

SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL STUDIES OF HETEROLEPTIC CO(II), NI(II), CU(II) AND ZN(II) COMPLEXES OF N-(2-HYDROXYBENZYLIDENE)PYRAZINE-2-CARBOXAMIDE

Chioma Festus

¹Department of Chemistry, Ignatius Ajuru University of Education, P.M.B 5047 Rumuolumeni, Port Harcourt, Rivers State, Nigeria

Corresponding Author: festchi@yahoo.com

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ABSTRACT

The divalent Co, Ni, Cu and Zn complexes with the Schiff base ligand; N-(2-hydroxybenzylidene)pyrazine-2-carboxamide (HL) and 2,2' bipyridine have been synthesized. The HL ligand and its metal (II) complexes were all synthesised using methanolic solvent at 55°C and constant stirring. The resulting heteroleptic complexes were characterized by magnetic moment and conductivity measurements, IR and UV-visible spectral studies. The Schiff base ligand, HL acts as a bidentate monobasic ligand, coordinating through the azomethine nitrogen and deprotonated naphthol oxygen atoms, while the bidendate 2,2' bipyridine ligand (L') coordinated through its aromatic nitrogen atoms with the metal ions respectively. The heteroleptic metal complexes were non-electrolytic in dimethylsulphoxide (DMSO). The analytical and spectral data indicates that all the complexes were mononuclear, covalent, and octahedral and coordinated with the ligands in 1:1:1 molar ratio respectively. The in vitro antibacterial activity of the synthesized compounds were investigated against strains of *Bacillus cereus*, *Proteus mirabilis*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsilla oxytoca* and *Pseudomonas aeruginosa*. The antibacterial activity of the Schiff base and the complexes compared favourably with that of standard drug, streptomycin against *Bacillus cereus*, *Proteus mirabilis* and *Pseudomonas aeruginosa*. The studied divalent cobalt and copper complexes had the best antibacterial activity against the screened microbes with inhibitory zone range of 23.3–28.3 mm.

Keywords: Pyrazine, Schiff base, Heteroleptic, Bidendate, In-vitro and Octahedral geometry

INTRODUCTION

Pyrazines occur ubiquitously in nature as part of various polycyclic compounds [1]. They constitute an important class of heterocyclic nitrogen-containing aromatic compounds. Derivatives of pyrazine have long been recognized to exhibit different biological and/or industrial applications as antimycobacterial, fungicides and growth inhibitors. They have also been used to impact flavour (odour) in pharmaceuticals, perfumes, cosmetics, and insecticides and in food systems [2-5]. Apparently, the presence of two nitrogen atoms in pyrazine compounds at positions 1 and 4 are responsible for their various pharmacological applications mostly against antibiotic resistant infections [6-7]. Synthetic substituted pyrazine derivatives are reported as good corrosion inhibitors, antioxidants, therapeutic drugs for viral, cancer, mycobacterial and auxin related diseases/behaviour

[8-9]. Synthesis of pyrazine Schiff base and their metal complexes have attracted considerable attention from bio-inorganic and medicinal chemists due their similarity to natural systems/products, DNA strand breakage activity and their influence to apoptosis [10]. Pharmacological activities displayed by a large number of structurally novel pyrazinyl derivatives suggest these compounds may affect the DNA function of many mammalian cellular systems.

It has been reported that, *O* and *N* atoms display important roles in coordination of metal atoms/ions at functional sites of metallo-biomolecules [11-12]. Aminopyrazines, typical amine compounds act as potent metal chelators and are reported to form stable Schiff base ligands [13]. Schiff base metal complexes generally have exhibited vital roles in pharmaceutical, agricultural and industrial sectors [14]. The importance of these complexes are not only limited to the development of coordination chemistry, but also in enzymatic and catalytic reactions, magnetism and molecular architectures as well as interesting biological activities. There are dealt of information on metal complexes of Schiff bases derived from pyrazine and its derivatives.

