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Antifungal Activities of Some Divalent and Trivalent Metal Chelates with 2-aminobenzoic acid and Schiff base derived from 4-dimethylaminobenzaldehyde and 2-aminophenol

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ABSTRACT: Five metal chelates of Co(II), Ni(II), Cu(II), Zn(II) and Cr(III) ions with mixed ligands of a Schiff base: Namely, (E)-2-(4-(dimethylamino)benzylidene)amino)phenol derived from 4-dimethylaminobenzaldehyde and 2-aminophenol as main ligand (HL1) and 2-aminobenzoic acid as co-ligand (HL2) have been synthesized and characterized by using several physiochemical tools. An octahedral structure was suggested for all the chelates. The antifungal activity the ligands and their mixed ligand chelates against some pathogenic fungi was studied by using agar well diffusion method. The obtained data showed that some of the chelates have most active against *A. niger, A. flavus, Alternaria alternata, Rhizopus stolonifer***.**

Keywords: Schiff base; fungicidal; 2-aminobenzoic acid and Antifungal Activity.

INTRODUCTION: The modified bio-ligands has increased and played a good rule in coordination chemistry[1]. The extensive characterization has been observed for potential biological activities of chelates. Schiff bases have very important role due to their physiological and pharmaceutical activities and also they are of well known structures for antimicrobial and antiviral agents[2]. Many metal chelates of Schiff bases were reported and exhibiting that their biological activities are more active than free Schiff bases. This attributed to complexation formation which decreases the polarity of the metal ions[3]. Five divalent transition metal chelates with a Schiff base formed from the reaction of 5-phenyl-1,3,4-thiadiazol-2-amine with 4-ethoxy-3-hydroxybenzaldehyde have been synthesized and investigated by using several techniques. The used techniques displayed the proper geometrical structures of the chelates. The synthesized Schiff base and its chelates were screened for their antifungal activity against *A. nigar, C. Albicans and C. Krusei* using Fluconazole as standard drug. It was found that the synthesized chelates exhibiting enhanced antifungal activity as compared to the free Schiff base[4]. Nair et al.,[5] Prepared and characterized four chelates with a Schiff base derived fromindole-3-carboxaldehyde and m-aminobenzoic acid. The antimicrobial studies of the Schiff base and its chelates were reported by diffusion method. The obtained data exhibited that the chelates were found to be more active than the free Schiff base.

The present study aims to study the effect of the Schiff base, 2-aminobenzoic acid and their mixed ligand chelates with Co(II), Ni(II), Cu(II), Zn(II) and Cr(III) ions on some fungi *A. niger, A. flavus, Alternaria alternata, Rhizopus stolonifer*

MATERIAL AND METHODS:

Synthesis of the Schiff base and its mixed ligand chelates: The Schiff base Namely: [(E)-2-((4-(dimethylamino)benzylidene)amino)phenol] derived from 4-dimethylaminobenzaldehyde and 2-aminophenol (Figure 1), 2-aminobenzoic acid (Anthranilic acid), Schiff base (HL1) and their mixed ligand chelates with Co(II), Ni(II), Cu(II), Zn(II) and Cr(III) ions were reported[6] (Figure 2).

Fungal species: Four test organisms, *Aspergillus niger, Aspergillus flavus, Alternaria alternata* and *Rhizopus stolonifer* were obtained from the Laboratory of Applied Microbiology, University of Omar AL-Mukhtar, Baida, Libya. They were cultured in Petri plates containing Potato dextrose agar (PDA) media

and incubated at 27°C for three days with periodic sub–culturing at 4°C.

