SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY SCREENING OF METAL (II) COMPLEXES OF SOME NITROGEN AND DIOXYGEN DONOR LIGANDS

OWALUDE, S.O.[1*], TELLA, A.C.[1], DUNTOYE, M.R.[2], ADIMULA, V.O.[2], EKE, U.B.[1] AND ODEBUNMI, E.O.[1]

[1]Department of Chemistry, [2]Department of Industrial Chemistry,
University of Ilorin, Ilorin, Nigeria.

ABSTRACT

A series of Ni(II) and Cu(II) complexes of Schiff base ligands derived from 4-aminobenzoic acid, 2-aminophenol, salicylaldehyde and 1H-indole-2,3-dione have been synthesized and characterized by elemental analysis, FT-IR, UV-vis and NMR spectroscopic analyses. Elemental analysis data were in agreement with a metal:ligand ratio of 1:1 for the complexes formed with HL^1, HL^3 and HL^4 in a tetrahedral geometry fashion while those with HL^2 results in complexes with metal:ligand ratio of 1:2 in octahedral arrangement. The antimicrobial activity of the Schiff base ligands and their metal complexes were investigated on the strains of gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Salmonella typhi*) as well as on the fungi strains (*Candida albicans, Aspergillus niger, Rhizopus stolonifer and Penicillium notatum*) using disc diffusion method. The results showed that the zones of inhibition of the metal complexes for both species were higher than that of the Schiff base ligands. This indicates that the metal complexes can be applied in drug design to control bacterial and fungal diseases.

Key words: Antimicrobial screening, metal complexes, Schiff bases, spectroscopic analysis.
***Correspondence:** owalude@unilorin.edu.ng

INTRODUCTION

Research into synthesis of novel Schiff base ligands has continued to attract the attention of Synthetic Inorganic Chemists over the years. This has been attributed to their simple synthetic methods, versatile coordination behavior and more importantly exceptional antibacterial, antifungal and antitumor activities [1]. Their anti-tumor activities have been explained in terms of their ability to interact with DNA which can often cause DNA damage in cancer cells, thereby blocking the division of cancer cells and resulting in cell death [2]. Transition metal complexes with coordinated Schiff base ligands have remained one of the most studied systems due to their rich structural diversity and broad therapeutic activity [3]. Transition metals have been proved to enhance the potency of drugs by providing additional stability and better means of delivery to their desired targets [4]. This has led to an increased research efforts towards the synthesis of novel transition metal complexes containing the Schiff base moieties and the studies of their potential applications in medicine and biotechnology.

Schiff bases are special class of ligands with variety of donor atoms exhibiting easy coordination with various metals [5]. The characteristic azomethine linkage in the Schiff bases has been reported as being responsible for their potent biological activities such as antitumor, antibacterial, antifungal and herbicidal activities [6]. Therefore, metal complexes constructed with azomethine unit in their structures are expected to be an important approach to the design of new drugs.1H-indole-2,3-dionein particular has been used over the years as a raw material for drug synthesis [7]. Their complexes with transition metals affect cell viability [8] and also exhibiting high antimicrobial properties [9].

These ligands and their metal complexes have also been investigated for a number of other important properties such as ability to reversibly bind oxygen [10], catalytic activity in hydrogenation of olefins [11], complexing ability toward some toxic metals [12] and photochemical activities [13,14].

In recent times, there is increasing incidence of resistance to the existing drugs by microbes; scientific literature is therefore replete with increasing emphasis on the screening of new potent and non-toxic antimicrobial drugs. The main objective of this study therefore is to prepare some new Schiff base ligands and their corresponding Cu(II) and Ni(II) complexes. The antimicrobial study of the synthesized complexes was investigated and the results showed that the metal complexes displayed higher antimicrobial activity against all the organisms comparing with Schiff bases.

MATERIALS AND METHODS

Materials

4-aminobenzoic acid, 2-aminophenol, salicylaldehyde, 1H-indole-2,3-dione, copper(II) chloride dihydrate and nickel(II) chloride hexahydrate were purchased from Aldrich and used without purification. Solvents used for spectroscopic studies were purified and dried by standard procedures before use [15].

Physical measurements

Melting points were carried out with the use of Gallen Kamp melting point apparatus. Elemental analysis was carried out in a Carlo Erba Model EA1108 elemental

analyzer at MEDAC Laboratory, UK. FT-IR spectra were obtained on a SHIMADZU Affinity 1S FTIR spectrophotometer with samples prepared as KBr pellets. High-resolution ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker Avance 600-MHz spectrometer at 298 K. The ^{1}H and $^{13}C\{^{1}H\}$ chemical shifts were calibrated to solvent peaks, which are reported relative to TMS. All other solvents were freshly distilled before use.

