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SYNTHESIS, SPECTRAL AND ANTIMICROBIAL ACTIVITY OF NOVEL SCHIFF BASES INCORPORATED WITH BENZOTHIAZOLE

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ABSTRACT

Heterocyclic Schiff bases of benzothiazole were prepared by the reaction of compounds such as heterocyclic amine resacetophenone, 2-hydroxy acetophenone, (pyrrole 2-aldehyde), (pyridine 2-aldehyde), (2-acetyl thiophene), (salicyldehyde), thiophene 2-aldehyde and 2-amino, 6-sulfamyl benzothiazole were refluxed. All these newly synthesized compounds were characterized by elemental analysis, spectral data and also screened for antimicrobial activity.

Key words: Benzothiazole, Heterocyclic Schiff bases, Spectral analysis, Antimicrobial study.

INTRODUCTION

In the recent years, there has been considerable interest in the chemistry of transition metal complexes of Schiff's bases[1,2]. They have played important role in the coordination chemistry[3]. Studies during the past few years on Schiff bases containing chelating groups in their structures (especially nitrogen, oxygen and sulphur) have attract attention, due to its activity as electrochemical compounds[4], photo-chromism[5], determining of some cations[6], complexing towards heavy metals[7], antimicrobial activities[8], intermediates for synthesis of heterocyclic compounds containing sulphur and nitrogen atoms[9] and catalytically active materials in asymmetric catalysis[10]. In this respect, encourage us to synthesis, spectroscopic and antimicrobial studies of some new heterocyclic Schiff bases. The structures of the compounds were characterized by using IR, NMR, Mass.

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EXPERIMENTAL

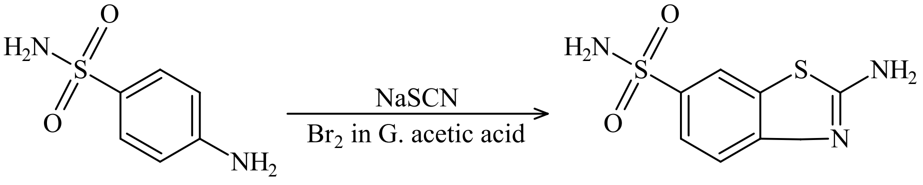
All the melting points were determined in an open capillary tube and are uncorrected. Completion of the reaction was monitored by thin layer chromatography on pre-coated sheets of silica gel-G. IR spectra were recorded on Shimadzu-FTIR spectrophotometer using KBr pellet method. ^{1}H-NMR spectra were recorded using TMS as an internal standard. The mass spectra were on Shimadzu-GC-MS spectrometer.

Synthesis of Schiff bases

In the present work, we have reported some new Schiff bases synthesized by the condensation of 2-amino-6-sulfamyl benzothiazole and respective hydroxy ketones, aldehydes.

(a) Synthesis of Benzothiazole

Synthesis of 2-Amino-6-sufamyl-benzothiazole was carried out by the method reported by Rojer Adams[11]. The method of thiocynation and bromination was adopted. (0.1 M) sulfanilamide and sodium thiocyanate (0.2 M) in 100 mL glacial acetic acid are mixed together maintaining 0°C temperature. (0.2 M) bromine in acetic acid (25 mL) was added to the above solution drop wise and the mixture was stirred continuously by a mechanical stirrer till the complete addition of bromine. The temperature was maintained below 10°C. The solid thus obtained after complete addition of bromine was filtered so as to remove excess of bromine and then dissolved in hot water. Again, it was filtered and filtrate then treated with alkali like NaOH or KOH for the precipitation of free base. The precipitate thus obtained was filtered, washed and dried. The product was recrystallized from ethanol M.P. 105°C, Yield –40%.