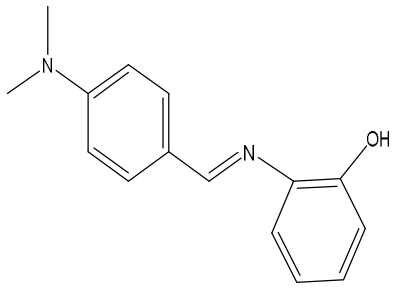
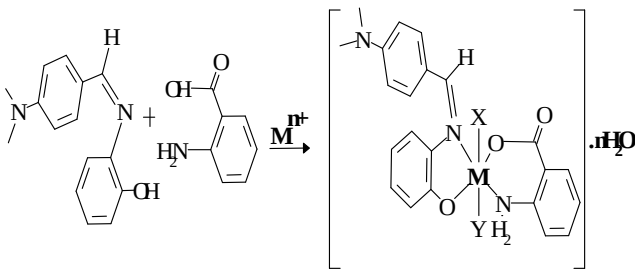


Figure1: Schiff base: (E)-2-((4-(dimethylamino) benzylidene) amino)phenol=HL1.

Screening for Antifungal Assay: ***Antifungal activity test:*** The antifungal activity of the ligands and their mixed ligand chelates were evaluated by the agar well diffusion method[7-9]. All fungi were subcultured and prepared for the assessment of ligands and their mixed ligand chelates activity. The compounds were dissolved in DMF solution. The PDA medium was poured into the sterile petriplates and allowed to solidify. The inoculum used was prepared using the fungal species from a 72 hour culture on (PDA). The fungal suspension of each test fungi was evenly spread over the media by sterile cotton swabs. The plates have been kept to dry and a sterile cork borer (7mm in diameter) was then used to punch wells in the agar medium. Subsequently, wells were filled with 20µl of each compound at various concentrations of 20, 40 and 60 mg/ml and allowed to diffuse at room temperature for 15 min. The plates were incubated at 27°C for 48-72 hrs. After the incubation, the plates were observed for formation of clear inhibition zone around the well indicated the presence of antifungal activity. The zone of inhibition was measured with a ruler.

RESULTS AND DISCUSSION: The combination of a Schiff base (HL1) and 2-aminobenzoic acid (HL2) with the metal ions [Co(II), Ni(II), Cu(II), Zn(II) and Cr(III)] ions is shown below:



M= Co(II), Ni(II), Zn(II) , X, Y= H_2O

M= Cr(III), X = H_2O , Y = OH^-
n = 1 for Ni(II) chelate and 6for Cr(III), Co(II) and Zn(II) chelates

Figure 2: The combination between the Schiff base and 2-aminobenzoic acid and the suggested geometrical structure for the complexes.

Synthesized and investigated of mixed ligands chelates above were reported in our study[6]. The ligands and their metal chelates were also evaluated for their ability to inhibit growth of bacteria[6].

Antifungal Activity: The Schiff base, 2-aminobenzoic acid ligands and their mixed ligands chelates were evaluated for their antifungal activities against fungal species named; *Aspergillus niger, Aspergillus flavus, Alternaria alternata* and *Rhizopus stolonifer*. The results of the antifungal activity of the Schiff base, 2-aminobenzoic acid ligands and their mixed ligand chelates against all tested fungal species are shown in Table 1, Charts (1-4) and Plates (1-4). The DMF solvent is used as negative control.

The ligands and their mixed ligand chelates show variable antifungal activities against the fungal species and increased in higher concentration.

All compounds (two ligands, solvent (DMF) and chelates) no activity observed against *A. flavus.*

Schiff base (HL1) exhibits moderate activity against *A. niger, Alternaria alternata* and *Rhizopus stolonifer*, but no activity observed against *A. flavus.*

The 2-aminobenzoic acid (HL2) did not show any activity against all a tested fungi.

The $[Ni(L1)(L2)(H_2O)_2].H_2O$ chelate reveals a moderate activity against *A. niger, Alternaria alternata* and *Rhizopus stolonifer*, but there is no activity against *A. flavus*.The$[Co(L1)(L2)(H_2O)_2]6H_2O$ and $[Zn(L1)(L2)(H_2O)_2]$ $6H_2O$ chelates display a moderate activity against *Rhizopus stolonifer*, less activity against *A. niger*, but had no activity against *A. flavus* and *Alternaria alternate* in all concentrations used.

