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Synthesis, Characterization and Antimicrobial Studies of Co(II), Ni(II), Cu(II) and Zn(II) Complexes of (E)-2-(4-Dimethylbenzydimino)-Glycylglycine, (Glygly-DAB) a Schiff Base Derived from 4-Dimethylaminobenzaldehyde and Glycylglycine

Maurice Kuate[1,2], Mariam Asseng Conde[2*], Katia N. Nchimi[1], Awawou G. Paboudam[1], Sally-Judith E. Ntum[1], Peter T. Ndifon[1]

[1]Department of Inorganic Chemistry, Faculty of Science, University of Yaounde 1, Yaoundé, Cameroon
[2]Department of Chemistry, Faculty of Science, University of Douala, Douala, Cameroon
Email: *conde_mame@yahoo.fr

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Abstract

A tridentate Schiff base ligand, (E)-2-(4-dimethylbenzydimino) glycylglycine (glygly-DAB), derived from the condensation of 4-Dimethylaminobenzaldehyde (DAB) and glycylglycine (glygly) together with its Co(II), Ni(II), Cu(II) and Zn(II) complexes have been synthesized and characterized using various physico-chemical methods including C,H,N elemental analysis, melting point determination, molar conductivity measurement, IR, ^{1}H NMR and UV-Vis. The ligand and metal complexes were screened *in vitro* for antimicrobial and antifungal activities on four bacterial strains (*Staphylococcus aureus*, *Escherichia coli*, *Salmonella thyphi and Pseudomonas aeruginosa*) and two fungal strains (*Candida albicans and Cryptococcus neoformans*). glygly-DAB showed remarkable antifungal activities on all the fungal strains and antibacterial activities on one bacterial strain.

Keywords

Schiff Base Ligand, Glycylglycine, Complexes, Antimicrobial Activities, Spectroscopy

1. Introduction

Schiff bases are an important class of ligands due to their synthetic flexibility, their selectivity, their ability to act as multidentate N- and O-donor ligands and their structural resemblance to natural biological substances [1] [2]. Schiff bases have been shown to exhibit a broad range of potential applications because of the diversity observed in their structures [1]-[6]. They are good chelators forming stable coordination compounds with transition metal ions using mostly the imine linkage, characteristic of the Schiff bases [1] [2] [3] [4]. The azomethine (N=CH-) linkage is essential for biological activity [6] [7] [8].

The emergence of drug-resistant bacterial strains has become a world-wide cause for concern [4]-[9]. The increasing resistance of microbes to antibacterial and antifungal drugs has necessitated the search for new compounds to target pathogenic microbes. The incorporation of metal-based systems into antibacterial molecules is expected to enhance the bactericidal or fungicidal properties of these drugs. Complexes of Schiff bases derived from amino acids have been extensively studied as potential antibacterial, antifungal and anticancer agents [4] [10] [11] [12]. Considerable effort has been devoted to the synthesis, characterization, and antimicrobial properties of metal complexes of Schiff bases derived from amino acids [4] [12] but little attention has been paid to systems involving simple peptides [13]. We report here the synthesis, characterization and antimicrobial activity of a Schiff base derived from the peptide, glycylglycine and 4-Dimethylaminobenzaldehyde and its Co(II), Ni(II), Cu(II) and Zn(II) complexes.

2. Experimental

2.1. Materials and Methods

All reagents were analytical grade, obtained from commercial sources and were used without further purification. The metal contents in the complexes were estimated by complexometric titrations. C, H and N elemental analyses were performed using a PE 2400 CHN/O/S Elemental Analyser. IR spectra were recorded using a KBr disc on an ALPHA-P spectrometer obtained from BRUKER in the 3800 ~ 400 cm^{-1} region. Electronic spectra were recorded on a HACH DR-3900 UV/VIS spectrometer. Molar conductance measurements of aqueous solutions of the complexes (10^{-3} M) were measured using a CD810 Solea Tacussel conductivity meter. The melting points of the compounds were determined using a KOFLER bench from LEICA VMHB. The micro-organisms were obtained from the Phytobiochemistry Laboratory of the University of Yaoundé 1.

