Nigerian Journal of Biochemistry and Molecular Biology 2014; 29(2): 170-178

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0189-4757/96 $3.0 + 0.00
Printed in Nigeria

Available online at http://www.nsbmb.org/

NJBMB/046/14

Synthesis, Characterization and Antimicrobial Activity of Amodiaquine and Sulphadoxine Mixed Ligand-metal Complexes

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Abstract: Four mixed ligand metal complexes $[Co(AMD)(SUL)Cl_2]$, $[Cu(AMD)(SUL)Cl_2]$, $[Ni(AMD)(SUL)Cl_2]$ and $[Zn(AMD)(SUL)Cl_2]$ of amodiaquine and sulphadoxine were synthesized. The complexes formed were characterized by solubility and melting point determination, conductivity measurements, infrared, ultraviolet and NMR spectroscopy and elemental analysis. The analytical and spectroscopic data revealed the formation of new complexes. The ligands used were found to acts as monodentates. Sulphadoxine, coordination occurs through the N atom of the NH_2 group in the complexes while for amodiaquine, coordination occurs also through the nitrogen of the quinoline group. Hence, tetrahedral geometry was assigned for all the synthesized complexes, since they also coordinate with the chloride ions. Investigation of the antibacterial study was also carried out which indicated that the synthesized complexes exhibits some inhibitory activities higher than their parent ligands most especially for the Co(II) and Cu(II) complexes.

KEYWORDS: Amodiaquine, Sulphadoxine, Ligand, Antibacterial

1.0 Introduction

Recent advances in medicinal inorganic chemistry demonstrate significant prospects for the utilization of metal complexes as drugs, presenting a flourishing arena for inorganic chemistry. The main targets of present day bioinorganic coordination chemists and pharmaceutical investigations is the discovery and development of better drugs to combat diseases, and this has led to numerous studies on drug-metal complexes (Ovig and Abrahams, 1999). Multi-drug resistance has already been developed in most parts of the world, and the World Health Organization recommends that combination treatment rather than monotherapy should be used in areas where multi-drug resistance is a problem (WHO, 2001). The continuous search for novel and innovative drug delivery systems is predominantly a consequence of the well established fact that the convectional dosage forms are not sufficiently effective in conveying the drug compound to its site of action and this have necessitated the needs to search for more potent drugs (Obaleye *et al.*, 2009). The recognition of the potential employment of coordination compounds in therapeutic application provides useful outlet for basic research in transition metal chemistry.

Over the past decades, there has been an increasing interest in metal-containing antimicrobials and antiplasmodials. This trend was in part initiated by the successes of metal-containing antitumor drugs such as cisplatin. Hence, interest in coordination complexes of known chemotherapeutic agents began to emerge (Farrel *et al.*, 1984; Sanchez-Delgado *et al.*, 1993).

Silver and mercury salts have a long history of use as antibacterial agents (Grier, 1983; Gupta *et al.*, 1999). The use of mercurochrome as a topical disinfectant is now discouraged. Silver sulfadiazine finds use for treatment of severe burns; the polymeric material slowly

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releases the antibacterial Ag+ ion. Silver nitrate is still used in many countries to prevent ophthalmic disease in newborn children (Clement and Jarrett, 1994). The mechanism of action of Ag and Hg is through slow release of the active metal ion-inhibition of thiol function in bacterial cell walls gives a rationale for the specificity of bacteriocidal action.

Air stable Ag(I), Co(II) and Cu(II) complexes of pyrimethamine have been synthesized and characterized (Idemudia and Ajibade, 2010). Based on their electronic spectral results, a linear geometry has been suggested for the Ag(I) complexes, tetrahedral geometry and an octahedral geometry for Co(II) and Cu(II) complexes. The antimicrobial screening of the complexes showed that the Ag(I) complexes have enhanced activity, with $\{[Ag_2(pyrm)2].0.7CH_3OH\}$ showing a stronger antimicrobial potential at an MIC value of 0.03125 mg/ml [1O]. Also, Cefotaxime complexes [M(cefotax)Cl] (M= Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Cd(II)) have been screened for antibacterial activity against several bacteria, and the results are compared with the activity of cefotaxime (Anacona and Silva, 2010).

In the present paper, we describe the synthesis, characterization and antimicrobial activity studies of mixed amodiaquine and sulphadoxine mixed ligand-metal complexes.