Preparation of the ligands

4-((2-oxoindolin-3-ylidene)amino)benzoic acid (HL^1): 1H-indole-2,3-dione (2.943 g, 20 mmol) and 4-aminobenzoic acid (2.743 g, 20 mmol) were dissolved separately in 40 mL of absolute methanol. The two solutions were mixed together in a 250 mL round bottomed flask and thereafter heated to reflux on a water bath for 4 hours in the presence of 0.5 mL glacial acetic acid. The clear orange solution formed was kept in ice over night after which an orange precipitate was obtained. After recrystallization from hot methanol, the orange product was collected by filtration, washed with methanol and dried at room temperature and then stored in the desiccator over $CaCl_2$. Yield 4.523 g (85%); m.p., 289 °C. Anal. Calcd for $C_{15}H_{10}N_2O_3$ (%): C, 67.67; H, 3.79; N, 10.52. Found (%): C, 66.46; H, 3.81; N, 10.32.IR (KBr disc): 3452br, 3371m, 1741m, 1693s, 1608s cm^{-1}. ^{1}HNMR (600 MHz, DMSO-d_6, δ ppm): 6.55(d, 2H); 6.91 (d, 1H); 7.02 (d, 2H); 7.35 (dd, 1H); 7.62 (d, 1H); 7.87(s,1H); 8.05 (s, 1H); 12.75 (s, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 167.8 (acid C=O), 163.7 (C=N), 158.9 (C–N), 153.6 (isatin C=O), 135.3-117.8 (aromatic C=C).

3-((2-hydroxyphenyl)imino)indolin-2-one (HL^2): This ligand was synthesized by following the procedure described for HL^1 above, using1H-indole-2,3-dione (3.678 g, 25 mmol) and 2-aminophenol (2.728 g, 25 mmol). The compound was obtained as brick red precipitate. Yield: 3.873 g (65%). m.p., 218 °C. Anal. Calcd for $C_{14}H_{10}N_2O_2$ (%): C,70.58; H, 4.23; N, 11.76. Found (%): C, 70.29; H, 4.19; N, 11.63.IR (KBr disc): 3441br, 3100w, 1728m, 1612m cm^{-1}. ^{1}HNMR (600 MHz, DMSO-d_6, δ ppm): 6.58 (s, 1H); 6.97 (d, 1H); 7.06 (d, 2H); 7.36 (dd, 1H); 7.45 (d, 1H); 7.64 (d,2H); 9.37 (s, 1H); 10.95 (s, 1H). ^{13}C NMR (DMSO-d^6, δ ppm): 164.2 (C=N), 159.0 (C=O), 154.1 (C–O), 137.5 (C–N), 134.4-117.1 (aromatic C=C).

4-((2-hydroxybenzylidene)amino)benzoic acid (HL^3): Salicylaldehyde (1.832 g, 15 mmol,) and 4-aminobenzoic acid (2.057 g, 15 mmol) each in 30 mL ethanol were mixed together in a 250 mL round bottomed flask. A large yellow mass was formed instantly, three drops of glacial acetic acid was added to the large mass and further heated under reflux for 6 hours. The large mass dissolved to form a clear yellow solution and on cooling, a deep yellow precipitate was obtained. The yellow precipitate was collected through filtration, washed with ethanol and dried at room temperature. The yellow crystalline solids were then stored in the desiccator over $CaCl_2$. Yield 3.078 g (85%). m.p., 263 °C. Anal. Calcd for $C_{14}H_{11}NO_3$ (%): C, 69.70; H, 4.60; N, 5.81 Found (%): C, 69.42; H, 4.51; N, 5.83. IR (KBr disc): 3442br, 1681sh, 1598s cm^{-1}. ^{1}HNMR (600 MHz, DMSO-d_6, δ ppm): 6.54 (d, 2H); 6.97 (d, 1H); 7.02 (d, 1H); 7.33 (dd, 1H); 7.48 (d, 2H); 8.01 (d,1H); 8.98 (s, 1H); 12.95 (s, 1H). ^{13}C NMR (DMSO-d^6, δ ppm): 165.3 (C=O), 160.9 (C=N), 152.6 (C–N), 133.1-117.2 (aromatic C=C).

2-((2-hydroxybenzylidene)amino)phenol (HL^4): This ligand was prepared following the procedure described for HL^1 with Salicylaldehyde (2.443 g, 20 mmol) and 2-aminophenol (2.183 g, 20 mmol). A clear orange solution was obtained and on cooling to room temperature, orange precipitate settled at the bottom of the flask. The precipitate was filtered, washed with methanol and dried at room temperature. The product obtained as orange crystalline solids were then collected and stored in the desiccator over $CaCl_2$.Yield 3.628 g (85%). m.p.,189°C. Anal. Calcd for $C_{13}H_{11}NO_2$ (%): C, 73.23; H, 5.20; N, 6.57. Found (%): C, 73.20; H, 5.12; N, 6.58. IR (KBr disc): 3423br, 1629m cm^{-1}. ^{1}HNMR (600 MHz, DMSO-d_6, δ ppm): 6.89 (d, 1H); 6.99 (d, 2H); 7.14 (d, 1H); 7.36 (dd, 1H); 7.53 (d, 1H); 7.62 (s,1H); 8.98 (s, 1H); 13.80 (s, 1H). ^{13}C NMR (DMSO-d^6, δ ppm): 162.3 (C–OH), 161.2 (C=N), 151.6 (phenolic C–OH), 135.4-117.2 (aromatic C=C).