2.2. Synthesis

2.2.1. Synthesis of Schiff Base Ligand, Glygly-DAB

The Schiff base ligand, glygly-DAB was synthesized according to the general synthetic procedure [7] [8] by the condensation of glycylglycine with

4-Dimethylaminobenzaldehyde.

An ethanolic solution of 4-Dimethylaminobenzaldehyde (5 mmol) was added drop wise to a solution of glycylglycine (5 mmol) and KOH (5 mmol) in ethanol and the mixture heated under reflux for 3 hours. After concentrating the solution, a yellowish precipitate was obtained which was filtered, washed several times with ethanol and air-dried at room temperature. Yield: 72%, m.p 56˚C; Anal. Calc. (Found): C: 51.81 (51.93); H: 5.35 (5.57); N: 13.94 (13.84). ^{1}H NMR (DMSO; ppm): δ 9.85 (s, 1H; -CH=N); 8.40 (s, 1H; N-H); 7.1 - 7.9 (m, 4H; phenyl ring H); δ 3.2 - 3.4 (s, 4H; $-CH_2$); 2.75 (m, 6H; $-CH_3$).

2.2.2. Synthesis of Metal Complexes

A methanoic solution of the metal Chloride (1 mmol) was added drop wise to a solution of (E)-2-(4-dimethylbenzydimino) glycylglycine (1mmol) in ethanol. The mixture was heated under reflux for 3hours and the coloured precipitates obtained were filtered, washed several times with methanol and air-dried at room temperature.

2.3. Antimicrobial Screening

In vitro Antimicrobial activity of the ligands and corresponding complexes were done in the Laboratory unit of Yaoundé Central Hospital and the phytobiochemistry laboratory of the University of Yaounde 1, and tested against four bacterial species: *Staphylococcus aureus*, *Escherichia coli*, *Salmonella thyphi* and *Pseudomonas aeruginosa* and two fungal species: *Candida albicans* and *Cryptococcus neoformans*.

2.3.1. Screening Method

The antimicrobial and antifungal screening were performed by the disc diffusion method [14]. This technique is based on the antimicrobial and antifungal agent's capacity to distribute to the surfaces of the inoculated nutrient agar, creating a zone of inhibition on the disc of which one can measure the diameter. Gentamycin was used as the standard antibacterial agent while Nystatin was used as the standard antifungal agent.

2.3.2. Preparation of the Discs and Incubation

40 mg of each compound was dissolved in 1 ml of 10% DMSO to obtain a final concentration of 40 mg/ml. A wattman N˚3 filter paper, 5mm diameter was placed on the surface of the sowed medium. 10μl of the compound was then added to every corresponding disc and allowed to stand for 15 minutes for pre-diffusion at room temperature before being hatched at 37˚C for 24 hours for the bacteria and 48 hours for the fungi. Every test was repeated three times. The antimicrobial and antifungal activities of each compound were determined by measuring its inhibition zone diameter in mm and the compounds with an inhibition zone diameter ≥ 13 mm are kept for the determination of their inhibitory minimal concentration [14] [15].

3. Results and Discussions

3.1. Synthesis and Characterization

The physical characterization and analytical data of the ligands and their complexes are given in **Table 1**. The synthesis of the Schiff base ligand was carried out according to the equation in **Figure 1**. The ligands had the characteristic yellow colour of Schiff base ligands and its complexes were all coloured. The Ligand, glygly-DAB melted at melted at 56˚C as shown on **Table 1** whereas the melting points of all its complexes were above 196˚C - 360˚C. glygly-DAB ligand and all its Complexes were soluble in distilled water. The high molar conductance values of all the metal complexes of glygly-DAB indicate that they behave as 1:1 electrolyte [13] as evidenced for the non-involvement of the counter ion group in coordination thus, showing the ionic character of the complexes.

Table 1. Physical properties and analytical data of the ligand and its complexes.

