungi, whereas the Schiff bases derived from sulpha drugs show high activity. However, the Schiff base L_1 are observed to be the more active (80-85%) against *Mucor and Candida albicans.*

The antimicrobial activity of the ligands are enhanced due to the mode of action of the ligands through the azomethine group with the active centers of cell constitutions, resulting in an interference with the normal cell process.

The enhancement of antimicrobial activity of the ligands as compared to sulpha drugs may be explained on the basis of Overtone's concept. According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favours the passage of only lipid soluble materials due to which liposoluble is considered to be an important factor that controls the antimicrobial activity. The large ring size of ligand moiety makes the complexes more lipophilic. This increased lipophilicity enhances the penetration of the Schiff bases into lipid membranes of the microorganisms and block metal binding sites in the enzymes.

The Schiff bases also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism. The variation in the activity of different compounds against different organisms depend either on the impermeability of the cells of the microbes or difference in ribosomes of microbial cells. Apart from this, other factors such as solubility, conductivity may also be the possible reasons for increasing this activity.

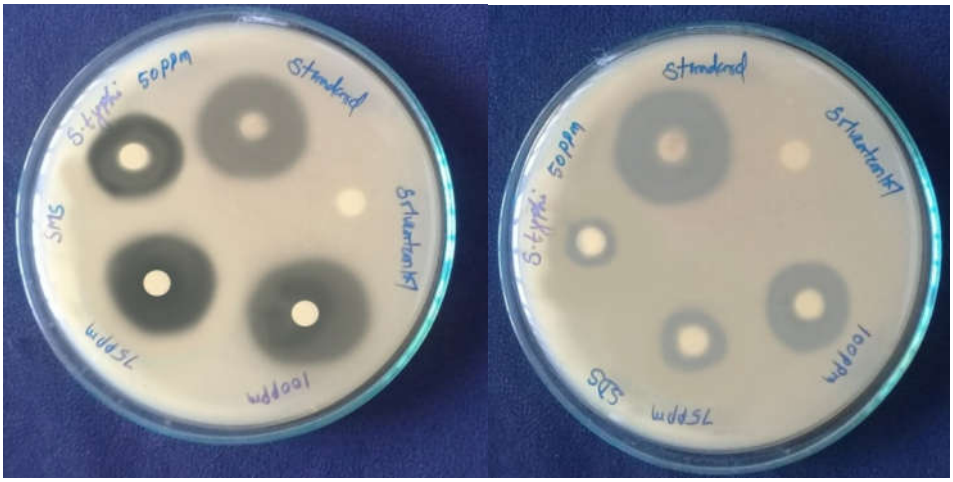


Figure 6. In *vitro* antibacterial screening of Schiff bases against *Salmonella typhi*.

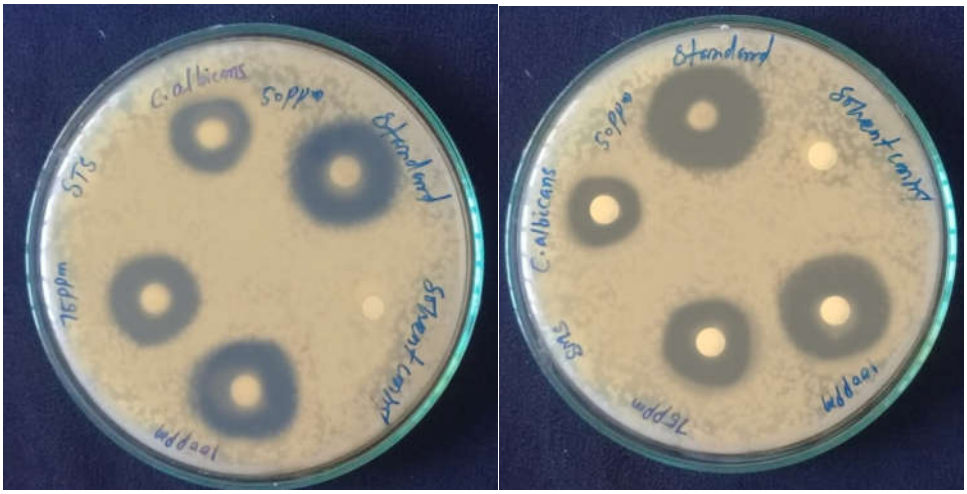


Figure 7. In *vitro* antifungal screening of Schiff bases against *Candida albicans*.