2.0 Materials and Methods

2.1 Metal Salts, Reagents and Chemicals

All metal salts, reagents and chemicals are of analytical grade and they were used without further purification. Amodiaquine and sulphadoxine were obtained from Emzor Pharmaceuticals Company Limited, Lagos. Metal salts used include Copper chloride dihydrate $[CuCl_2.2H_2O]$, Cobalt chloride hexahydrate $[CoCl_2.6H_2O]$, Nickel (II) chloride $[NiCl_2.6H_2O]$ and Zinc (II) chloride $[ZnCl_2.H_2O]$were products of sigma and Aldrich, UK. Cultures of the micro-organism used were obtained from the University Teaching Hospital and Department of Microbiology, University of Ilorin, Ilorin, Nigeria. This study was carried out in the STEP B Laboratory, Department of Chemistry, University of Ilorin, Ilorin, Nigeria.

2.2 Instrumentation

The IR spectra of the samples in KBr pellets were obtained in the ranges of 4000-400 cm^{-1} using an IR-435 Shimadzu spectrometer. Metal Analyses were determined by atomic absorption spectroscopy with Perkin-Elmer Spectrometer, model 3110. UV-Vis spectra were obtained on Aquamate v4.60 spectrophotometer. Microanalyses for C, H, N were performed on Perkin Elmer 204C micro-analyser, while NMR measurements were also carried out on a Bruker AV 400 NMR Spectrophotometer.

2.3 Synthesis of Metal Complexes

The complexes were prepared following the reported literature procedures with slight modification (Ibrahim *et al.*, 1995; Obaleye *et al.*, 2007).

2.3.1 Synthesis of $[Cu(AMD)(SUL)Cl_2]$ Complex:

Amodiaquine and Sulphadoxine (2mmol each) were dissolved in 10ml of each of methanol and acetone in a conical flask and 1mmol of $[CuCl_2.2H_2O]$ in 10ml of ethanol in another flask. The bluish coloured solution observed after refluxing for 4 hours was concentrated at 50°C. Precipitate formed was allowed to cool, was filtered, washed and dried. The product formed arising from the following equation was labelled for analysis/characterization.

$$CuCl_2.2H_2O + AMD + SUL \xrightarrow[\text{reflux/4 hrs}]{\text{methanol/acetone}} [Cu(AMD)(SUL)Cl_2]$$

2.3.2. Synthesis of $[Co(AMD)(SUL)Cl_2]$ Complex

Amodiaquine and Sulphadoxine (2mmol each) were dissolved in 10ml of each of methanol and acetone in a conical flask and 1mmol of $[CoCl_2.2H_2O]$ in 10ml of ethanol in another flask. The brown coloured solution observed after refluxing for 4 hours was

concentrated at 50°C and left to stand for 4 days for precipitate formation. Precipitate formed was filtered, washed and dried. The product as represented by the following chemical equation was labelled for analysis/characterization.

$$CoCl_2.2H_2O + AMD + SUL \xrightarrow[\text{reflux/4 hrs}]{\text{methanol/acetone}} [Co(AMD)(SUL)Cl_2]$$

2.3.3 Synthesis of [Zn(AMD)(SUL)Cl_2] Complex

Amodiaquine and Sulphadoxine (2mmol each) were dissolved in 10ml of each of methanol and acetone in a conical flask and 1mmol of [$ZnCl_2.H_2O$] in 10ml of ethanol in another flask. The cream coloured solution observed after refluxing for 4 hours was concentrated at 50°C and left for 48hrs for precipitate formation. The cream coloured precipitate formed was filtered, washed and dried. The product according to the following equation was labelled for analysis/characterization.

$$ZnCl_2.2H_2O + AMD + SUL \xrightarrow[\text{reflux/4 hrs}]{\text{methanol/acetone}} [Zn(AMD)(SUL)Cl_2]$$

2.3.4 Synthesis of [Ni(AMD)(SUL)Cl_2] Complex

Amodiaquine and Sulphadoxine (2mmol each) were dissolved in 10ml of each of methanol and acetone in a conical flask and 1mmol of [$NiCl_2.6H_2O$] in 10ml of ethanol in another flask. The green coloured solution observed after refluxing for 4 hours was concentrated at 50°C and left to stand for 48hrs for precipitate formation. The army green precipitate formed was filtered, washed and dried. The product represented by the chemical reaction was labelled for analysis/characterization.