Compounds	Formula	Color	Molar conductance ($\Omega^{-1}\cdot cm^2\cdot mol^{-1}$)	Melting point (˚C)	Analysis % calculated (found)		
					C	H	N
GLYGLY-DAB (L)	$C_{13}H_{16}N_3O_3K$	yellow	/	56	51.81 (51.93)	5.35 (5.57)	13.94 (13.84)
[ZnL(H_2O)]$_2$$SO_4$·2$H_2O$	$ZnC_{13}H_{22}N_3O_{10}S$	white	238.8	>260	32.68 (32.02)	4.64 (5.18)	8.79 (8.93)
[CuL(H_2O)]Cl·5H_2 O	$CuC_{13}H_{20}N_3O_5Cl$	blue	119.2	224	33.27 (33.33)	6.01 (6.08)	8.95 (8.55)
[CoL(H_2O)]Cl·3H_2 O	$CoC_{13}H_{24}N_3O_7Cl$	Pink	159.2	>260	36.42 (36.09)	5.64 (4.13)	9.80 (8.97)
[NiL(H_2O)]Cl·5H_2 O	$NiC_{13}H_{28}N_3O_9Cl$	Pale green	159.0	196	33.61 (33.77)	6.03 (5.21)	9.05 (8.26)

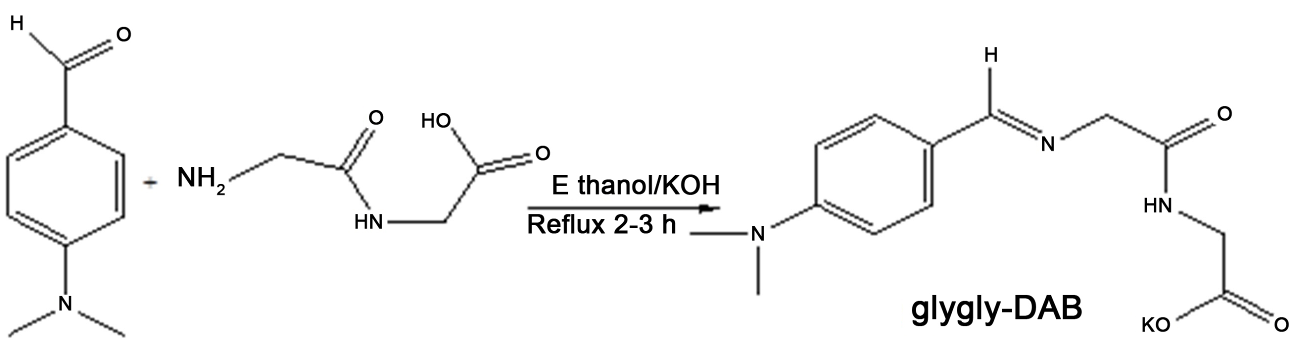

Figure 1. Equation for the synthesis of glygly-DAB.

3.2. ^{1}H-NMR of Glygly-DAB

The ^{1}H-NMR spectrum of *glygly-DAB* was recorded on an AC 250 NMR spectrometer using DMSO as internal standard in the 3 - 10 ppm region.^{1}H-NMR spectrum of *glygly-DAB* shows the azomethine proton (H-C=N) signal at 9.8 ppm and amide proton (-CONH-) signal at 8.4 ppm. The aromatic protons show the multiplet (aromatic-CH, CH-) at 6.8 - 7.5 ppm. The two aliphatic protons (-CH_2-) in the chain show the multiplet signal at 3.2 - 3.7 ppm and the methyl group signal (-CH_3) appear at 2.75 ppm. Based on the above analysis, the ^{1}H-NMR spectrum and proposed structure of glygly-DAB is given in **Figure 2**.