Synthesis of the metal complexes

A general procedure was used for the synthesis of the metal complexes under investigation as described here for 1a:

$[NiHL^1H_2O]Cl_2.H_2O$ (**1a**): $NiCl_2.6H_2O$ (0.238 g, 1 mmol) dissolved in 20 mL hot methanol was added to a 20 mL hot methanolic solution of HL^1 (0.266 g, 1 mmol) in a 100 mL round bottom flask. The resulting solution was then heated to reflux on a water bath for 3 hours. The pH of the mixture was adjusted to 7.2 by adding 10% alcoholic ammonia. The brown precipitate obtained was filtered, washed several times with methanol and dried in air at room temperature. Yield 0.235 g (55%). m.p., decomp. > 280°C. Anal. Calcd for $C_{15}H_{13}O_5N_2Cl_2Ni$ (%): C, 41.79; H, 3.02; N, 6.50. Found (%): C, 42.04; H, 3.73; N, 6.31. IR (KBr disc): 3444br, 3452m, 1716m, 1620s, 1600s, 678w, 522w cm^{-1}.

$[CuHL^1H_2O].H_2O$ (**1b**)**:** Green solids, Yield 0.235 g (65%). m.p., decomp. > 312°C. Anal. Calcd for $C_{15}H_{14}O_5N_2Cu$ (%): C, 49.37; H, 3.57; N, 7.68. Found (%): C, 48.02; H, 3.51; N, 8.23. IR (KBr disc): 3450br, 3253m, 1707m, 1608s, 1571m, 638s, 443s cm^{-1}.

$[Ni(HL^2)_2].4H_2O$ (**2a**): Purple solids, Yield 0.350 g (58%). m.p., decomp. > 332°C. Anal. Calcd for $C_{28}H_{26}O_8N_4Ni$ (%): C, 55.52; H, 4.29; N, 9.25. Found

(%): C, 56.83; H, 3.64; N, 8.83. IR (KBr disc): 3450br, 3100w, 1697sh, 1618s, 586w, 480w cm^{-1}. ^{1}HNMR (600 MHz, DMSO-d_6, δ ppm): 6.57 (d, 2H); 6.96 (d, 1H); 7.06 (d, 2H); 7.34 (dd, 1H); 7.49 (d, 1H); 7.64 (s, 1H).

$[Cu(HL^2)_2].2H_2O$ (**2b**): Black solids, Yield 0.310 g (53%). m.p., decomp. > 359 °C. Anal. Calcd for $C_{28}H_{22}O_6N_4Cu$ (%): C, 55.58; H, 3.84; N, 9.76. Found (%): C, 56.83; H, 3.64; N, 8.83. IR (KBr disc): 3448br, 3110w, 1730s, 1618s, 600w, 490w cm^{-1}.

$[Ni(HL^3)H_2O]Cl_2.H_2O$ (**3a**): Lemon-green solids, Yield 0.307 g (75%). m.p., decomp. > 270 °C. Anal. Calcd for $C_{14}H_{13}O_5NCl_2Ni$ (%): C, 41.58; H, 3.21; N, 3.45. Found (%): C, 39.98; H, 2.91; N, 2.74. IR (KBr disc): 3454br, 1612s, 1543m, 684w, 455w cm^{-1}.

$[Cu(HL^3)H_2O]Cl_2$ (**3b**): Green solids, Yield 0.275 g (70%). m.p., 352 °C. Anal. Calcd for $C_{14}H_{11}O_4NCl_2Cu$ (%): C, 42.88; H, 2.81; N, 3.57. Found (%): C, 43.21; H, 2.63; N, 3.74. IR (KBr disc): 3350br, 1604s, 1541s, 696w, 474w cm^{-1}.

$[Ni(HL^4)H_2O]Cl_2.H_2O$ (**4a**): Brown solids, Yield 0.286 g (75%). m.p., decomp. > 294 °C. Anal. Calcd for $C_{13}H_{13}O_4NCl_2Ni$ (%): C, 41.39; H, 3.45; N, 3.71. Found (%): C, 40.30; H, 2.57; N, 3.54. IR (KBr disc): 3448br, 1614m, 522w, 464w cm^{-1}.

$[Cu(HL^4)H_2O]Cl.H_2O$ (**4b**): Green solids, Yield 0.247 g (70%). m.p., decomp. > 372 °C. Anal. Calcd for $C_{13}H_{13}O_4NClCu$ (%): C, 45.05; H, 3.75; N, 4.04. Found (%): C, 46.12; H, 2.72; N, 4.55. IR (KBr disc): 3452br, 1622m, 550w, 468w cm^{-1}.