The $[Cr(L1)(L2)(OH)(H_2O)]6H_2O$ chelate according to the results presented in table 1, it was found that this chelate has no effect on the tested fungi in all concentrations used. Generally, the ligands and their metal chelates were evaluated for their ability to inhibit growth of fungi in the following order; Schiff base HL1 ≈ $[Ni(L1)(L2)(H_2O)_2]H_2O$>$[Co(L1)(L2)(H_2O)_2]6H_2O$≈ $[Zn(L1)(L2)(H_2O)_2]6H_2O$>$[Cr(L1)(L2)(OH)(H_2O)]6H_2O$ = 2-aminobenzoic acid = DMF(control) See Table 1.

Table 1: Antifungal activity of the Schiff base, 2-aminobenzoic acid ligands and their mixed ligand chelates.

S.No.	Fungal sp. / Compounds	Diameter of inhibition zone of fungi (mm)											
		Concentration in mg/mL											
		A. niger			*A. flavus*			*Alternaria alternata*			*R. stolonifer*		
		20	**40**	**60**	**20**	**40**	**60**	**20**	**40**	**60**	**20**	**40**	**60**
1	Schiff base L1	10	11	13	-	-	-	-	16	17	8	11	13
2	2-aminobenzoic acid (L2)	-	-	-	-	-	-	-	-	-	-	-	-
3	$[Ni(L1)(L2)(H_2O)_2]H_2O$	9	9	13	-	-	-	9	16	19	12	13	15
4	$[Co(L1)(L2)(H_2O)_2]6H_2O$	-	4	8	-	-	-	-	-	-	-	10	14
5	$[Zn(L1)(L2)(H_2O)_2]6H_2O$	6	6	8	-	-	-	-	-	-	8	10	13
6	$[Cr(L1)(L2)(OH)(H_2O)]6H_2O$	-	-	-	-	-	-	-	-	-	-	-	-
7	DMF	-	-	-	-	-	-	-	-	-	-	-	-

Control (DMF): = No activity (there is no zone of inhibition)

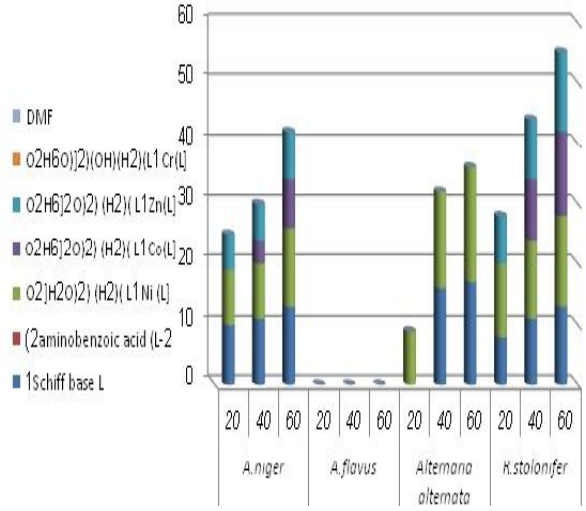


Chart 1: Chart of comparison of all compounds against the four fungal species in (Concentration 20, 40 and 60 mg/mL via DMF as control.

