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Synthesis and Antibacterial Study of Some Schiff Bases Complexes

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Abstract. Novel Schiff bases *(E)*-N-(4-chlorobenzylidene)-2-(2,4-dichlorophenyl) acetohydrazide and *(E)*-2-(2,4-dichlorophenyl)-N'-((1-methoxynaphthalen-2-yl)methylene) acetohydrazide were synthesized and further used for the synthesis of metal complexes. All these synthesized Schiff bases and metal complexes were characterized and screened for antimicrobial activity against bacteria *Escherichia coli, Pseudomonas aeruginosa,* and *Bacillus subtilis*.

Keywords: Schiff bases, metal complex, antimicrobial activity etc.

1 Introduction

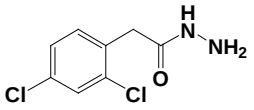
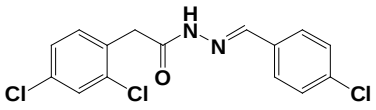
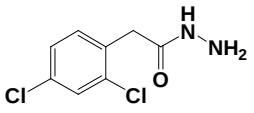
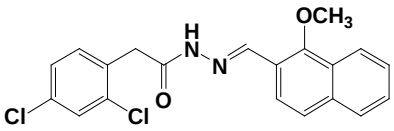
Schiff bases and their complexes are of high interest among the researchers because of their biological activity including anti-tumor, antibacterial, fungicidal, antidepressants, antiphlogogistic, nematocide, anti-carcinogenic and catalytic activity [1-2].

The microorganisms adsorb metal ions on their cell walls and through respiration process of cells these ions are disturbed and the process of protein synthesis is blocked which is the requirement for further growth of organisms. Gram-negative bacteria membrane is surrounded by an outer lipopolysaccharide membrane. Schiff base metal complexes combine with the lipophilic layer to enhance the membrane permeability of the Gram-negative bacteria. The lipid membrane surrounding the cell favours the passage of lipid soluble materials only; thus the lipophilicity is an important factor that controls the antimicrobial activity. Increase in lipophilicity enhances the penetration of Schiff base and its metal complexes into the lipid membranes and thus restricts growth of the organism [3].

Synthesis of new coordination compounds for cobalt (II), nikel (II) and copper (II) with Schiff base ligand derived from 4-Amino antipyrine, sulphadiazine and acetoacetanilide has been studied [4]. Copper (II) complexes derived from 4-nitro-2-[(2-diethylaminoethylimino)-methyl]-phenol as the Schiff base ligand was reported by Wei *et al.* [5]. Metal complexes of Fe (II), Co (II), Ni(II), Cu(II), Zn(II) or Cd (II) with Schiff base like N-(2-thienylmethylidene)-2-aminopyridine have been studied by Spinu *et al* [6]. Synthesis and antibacterial activity of schiff bases and transition metal complexes derived from 2, 3-diminopyridine and ortho-vanillin has been studied by Henri *et al.*[7]. Anil Kumar *et al.* [8] described the synthesis and antimicrobial activity of new metal [Mg(II), Fe(II), Co(II), Ni(II), Zn(II) and Cd(II)] complexes from 2-(1'/2'-hydroxynaphthyl) benzoxazoles. Gudasi *et al.*[9] synthesized and studied biological activity of dioxouranium(II) and thorium(IV) complexes of Schiff base derived from 2-amino pyridine and acetophenones. Chittilappilly *et al.* [10] have reported the synthesis and biological activity of ruthenium (III) Schiff base complexes derived from 3-hydroxy quinoxaline-2-carboxaldehyde and salicylaldehyde. In continuation of our previous work [11-12], we prompted to synthesize new Schiff bases and their complexes.

Herein, we synthesized novel Schiff bases *(E)*-N-(4-chlorobenzylidene)-2-(2,4-dichlorophenyl) acetohydrazide and *(E)*-2-(2,4-dichlorophenyl)-N'-((1-methoxynaphthalen-2-yl)methylene) acetohydrazide by the condensation of novel hydrazides with aromatic aldehydes Table 1.

