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ORIGINAL RESEARCH

Copper(II) complexes of Substituted Salicylaldimines with benzimidazole nucleus: Synthesis, characterization and antimicrobial activity

Abdullahi Owolabi Sobola[1, 2] and Gareth Mostyn Watkins[2]

[1]*Department of Chemistry, Faculty of Science, Lagos State University, Nigeria*

[2]*Department of Chemistry, Rhodes University,* Grahamstown 6140, South Africa.

Correspondence
Abdullahi Owolabi Sobola, Department of Chemistry, Faculty of Science, Lagos State University, Nigeria.
email: abdullahi.sobola@lasu.edu.ng

Abstract:
Introduction: Most branded antifungal and anthelmintic agents contain the benzimidazole nucleus. Studies have shown that the substitution of the benzimidazole nucleus at the 1, 2, and 5 positions is important to the pharmacological effects of the benzimidazole based drugs. Furthermore, it has been reported that the biological activity of bioactive compounds may be enhanced in the presence of metal ions.
Aims: The aim of this study was to synthesize and evaluate the antimicrobial activity of Cu(II) complexes of some substituted salicylaldimines with benzimidazole nucleus.
Materials and Methods: The salicylaldimine ligands were prepared by condensing 2-aminobenzimidazole with salicylaldehyde, *o*-vanillin and *p*-vanillin. All the compounds and the Cu(II) complexes were characterized by CHNS, electronic, infrared and conductivity data. In addition, the structures of the ligands were confirmed with ^{1}H-NMR and ^{13}C-NMR spectral data. Both the ligands and the Cu(II) complexes have been screened for their in vitro antimicrobial activity against *Staphylococcus aureus subsp. aureus* ATCC® 6538™, *Bacillus substillis subsp. spizizenii* ATCC® 6633™*, *Escherichia coli* ATCC® 8739™*) and *Candida albicans* ATCC® 2091™* using agar diffusion and broth dilution techniques
Results: The ligands coordinated to the Cu(II) ion in 1:2 (M:L) as tridentate monobasic species via the imine-N, the imidazole-N and the phenolic–O to give six-coordinate Cu(II) complexes. All the benzimidazole compounds exhibited significant potency, especially antifungal activity, against the tested microorganisms.
Conclusion: The presence of the Cu(II) ions did not have a regular effect on the activity of the compounds, but the ortho-methoxy substituent enhanced the biological activity of the imidazole nucleus.

Keywords: Schiff bases, *o*-vanillin, antifungal activity, Cu(II) complexes,

All co-authors agreed to have their names listed as authors.

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1. INTRODUCTION

The chemistry of compounds containing the benzimidazole nucleus has received an unending interest because of its numerous and profound pharmacological activity. It has been established that benzimidazole compounds have a wide spectrum of biological activity comprising antibacterial, antifungal, anti-inflammatory, antiviral, anti-tumour, anti-oxidant and anthelmintic activity [1-5]. The discovery of new antibacterial and anthelmintic agents has added momentum to investigations in these areas. Many of these pharmacological agents have pronounced potency and have been in use for decades under different trade names (R Skeela, Cochin University of Science and Technology, Kerala, PhD Thesis). Examples include thiabendazole, mebandazole, cambendazole, fuberidazole, clemizole and bezitramide. In particular, studies have shown that compounds containing the benzimidazole ring with substitution at 1, 2, and 5 positions exhibit enhanced pharmacological effects [6]. Likewise, Schiff bases, derived mostly from variety of heterocyclic rings, were reported to possess a wide variety of biological activities including antiviral, anticancer, cytotoxic, antimicrobial and anticonvulsant among others [7]. Schiff bases are condensation product of reaction between a primary amine and an aldehyde or ketone.