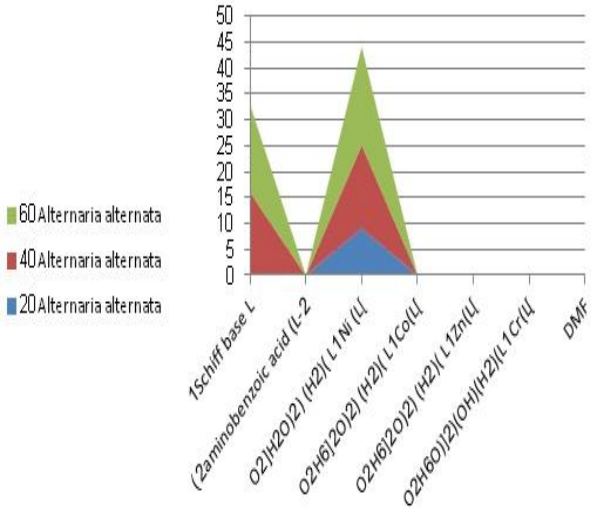


Chart 3: Chart of comparison of all compounds against the *Alternaria alternata* in (20, 40, 60) mg/ml concentration via DMF as control.

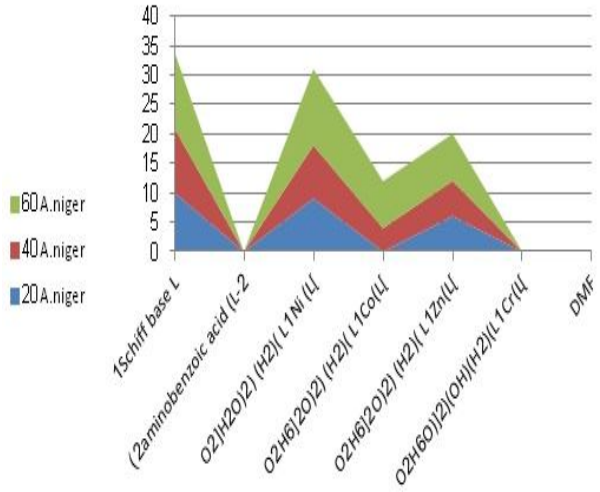


Chart 2: Chart of Comparison of all compounds against the *A. niger* in (20, 40, 60) mg/ml concentration via DMF as control.

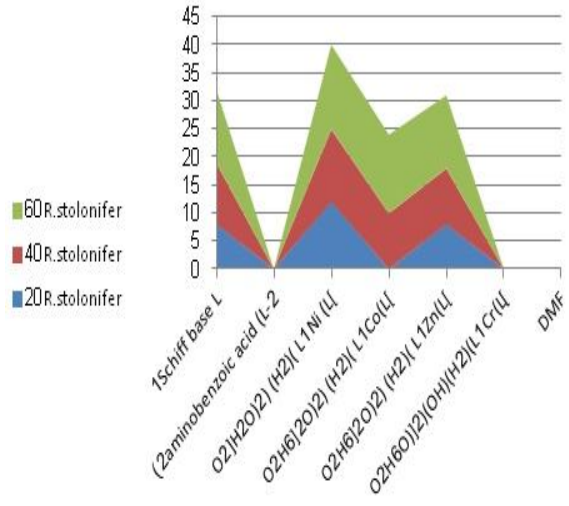


Chart 4: Chart of comparison of all compounds against the *R. stolonifer* in (20, 40, 60) mg/ml concentration via DMF as control.

The biological activity of a Schiff base is altered many fold on its coordination with suitable metal ions. The increase in antifungal activity of the metal chelate may be due to the effect of a decrease in the polarizability of the metal could enhance the lipophilicity of the chelates, which leads to a breakdown of the permeability of the cells, resulting in interference with normal cell processes[10-13], or cell permeability is an important factor that control antifungal activity. The lipid membrane that surrounds the cell favors the passage of lipid soluble materials[14, 15].

The introduction of nitrogen atoms into the structure of organic compounds often resulted in important changes in their behavior towards metal ions.

In case of $[Cr(L1)(L2)(OH)(H_2O)].6H_2O$ Chelate and 2-aminobenzoic acid, many investigations were under taken of the interaction of metal ions with ligands containing oxygen(-OH-group) and nitrogen ($-NH_2$) as donor atoms[16-19].