Biological investigations

Agar diffusion-pour plate method for bacteria: An overnight culture of each of the organisms was prepared by taking a loop full of the organism from stock and inoculated each into the sterile nutrient broth of 5 mL each incubated for 18-24 hr at 37°C. From overnight culture, 0.1 mL of each of the organisms was taken and put into 9.9 mL of sterile distilled water to get 1:100 (10^{-2}) of the dilution of the organism. From the diluted organism, 0.2 mL was taken into the prepared sterile nutrient agar which was at 45°C, and aseptically poured into sterile petri dishes and allowed to solidify for about 45-60 min. Using a sterile cork-borer of 8 mm diameter, the wells were made according to the number of graded concentration of the sample. In each well, the different graded concentrations of the sample were produced, this was done in duplicates. The plates were allowed to stay on the bench for 2 hr to allow pre-diffusion. The plates were incubated uprightly in the incubator for 18-24 hours at 37°C.

Agar diffusion-surface plate method for fungi: A sterile sabouraud dextrose agar (62 g/L) was prepared accordingly and aseptically poured into the sterile plates in duplicates and allowed to solidify properly. 0.2 mL of the 10^{-2} of the organism was spread on the surface of the agar using petri dish to cover all the surface of the agar. Eight wells were bored using a sterile cork-borer of 8 mm diameter. The graded concentrations of the extract were put into the wells accordingly, including the controls. All the plates were left on the bench for 2 hours to allow the extract to diffuse properly into the agar i.e. pre-diffusion. The plates were incubated at 25 °C for 72 hr. Dimethylsulphoxide (DMSO) was used as control, while gentamycin (10 µg/mL) and tioconazole (0.7 µg/mL) were used as standard reference drugs in the study.

RESULTS AND DISCUSSION

The Schiff base ligands were prepared by simple condensation reaction between one equivalent of 1H-indole-2,3-dione and salicylaldehyde with either 4-aminobenzoic acid or 4-aminophenol in absolute methanol. The ligands obtained were pure with sharp melting points and had good agreement between the theoretical and experimental elemental analysis data. The complexes have been synthesized by the reaction of the ligand with copper(II) chloride dehydrate and nickel(II) hexahydrate in hot methanol. The complexes were coloured, stable in air and readily soluble in DMSO and DMF but insoluble in distilled water and most organic solvents.

IR spectra analyses

FT-IR spectra of the ligands show a number of weak bands between 2300 and 3000 cm^{-1} assigned to *ν*C–H [16]. These bands did not show any appreciable change in the complexes. The C=N bond stretching frequency appeared as strong bands at 1608, 1612, 1598 and1629 cm^{-1}in HL^1, HL^2, $HL^3$and HL^4 respectively. In the complexes, these bands were shifted to lower frequencies indicating coordination through the nitrogen of the azomethine group of the Schiff base ligands. For example, the azomethine *ν*C=N band at 1608 cm^{-1} in $HL^1$was shifted to lower frequencies 1600 cm^{-1} and 1571 cm^{-1} in Figs 1a and 1b respectively and the same trend were observed in the other complexes. This confirms the retention of C=N bond in all the complexes. In the spectra of the metal complexes, there is a complete disappearance of the band appearing at around 3450 cm^{-1} assigned to *ν*(OH) in the ligands, suggesting deprotonation of the acidic proton of the hydroxyl group due to coordination through the oxygen [17]. The presence of coordinated water molecules in the complexes can also be inferred from bands appearing in the range 3444 to 3450 cm^{-1}which is supported by the elemental analysis data [18].

The complexes show new sharp bands of medium intensity at around 550 to 700 cm^{-1} for the characteristic *ν*M–O band suggesting the coordination of the ligands through the various oxygen donor atoms present in their structures [19]. Appearance of new bands in the range 450 to 520 cm^{-1} in the spectra of all

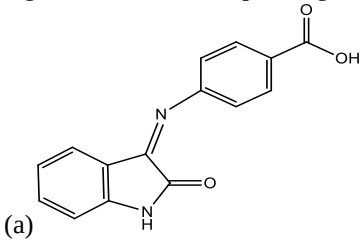
the complexes assignable to *ν*M–N also indicates coordination through the nitrogen donor atoms present in the ligands. These bands were absent in the spectra of the ligands as expected.

The IR and elemental analysis data of the metal complexes suggests tetrahedral geometry for all the complexes, except for the metal complexes of HL^2 which exhibits an octahedral geometry. All the ligands are bonded to the metal ions in a tridentate fashion through NOO donor atoms. Further evidence of coordination through NOO atoms of the Schiff bases with the respective metal ions were provided by the appearance of new bands due to ν(M-N) and ν(M-O) in the metal complexes [20].