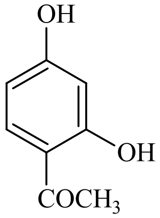


Sulfamyl amide

2-Amino-1,3-benzothiazole-6-sulfon amide
or 2-amino 6-sulfamyl benzothiazole

(b) Synthesis of Resacetophenone

The method of synthesis of resacetophenone was as given by Vogel[12]. $ZnCl_2$ (40 g) and glacial acetic acid (20 mL) were taken in a round bottom flask. The contents in the flask were refluxed till whole of the $ZnCl_2$ dissolved. The dissolved $ZnCl_2$ was then added to the resorcinol (20 g) beaker with constant stirring. Heating of the contents in the beaker was done on a sand bath till the separation of the solid. Solid thus obtained was then removed from sand bath 1:1 HCl (50 mL) solution was added to it. It was then allowed to cool, filtered, washed with water, dried and recrystallized from 10% HCl. M.P. 140°C, yield – 75-80%.



Resacetophenone

(c) Synthesis of Schiff bases

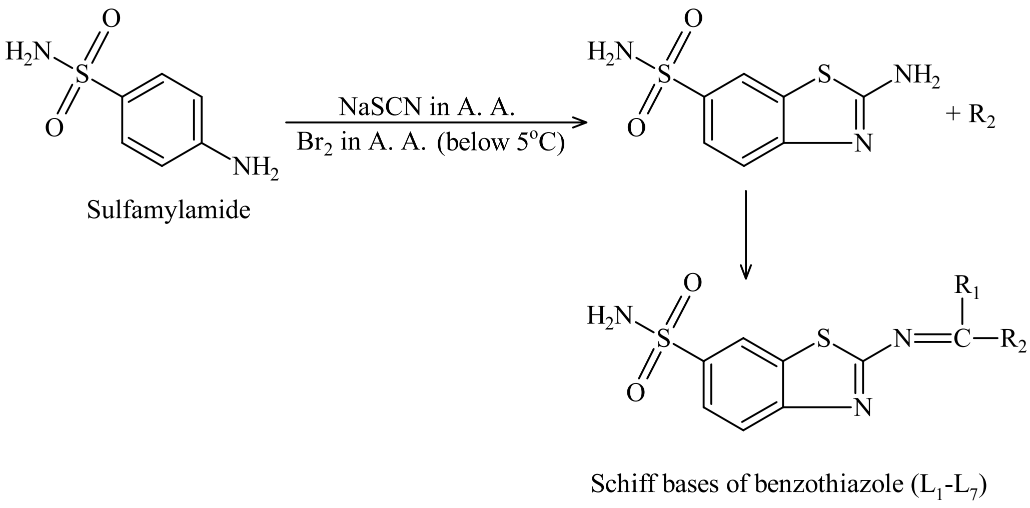
Schiff bases were synthesized by taking equimolar ethanolic solutions of heterocyclic amine and hydroxyketone/aldehyde in 50 mL ethanol and refluxing for 3-4 hrs. The reaction progress was monitored by TLC. After confirming the completion of the reaction by TLC, the reaction mixture was poured on crushed ice or cold water and the solid separated was then filtered, washed with distilled water and dried, recrystallised from ethanol. The product collected was tested for $–NH_2$ group, >C=O group, -SCN group, -OH group for the sake of the purity of the product.

Synthesis of L_1, L_2 and L_5

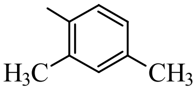
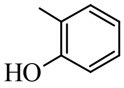
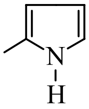
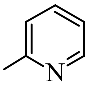
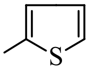
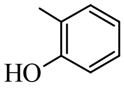
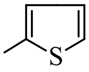
Equimolar ethanolic solutions of the heterocyclic amine i.e., 2-amino-6 sulfamyl benzothiazole and (L_1) resacetophenone, (L_2) 2-hydroxy acetophenone, (L_5) 2-acetyl thiophene was refluxed on water bath for 3-4 hrs. Then the reaction mixture was poured on ice cold water/crushed ice and then the separated solid was collected by filtration, washing and drying, recrystallized from ethanol. The melting points were also recorded.