CONCLUSION: The mixed Co(II), Ni(II), Cu(II), Zn(II) and Cr(III) ions chelates of the Schiff base derived from 4-dimethylaminobenzaldehyde with 2-aminophenol and 2-aminobenzoic acid are non-electrolytes, Schiff base behaves as uninagative bidentate ligand and is coordinated to the central metal ion through the nitrogen atom of azomethine group and oxygen atom of phenol group. 2-aminobenzoic acid ligand coordinated to the metal ion as uninagative bidentate ligand through the oxygen atom in the carboxyl group (COO^-) and the nitrogen atom of the $-NH_2$ of the ligand in chelation process. The antifungal activity of the Schiff base and its mixed ligand chelates are shown in plates 1-4.

Plate 1: Effect of Schiff base (HL1) on 1- *Aspergillus niger*, 2-*Alternaria alternata* and 3- *Rhizopus stolonifer* at 20, 0 and 60 mg/ml concentration, respectively (from right to left) compared with control.

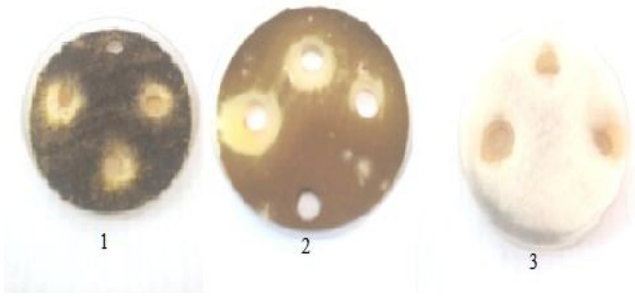


Plate 2 : Effect of [Ni (L1)(L2) $(H_2O)_2$]H_2O on 1- *Aspergillus niger*, 2-*Alternaria alternata* an 3- *Rhizopus stolonifer* at 20, 40 and 60 mg/ml concentration, respectively (from right to left) compared with control.

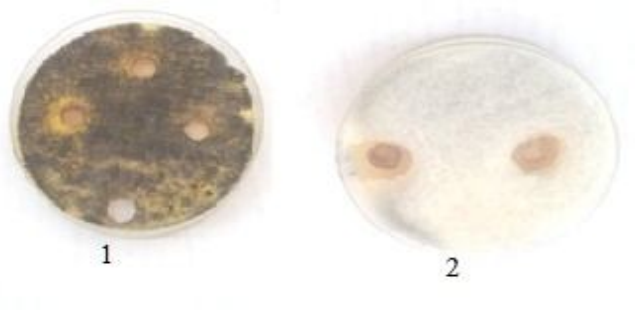


Plate 3: Effect of [Co(L1)(L2) $(H_2O)_2$]$6H_2O$ on 1- *Aspergillus niger* and 2- *Rhizopus stolonifer* at 20, 40 and 60 mg/ml concentration, respectively (from right to left) compared with control.

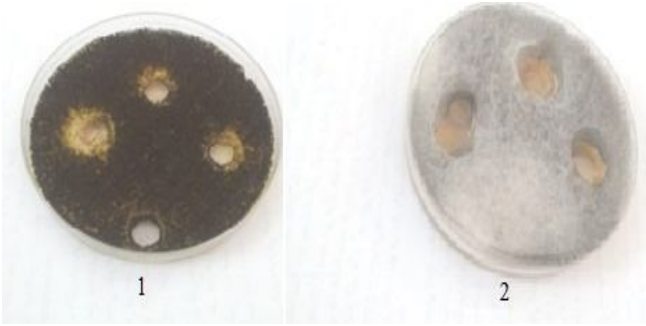


Plate 4: Effect of [Zn(L1)(L2) $(H_2O)_2$]$6H_2O$ ion on 1- *Aspergillus niger* and 2-*Rhizopus stolonifer* at 20, 40 and 60 mg/ml concentration, respectively (from right to left) compared with control.

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