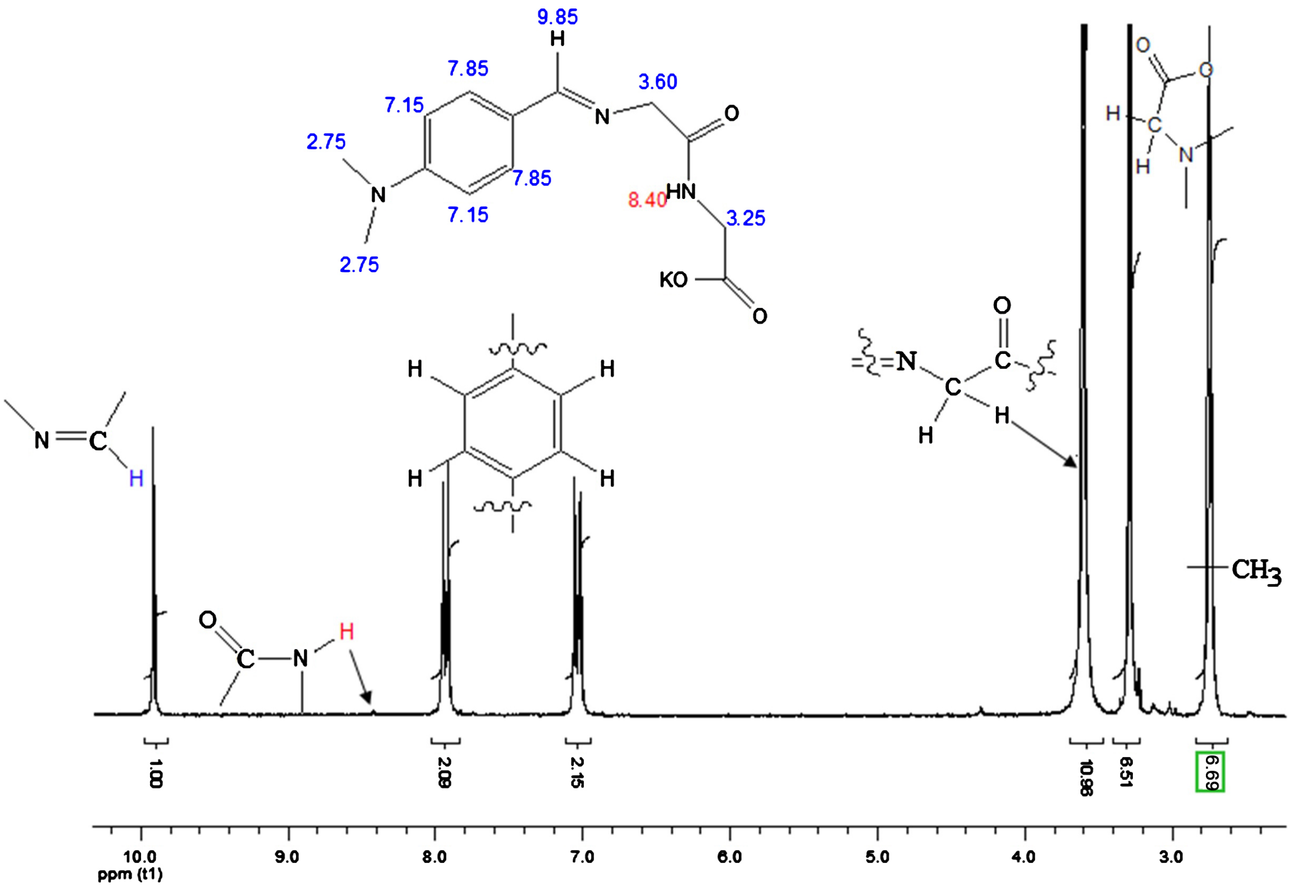

Figure 2. The [1]H-NMR spectrum and proposed structure of glygly-DAB ligand (L).