NMR spectral analyses

In the ^{1}H NMR spectra of the ligands, the signal due to the HC=N group is observed at the expected range between 8.05 and 9.37 ppm. The carbon signal corresponding to this group is observed as a single line around 146 ppm in the ^{13}C NMR spectra of the ligands. This indicates that the Schiff base ligands contain the characteristic azomethine group in their structures. The protons of aromatic units were observed as multiple peaks in the range 6.6-8.5 ppm in all the ligands and remain almost unchanged in all the complexes. The proton signal due to COOH was observed at 11.03 and 12.95 ppm respectively for HL^1 and HL^3 while the phenolic OH protons in HL^2 and HL^4 appeared at 10.95 and 13.08 respectively. In the ^{13}C NMR spectra of the ligands, the C=O of the acid is observed at 167.4 ppm in HL^1 and HL^3 which is retained in the corresponding complexes [21]. The integration ratios in the ^{1}H NMR of the ligands as well as the complexes combined with the elemental analysis data support the stoichiometry proposed in Figs. 1-4. The signal due to COOH is absent in the ^{1}H NMR spectra of compounds **3a** and **3b**, which suggests that the carboxyl group is deprotonated and coordinates to the central metal atom. In the spectra of the two complexes, the HC=N group is shifted by almost 1 ppm unit, which clearly indicates the coordination of the azomethine nitrogen to the metal atoms. The NMR spectra of the other complexes could not be obtained due to their poor solubility in DMSO-d_6 and other common NMR solvents.

Based on the analytical and the spectroscopic data, the following structures are proposed for the Schiff base ligands and the corresponding complexes:



(a)

(b)

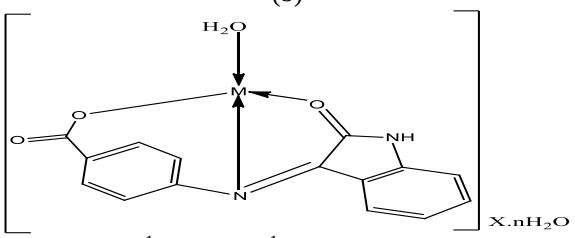
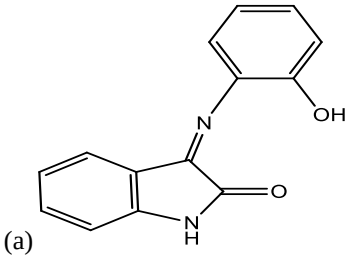
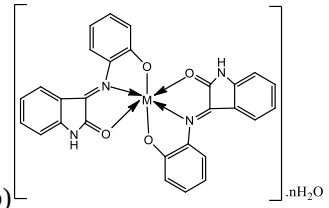


Fig. 1: (a) HL^1 (b) $[NiHL^1H_2O]Cl_2.H_2O$ when M = Ni; X = Cl_2, n = 1 and $[CuHL^1H_2O].H_2O$ when M = Ni; X = 0, n = 1.

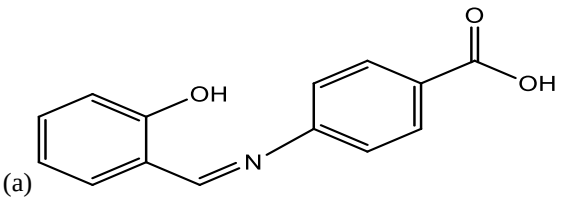


(a)



(b)

Fig. 2: (a) HL^2 (b) $[Ni(HL^2)_2].4H_2O$ when M = Ni; n = 4 and $[Cu(HL^2)_2].2H_2O$ when M = Cu; n = 2.



(a)

(b)

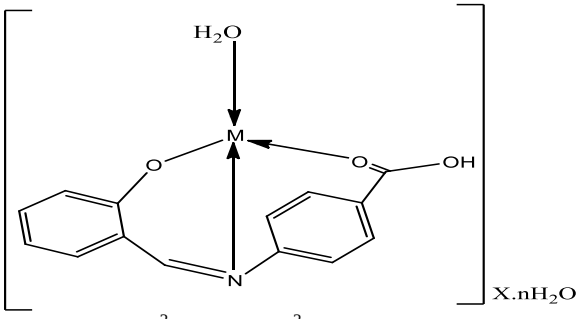


Fig. 3: (a) HL^3 (b) $[Ni(HL^3)H_2O]Cl_2.H_2O$ when M = Ni; n = 1; X = Cl_2 and $[Cu(HL^3)H_2O]Cl_2$ when M = Cu; n = 0; X = Cl_2.

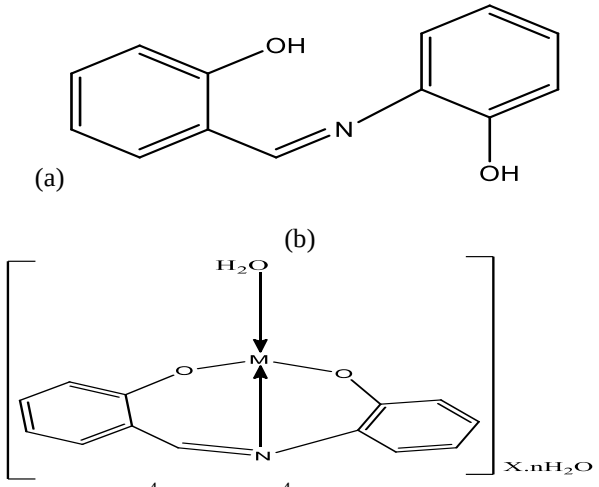


Fig. 4: (a) HL^4 (b) $[Ni(HL^4)H_2O]Cl_2.H_2O$ when M = Ni; n = 1; X = Cl_2 and $[Cu(HL^4)H_2O]Cl.H_2O$ when M = Cu; n = 1; X = Cl.