Synthesis of L_3, L_4, L_6 and L_7

Equimolar ethanolic solution of L_3 (pyrrole 2-aldehyde) L_4 (pyridine 2-aldehyde) L_6 (salicyldehyde) and L_7 (thiophene 2-aldehyde) and 2-amino, 6-sulfamyl benzothiazole were refluxed for 3-4 hrs on water-bath and the reaction mixture was poured on ice cold water and the separated solid was collected by filtration, washing and drying, recrystallised from ethanol and M.P. were also recorded.



Scheme

S. No.	Compound	Substituents	
		R_1	**R_2**
1	**L_1**	**CH_3**	
2	**L_2**	**CH_3**	
3	**L_3**	**H**	
4	**L_4**	**H**	
5	**L_5**	**CH_3**	
6	**L_6**	**H**	
7	**L_7**	**H**	

Characterisation of Schiff bases

The characterization of Schiff bases was done by analytical and spectral methods. The synthesized Schiff bases are found to be stable in air and moisture, soluble in ethanol, chloroform, DMF and DMSO and insoluble in water. The structural features of the Schiff bases are elucidated with the help of elemental and spectral analysis.

(a) Elemental analysis

The elemental analysis of Schiff bases was carried out by micro compound method using CHNS, EA-1108 analyser. The melting points were reported by open capillary method. The data of elemental and analytical analysis is tabulated in Table 1.

Table 1: Physical and analytical data of synthesized Schiff bases (Ligands)

S. No.	Comp.	Mol. formula	Mol. wt.	Yield %	Colour	M.P. (^{o}C)	Elemental analysis in% Found (Cal.)		
							C	H	N
1	**L_1**	$C_{15}H_{13}O_4N_3S_2$	363	40	Pale Gold	180	49.37 (49.58)	3.75 (3.58)	11.65 (11.57)
2	**L_2**	$C_{15}H_{13}O_3N_3S_2$	347	45	Vanilla	170	51.59 (51.87)	3.83 (3.74)	12.34 (12.10)
3	**L_3**	$C_{12}H_{10}O_2N_4S_2$	306	70	Pink orange	160	46.87 (47.05)	3.47 (3.26)	18.49 (18.30)
4	**L_4**	$C_{13}H_{10}O_2N_4S_2$	318	40	Royal Yellow	165	48.98 (49.05)	3.21 (3.14)	17.77 (17.61)
5	**L_5**	$C_{13}H_{11}O_2N_3S_3$	337	45	yellow	180	46.11 (46.29)	3.32 (3.26)	12.63 (12.46)
6	**L_6**	$C_{14}H_{11}O_3N_3S_2$	333	45	Topaz	175	50.22 (50.45)	3.42 (3.30)	12.82 (12.61)
7	**L_7**	$C_{12}H_9O_2N_3S_3$	323	45	Brown	180	44.23 (44.58)	2.97 (2.78)	13.12 (13)

(b) Spectral analysis

The IR spectra were recorded by Shimadzu-FTIR spectrophotometer by KBr pellet method. ^{1}H-NMR spectra were recorded at IICT, Hyderabad using TMS as an internal standard. The mass spectra were recorded at IICT, Hyderabad on Shimadzu-GC-MS spectrometer. The values for respective spectra for compounds are given below, which are in good agreement with that of the theoretical values, which specifies the structures of the synthesized compounds.

Spectral data of synthesized Schiff bases

(i) L_1

IR (KBr) ʋ in cm^{-1}: 3416 (-NH_2 and –OH), 2925 and 2855 (aliphatic -C-H), 1603 (-C=C- ring), ~1580 (-C=N- azomethine), 1519 (- C=N- ring stretch), 1325 (asymmetric strecth -SO_2), 1158 (symmetric stretch SO_2), 1241 (phenolic -OH), 909 and 832 (C-H out of plane), 832-740 (thiazole C-S-C); ^{1}H-NMR δ ppm: 7.00-8.3 (m, Ar – H), 5.3 (s, Ar–O– H), 5.3 (s, Ar–O– H), 2.6 (s – NH_2), 0.9 (s – CH_3). Mass (M/z) 363.