3.3. Infrared Spectral Studies

The IR spectra of glygly-DAB and its complexes are given in **Figure 3** and the characteristic IR spectral bands are shown in **Table 2**. The Schiff base ligand glygly-DAB show $\nu_{(C=N)}$ azomethine band at 1625 cm^{-1}. Upon complexation, this band is shifted to a lower frequency, indicating that the azomethine nitrogen is coordinated to the metal ions [16] [17]. The peptide (N-H) band appears at 3412 cm^{-1} on the spectrum of the ligand glygly-DAB; which is red shifted on the spectra of the complexes thus confirming the involvement of the peptide nitrogen in bonding to the metal ions [18]. The spectrum of the ligand glygly-DAB also shows a band at 1382 cm^{-1}, attributed to the $\nu_{(C-O)}$ of the carboxyl group which is shifted to a lower frequency on the spectra of the complexes, indicating the coordination of the carboxyl oxygen to the metal ion [18]. The spectra of the complexes present broad bands in the range 3417 - 3301 cm^{-1}, attributed to O-H stretching vibration of coordinated water molecules [2]. The bands at 649 - 465 and 399 - 415 cm^{-1} in the spectra of the complexes absent in the spectrum of the ligand thus suggesting then ν(M-O) and ν(M-N) vibrations respectively [2] [19] [20]. The IR spectra indicate that the Schiff base ligand glygly-DAB in all the complexes is tridentate with the azomethine nitrogen, peptide nitrogen and carboxylato oxygen atoms as binding sites.

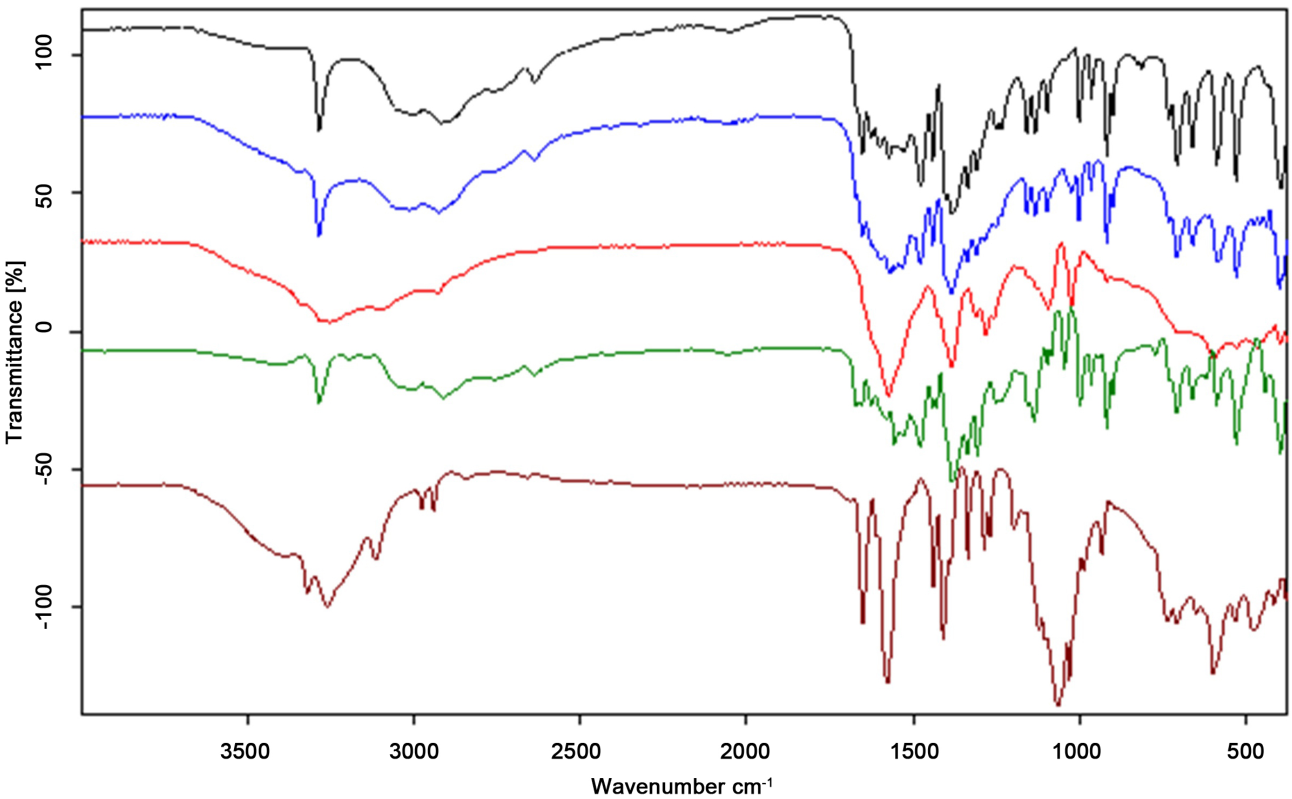

Figure 3. IR spectra of glygly-DAB(L) and its complexes.