Biological activity studies

The ligands and their corresponding metal complexes were investigated for antibacterial and antifungal activities and the results are recorded in Table 1. All the Schiff base ligands exhibited antibacterial properties on all the six test bacteria species except HL^2 which was not effective against *Klebsiella pneumoniae* (gram negative). In the test for antifungal activities, all the compounds demonstrate high activity against the test organisms except HL^2 that exhibit no activity against *Candida albicans*, *Penicillium notatum* and *Rhizopus stolonifer*. The ligand HL^4 was also not active against *Penicillium notatum* and *Rhizopus stolonifer*. It was generally observed that the activities of the ligands and their corresponding metal complexes were comparable to the reference drugs viz: gentamycin for bacteria and tioconazole for fungi). The increase in activity measured by the size of the zones of inhibition of the Schiff base ligands are in the order $HL^1 > HL^2 > HL^3 > HL^4$. The corresponding metal complexes followed exactly the same order of activity.

Table 1: Antibacterial and antifungal activities of the ligands and their metal complexes

Compounds	Concentration (µg/mL)	*S.a*	*E.c*	*B.s*	*P.a*	*S.t*	*K.p*	*C.a*	*A.n*	*P.n*	*R.s*
		Bacteria (mm)						Fungi (mm)			
HL^1	50	17±1	16±0	15±1	12±0	14±0	16±0	14±0	12±0	12±0	12±0
	100	19±1	18±0	17±1	15±1	16±0	18±0	18±0	14±0	14±0	16±0
	200	22±2	22±0	19±1	18±0	18±0	20±0	20±0	18±0	16±0	18±0
	50	17±1	21±1	18±0	18±0	15±1	17±0	18±0	18±0	16±0	15±1
1a	100	21±1	23±1	21±1	21±1	21±1	18±0	23±1	21±1	18±0	17±1
	200	25±1	26±2	24±0	23±1	23±1	22±0	23±1	23±1	20±0	20±0
	50	24±0	23±1	21±1	21±1	22±0	19±1	19±1	19±1	18±0	18±0
1b	100	26±0	26±0	24±0	23±1	25±1	22±0	22±0	21±1	20±0	20±0
	200	28±0	28±0	26±0	25±1	25±1	24±0	24±2	23±1	22±0	22±0
	50	13±1	13±1	14±0	13±1	13±1	-	-	12±0	-	-
HL^2	100	15±1	15±1	16±0	14±0	14±0	-	-	14±0	-	-
	200	17±1	17±1	19±1	17±1	17±1	-	-	17±1	-	-
	50	18±0	17±1	15±1	14±0	16±0	16±0	15±1	14±0	13±1	14±0
2a	100	21±1	20±2	18±0	16±0	18±0	19±1	17±1	16±0	15±1	16±0
	200	25±1	23±1	21±1	18±0	21±1	23±1	20±0	19±1	17±1	19±1
	50	20±0	19±1	17±1	16±0	18±0	18±0	17±1	16±0	15±1	16±0
2b	100	23±1	22±0	20±0	18±0	20±0	21±1	19±1	18±0	17±1	18±0
	200	27±1	25±1	23±1	20±0	23±0	25±1	21±1	21±1	19±1	21±1
	50	12±0	12±0	12±0	10±0	10±0	12±0	12±0	10±0	10±0	10±0
HL^3	100	14±0	14±0	14±0	12±0	13±1	15±1	14±0	12±0	12±0	12±0
	200	17±1	17±1	17±1	15±1	15±1	17±1	17±1	15±1	14±0	15±1
	50	16±0	14±0	15±1	15±1	13±1	12±0	12±0	12±0	10±0	10±0
3a	100	18±0	17±1	17±1	18±0	16±0	15±1	14±0	14±0	12±0	13±1
	200	21±1	20±0	21±1	21±1	18±0	17±1	16±0	17±1	15±1	15±1
	50	18±0	17±1	17±1	17±1	13±1	13±1	13±1	13±1	12±0	12±0
3b	100	20±0	19±1	19±1	20±0	18±0	17±1	16±0	16±0	14±0	15±1
	200	23±1	22±2	23±1	23±1	20±0	19±1	18±0	19±1	17±1	17±1
	50	11±1	10±0	10±0	10±0	10±0	10±0	10±0	10±0	-	-
HL^4	100	13±1	12±0	16±0	13±1	10±0	10±0	10±0	10±0	-	-
	200	15±1	14±0	18±0	15±1	13±1	13±1	13±1	14±2	-	-
	50	13±1	12±0	13±1	12±0	10±0	10±0	10±0	10±0	-	-
4a	100	15±1	14±0	16±0	13±1	12±0	12±0	12±0	12±0	-	-

