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Synthesis and characterization of Schiff base ligands and their antimicrobial activity

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ABSTRACT

A new Schiff base ligand derived from sulphonamide salicylaldehyde and substituted salicylaldehyde have been synthesized. The ligands were characterized by M.P, elemental analysis, TLC and IR spectra. The Schiff base ligands were screened for antifungal activity against Aspergillus niger and antibacterial activity tested against Escherichia coli

Keywords: Schiff base, antibacterial, fungicidal activity

INTRODUCTION

The sulphonamide functional group is $S(=O_2)$-NH_2,a sulfone group connected to an amine group. A sulphonamide is a compound that contains this group. The general formula is RSO_2NH_2 where R is some organic group. Sulphonamides were amongst the first clinically useful antibacterial agents to be discovered[1]. The antibacterial sulphonamides continue to play an important role in chemotherapy, alone or in combination with other drugs[2-4].
Sulphonamides were discovered by Gerhard Domagk, a young physician on the staff of Bayer Laboratory in Elberfeld, Germany in December 1932[3]. His work, incidentally brought him a Nobel Prize in 1939.He tested a new red dye named Protonsil ruburum containing sulphonamide group on mice. It was soon learned that the protonsil was degraded in vivo to sulphonamide which leads to the activity of protonsil as drug is due to presence of sulphonamide group.

This drug is now generally accepted as of great value in the treatment of many infections, especially those due to betahaemolytic streptococci, especially in streptococcus septicemia, meningitis, pharyngitis, tonsillitis, otitis media, mastoiditis, puerperal fever and erysipelas. It is also potent against the meningococcus the majority of organism causing urinary infections[5]. The name sulphanilamide for para amino-sulphonamide has been adopted by the council of pharmacy of the American Medical Association[5]. The antibacterial sulphonamides continue to play an important role in chemotherapy, alone or in combination with other drugs[6, 7, 8].

Schiff bases derived from sulphonamides have also acquired wide interest in connection to biological systems. Most of their complexes proved to be biologically active (antibacterial, hypoglycemic and anti-inflammatory) is evidenced by pharmacological tests[9].

MATERIALS AND METHODS

This section describes the experimental methods used for the synthesis of sulphonamide and it's Schiff bases.For the sake of convenience Schiff bases in the present work are divided into groups.

1) Those which are prepared by salicylaldehyde
2) Those which are prepared by substituted salicylaldehyde i.e.2,4-dihydroxybenzaldehyde.

Group A-
R_1-4-(2'-hydroxybenzylidene amino)benzene sulphonamide
R_3-2-methyl-5-(2'-hydroxybenzylidene amino) benzene sulphonamide
R_5-2-methoxy-3-(2'-hydroxybenzylidene amino) benzene sulphonamide

Group B-
R_2-4-(2' 4'-dihydroxybenzylidene amino) benzene sulphonamide
R_4-2-methyl-5-(2' 4'-dihydroxybenzylidene amino) benzene sulphonamide
R_6-2-methoxy-3-(2' 4'-dihydroxybenzylidene amino) benzene sulphonamide

Preparation of p-acetamidobenzene sulphonyl chloride-
Dry acetanilide (0.1ml)was taken in a 500ml two necked flask with a dropping funnel and a reflux condenser. The top of the reflux condenser was attached to a device for absorption of HCl gas. Chlorosulphonic acid (0.52 mol) was placed in a dropping funnel and calcium chloride guard tube was inserted into the dropping funnel. Chlorosulphonic acid was added in small portions and the flask was shaken to ensure thorough mixing. When the addition was completed; the reaction mixture was heated on a water bath for one hour in order to complete the reaction. The reaction mixture was allowed to cool at room temperature; then the oily mixture was poured in a thin stream with stirring into 300 gm crushed ice. This operation was carried out carefully in a fume cupboard since the excess of chlorosulphonic acid reacts with water vigorously. The solid i.e. p-acetoamido benzene sulphonyl chloride was filtered off at the pump and washed with cold water. The crude product was used immediately for the next step.

A) **Preparation of p-acetamidobenzene sulphonamide-**
Crude p-acetamidobenzene sulphonyl chloride was taken in a beaker. A mixture of (47.5 ml) conc. ammonia solution and (47.5 ml) water was added in a beaker. The contents were mixed thoroughly and heated for 15 mins.in a water bath. The suspension was cooled in ice bath. The product i.e. P-acetamidobenzene sulphonamide was filtered off and washed with cold water. The crude product was used for the next step.

B) **Preparation of p-amino benzene sulphonamide-**
The crude product of p-acetamidobenzene sulphonamide,10ml of concentrated hydrochloric acid and 30ml of water was taken in a round bottomed flask. The reaction mixture was boiled gently under reflux for 30-45 mins. Then allowed to cool at room temperature and 2 gm decolorizing carbon was added in a cooled solution. The solution was heated and filterer off with suction. The filtrate was cooled and solid sodium bicarbonate was added to make the solution neutral. The product was filtered, washed with water and recrystallized from alcohol.

C) **Preparation of Schiff bases-**
P-amino benzene sulphonamide (0.1mol)and catalytic amount of zinc chloride was taken in a round bottomed flask. Salicylaldehyde (0.1mol) dissolved in ethanol was added slowly to the round bottomed flask. The resulting mixture was refluxed for 2-3 hours at 60-70^{O} C. Then resulting mixture was allowed to cool at room temperature, solid product of Schiff base separated out was filtered and washed with ethanol. The Schiff bases thus formed were crystallized in to fine yellow crystals. The purity was checked by melting points, elemental analysis, and TLC and IR spectra.