Consequently, in recognition of the versatile significance of pyrazine and its derivatives, the authors herein report the synthesis, characterization and antibacterial studies of the Schiff base ligand, HL (derived from 2-hydroxybenzaldehyde and pyrazine-2-carboxamide) and their heteroleptic Co(II), Ni(II), Cu(II) and Zn(II) complexes with bidentate 2,2'-bipyridine. This work is thus an extension of our previous studies [15], in which there was no mixed ligand systems in order to investigate the effect of the mixed-electron ligand system on geometries and physico-chemical properties and to derive divalent metal complexes with better antibacterial, antifungal and antioxidant activities.. The ligand and its divalent metal complexes are new, being reported for the first time.

MATERIAL AND METHODS

Chemicals

The reagents: Salicylaldehyde (2-hydroxybenzaldehyde), pyrazine-2-carboxamide, cobalt (II) chloride hexahydrate, nickel(II) chloride hexahydrate, copper (II) chloride dehydrate, zinc (II) acetate dehydrate, acetic acid and triethylamine were all analytical grade products and purchased from Sigma-Aldrich, British Drug Houses (BDH) or Merck chemicals.

All the chemical solvents were used as received without further purifications exception of methanol that was purified by distillation.

Physical measurements

The ultraviolet (190-400 nm) and visible (400-900 nm) absorption (UV-Vis) spectra have been obtained on a Perkin Elmer λ 25 spectrophotometer. The infrared spectra of HL, L^I and their divalent-heteroleptic metal complexes (KBr pellets) were obtained at the range 4000-400 cm⁻¹ on a Perkin Elmer FT-IR spectrum BX spectrophotometer. Magnetic susceptibilities were measured on a Sherwood susceptibility balance MSB Mark 1 at room temperature of 29°C and diamagnetic corrections were calculated using Pascal's, constant [16], while electrolytic conductivities of the synthesized compounds in DMSO (1×10⁻³ M) were obtained on a HANNA HI 991300 conductivity meter with a cell constant of 1.0. The ligands and their heteroleptic metal (II) complexes were evaluated for melting points (uncorrected) using Digital melting point machine in an open glass capillary tubes. Complexometric titration with EDTA was employed for the quantitative percentage determination of divalent Co, Ni, Cu and Zn in the synthesized complexes. The synthesized compounds were also tested for solubility in polar and non-polar organic solvents. All the physical measurements were carried out at the Department of Chemistry, University of Ibadan, Nigeria.

SYNTHESIS

Synthesis of *N*-(2-hydroxybenzylidene)pyrazine-2-carboxamide; HL

A homogeneous solution of pyrazine-2-carboxamide (0.017mol, 3.0g) and salicylaldehyde (0.017mol, 2.1g) in 45 mL methanol was refluxed for 4 h with the addition of few drops of glacial acid (catalyst). The product *N*-(2-hydroxybenzylidene)pyrazine-2-carboxamide obtained on cooling in ice (300 K), was filtered, washed with methanol and dried in *vacuo* over anhydrous calcium chloride in a desiccator.

Syntheses of the Heteroleptic Divalent Metal Complexes

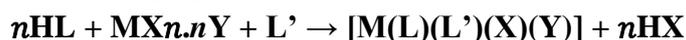
The heteroleptic divalent metal complexes were synthesized as described by literature [17] with little modifications. The Co(II) complex was synthesised by refluxing a warm methanolic solution (60°C) of the appropriate metal(II) chloride (Co; 0.0018mol, 0.42g), the Schiff base (HL; 0.4g, 0.017mol) and 2,2' bipyridine (L'; 0.27g, 0.00176mol) in the mole ratio 1:1:1. The reaction mixture was refluxed for 6 h. The solid precipitates formed were collected on filtration, recrystallized with MeOH and dried over anhydrous calcium chloride in desiccator. The Ni(II) and Cu(II) complexes were synthesized from their chloride salts, while Zn(II) complex was synthesized from its acetate salt using the procedure described by Osowole and Festus [16]. The analytical data are presented in Table 1 below