Table 2. IR spectral data (cm^{-1}) of Schiff base ligand and its complexes.

composes	$\nu_{(C=N)}$	$\nu_{(N-H)}$	$\nu_{(C-O)}$	$\nu_{(M-O)}$	$\nu_{(M-N)Azomethine}$	$\nu_{(M-N)peptide}$	$\nu_{(O-H)}$
glygly-DAB (L)	1625	3412	1382	/	/	/	/
$[ZnL(H_2O)]_2SO_4$	1587	3385	1064	649	476	415	3303
$[CuL(H_2O)]Cl$	1587	3396	1337	618	442	396	3414
$[CoL(H_2O)]Cl$	1568	3349	1336	475	457	438	3237
$[NiL(H_2O)]Cl$	1585	3334	1280	481	465	399	3301

3.4. Electronic Spectral Measurements

The UV-Visible spectrum of the ligand and its complexes were measured in distilled water at room temperature and the obtained spectra of the complexes are given in **Figure 4**. The UV/Vis spectrum of *glygly-DAB* exhibits an absorption band at 363 nm which can be attributed to a π-π* transition of the azomethine chromophore. Upon complexation, this band was shifted to lower wavelength regions, in the spectra of the complexes suggesting the involvement of azomethine nitrogen in the complexation [7] [8]. The spectrum of Co(II) complex shows a peak with a λ_{max} value of 519 nm attributed to $^4A_2(F) \rightarrow {}^4T_1(P)$ transition; which is indicative of a tetrahedral environment around the metal ion. In general, due to Jahn-Teller distortion, square planar Cu(II) complexes give a broad absorption band between 600 and 700 nm [19] [20]. This is observed in the spectrum of the Cu(II) complex which shows a maximum at 635 nm. The spectrum of Ni(II) complex shows an absorption band at 646 nm. This peak corresponds to the transition ${}^3T_1(F) \rightarrow {}^3T_1(P)$ which indicates the tetrahedral environment of the ligand surrounding Ni(II) in the complex. The four-coordinate Zn(II) complexes would have a tetrahedral geometry. Based on the above characterization, proposed structure of glygly-DAB metal complexes are given in Figure 5.

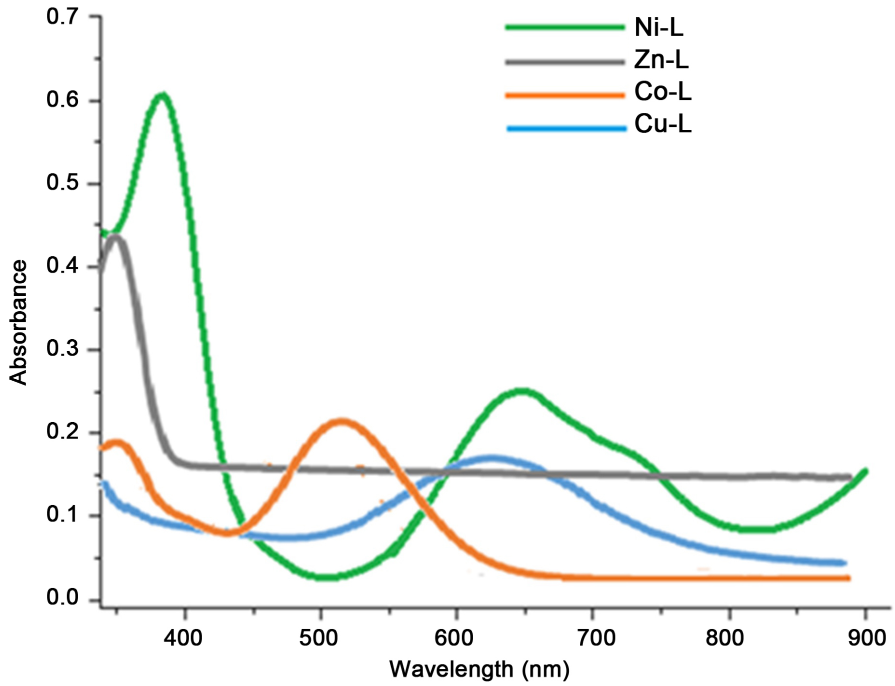

Figure 4. UV-vis spectra of glygly-DAB metal complexes.