Schiff base ligands have been used to prepare several metal complexes and have consequently been evaluated for their biological activity. Mohammed and Abd El-Wahab [8] reported the study of metal complexes of Schiff bases derived from salicylaldehyde and 2-aminobenzimidazole while Liu et al. [9] worked on Cu(II) complex of N-(methyl-2-benzimidazolmethylidene)- 2-hydroxylaniline. Chhonker et al. [10] has equally reported the antimicrobial activity of Schiff base compounds derived from 2-aminophenylbenzimidazole. Furthermore, Hranjec et al. [11] studied the biological activity of some substituted 2-aminobenzimidazole Schiff bases. The focus of this research, therefore, was to investigate the effect of methoxyl substituent on the antimicrobial activity of the 2-aminobenzimidazole-derived salicylaldimines Schiff bases using 2-hydroxybenzaldehyde (salicylaldehyde), 2-hydroxy-3-methoxybenzaldehyde (*o*-vanillin) and 2-hydroxy-4-methoxybenzaldehyde (*p*-vanillin).

2. MATERIAL AND METHODS

All the chemicals and reagents used were of reagent grade and used as supplied. The ^{1}H- and ^{13}C- NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Bruker Avance NMR equipment operating at 400 MHz. The mid-infrared absorption frequencies (4000 - 700 cm^{-1}) were recorded on a Perkin Elmer Spectrum 100 FT-IR equipped with universal attenuated total reflectance (ATR) accessory while the far-infrared (700 - 30 cm^{-1}) spectra were recorded in nujol mull on a Perkin Elmer Spectrum 400 FT-IR. The electronic spectra were obtained from PerkinElmer Lambda 25 spectrophotometer. The elemental analysis, CHN, was done on Vario MICRO V1.6.2 elemental analysen systeme GmbH while the percentage metal content was determined on PerkinElmer Analyst atomic absorption spectrometer. Molar conductivity measurement for the complexes was done in DMF, using Az® 86555 pH/mV/Cond./TDS/Temp. The melting points (uncorrected) of the compounds were determined using Galenkemp melting point apparatus. The micro-organisms were purchased from Microbiologics, Cape Town.

2.1 Synthesis of the Schiff base ligands

The ligands, L^1 – L^3 were synthesized according to the general synthetic procedure in the literature [8] by reacting equimolar amounts of the aldehyde with the 2-aminobenzimidazole under reflux for 2 hr.

Ligand L^1 was prepared by refluxing 10 mmol (1.07 mL) ethanol solution of salicylaldehyde with 10 mmol (1.332 g) ethanol solution of 2-aminobenzimidazole in a 100 mL round bottom flask for 2 hr. The resulting yellow solution was reduced using rotavapor to obtain some yellow precipitates. The precipitate was filtered under suction, washed with ethanol and dried over silica gel. The same procedure was used for all the ligands.

2.2 Synthesis of the Cu(II) complexes

All the Cu(II) complexes of the 2-aminobenzimidazole derived Schiff base ligands were prepared by reacting the ligands with Cu(II) acetate monohydrate $Cu(OAc)_2.H_2O$ in a ratio 2:1. Hot ethanol solution of $Cu(OAc)_2.H_2O$ was gradually added to a hot solution of the ligands in the same solvent in a ratio 1:2 to obtain complexes of the form $[ML_2].xH_2O$. The resulting solution was stirred for 30 minutes with slight heating to obtain a brown precipitate. The precipitate was filtered under suction, washed with ethanol and dried in a vacuum desiccator over silica gel.

3. RESULTS AND DISCUSSION

3.1 Analytical and spectral data

The analytical and spectral data for the synthesized compounds are given below.

3.1.1 Ligand L^1

Yield (1.33 g) 56%. M.Pt: 216-218 ^{o}C. Anal. Cal. For $C_{14}H_{11}N_3O$: C 70.89, H 4.67, N 17.72; found: C 71.75, H 4.52, N 17.71. ^{1}H-NMR (400 MHz, DMSO, δ): 12.76 (1H, s, -OH), 12.12 (1H, s, -NH), 9.67 (HC=N), 7.88 (4H, d), 7.50 (2H, t), 7.03 (2H, t). ^{13}C- NMR (400 MHz, DMSO, δ): 166.40, 161.43, 154.82, 135.57, 133.24, 123.04, 120.30, 117.76. IR (ATR, cm^{-1}): 3175-2344, 1619, 1606, 1276. UV/Visible (DMF, nm): 367