(ii) L_2

IR (KBr) ʋ in cm^{-1}: 3320-3269 - (-NH_2 and –OH), 2925, 2855(aliphatic - C-H), 1600, (-C=C-), ~1580 (-C=N- azomethine), 1519 (-C=N- ring stretch), 1325 (asymmetric strecth - SO_2) and 1158 (symmetric strecth -SO_2), 1241 (phenolic -OH), 909 and 832 (C-H out of plane bend), 832-740 (thiazole C-S-C); ^{1}H-NMR δ ppm: 6.9-8.2 (m, Ar-H), 5.3 (s,-OH), 2.5 (s-NH_2), 0.9 (s, -CH_3); Mass (M/z) % rel. Intensity: 347.

(iii) L_3

IR (KBr) ʋ in cm^{-1}: ~3400-3295 (NH_2), 2923-2855 (aliphatic-C-H stretch), 1598 (C=C), 1586 (C=N azomethine), 1519 (C=N ring stretch), 1326 (asymmetric stretch -SO_2), 1160 (symmetric stretch -SO_2), 910-826 (C-H out of plane bend) 780-735 (C-S-C); ^{1}H-NMR δ ppm: 7.2-8.3 (m, Ar-H), 6.2 (s, = C-H), 5. (s, N-H) 2.5 (s -NH_2); Mass (M/z) % rel. intensity: 307.

(iv) L_4

IR (KBr) ʋ in cm^{-1}: ~3330-3253 (-NH_2), ~3000 (Ar-C-H), ~2925 and ~2855 (aliphatic -C-H), 1592 (C=N azomethine), 1515 (–C=N ring stretch), 1330 (asymmetric strecth -SO_2), 1156 (symmetric stretch SO_2), 904 and 831 (C-H out of plane), 831-741 (thiazole C-S-C); ^{1}H-NMR δ ppm 7.2-8.4 (m, Ar-H), 6.2 (s, =C-H), 2.5 (s -CH_3); Mass (M/z) % rel. Intensity: 318.

(v) L_5

IR (KBr) ʋ in cm^{-1}: ~3340-3261 (NH_2), ~3000 (Ar-C-H), 2923 and ~2860 (aliphatic C-H), 1630 (C=C), 1593 (C=N azomethine), 1517 (C=N ring stretch), 1325 (asymmetric stretch SO_2), 1157 (symmetric stretch SO_2), 908 and 830 (C-H out of plane), 830-736 (thiazole C-S-C); ^{1}H-NMR δ ppm 7.2, 8.30 (m, Ar-H), 2.3 (s, – NH_2), 1.00 (s, – CH_3); Mass (M/z) % rel. Intensity: 337.

(vi) L_6

IR (KBr) υ in cm^{-1}: ~3380 and 3295 (-NH_2 and –OH), ~3000 (Ar-C-H), 2925 and 2855 (aliphatic -C-H), 1599 (C=C), 1592 (C=N azomethine), 1521 (–C=N ring stretch), 1328 (asymmetric strecth -SO_2), 1161 (symmetric stretch SO_2), 910 (C-H out of plane), 735 (thiazole C-S-C); ^{1}H-NMR δ ppm: 7.3, 8.6 (m, Ar-H), 6.00 (s, = C-H), 5.1 (s, -OH), 2.5 (s, NH_2); Mass (M/z) % 333.

Antimicrobial activity

Antifungal activity was performed by poison plate method. The medium used was Potato Dextrose Agar (Himedia). The medium was prepared and sterilized at 10 Psi in autoclave for 15 minutes. Then the compound to be tested is added to the sterile medium in aseptic condition so as to get final concentration as 1%. A plate with DMSO was prepared as blank (negative control). Similarly a plate with 1% Grysofulvin was prepared as standard reference plate (positive control). *Aspergillus niger*, *Pencillium chrysogenum*, *Fusarium moneliforme*, *Aspergillus flavus* were selected as test fungal cultures. They were allowed to grow on slant for 48 hrs so as to get profuse sporulation. 5 mL of 1:100 aqueous solution of teen 80 was added to the slant and spores were scraped with the help of nicrome wire loop to form suspension. The fungal suspension was spot inoculated on the plate's prepared using compound with the help of nicrome wire loop. The plate was incubated at room temperature for 48 hrs. After incubation plates were observed for the growth of inoculated fungi. Results were recorded as a growth of fungi (no antifungal activity), reduced growth of fungi (moderate antifungal activity), and no growth of inoculated fungi (antifungal activity).