$$NiCl_2.6H_2O + AMD + SUL \xrightarrow[\text{reflux/4 hrs}]{\text{methanol/acetone}} [Ni(AMD)(SUL)Cl_2]$$

2.4 Antibacterial Activity

The inhibitory activities of the mixed ligand and the metal complex synthesized were determined according to previously reported procedures with slight modification (Adediji *et al.*, 2009; Mohamed and Abdel-Wahab, 2005). The ligand and complexes were screened against three human pathogenic bacteria viz; *Bacillus substilis*, *Escherichia coli*, and *klebsiella pneumonia*.

The filter paper disc agar diffusion method was used. Pure Amodiaquine and Sulphadoxine were used separately as standard for antibacterial activities test. Nutrient agar (NA) was used as basal medium for the cultured bacteria. 0.1cm^3 of each of the compounds was applied to the agar media on which 1.0 cm diameter wells were punched and incubated at 37°C for one to three days. 1.0% w/v of the sterile filtered solutions of the ligands and the metal complexes were made using methanol. Discs with only methanol were used as control. Inhibitory activities were measured (mm) as the diameter of the observed inhibition zone formed around the wall of the seeded agar plates. The antibacterial activities were based on percentage inhibition calculated by using the average diameter of bacterial colony on the growth medium compared with their respective control.

3.0 Results and Discussion

The Cu(II), Co(II), Zn(II) and Ni(II) complexes of Amodiaquine- Sulphadoxine ligands were synthesized by reaction of the metal chlorides with mixed Amodiaquine and Sulphadoxine. The complexes were characterized by AAS, Conductivity, TLC, Infrared, UV-Visible and NMR spectroscopy and antimicrobial studies was investigated. The complexes are generally soluble in methanol, ethanol, acetone and DMSO but insoluble in non-polar organic solvents. The complexes are non-hygroscopic solids with melting points higher than the parent ligands. The physical properties of the various complexes are collected in Tables 1and Table 2. The molar conductance values measured in DMSO solution (1^{-3} M) for these complexes are 4.41×10^{-6}, 3.54×10^{-6}, 5.31×10^{-6} and 3.45×10^{-6} for the Cu, Co, Zn and Ni complexes respectively (Table 2). Similarly, from the results, the complexes are non-electrolytes. Determination of stoichiometric ratio using job's method (Clement and Jarrett, 1994) suggests a 1:2 metal to ligand stoichiometry for the complexes.

Table 1: Solubility of the ligands and drug-metal complexes

COMPOUND	Distilled H_2O		Methanol		Acetone		Ethanol		DMSO	
	Cold	Hot	Cold	Hot	Cold	Hot	Cold	Hot	Cold	Hot
Amodiaquine	NS	NS	NS	NS	NS	S	NS	NS	SS	S
Sulphadoxine	NS	NS	NS	NS	NS	NS	NS	NS	SS	S
[Cu(AMD)(SUL)Cl_2]	NS	NS	NS	NS	NS	NS	NS	NS	S	S
[Co(AMD)(SUL)Cl_2]	NS	NS	NS	S	NS	S	NS	NS	S	S
[Zn(AMD)(SUL)Cl_2]	NS	NS	NS	SS	NS	S	NS	NS	SS	S
[Ni(AMD)(SUL)Cl_2]	NS	NS	NS	S	NS	S	NS	NS	S	S

Table 2: Some Physical Properties of ligands and drug-metal complexes

COMPOUND	Colour	Melting point (°C)	Conductivity $\Omega^{-1}mol^{-1}cm^2$	% Yield	TLC R_f
Amodiaquine	Yellow	210-212	6.10	-	0.34
Sulphadoxine	White	237-238	4.83	-	0.47
[Cu(AMD)(SUL)Cl_2]	Blue	267-269	3.46	68	0.35
[Co(AMD)(SUL)Cl_2]	Brown	270-271	4.10	61	0.34
[Zn(AMD)(SUL)Cl_2]	Cream	251-253	4.31	77	0.36
[Ni(AMD)(SUL)Cl_2]	Green	310-312	3.58	64	0.48