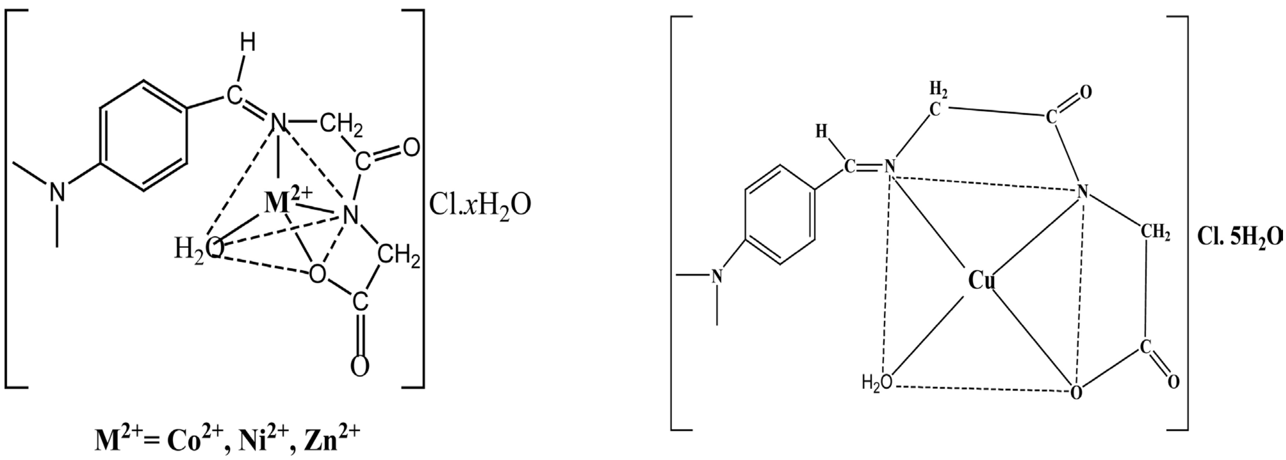

Figure 5. Proposed structures for glygly-DAB metal complexes.

3.5. Antimicrobial Studies

The antibacterial and antifungal activities of glygly-DAB and its metal complexes were tested against *E. coli*, *S. thyphi*, *C. albicans*, *P. aeruginosa*, *S. aureus* and *C.*

néoformans. The susceptibility of these strains of bacteria and fungi towards these compounds was judged from the measurement of the size of the inhibition diameter growth. The results obtained are presented in **Table 3**.

The Schiff base ligand, glygly-DAB was more active against *E. coli*, *S. thyphi*, *C. albicans*, *C. néoformans* and no activity against *P. aeruginosa*, *S. aureus.* The Co(II) complex show greater activity on *E. coli and C. néoformans* than the free ligand *glygly-DAB*. In the same way, the Cu(II) complex shows greater activity on *E. coli*; *P. aeruginosa*; *C. albicans* and *C. néoformans* compared to the free ligands while the Ni(II) complex shows greater activities on *S. thyphi*; *S. aureus and C. néoformans* compared to the free ligands. This increase in activity on chelation might be due to the delocalization of charge on the metal in the chelated complex thus increase in the lipophilic character of the metal chelate. Cu(II) and Ni(II) complexes show better activity on *C. néoformans* than the standard antibiotic, *fluconazole*. Compounds with a diameter of zone of inhibition ≥ 13 mm were used for the determination of their inhibitory minimal concentration.

Table 3. Diameter of inhibition zone (mm).