The cup plate agar diffusion method[13,14] was employed for determining the antibacterial activity of the newly synthesised ligands. The antibacterial activity was measured by agar cup method. Nutrient agar (Himedia) was prepared and sterilized at 15 Psi for 15 minutes in the autoclave. It was allowed to be cool below 45°C and seeded with turbid suspension of test bacteria separately prepared from 24 hrs old slant cultures. 3% incula were used every time. The bacterial culture selected where, two gram negative culture viz. Staphylococcus aureus, Bacillus subtilis. This seeded preparation was then poured in sterile Petri plate under aseptic condition and allow it to solidify. Cup of 10 mm diameter were borered in the agar plate with sterile cork borer. 100 µL of compound solution prepared in dimethyl sulphoxide (1%) was added in the cup under aseptic condition with the help of micropipette.100 µL of DMSO was also placed in one of the cup as a blank (negative control). A standard antibiotic disk impregnated with 10 units of pencillin was also placed on the seeded nutrient agar surface as standard reference antibiotic (positive control).

The plates were kept in refrigerator for 15 minutes to allow diffusion of the compound from agar cup into the medium. Then the plates were shifted to incubator at 37°C and incubated for 24 hrs. After incubation plates were observed for the zone of inhibition of bacterial growth around agar cup. Results were recorded by measuring the zone of inhibition in milimeters (mm) using zone reader.

Table 2: Antimicrobial activity

S. No.	Compound	Fungal Strain				Bacterial Strain			
		An	Pc	Fm	As	Ec	St	Sa	Bs
1	L_1	RG	-ve	RG	+ve	14	18	-ve	17
2	L_2	+ve	RG	+ve	RG	15	24	-ve	30
3	L_3	RG	RG	RG	+ve	20	15	12	20
4	L_4	+ve	+ve	+ve	+ve	18	-ve	20	19
5	L_5	+ve	RG	+ve	RG	16	-ve	16	18
6	L_6	RG	RG	+ve	+ve	17	-ve	19	19
7	+ve Control	+ve	+ve	+ve	+ve	NA	NA	NA	NA
8	-ve Control (Grysofulvin)	-ve	-ve	-ve	-ve	NA	NA	NA	NA
9	DMSO	NA	NA	NA	NA	-ve	-ve	-ve	-ve
10	Penicillin	NA	NA	NA	NA	13	22	36	18

Ec-E.coli, *St-S.typhi*, *Sa- S.aureus*, *Bs-B.subtilis*; *An-A.niger*, *Pc-P.chrysogenum*, *Fm-F.moneliformae*, *Ca-C.albicans*; -ve: No growth of fungi,+ve; Growth of fungi, RG-Reduced growth, NA-Not Applicable, Zone of inhibition was measured in mm

RESULTS AND DISCUSSION

In this present paper, a series of various substituted Schiff bases were synthesized. The products were confirmed by their spectral analysis. Appearance of IR bands at 3416-3295 cm^{-1} (-NH_2 and-OH) and 1518-1599 cm^{-1} (>C=O) supported the structure. ^{1}H NMR spectra, the multiplate around the δ 6.9-8.6 ppm assigned to the aromatic protons. The -OH proton appeared as singlet at δ 5-5.3 ppm, -NH_2 proton appeared as singlet at δ 2.3-2.5 ppm, while other aliphatic protons are appeared at excepted regions. The mass spectra of the compounds showed corresponding molecular ion peaks, which was correlated with their molecular weight of that respected compound. The results of antimicrobial data revealed that most of the compounds were found to be active against all the tested fungi and bacteria.

CONCLUSION

In summary, we have synthesized some novel heterocyclic Schiff bases. All the synthesized compounds gave satisfactory spectral and analytical data. The screening of antimicrobial data revealed that most of the compounds showed good antifungal and antibacterial activity.

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