	200	17±1	16±0	18±0	17±1	15±1	15±1	15±1	14±0	-	-
	50	14±0	13±1	14±0	14±0	12±0	12±0	12±0	12±0	-	-
4b	100	17±1	16±0	18±0	16±0	14±0	14±0	14±0	14±0	-	-
	200	19±1	18±0	20±0	19±1	17±1	17±1	17±1	16±0	-	-
DMSO		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
STD		40±0	40±0	39±1	38±0	39±1	38±0	28±0	28±0	27±1	27±1

S.a = *Staphylococcus aureus*; E.c = *Escherichia coli*; B.s = *Bacillus subtilis*; P.a = *Pseudomonas aeruginosa*; S.t = *Salmonella typhi*; K.p = *Klebsiella pneumoniae*; C.a = *Candida albicans*; A.n =*Aspergillus niger*; P.n =*Penicillium notatum*; R.s =*Rhizopus stolonifer*

The zones of inhibitions of the metal complexes for both the bacterial and the fungi species were higher than that of the corresponding Schiff base ligands as reported in Table 1, this increase in activity of the complexes may be explained on the basis of chelation theory. On chelation, there is a drastic reduction in the polarity of the metal ion attributable to the overlap of the ligand orbital and metal ion with donor groups [22]. The mode of action of the compounds may also involve the formation of intermolecular hydrogen bonds with the active centers of the cell constituents of the test organisms through the azomethine groups, resulting in interference with the normal cell process [23]. The observed toxicity of the complexes has been explained in terms of the strength of the metal-ligand bond and a combined effect of the metal and the ligands for activation of the bio-molecules [24]. In general, the activities were higher as the concentration of all the samples increases and the sensitivities of both the test bacteria and fungi species were concentration dependent.

CONCLUSION

The ligands were synthesized by the condensation reaction of 1H-indole-2,3-dione and 4-aminobenzoic acid (HL^1), 1H-indole-2,3-dione and 2-aminophenol (HL^2), salicylaldehyde and 4-aminobenzoic acid (HL^3) as well as salicylaldehyde and 2-aminophenol (HL^4). The metal complexes in Fig. 1a-4b were prepared by the reaction of equimolar amount of the ligands with either $NiCl_2.6H_2O$ or $CuCl_2.2H_2O$ salts. Compound **3b** has a sharp melting point at 352 °C while the others decomposed at various temperatures between 270 to 372 °C. Elemental analysis established a metal to ligand ratio of 1:1, except HL^2 which displayed a metal to ligand ratio of 1:2 for both Ni(II) and Cu(II) ions, all in tridentate manner. The compounds exhibit high potent activities against some selected bacteria and fungi species and the results showed that they can be applied in drug design to control bacterial and fungal diseases.

REFERENCES

1. BAGIHALI, G.B., AVAJI, P.G., PATIL, S.A. & BADAMI, P.S. (2008). Synthesis, spectral characterization, *in vitro* antibacterial, antifungal and cytotoxic activities of Co(II), Ni(II) and Cu(II) complexes with 1,2,4-triazole Schiff bases. *European Journal of Medicinal Chemistry*, **43:** 2639-2649.
2. YIN, H., LIU, H. & HONG, M. (2012). Synthesis, structural characterization and DNA-binding properties of organotin(IV) complexes based on Schiff base ligands derived from 2-hydroxy-1-naphthaldy and 3- or 4-aminobenzoic acid. *Journal of Organometallic Chemistry*, **713:** 11-19.
3. SHAHZADI, S. & ALI, S. (2008). Structural chemistry of organotin(IV) complexes. *Journal of the Iranian Chemical Society*, **5:** 16-28.
4. SÁNCHEZ-DELGADO, R.A., NAVARRO, M., PÉREZ, H.A. & URBINA, J.A. (1996). Toward a novel metal-based chemotherapy against tropical diseases. 2. Synthesis and antimalarial activity *in vitro* and *in vivo* of new ruthenium- and rhodium-chloroquine complexes. *Journal of Medicinal Chemistry* **39:** 1095-109.
5. PANDA, B.K. & CHAKRAVORTY, A. (2005). Spectroscopic properties of inorganic and organometallic compounds. *Journal of Organometallic Chemistry*, **690:** 3169-3175.
6. REKHA, S. & NAGASUNDARA, K.R. (2006). Complexes of the Schiff base derived from 4-amino-phenyl benzimidazole and 2,2'-dehydropyrollidene-*N*-aldehyde with Zn(II), Cd(II) and Hg(II) halides. *Indian Journal of Chemistry*, **45:** 2421-2425.
7. CERCHIARO, G., MICKE, G.A., TAVARES, M.F.M. & FERRIERA, A.M.(2004). Kinetic studies of carbohydrate oxidation catalyzed by novel isatin–Schiff base copper(II) complexes. *Journal of Molecular Catalysis A: Chemical* **221:** 29-39.
8. CERCHIARO, G., AQUILANO, K., FILOMENI, G., ROTILIO, G., CIRIOLO, M.R. & FERRIERA, A.M. (2005). Isatin-Schiff base copper(II) complexes and their influence on cellular viability. *Journal of Inorganic Biochemistry*, **99:** 1433-1440.
9. BACCHI, A., CARCELLI, M., PELAGATTI, P., PELIZZI, G., RODRIGUEZ-ARGUELLES, M.C., ROGOLINO, D., SOLINAS, C. & ZANI, F. (2005). Antimicrobial and mutagenic properties of organotin(IV) complexes with isatin and *N*-alkylisatinbisthiocarbonohydrazones. *Journal of Inorganic Biochemistry*, **99:** 397-408.
10. CHEN, D. & MARTELL, A.E. (1987). Dioxygen affinities of synthetic cobalt Schiff base