The ligands prepared are

	Ligand	
	Group A	
R_1	4-(2'-hydroxybenzylidene amino) benzene sulphonamide	$C_{13}H_{12}O_3N_2S$
R_3	2-methyl-5-(2'-hydroxybenzylidene amino) benzene sulphonamide	$C_{14}H_{14}O_3N_2S$
R_5	2-methoxy-3-(2'-hydroxybenzylidene amino) benzene sulphonamide	$C_{14}H_{14}O_4N_2S$
	Group B	
R_2	4-(2',4'-dihydroxybenzylidene amino) benzene sulphonamide	$C_{13}H_{12}O_4N_2S$
R_4	2-methyl-5-(2',4'-dihydroxybenzylidene amino) benzene sulphonamide	$C_{14}H_{14}O_4N_2S$
R_6	2-methoxy-3-(2',4'-dihydroxybenzylidene amino) benzene sulphonamide	$C_{14}H_{14}O_5N_2S$

The general structural formulae for the Schiff bases are represented in fig 2.1

RESULTS AND DISCUSSION

ANALYTICAL DATA OF THE SCHIFF BASES

Sr No	Ligand	M.P. ^{O}C	% of carbon		% of hydrogen		% of Nitrogen		% of Sulphur	
			cal	found	cal	found	cal	found	cal	found
R1	$C_{13}H_{12}O_3N_2S$	156 ^{O}C	56.52	56.00	4.34	4.45	10.14	10.25	11.59	11.50
R_2	$C_{13}H_{12}O_4N_2S$	150 ^{O}C	53.42	53.53	4.11	4.14	9.59	9.45	10.95	11.00
R_3	$C_{14}H_{14}O_3N_2S$	Decomposes at 130 ^{O}C	57.93	57.24	4.83	4.82	9.65	7.25	11.03	11.20
R_4	$C_{14}H_{14}O_4N_2S$	172 ^{O}C	54.90	54.75	4.58	4.61	9.15	9.00	10.46	10.60
R_5	$C_{14}H_{14}O_4N_2S$	176 ^{O}C	54.90	54.75	4.58	4.67	9.15	9.00	10.45	10.25
R_6	$C_{14}H_{14}O_5N_2S$	132 ^{O}C	52.17	52.30	4.34	4.24	8.70	8.60	9.94	9.99

Aspergillus niger-

Conidia of *Aspergillus niger* are always present in the air and cause contamination in laboratory cultures of bacteria and fungi. It is also called as 'weed of the laboratory'. Over 30 species of *Aspergillus niger* have been recorded so far in India. Thom and Raper [10] recognized more than 78 species of *Aspergillus.*

These are of great importance because of their harmful as well as useful activities. When *Aspergillus* infects lungs in human being[11] the symptoms resemble tuberculosis[12].

*Aspergilli*are now known to produce several deadly toxins on various food feed-stuffs which when eaten cause mycotoxicoses in animals and human beings. The fungi are always associated with fruits, vegetables. Food grains during storage and cause spoilage to these stored products. Strains of *Aspergillus niger* are used in the manufacture of citric acid, gluconic acid and itanoic acid [13]. Species of *Aspergillus* are used for hydrolysis of starch in alcoholic fermentation by yeasts. Itis used in the study of many biological processes and can detect even very minute qualities of trace elements Cu, Mn, Fe, Zn, Mo etc.in an unknown sample.

STUDY OF ANTIFUNGAL ACTIVITY OF SCIHFF BASES AGAINST *A .NIGER*

Sample No	Mycelial dry weight(in mg)at		
	Conc (250 ppm)	Conc (500 ppm)	Conc (1000 ppm)
Control(C)	60	60	60
R_1	34	25	18
R_2	45	54	69
R_3	73	66	41
R_4	85	101	45
R_5	65	39	85
R_6	51	80	61

Antibacterial activity-

Antibacterial activity of all ligands, sulphonamides and substituted sulphonamides against *Escherichia Coli* species were screened by disc diffusion method. The test compounds were dissolved in THF. For each compound 100ug/ml was taken for microbial screening against the *Escherichia Coli.* The bacteria were maintained in Nutrient agar Medium (NAM). Aseptic techniques were employed to prepare the culture medium of the test microorganisms were maintained on nutrient agar slant at 4^{o}C temperature.

Table 2. Antibacterial activity of ligands at concentration 100ug/ml at temperature 37°C+1°C and at 28 hours
Test species - Escherichia Coli

	Test compound	Diameter of inhinbition zone (mm)
1	Control Ciprofloxacin	30
2	p-amino benzene sulphonamide	25
3	2-methyl-5-amino benzene sulphonamide	22
4	2-methoxy-3-amino benzene sulphonamide	20
5	4-(2' -hydroxybenzylidene amino) benzene sulphonamide	15
6	4-(2' 4'-dihydroxybenzylidene amino) benzene sulphonamide	15
7	2-methyl-5-(2' -hydroxybenzylidene amino) benzene sulphonamide	13
8	2-methyl-5-(2' 4'-dihydroxybenzylidene amino) benzene sulphonamide	11
9	2-methoxy-3-(2' -hydroxybenzylidene amino) benzene sulphonamide	10
10	2-methoxy-3-(2' 4'-dihydroxybenzylidene amino) benzene sulphonamide	09

From the table 2.20 it can be seen that all ligands show antibacterial activity against *Escherichia Coli.* As substitution on sulphonamide moiety increases it's antibacterial activity decreases .The Schiff bases have less antibacterial activity than its parent sulphonamides.

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