Table 1. List of the synthesized Schiff base ligands

Entry	Hydrazides	Schiff base	Time (h)	Yield (%)
1			5	80
2			6	85

These Schiff base ligands were heated with different metals for the formation of corresponding complexes. Further the Schiff bases and complexes were screened for antimicrobial activity against bacteria *Escherichia coli, Pseudomonas aeruginosa,* and *Bacillus subtilis.*

2 General Procedure for the Synthesis of Schiff Base

In order to prepare Schiff base firstly esters of substituted phenylacetic acid were prepared, which were further reacted with hydrazine hydrate to obtain hydrazides from which Schiff base were prepared.

a) General procedure for the synthesis of esters:

To a magnetically stirred ice cold solution of carboxylic acid (20 mmol) in methanol (20 mL), a catalytic amount of concentrated H_2SO_4 (2-3 drops) was added dropwise. The contents were gently warmed to room temperature and then refluxed for 2-3 h. After completion of the reaction as indicated by TLC (20% ethyl acetate: n-hexane); excess methanol was removed under reduced pressure on rotary evaporator. The reaction mixture was cooled to 0 °C, basified with saturated aqueous $NaHCO_3$ and finally extracted with dichloromethane (3x15 mL). The combined organic layer was washed with water, separated, dried over sodium sulphate and concentrated on rotary evaporator to afford the corresponding esters as oily liquids (**Table-1**).

b) General procedure for the synthesis of hydrazides:

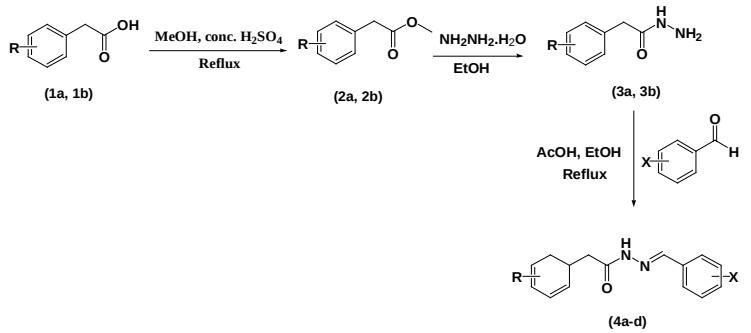
A mixture of carboxylic ester (20 mmol) and hydrazine hydrate (100 mmol) was refluxed at 100 °C for 1h. Progress of the reaction was monitored by TLC (50 % ethyl acetate: n-hexane). After completion of reaction; the excess amount of hydrazine hydrate was evaporated under reduced pressure. The crude product was triturated with petroleum ether under ice-cold condition, washed several times with water and dried by toluene azeotrope to get the corresponding hydrazide as the crystalline white solid.

c) General procedure for the synthesis of Schiff base:

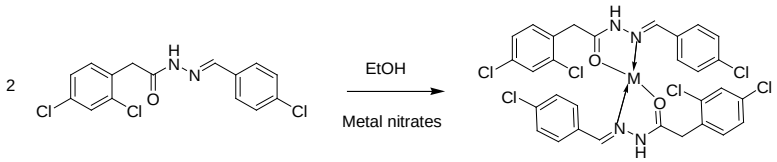
To an equimolar mixture of aldehyde (2 mmol) and hydrazide (2 mmol) in ethanol (5 mL), 2-3 drops of glacial acetic acid were added at room temperature and the content was refluxed till completion of reaction for appropriate time as specified in **Table-1**. After completion of the reaction as monitored by TLC (3:7 ethyl acetate : n-hexane), excess of ethanol was evaporated on rotary evaporator and the contents of the flask poured over crushed ice. The solid obtained was filtered, washed with cold water, dried and finally recrystallized from chloroform: hexane (1:1).

3 General Procedure for Preparation of Schiff Bases Metals-Complex

A mixture of Schiff base (2 mmol) and metal nitrates (1 mmol,) in ethanol (5 ml) was refluxed for 6-8 hours. The pH of solution is adjusted to 7-8 by using alcoholic ammonia solution. The progress of reaction is monitored on thin layer chromatography (TLC) using petroleum ether: ethyl acetate (7:3 ml) elute. The colored products were isolated after reduction of volume by evaporation. It was filtered, washed with ethanol, dried under vacuum and further recrystallized in ethanol Table 2.