3.1.2 Ligand L^2

The synthetic procedure was the same as ligand L^1 using 2-hydroxyl-3-methoxybenzaldehyde (*o*-vanillin) instead of salicylaldehyde. Yield: (1.74 g) 65%. M.Pt: 216-218 ^oC. Anal. Cal. For $C_{15}H_{13}N_3O_2$: C 67.40, H 4.92, N 15.72; found: C 67.67, H, 4.92, N, 15.64. ^{1}H-NMR (400 MHz, DMSO, δ): 12.74 (1H, s, -OH), 12.04 (1H, s, NH), 9.66 (1H, s, HC=N), 7.55 (1H, t), 7.45 (2H, d), 7.19 (2H, d), 6.96 (2H, t) 3.86 (3H, s, $-OCH_3$). ^{13}C-NMR (400 MHz, DMSO, δ): 166.58, 154.74, 151.42, 148.89, 124.33, 123.06, 120.13, 117.33, 56.77. IR (ATR, cm^{-1}): 3296, 3087-2339, 1623, 1600, 1249. UV/Visible (DMF, nm): 282, 357.

3.1.3 Ligand L^3

The synthetic procedure was the same as ligand L^1 using 2-hydroxyl-4-methoxybenzaldehyde (*p*-vanillin) instead of salicylaldehyde. Yield: (1.60 g) 60%. M.Pt: 206-207 ^oC. Anal. Cal. For $C_{15}H_{13}N_3O_2$: C 67.40, H 4.92, N 15.72; found: 67.39, H, 4.92, N, 15.64. ^{1}H-NMR (400 MHz, DMSO, δ): 12.70 (1H, s, -OH), 12.63 (1H, s, NH), 9.54 (1H, s, HC=N), 7.76 (2H, d), 7.50 (2H, d), 7.19 (2H, t), 6.63 (1H, d), 6.58 (1H, s), 3.85 (3H, s, $-OCH_3$). ^{13}C-NMR (400 MHz, DMSO, δ): 166.03, 165.71, 164.04, 154.89, 135.55, 122.83, 113.77, 108.64, 101.76, 56.55. IR (ATR, cm^{-1}): 3261, 3109-2287, 1624, 1278. UV/Visible (DMF, nm): 284, 370.

3.1.4 $Cu(L^1)_2.\frac{1}{2}H_2O$

Yield: 73%. M.Pt: 228 ^oC (decomposed). Anal. Cal. For $CuC_{28}H_{20}N_6O_2.\frac{1}{2}H_2O$: C 61.70, H 3.88, N 15.42, Cu 11.16; found: 61.75, H 3.57, N 15.34, Cu 11.32. Λ_M (DMF, $\Omega^{-1}cm^2mol^{-1}$): 13.13. IR (ATR, cm^{-1}): 3357, 1622, 1321, 445, 436, 393, 339. UV/Visible (DMF, nm): 317, 322, 359, 415, 692.

3.1.5 $Cu(L^2)_2.H_2O$

Yield: 80%. M.Pt: 241 ^oC (decomposed). Anal. Cal. For $CuC_{30}H_{24}N_6O_4.H_2O$: C 59.55, H 4.17, N 13.80, Cu 10.35; found: 58.93, H 4.00, N 13.65, Cu 10.10. Λ_M (DMF, $\Omega^{-1}cm^2mol^{-1}$): 7.73. IR (ATR, cm^{-1}): 3291, 1606, 1276, 466, 435, 399, 364. UV/Visible (DMF, nm): 352, 412, 755.

3.1.6 $Cu(L^3)_2$

Yield: 72%. M.Pt: 241 ^oC (decomposed). Anal. Cal. For $CuC_{30}H_{24}N_6O_4$: C 60.44, H 4.06, N 14.10, Cu 10.66; found: 60.17, H 4.11, N 14.00, Cu 10.43. Λ_M (DMF, $\Omega^{-1}cm^2mol^{-1}$): 7.46. IR (ATR, cm^{-1}): 3301, 1614, 1313, 513, 468, 389, 339. UV/Visible (DMF, nm): 319, 375, 702.