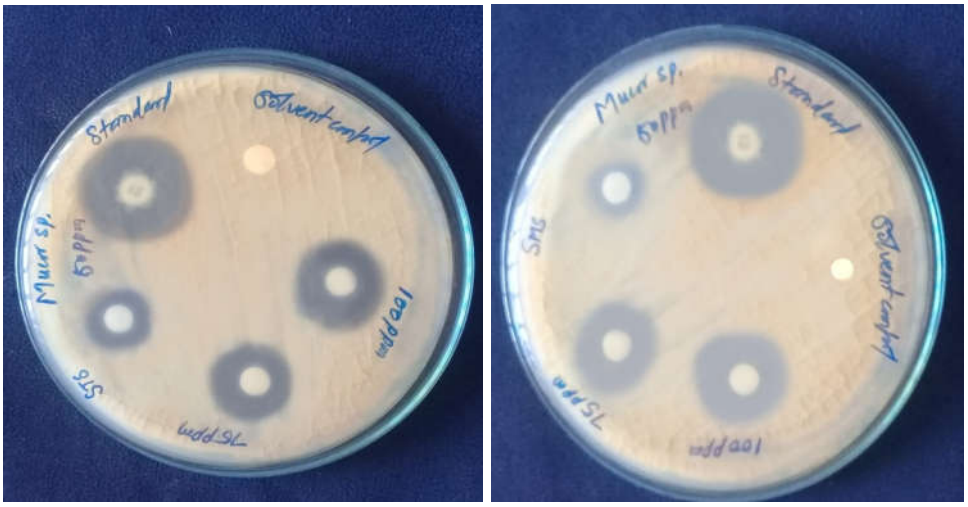


Figure 8. In *vitro* antifungal screening of Schiff bases against *Mucor*.

Minimum inhibitory concentration

The data obtained after preliminary antimicrobial screening showed that the following complexes were most active against the specified species. (1) Even at lower concentration, 50 ppm, 4-((2-hydroxybenzylidene)amino)-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide) L_2 are active against *Salmonella typhi* and *Candida albicans*. (2) 4-((2-hydroxybenzylidene)amino)-N-(1,3-thiazol-2-yl)benzenesulfonamide) L_1, 4-((2-hydroxybenzylidene)amino)-N-(5-methyl-1,2-oxazol-3-yl) benzenesulfonamide) L_2 are highly active at 75 ppm against *Salmonella typhi.* (3) The three synthesized Schiff bases exhibited varying degree of inhibitory effects on the *Salmonella typhi* and *Candida albicans.* On comparing the activity of ligands 4-((2-hydroxybenzylidene)amino)-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide) L_2 is more active than the 4-((2-hydroxybenzylidene) amino)-N-(1,3-thiazol-2-yl)benzenesulfonamide) L_1, 4-((2-hydroxybenzylidene)amino)-N-(4,6-dimethylpyrimidin-2-yl) benzenesulfonamide) L_3. The order of activity is $L_2 > L_1 > L_3$. The greater activity of L_2 may be due to the presence of oxazole moiety in the ligand [23].

CONCLUSION

In conclusion, the bidentate coordination ability of the newly synthesized azo Schiff base was proved by IR, UV, NMR and mass spectra confirms two donor sites azomethine nitrogen and phenolic oxygen. The synthesized Schiff bases were subjected to antimicrobial activity at a concentration of 50 ppm. The order of activity is $L_2 > L_1 > L_3$. The greater activity of L_2 may be due to the presence of oxazole moiety in the ligand.

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