ANTIBACTERIAL STUDIES

Antibacterial assay: The antibacterial activity of the ligands (HL and L') and their heteroleptic Co(II), Ni(II), Cu(II) and Zn(II) complexes against *Bacillus cereus*, *Proteus mirabilis*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsilla oxytoca* and *Pseudomonas aeruginosa* were determined as described by Aderoju and Chioma [17] with slight modifications. Employing Agar well diffusion method, 0.3 mL of 18-20 h old standard test bacteria cultures were uniformly inoculated on the surface of the Muller Hinton's agar in petri dish [18] 0.06 mL of the 10 mg/mL solution of each complex prepared in dimethyl sulphoxide (DMSO) was poured into 6mm wells bored on the agar. The plates were allowed to stand on the bench for 45min. before incubation at 35°C for 48 h after which inhibition zone growth in diameter (mm) was measured as antibacterial activity. All antibacterial activities were calculated as mean of three replicates with streptomycin used as reference drug. The results are presented in Table 3.

RESULTS AND DISCUSSION

The reaction of the ligands (HL and L') and the divalent transition metal atoms in methanolic solution proceeded in a 1:1:1 stoichiometric ratio to afford heteroleptic metal complexes as represented by the equation below [19].



where $n = 1(\text{HL}), = 2(\text{X}), = 6(\text{Y for Co and Ni}), = 2(\text{Y for Cu and Zn})$; M = Co(II), Ni(II), Cu(II) and Zn(II); HL = Schiff base; L' = 2,2'-bipyridine; X = corresponding anion of metal salt and Y = H₂O molecule(s). All the synthesized compounds exhibited various shades of colours, melting points, and solubility different from that of the starting materials. Low molar conductance values (9.01-15.4 Ohm⁻¹cm²mol⁻¹) of the heteroleptic divalent metal complexes in DMSO, indicate their non-electrolytic nature and corroborates covalence [20]. The analytical data are presented in Table 1.

Table 1. Analytical Data for the Ligands, HL and L' and their Divalent Metal Complexes

Compound (Empirical Formula)	Colour	Molecular Weight (g/mol)	Yield (%)	M.Pt/ D.T. (°C)	BM (μ_{eff})	% Metal (Cal.)	Λ_m
HL	Bright	227.218	58.5	213-	-	-	-
$C_{12}H_9N_3O_2$	Yellow			215			
L'	White	156.18	-	63-65	-	-	-
$C_{10}H_8N_2$							
[Co(L)(L')(Cl)(H ₂ O)]	Ochre	512.852	74.9	337-	4.87	11.78	15.4
[Co(C ₂₂ H ₁₈ N ₅ O ₃ Cl)].H ₂ O	Brown			339		(11.49)	
[Ni(L)(L')(Cl)(H ₂ O)]	Scarlet	494.618	69.2	348-	3.69	11.52	10.0
[Ni(C ₂₂ H ₁₈ N ₅ O ₃ Cl)]	Red			350		(11.86)	5
[Cu(L)(L')(Cl)(H ₂ O)]	Platinum	517.462	57.1	297-	2.04	11.93	9.01
[Cu(C ₂₂ H ₁₈ N ₅ O ₃ Cl)].H ₂ O	Gray			299		(12.27)	
[Zn(L)(L')(CH ₃ CO ₂)]	Coral	506.804	63.7	321-	D	12.61	11.9
[Zn(C ₂₄ H ₁₉ N ₅ O ₄)]	Pink			323		(12.89)	

Cl = Chloride; L' = 2,2'-Bipyridine; HL = Schiff Base Ligand, M.Pt/D.T(°C) = Melting Point / Decomposition Temperature, BM(μ_{eff}) = Bohr Magneton, Λ_m = Molar Conductance