Table 3: UV-Visible spectra of the ligands and drug-metal complexes

COMPOUND	WAVELENGTH (nm)	ENERGIES (cm^{-1})	ASSIGNMENT
Amodiaquine	205	48780	$\pi \rightarrow \pi^*$
	325	33223	$n \rightarrow \pi^*$
	364	27473	$n \rightarrow \pi^*$
Sulphadoxine	235	42553	$\pi \rightarrow \pi^*$
	304	32895	$n \rightarrow \pi^*$
[Cu(AMD)(SUL)Cl_2]	325	30769	$n \rightarrow \pi^*$
	820	12195	$^2E_g \rightarrow {}^2T_{2g}$
[Co(AMD)(SUL)Cl_2]	499	20040	$^4T_{1g} \rightarrow {}^4A_{2g}$
	679	14738	$^4T_{1g} \rightarrow {}^4T_{2g}$
[Zn(AMD)(SUL)Cl_2]	256	39063	$\pi \rightarrow \pi^*$
	430	23256	$^2T_2g \rightarrow {}^2Eg$
[Ni(AMD)(SUL)Cl_2]	562	17800	$^3T_1(F) \rightarrow {}^3T_1(P)$
	602	16600	$^3T_1(F) \rightarrow {}^3T_2(F)$

Table 4: Infrared spectra data for the ligands and drug-metal complexes

COMPOUND	ν(N-H)	ν(S=O)	ν(C=O)	ν(C-O)	ν(C-N)	ν(O-H)	ν(M-N)
Amodiaquine	3356.02 s	-	1262.31 s	1270.10 s,b	1220.98 b	3426.04 s,b	-
Sulphadoxine	3625.80 m,b	1195.76w ,b	1396.79 s	1218.19 s,b	1173.60 s	3484.29 s,b	-
[Cu(AMD)(SUL)Cl_2]	3538.68 s	1184.82 s,b	1268.55 s	1126.52 m,b	1108.47 m	3429.94 s,b	697.52 m,b
[Co(AMD)(SUL)Cl_2]	3413.14 s	1205.93w ,b	1356.61 s	-	1127.76 m	3452.17 w,b	687.45 m
[Zn(AMD)(SUL)Cl_2]	3403.53 s	1196.55 w,b	1357.77 s	1157.71 s	1127.56 w	3441.04 s	689.10 m
[Ni(AMD)(SUL)Cl_2]	3465.73 s	1212.45	1326.32 s	1157.77 w	1108.15 w	3425.03 s,b	691.34 m

Table 5: NMR spectra data of the ligands and drug-metal complexes

COMPOUND	CH(δ,ppm) I-benzene	CH(δ,ppm) Quinoline	CH (δ, ppm) 4-pyrimidine	CH_3(δ,ppm) Methyl	NH(δ,ppm) Aromatic C-NH	OH(δ, ppm) Hydroxyl
Amodiaquine	7.26	8.00	-	1.00	4.00	5.00
Sulphadoxine	6.78	-	7.64	3.73	4.10	-
[Cu(AMD)(SUL)Cl_2]	7.26 6.74	8.64 8.00	7.64	1.20 3.73	4.12	5.00
[Co(AMD)(SUL)Cl_2]	7.22 6.71	8.64 8.00	7.44	1.20 3.72	4.18	5.00
[Zn(AMD)(SUL)Cl_2]	7.26 6.74	8.64 8.00	7.66	1.22 3.72	4.12	5.00
[Ni(AMD)(SUL)Cl_2]	7.26 6.74	8.64 8.00	7.40	1.20 3.70	4.10	5.00

Table 6: Elemental constituents of the ligands and drug-metal complexes

COMPOUND	Carbon found (Calc.)	Hydrogen found (Calc.)	Nitrogen found (Calc.)	Metal content found (calculated)
Amodiaquine	67.01 (67.50)	6.20 (6.23)	11.48 (11.81)	-
Sulphadoxine	48.90 (46.44)	6.43 (4.55)	18.62 (18.05)	-
[Cu(AMD)(SUL)Cl_2]	48.93 (48.13)	4.31 (4.29)	12.34 (12.28)	8.14 (7.96)
[Co(AMD)(SUL)Cl_2]	49.20 (48.41)	4.64 (4.32)	12.68 (12.35)	7.69 (7.42)
[Zn(AMD)(SUL)Cl_2]	48.86 (48.01)	4.30 (4.28)	12.38 (12.25)	8.56 (8.17)
[Ni(AMD)(SUL)Cl_2]	48.61 (48.42)	4.45 (4.32)	12.62 (12.35)	8.56 (7.39)