3.2 Elemental analysis

The Schiff base ligands and the complexes were obtained in high purity as indicated by the micro-analytical (CHNS) data. The experimental data were very close to the theoretical values. Furthermore, the data indicated that the Schiff base ligands coordinated to the Cu(II) ion in a ratio 1:2, with x molecule of water (x = 0, 0.5, 1.0). The complexes, therefore, have the molecular formula $CuL_2.xH_2O$. Previous study on metal complexes of Schiff base ligand derived from salicylaldehyde and 2-aminobenzimidazole reported a 1:1 coordination for the Cu(II) ion and the Schiff base ligand [8]. The complexes are poor electrolyte as indicated by the conductivity values [12] and thus supporting the neutral nature of the complexes.

3.3 ^{1}H-NMR and ^{13}C-NMR

The assignment of the nuclear magnetic resonance (NMR) spectral data for the ligands is presented in section 3.10, while the individual spectra are presented as supplementary data. The strong singlet signal at 9.54 - 9.67 ppm corresponds to the azomethine proton (HC=N) of the Schiff base ligands [11]. The hydroxyl (OH) and the amino protons (NH) were, however, observed as broad signals between 12.70 – 12.04 ppm due to strong intra-molecular hydrogen bonding. The multiple signals between 6.94 ppm and 7.89 ppm are due to the aromatic protons of the Schiff base ligands while the prominent signal at 3.85 ppm corresponds to the methoxyl ($-OCH_3$) protons of the *o*-vanillin and *p*-vanillin ligands. In addition, the ^{13}C-NMR spectral data corroborate the structures of the Schiff bases ligands. The azomethine carbon was observed at 166.58 - 161.43 ppm while the signal at 56.77 - 56.55 ppm corresponds to the methoxyl carbon of ligands L^2 and L^3. The absence of any signal between 180 – 200 ppm due to the aldehyde carbon showed that the ligands were obtained in pure form.

3.4 Infrared spectral study

The assignment of the infrared spectral data for the ligands and the corresponding Cu(II) complexes gave an insight into the bonding pattern of the Schiff base ligands. The values are presented above in section 3.10, while the individual spectra are presented as supplementary data.

The $\nu_{C=N}$ of the azomethine group was observed as a strong band at 1624 – 1619 cm^{-1} while the benzimidazole -NH stretch absorbed as a medium band at 3296 – 3261 cm^{-1}. The hydroxyl (OH) group, however, absorbed as a very weak and broad band at 3175 – 2287 cm^{-1} due to strong intra-molecular hydrogen bonding within the orthohydroxybenzaldimine Schiff base ligands [13, 14]. In addition, the C-O stretch band for the phenolic OH was observed as a strong band at 1278 - 1249 cm^{-1}.
The spectra of the Cu(II) complexes showed a red shift (- 5 cm^{-1}) for the azomethine frequency of the Schiff ligands indicating coordination via the imine-N of the ligands [8, 14, 15]. In addition, the C-O stretch of the free ligands was observed at a higher frequency in the spectra of the Cu(II) complexes, suggesting coordination of the Schiff base ligands through the deprotonated phenolic–O [8, 14, 16]. This was substantiated by the disappearance of the weak phenolic OH band in the spectra of the complexes. The mode of coordination of the Schiff base ligands

was further corroborated by the appearance of bands in the far-infrared spectra of the complexes due to the M-N and M-O bonds.

The band at 510 - 450 cm^{-1} corresponds to the ν_{Cu-O} of the complexes, while the band due to ν_{Cu-N} was observed at 440 - 390 cm^{-1} [17, 18]. In addition, the band at 360 – 331 cm^{-1} is tentatively assigned to the ν_{Cu-N} of the imidazole ring [19]. Thus, indicating that the Schiff base ligands coordinates as monobasic tridentate (ONN) ligands via the deprotonated –O, imine – and the imidazole-N. The proposed structure for the Cu(II) complexes is presented in figure 1 below.