Infrared Spectra

Infrared spectral studies have great significance in the evaluation of important characteristic frequency needed for comparative interpretation of the bond nature of Schiff base ligands and their metal complexes, molecular symmetry, electron distribution and stability of the formed complexes. The infrared spectra comparative analyses for the free ligands (HL and L) and their divalent metal complexes are shown in Table 2. The intense absorption band characteristic of azomethine group ($-C=N-$) stretching vibrations was observed at 1631 cm^{-1} in the spectrum of the Schiff base ligand. However, the band due to $-C=N-$ shifted towards higher wavenumbers ($1644 - 1663\text{ cm}^{-1}$) in the spectra of the heteroleptic divalent metal complexes [21]. This confirms coordination of the nitrogen atom of this moiety ($-C=N-$) with the divalent metal ions [22]. The 2-hydroxybenzaldehyde also known as salicylaldehyde exhibits bands around 1700 cm^{-1} characteristic of $C=O$, while the amide $C=O$ band of the pyrazine-2-carboxamide was observed as a doublet at 1623 cm^{-1} indicative of its partially overlap with the N-H band [23-24]. The amide ($C=O$) band remained un-shifted both in the spectra of the HL ligand and metal complexes corroborating non-participation of the amide oxygen atom in the HL ligand and metal complexes formations. A broadband observed at 3439 cm^{-1} assignable to $\nu O-H$ in the free Schiff base was not observed in the spectra of the investigated heteroleptic divalent metal complexes. Rather the appearance of non-ligand band around 1269 cm^{-1} attributable to $\nu(C-O)$ stretching vibrations was observed in the spectra of the divalent metal complexes. The observed non ligand bands indicate deprotonation and coordination of the hydroxyl oxygen atom of the HL ligand to the divalent metal ions [25]. The broadness of the band was attributed to intra-molecular hydrogen bonding [26]. However, the broad bands observed around $3328 - 3381\text{ cm}^{-1}$ in all complexes were characteristic of νOH of hydrated water molecules in the inner sphere of metal complexes [27]. Subsequently, the bands around $337-362\text{ cm}^{-1}$ region were attributed to $\nu(M-Cl)$ bond formation in heteroleptic divalent metal complexes and corroborates the involvement of chloride atom in coordination [28]. Furthermore, evidence of coordination of the bidentate ligands (HL and L) with the divalent metal ions was indicated by the appearance of weak to medium low wavenumber non-ligand bands. These bands

observed in the ranges 559-566 cm^{-1} and 458- 467 cm^{-1} due to metal-nitrogen $\nu(\text{M-N})$ and metal-oxygen $\nu(\text{M-O})$ vibrations [29] confirmed the participation of the oxygen and azomethine nitrogen atoms in the coordination respectively.

Table 2: Selected Infrared (cm^{-1}) and Electronic ($1000 \text{ cm}^{-1} = 1\text{kk}$) Spectral Data of the Compounds

Compound	νOH	$\nu(\text{C=N})+$ $\nu(\text{C=C})$	$\delta\text{C-H}$	$\nu(\text{M-N})$	$\nu(\text{M-O})$	$\nu(\text{M-Cl})$	Electronic spectra (cm^{-1})
HL	3439	1631, 1415	1050	-	-	-	35100, 27800
L'	-	1644, 1417	1035	-	-	-	34900
[Co(L)(L')(Cl)(H ₂ O)].H ₂ O	3328	1655, 1425	963	563	467	362	38550, 25700, 18600, 15100, 11780
[Ni(L)(L')(Cl)(H ₂ O)]	3381	1652, 1422	965	566	458	335	41500, 33700, 27.400 21720, 16100, 11.900
[Cu(L)(L')(Cl)](H ₂ O)].H ₂ O	3364	1648, 1423	964	560	464	353	34150, 25300, 13800
[Zn(L)(L')(CH ₃ CO ₂)]	3339	1663, 1424	963	559	461	347	38.20, 13.75 (MLCT)

Electronic spectroscopy

The ultraviolet spectra of the ligands (HL and L') and their heteroleptic divalent metal complexes are generally characterized by three transition bands. These bands include intra-ligand bands: $n-\pi^*$ and $\pi-\pi^*$ transitions in the ranges 25300–27800 cm^{-1} and 34100–38550 cm^{-1} of $-\text{C}=\text{O}$, $-\text{C}=\text{N}$ - and $-\text{C}=\text{C}$ - chromophores respectively, and charge transfer transitions in the range 40340-49800 cm^{-1} [30].