Table 7: Zones of inhibition of the bacterial species by the ligands and drug-metal complexes

COMPOUNDS	*Escherichia coli (mm)* (-ve)				*Staphylococcus (mm)* (-ve)				*Klebsiella (mm)* (-ve)			
	20	40	50	100	20	40	50	100	20	40	50	100
Amodiaquine	0	0	4.2	7.8	0	0	0	4.5	0	4.5	0	0
Sulphadoxine	0	3.4	0	2.0	2.5	2.7	6.2	0	4.5	0	0	0
$[Cu(AMD)(SUL)Cl_2]$	26.8	22.2	13.5	37.0	0	0	0	0	15.5	17.0	7.8	17.6
$[Co(AMD)(SUL)Cl_2]$	23.4	25.6	14.4	38.5	0	0	0	0	16.5	15.7	7.2	15.3
$[Zn(AMD)(SUL)Cl_2]$	0	0	34.9	35.6	0	0	0	3.1	15.7	16.9	8.9	16.9
$[Ni(AMD)(SUL)Cl_2]$	26.8	22.2	13.5	37.0	0	0	8.4	0	15.5	17.9	7.8	17.0

The proposed structures of the complexes are shown in Figures 1.

The results of the UV-Vis spectra of amodiaquine in methanol present three absorption bands maxima at 205, 325 and 364 which were assigned to $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions respectively. The UV-Vis spectra of sulphadoxine in acetone present two absorption band maxima at 235 and 304 which were also assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions respectively. Copper (II) complex exhibits two absorption bands at 325nm and 820nm which may be tentatively assigned to $n \rightarrow \pi^*$ and $^2E_g \rightarrow {}^2T_{2g}$ transitions respectively. The cobalt (II) complex also exhibits two bands at 499 nm and 679 nm. These bands are assigned to $^4T_{1g} \rightarrow {}^4A_{2g}$ and $^4T_{1g} \rightarrow {}^4T_{2g}$ transitions respectively. Zinc (II) exhibits two absorption bands centered at 256nm and 430nm which may also be assigned to $n \rightarrow \pi^*$ and $^2T_2g \rightarrow {}^2Eg$ transitions respectively. All these characteristic bands observed in the UV-Vis. spectra confirm tetrahedral configuration for Cu (II), Co(II), Zn(II) and Ni(II) complexes respectively.

From the infrared results data, the coordination of Amodiaquine occurs through the nitrogen of the secondary amine group while in Sulphadoxine, coordination occurs also through nitrogen of the primary amine group as shown on the Infrared spectra data. The IR frequency values of both ligands and their complexes have been assigned mainly for those specific frequencies directly involved in complex formation. The infrared spectra of the ligands were compared with those of the metal complexes (Table 4). The spectra data of the ligands and their metal complexes are in agreement with the expected range. The strong band in the range of 3413 to 3625cm^{-1} was attributed to (N-H) stretching vibration (Clement and Jarrett, 1994; Gupta *et al.*, 1999). The same band was observed in the metal complexes spectra at lower wavelength $[Cu(AMD)(SUL)Cl_2]$ (3538.7cm^{-1}), in $[Co(AMD)(SUL)Cl_2]$ (3413.1cm^{-1}), $[Zn(AMD)(SUL)Cl_2]$ (3403.5cm^{-1}) and in $[Ni(AMD)(SUL)Cl_2]$ (3465.7cm^{-1}). The shifting of this group to lower frequency when compared with the Amodiaquine and Sulphadoxine free ligands suggesting a coordination of Cu(II), Co(II) Zn(II) and Ni(II) ions, respectively through nitrogen atom of the respective amine group (Anacona and Silva, 2010; Idemudia and

Ajibade, 2010). However, this observation was confirmed by C-N bending vibration which appeared as medium band at 1120.9cm^{-1} in Amodiaquine and 1173.6 cm^{-1} in Sulphadoxine. The band was observed to have shifted to lower frequencies in the metal complexes coupled with reduction in intensity (Obaleye *et al.*, 2007).