complexes. *Inorganic Chemistry*, **26:** 1026-1987.

11. ALEXANDER, S., UDAYAKUMAR, V. & GAYATHRI V. (2009). Hydrogenation of olefins by polymer-bound palladium(II) Schiff base catalyst. *Journal of Molecular Catalysis A: Chemical*, **314:** 21-27.
12. ZHAO, J., ZHAO, B., LIU, J., XU, W. & WANG, Z. (2001). Spectroscopy study on the photochromism of Schiff bases *N,N*'-bis(salicylidene)-1,2-diaminoethane and *N,N*'-bis(Salicylidene)-1,6-exanediamine. *Spectrochimica Acta Part A*: *Molecular and Biomolecular Spectroscopy*, **57:** 149-154.
13. YOUSIF, E., AL-AMIERY, A.A., KADIHUM, A., KADHUM, A.A.H. & MOHAMAD, A. (2015). Photostabilizing efficiency of PVC in the presence of Schiff bases as photostabilizers. *Molecules*,**20:** 19886-19899.
14. SAWODNY, W.J. & RIEDERER, M. (1977). Addition com-pounds with polymeric chromium(II)-Schiff base complexes. *Angewandte Chemie*, **16:** 859-860.
15. ARMAREGO, W. L. F. & PERRIN, D.D. (2000). *Purification of Laboratory Chemicals*, 4th Ed., Butterworth-Heinemann, Oxford, U.K., 196 pp.
16. ROY, P. (2009). Synthesis, characterization, and fluorescence properties of dinuclear cadmium(II) complexes. *Journal of Coordination Chemistry*, **62:** 2003-2011.
17. YIN, H., LIU, H. & HONG, M. (2012). Synthesis, structural characterization and DNA-binding properties of organotin(IV) complexes based on Schiff base ligands derived from 2-hydroxy-1-naphthaldy and 3- or 4-aminobenzoic acid. *Journal of Organometallic Chemistry*, **713:** 11-19.
18. TELLA, A.C., OWALUDE, S.O., ALIMI, L.O., OLADIPO, A.C., OLATUNJI, S.J. & ADEYEMI, O.G. (2016). Facile synthesis and vapochromic studies of Co(II) complexes bearing NO and OO donor ligands. *Egyptian Journal of Basic and Applied Sciences*, **3:** 125-133.
19. GUY, J.T., COOPER, J.C., GILARDI, R.D., FLIPPEN-ANDERSON, J.L. & GEORGE, C.F. (1988). Transition metal promoted oxidation of organic sulfides. Synthesis, characterization, and structure of (μ^4-oxo)hexakis(μ^2-chloro)tetrakis(dialkylsulfoxide)tetracopper(II) . *Inorganic Chemistry*, **27:** 635-638.
20. SINGH, K., BARWA, M.S. & TYAGI, P. (2006). Synthesis, characterization and biological studies of Co(II), Ni(II), Cu(II) and Zn(II) complexes with bidentate Schiff bases derived by heterocyclic ketone, *European Journal of Medicinal Chemistry*, **41:** 147-153.
21. YOUSIF, A., MEHDI, B.I., YUSOP, R., SALIMON, J., SALIH, N. & ABDULLAH, B.M. (2014). Synthesis, structure and antibacterial activity of some triorganotin(IV) complexes with a benzamido alanine ligand. *Journal of Taibah University for Science*, **8:** 276-281.
22. MAHDI, R.A., AL-NOOR, T.H. & ISMAIL, A.H. (2014). Preparation, characterization, and antibacterial properties of mixed ligand complexes of L-leucine and Sulfamethoxazole with Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) ions. *Advances in Physics Theories and Applications*, **27:** 8-19.
23. NATH, M. & YADAV, R. (1998). Studies of Organotin(IV) derivatives of DL-methhionine and L.-asparagine. *Bulletin of the Chemical Society of Japan*, **71:** 1355-1362.
24. JOSH, A., VERMA, S., GAUR, R.B. & SHARMA, R.R. (2005). Di-n-butyltin(IV) complexes derived from heterocyclic β-diketones and *N*-phthaloyl amino-acids: Preparation, biological evaluation, structural elucidation based upon spectral [IR, NMR (^{1}H, ^{13}C, ^{19}F and ^{119}Sn)] studies. *Bioinorganic Chemistry and Application*, **3:** 201-215.