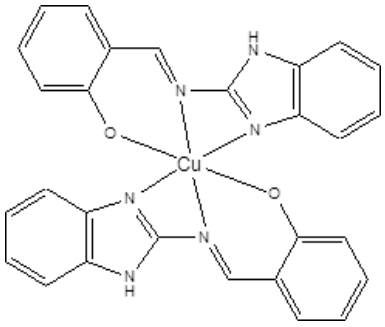


Fig. 1: Proposed molecular structure for the aminobenzimidazole Schiff base Cu(II) complexes

3.5 Electronic spectral study

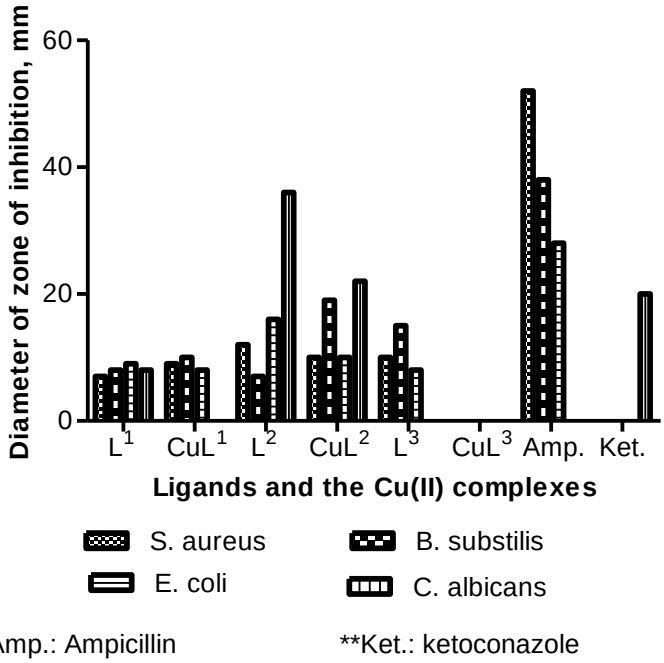
The UV/Visible spectral for the ligands and the Cu(II) complexes are recorded in DMF and the data are presented in section 3.10. The spectra of the ligands exhibit two distinct bands at 282-284 nm and 383- 387 nm corresponding to π→π* and n→π* transitions of the azomethine functional group respectively [20, 21]. The bands, however, undergone red shift in the spectra of the complexes indicating coordination of the Schiff base ligands to the Cu(II) ions. In addition, the spectra of the complexes exhibit two additional bands at 415 - 412 nm and 702 – 692 nm corresponding to charge transfer and d - d transition respectively [17].

3.6 Biological study

The Schiff base ligands and the corresponding Cu(II) complexes were evaluated for their *in vitro* antimicrobial activity against three pathogenic bacterial (*Staphylococcus aureus subsp. aureus* ATCC® 6538™*, *Bacillus subtilis subsp. spizizenii* ATCC® 6633™* and *Escherichia coli* ATCC® 8739™*) and one fungal strains (*Candida albicans* ATCC® 2091™*).

3.6.1 Disc diffusion test

The qualitative susceptibility testing was evaluated using the disc diffusion technique [22]. Each test organism was inoculated onto a nutrient agar plate and incubated at 37 ℃ for 24 hr to obtain the primary culture. Several discrete colonies were harvested from the culture to make a bacterial suspension (10 mL) in a test tube using saline water. The cell density of the suspension was standardized using 0.5 McFarland barium sulphate turbidity standards. The bacterial suspension (0.1 mL) was inoculated onto Mueller Hinton plate and the sterile discs that have been impregnated with the test compounds were firmly placed on it. The assay was inoculated at 37 ℃ for 16 hr and the zone of inhibition was measured as millimeters diameter. Ampicillin and dimethylformamide (DMF) were used as the standard antibacterial drug and control solvent respectively. The test was repeated two more times for those compounds that showed activity of more than 6 mm and their activity was recorded as average zone of inhibition and presented in figure 4 below. The fungus was grown on potato disc assay (PDA) and the incubation was done at 28 ℃ for 48 hr. Ketoconazole was used as standard antifungal drug and the zone of inhibition was measured as millimeters diameter. The result of the disc diffusion test is presented in figure 2.