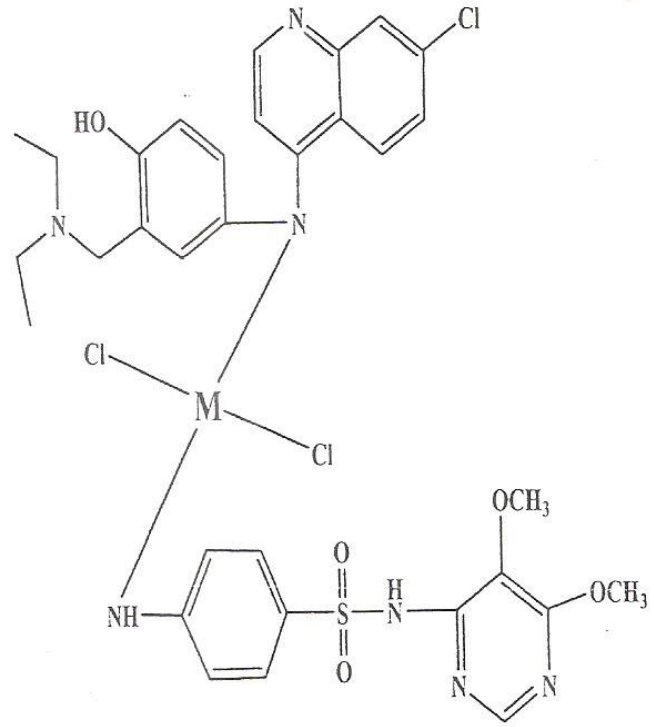
The appearance of C-N bending at this position further supports the involvement of nitrogen atoms in complexation with metal ions under investigation (Gupta *et al.*, 1999). Also, the infrared spectra display strong absorption band at 697.5cm^{-1} [Cu(AMD)(SUL)Cl_2], 687.5cm^{-1} [Co(AMD)(SUL)Cl_2], 689.1cm^{-1} [Zn(AMD)(SUL)Cl_2] and at 691.3 cm^{-1} [Ni(AMD)(SUL)Cl_2] attributed to M-N vibration[12]. The band was conspicuously absent in the spectra of the ligands. The appearance of M-N vibration further supports the involvement of nitrogen in the complexation. Thus, indicating that these amine groups are involved in coordination of all complexes. Other bands observed in the spectra of the ligands were also observed in the metal complexes with shifting in their position due to the effect of complexation.

The results of the C, H, N elemental analysis (as shown in Table 6) of the complexes also agreed well with 1:1:1 metal to ligands stoichiometry for all the complexes.

From the result in Table 7, it is evident that the overall zone of inhibition against bacterial species is highest in Co(II) complex, followed by Cu(II) complex while Zn(II) complex appears to have the least zone of inhibition. The synthesized complexes showed least or no inhibition activity against the staphylococcus species. It is also evident that nearly all the metal complexes posses significant zone of inhibition acting against bacterial species than their parent ligands thus, giving the metal-chelators potentiality as antidotes for metal-overload.

The results obtained from spectroscopic analysis for this study revealed that coordination of Amodiaquine occurs through the nitrogen of the quinoline group while in Sulphadoxine, coordination occurs through the N atom of the NH_2 group for all the metal complexes of [Co(AMD)(SUL)Cl_2], [Cu(AMD)(SUL)Cl_2], [Ni(AMD)(SUL)Cl_2] and [Zn(AMD)(SUL)Cl_2] synthesized to give an tetrahedral geometry, with each ligand acting as monodentate. This mode of coordination corresponds with those in literature (Adediji *et al.*, 2009; Mohamed and Abdel-Wahab, 2005). Evidence of formation of complex was demonstrated by examining the IR and UV spectra carefully. The suggested structure is shown in Figure 1.

In conclusion, the future development of medicinal inorganic chemistry requires an understanding of the physiological processing of metal complexes, to provide a rational basis for the design of new metal-based drugs. Application of new methodologies such as combinatorial chemistry, extensively used in organic drug discovery, will be beneficial for the development of inorganic compounds as therapeutics. This research has provided added data in the quest for novel metallotherapeuticals of mixed ligand complexes. The synthesized complexes shows enhanced inhibitory activities against the tested micro-organisms than the parent ligand.



Where M = Cu(II), Co(II), Zn(II) and Ni(II)

Figure 1: The proposed structure of the Complex

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