	Bacterial species				Fungal species	
compound	*E. coli*	*S. thyphi*	*P. aeruginosa*	*S. aureus*	*C. albicans*	*C. néoformans*
glygly-DAB (L)	07	12	00	00	09	13
Zn-*glygly-DAB*	05	00	07	16	00	00
Cu-*glygly-DAB*	09	08	07	00	10	00
Co-*glygly-DAB*	09	09	00	00	00	06
Ni-*glygly-DAB*	00	15	00	00	00	00

3.6. Determination of Minimal Inhibitory Concentration (MIC)

The minimal concentration at which the compound inhibits 100% visible growth of microorganism, (MIC) was further determined using the compounds with a diameter of inhibition zone greater than 13 mm [14]. MIC was determined using the Micro Dilution method in liquid environment. The microorganism was placed in the presence of the antimicrobials (glygly-DAB, Zn-glygly-DAB, Ni-glygly-DAB), in a decreasing order of concentration, in the wells of the micro plates. After incubation, the lowest concentrations of the antimicrobials in which there are no visible growth of the microorganism represent their minimal inhibition concentration. The results given in **Table 4** show that glygly-DAB, Zn-glygly-DAB and Ni-glygly-DAB are the most active against *C. néoformans*, *S. aureus* and *S. thyphi* respectively. **Figure 6** depicts a histogram of the zone of diameter of inhibition.

Table 4. Minimum inhibitory concentration (mg/ml).

Compound	Bacterial species		Fungal species
	S. thyphi	*S. aureus*	*C. néoformans*
glygly-DAB	/	/	2×10^{-2}
Zn-*glygly-DAB*	/	2×10^{-3}	/
Ni-*glygly-DAB*	2.5×10^{-2}	/	/

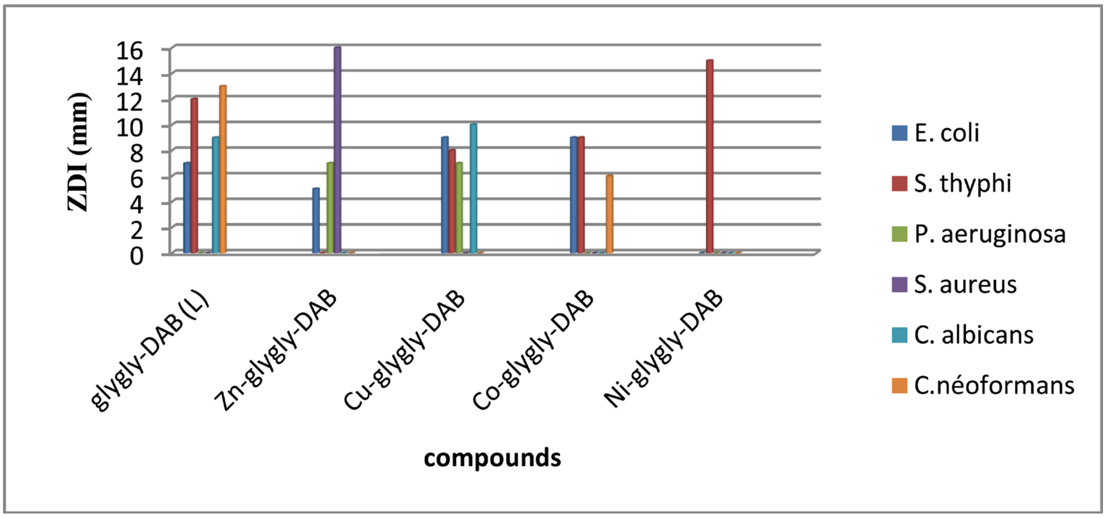

Figure 6. Histogram representing the zone of diameter of inhibition (ZDI) in mm of compounds.

4. Conclusion

The (E)-2-(4-dimethylbenzydimino) glycylglycine Schiff base ligands and their Co(II), Ni(II), Cu(II) and Zn(II) complexes have been synthesized and characterized. The Schiff base ligand glygly-DAB is tridentate, bonding using the azomethine nitrogen, peptide nitrogen and carboxyl oxygen, forming Tetrahedral complexes except Cu(II) complex which is square planar. Antimicrobial tests show that some of the complexes are more active as compared to the free ligand.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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