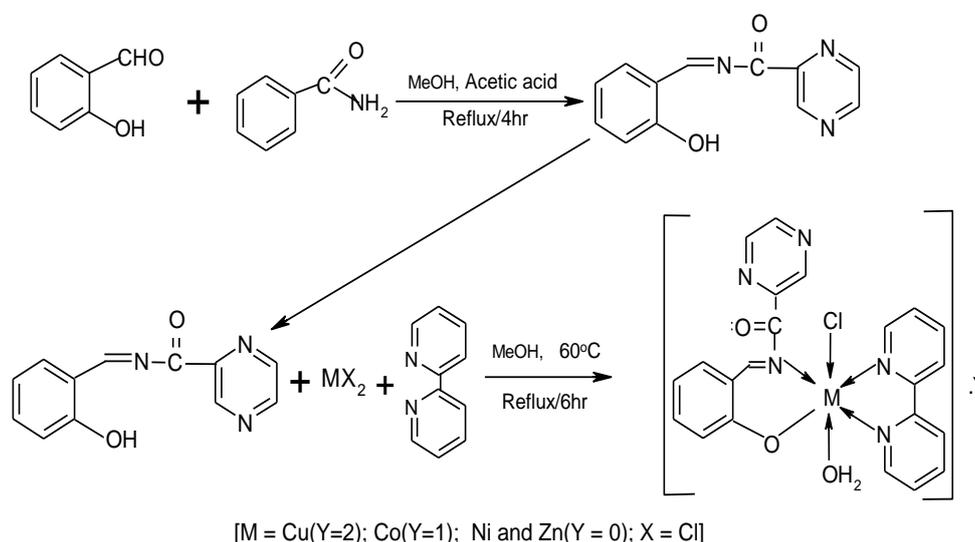
Divalent cobalt forms various complexes of different stereochemical types since ligand field stabilization energies for d^7 configuration do not favour a particular ligand arrangement. The Co (II) ion has a $3d^7$ electronic ($t_{2g}^6 e_g^1$) configuration which in octahedral fields may give rise to either high spin $t_{2g}^5 e_g^2$ or low spin $t_{2g}^6 e_g^1$ complexes with magnetic moment values in the range 4.7-5.2 B.M. The electronic spectrum of the divalent [Co(L)(L')(Cl)(H₂O)].H₂O complex studied displayed three strong bands at 18600, 15100 and 11780 cm^{-1} attributable to ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{2g}$, ${}^4\text{T}_{1g} \rightarrow {}^4\text{A}_{2g}$, and ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{1g}(\text{P})$ transitions respectively and corroborates high spin octahedral geometry around the Co(II) ion [31]. The complex exhibited a magnetic moment of 4.87 BM which is expected for 6-coordinate octahedral geometry and was due to considerable orbital contribution arising from the intrinsic orbital angular momentum in the ground state [32].

Six coordinate octahedral Ni(II) complexes are always high spin complexes with either regular or distorted stereochemistries. However, three spin transitions; ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{2g}$ assigned to the 9000-13000 cm^{-1} band, ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}$ assigned to 14000-20000 cm^{-1} and a band at 21000-27000 cm^{-1} giving the transition ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{P})$ with magnetic moments usually close to the spin-only value of 2.83 B.M are often associated with octahedral Ni(II) complexes. The heteroleptic [Ni(L)(L')(Cl)(H₂O)] complex in the present study exhibited three sharp absorption bands at 21720, 16100 and 11900 cm^{-1} assigned to ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{P})$, ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}$ and ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{2g}$ transitions complementary of octahedral

geometry [33-34]. A magnetic moment of 3.69 B.M. indicates the existence of octahedral \leftrightarrow tetrahedral equilibrium.

The visible electronic spectrum of the d^9 heteroleptic copper complex displayed a single broad absorption band around 13750 cm^{-1} attributed to ${}^2E_g \rightarrow {}^2T_{2g}$ transition consistent with octahedral geometry. The broadness and asymmetric nature of the band indicates that the complex is Jahn Teller distorted from the regular stereochemistry [35]. The latter is due to the presence of the 9th $3d$ electron in the eg -orbital. The Cu (II) complex exhibited a magnetic moment of 2.04 B.M. which was slightly above spin only value corroborates octahedral geometry and consequently mononuclear [36].

The $[\text{Zn}(\text{L})(\text{L}')(\text{CH}_3\text{CO}_2)]$ complex was expectedly diamagnetic in nature with a moment of 0.37 B.M. The electronic spectrum of the synthesized divalent zinc complex exhibited no d-d bands as expected for a d^{10} system but was assigned an octahedral geometry on the basis of analytical and spectral data [37].