*Amp.: Ampicillin **Ket.: ketoconazole

Fig. 2: Disc diffusion result showing the antimicrobial activity of the compounds against the tested micro-organisms.

The disc diffusion result for the aminobenzimidazole derived Schiff base ligands showed that the *o*-vanillin analogue exhibited the highest antimicrobial activity against the tested micro-organisms. The ligand was prominently potent against the anti-fungal strain, *Candida albicans*; exhibiting higher activity than the commercially available antifungal drug, ketoconazole. The Salicylaldehyde based ligand was moderately active against the micro-organisms. It can, therefore, be suggested that the presence of the methoxy group enhanced the antimicrobial activity of the salicylaldimine Schiff base ligand. Furthermore, the *p*-vanillin analogue was almost inactive, less active than the salicylaldimine ligand. This establishes the effect of electronic effect of the 2-methoxy group on the antimicrobial activity of the Schiff base ligands. In the

same vein, the study conducted by Eisa etal [23] indicated that the incorporation of 1,3,4-oxadiazole or 1,2,4-triazole at the 2-position enhanced the antimicrobial activity of the benzimidazole-based compounds. On chelation, however, the presence of the Cu(II) ion did not have a regular effect on the antimicrobial activity of the free ligands. Chelation reduced the antimicrobial activity of the *p*-vanillin ligand and specifically the antifungal activity of the free ligand.

3.6.2 Minimum inhibitory concentration (MIC)

The quantitative antimicrobial activity of the test compounds was evaluated using macro dilution broth method [23]. Two-fold serial dilutions of the compounds were prepared in 96 micro wells plates using sterile nutrient broth as diluent. The plates were inoculated with 5 µL bacterial suspensions containing 106-108 CFUs and incubated at 37 ℃ for 16 – 18 hr. The MIC value was defined as the lowest concentration of the compounds giving complete inhibition of visible growth; the result is presented in table 1 below. The MIC values for the salicylaldimines and the *o*-vanillin compounds varied from 9.766 x 10^{-1} - 3.906 mg/mL, while the *p*-vanillin ligand required 3.906 – 250 mg/mL.

Table 1: MIC values for the compounds, mg/mL

Compounds	*S. aureus*	*B. substilis*	*E.coli*
L^1	7.8125	7.8125	7.8125
$Cu(L^2)_2.H_2O$	1.9531	0.9766	7.8125
L2	7.8125	1.9531	1.9531
$Cu(L^2)_2.H_2O$	3.9063	1.9531	62.50
L^3	125	3.9063	250

4. CONCLUSION

The salicylaldimine Schiff base ligands containing benzimidazole nucleus have been synthesized and characterized with analytical and spectroscopic spectral data. The preliminary study involving molar conductivity and infrared study indicated that the Schiff base ligands coordinated to the Cu(II) ion as monobasic terdentate ligands via the imine-N, the phenolic-O and the azine-N of the benzimidazole moiety. The free ligands exhibited varying antimicrobial activity on the tested organisms from low activity to significant potency. The enhancement of the antimicrobial activity of the salicylaldimine ligand was found to be related to the presence and position of the methoxyl group on the salicylaldehyde moiety. The fungal strain, *Candida albicans*, was significantly susceptible to the 2-methoxyl salicylaldimine analogue. This finding, therefore, may be considered to be the focus for further research in pursuant of the discovery of novel antifungal drug. Lastly, chelation did not enhance the antimicrobial activity of the Schiff base ligands.

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COMPETING INTERESTS

We declare that no compete interests exist for this study.

AUTHORS' CONTRIBUTIONS

Sobola AO designed the study under the guidance of Professor Watkins GM. Sobola AO synthesized the compounds and performed the antimicrobial bioassay. Professor Watkins GM supervised the project. Sobola AO wrote the first draft of the manuscript.

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