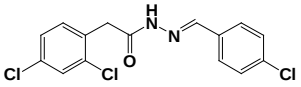
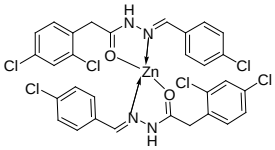
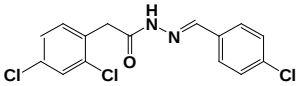
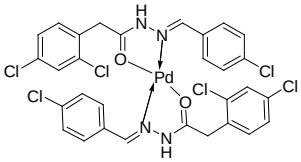
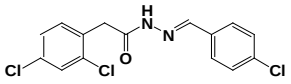
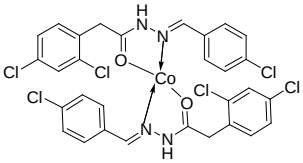
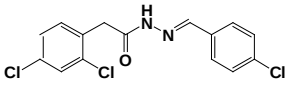
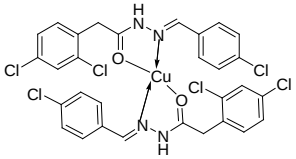
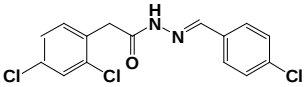
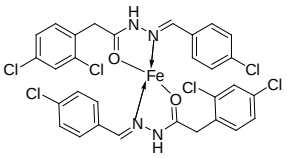


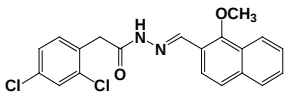
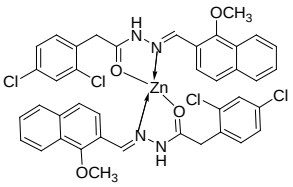
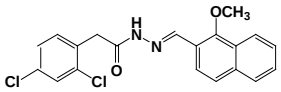
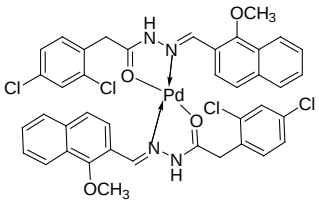
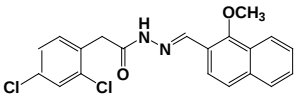
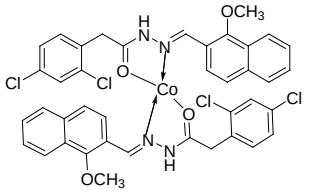
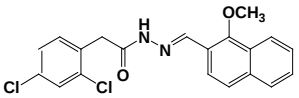
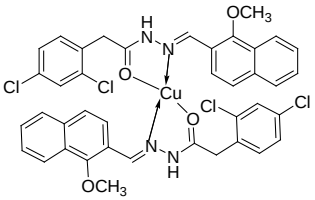
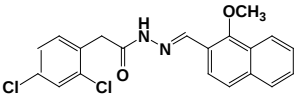
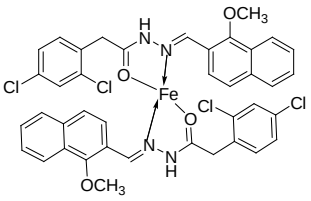
Scheme 1



Scheme 2

Table 2. List of synthesized Schiff base metal complexes

Entry	Schiff base	Complex	Time (h)	Yield (%)
1			7.0	80
2			8.0	78
3			6.5	85
4			6.0	91
5			6.5	90

6			6.5	82
7			7.5	85
8			7.0	87
9			6.5	90
10			7.0	89

Spectral Analysis of Schiff Bases:

(2,4-Dichloro-phenyl)-(4-chloro-benzylidene)-acetohydrazide:

IR v max cm^{-1} 767, 824, 1099, 1250, 1384, 1560, 1609, 2972, 3099; ^{1}H NMR (400 MHz, DMSO-d6) δ ppm δ 2.5 (s, 2H, Ar-CH_2-), δ 4.2 (s, 1H, -NH-N-), δ 7.35-7.80 (m, 7H, Ar-H), δ 8.05 (s, 1H, -N=CH); ^{13}C NMR (400 MHz, DMSO-d6) δ ppm 40, 127.53, 128.81, 129.11, 129.33, 132.55, 133.16, 133.56, 133.99, 134.68, 135.30, 142.3, 145.61, 165.68, 171.24; EI-MS: m/z (% Relative intensities) 341.2 (96%), 339(100%).

(2,4-Dichloro-phenyl)-(1-methoxy-naphthalen-2-ylmethylene)-acetohydrazide:

IR v max cm^{-1} 754, 812, 1084, 1196, 1261, 1378, 1595, 1669, 2896, 2983, 3084; ^{1}H NMR (400 MHz, DMSO-d6) δ ppm δ 2.45 (s, 3H, Ar-OCH_3), δ 3.60 (s, 2H, Ar-CH_2-), δ 4.0 (b, 1H, -NH-N-), δ 7.25-7.65 (m, 9H, Ar-H), δ 8.78 (s, 1H, -N=CH); ^{13}C NMR (400 MHz, DMSO-d6) δ ppm 40, 48.5, 113.80, 124.40, 124.48, 125.55, 126.22, 128.36, 128.43, 129.18, 131.45, 132.74, 133.13, 135.21, 141.57, 144.60, 157.98, 158.16, 166.46, 172.12; EI-MS: m/z (% Relative intensities) 388 (M+, 65 %), 385.3 (100%).

Spectral Analysis of Metal Complexes:

Characterization of all the prepared hydrazone-based Schiff base ligands complexes with metals Zn(II), Pd(II), Co(II), Cu(II), and Fe(II) were done.

Bis-(2,4-Dichloro-phenyl)-(4-chloro-benzylidene)-acetohydrazide copper complex:

IR v max cm^{-1} 470, 530, 767, 824, 1099, 1250, 1380, 1560, 1609, 2972, 3099; ^1H NMR (400 MHz, DMSO-d6) δ ppm δ 2.47 (s, 2H, Ar-CH_2-), δ 7.35-7.84 (m, 7H, Ar-H), δ 8.09 (s, 1H, -N=CH); Metal Cu %: 7.65 %; UV λmax: 323 nm; XRD: monoclinic.

4 Antibacterial Activity

Antibacterial activity of synthesized Schiff bases and their complexes has been screened against bacteria *Escherichia coli, Bacillus subtilis & Salmonella aeruginosa.* Selective media (HiMedia) were used for each type of bacteria.The antibacterial activity was evaluated using agar plate method. Agar plate's surface was inoculated by spreading a standardized inoculum of the test microorganism over entire surface. Then, a hole with a diameter of 6 mm is punched aseptically with a sterile cork borer or a tip, and a volume (20 µL) of the test compound solution is introduced into the well. The Petri dishes are incubated under suitable conditions. The test compounds diffuse into the agar and inhibits germination and growth of the test microorganism and then the diameters of inhibition growth zones are measured as a zone of inhibition [13, 14]. Results of the ligands and complexes prepared were showed moderate to excellent activity as compared to standard Penicillin Table 3.

When compared with standard drug as penicillin the compound A8 does not show any antibacterial activity against all three types of bacteria. Compound A6 shows week antibacterial activity. Compound A1, A2 and A4 show comparable antibacterial activity against *Escherichia coli* and *Bacillus subtilis* but not for *Pseudomonas aeruginosa.* On the other hand compound A9 possesses comparable activity against *Escherichia coli and Pseudomonas aeruginosa* but not against *Bacillus subtilis.*

Table 3. Anti-bacterial activity of ligand and complexes

Sr. No.	Compound	Zone of inhibition (mm)		
		Escherichia coli	*Pseudomonas aeruginosa*	*Bacillus subtilis*
1	L1	15	17	20
2	L2	10	12	29
3	A1	20	22	27
4	A2	20	25	25
5	A3	19	17	22
6	A4	25	19	30
7	A5	18	19	25
8	A6	05	08	11
9	A7	16	13	18
10	A8	00	00	00
11	A9	22	29	21
12	A10	17	19	18
Std.	Penicillin	23	28	30

5 Conclusion

In conclusion we have synthesized novel Schiff bases and their metal complexes. These synthesized metal complexes were screened for antibacterial activity and found to exhibit good to moderate activity for complex A1, A2, A4 and A9. Complex A8 does not show any antibacterial activity while compound A6 showed very week antibacterial property. All other compounds were variable but have less than standard antibacterial activity.

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