Scheme 1: Schematic Representation of Schiff Base and Metal Complexes' Formation

Antibacterial Activities

The antibacterial activities of the ligands and their divalent metal complexes are presented in Table 3 as mean values. Generally, values less than 7mm were considered inactive. The \pm figures are standard deviation values of the duplicate experiments values. Six different microbes; *B. cereus*, *P. mirabilis*, *E. coli*, *S. aureus*, *K. oxytoca* and *P. aeruginosa* were used in the antibacterial screening. The Schiff base ligand, *N*-(2-hydroxybenzylidene)pyrazine-2-carboxamide was more active against two bacteria; *B. cereus* and *S. aureus* with inhibitory zones of 27.4 and 19.4 mm, respectively. Its toxicity was resisted by *P. mirabilis*, *E. coli*, *K. oxytoca* and *P. aeruginosa* and could be attributed to Schiff base ligand's non-permeation through lipid layers of the gram positive bacteria cell wall and the detoxification of the HL ligand by the gram-negative microbes through the secretion of beta lactamase. The 2,2' bipyridine ligand was moderately active against all the screened microbes. The $[\text{Zn}(\text{L})(\text{L}')(\text{CH}_3\text{CO}_2)]$, $[\text{Co}(\text{L})(\text{L}')(\text{Cl})(\text{H}_2\text{O})] \cdot \text{H}_2\text{O}$ and $[\text{Cu}(\text{L})(\text{L}')(\text{Cl})](\text{H}_2\text{O}) \cdot 2\text{H}_2\text{O}$ complexes exhibited enhanced antibacterial activity against *P. mirabilis* and *P. aeruginosa* bacteria, compared with the Schiff base ligand with inhibitory zones of 20.0, 23.3 and 28.3 mm respectively. The latter

is in agreement with chelation theory which increases antibacterial activity due to partial sharing of the metal ion positive charge with donor groups of the ligands, and in turn reduces its polarity and the possible π -electron delocalization over the aromatic rings of the ligands. Thus, it increases the lipophilic character of the complex, and favours its permeation through lipid layers of the bacterial membrane [38]. Generally, the divalent heteroleptic metal complexes were most expectedly effective than the free ligands, exceptions of Cu(II) and Ni(II) complexes that had no activity against *P. mirabilis*, *K. oxytoca* and *P. aeruginosa*.

Table 3: Zones of Inhibition (mm) for the Ligands and their Complexes against screened microbes

Compound	Antibacterial Activities					
	<i>B. cereus</i>	<i>P. mirabilis</i>	<i>E. coli</i>	<i>S. aureus</i>	<i>K. oxytoca</i>	<i>P. aeruginosa</i>
HL	27.4±2.1	21.3±2.1	15.5±1.4	19.4±0.7	7.5±0.7	12.5±2.1
L'	17.5±0.9	19.5±2.1	12±1.4	15.5±2.8	13±0.7	17.0±1.4
[Co(L)(L')(Cl)(H ₂ O)].H ₂ O	17.2±1.4	23.3±3.5	17.5±2.1	11.5±0.7	0.0±0.0	9.5±0.7
[Ni(L)(L')(Cl)(H ₂ O)]	12.1±1.4	0.0±0.0	6.5±0.7	14.3±1.4	16.5±1.4	0.0±0.0
[Cu(L)(L')(Cl)](H ₂ O)].H ₂ O	16.3±1.4	15.0±2.5	18±2.8	9.4±0.7	12.1±1.4	28.3±2.1
[Zn(L)(L')(CH ₃ CO ₂)]	18.2±4.2	20±1.4	13.5±2.8	17.5±2.1	0.0±0.0	16.0±0.7
+streptomycin	44.1±5.6	47.0±1.4	35.5±1.4	30±1.4	46.0±5.6	34.5±2.8

KEY: + = positive control, HL= Schiff base. L' = 2,2'-bipyridine

CONCLUSION

The synthesized divalent heteroleptic Co, Ni, Cu and Zn complexes of the Schiff base ligand, *N*-(2-hydroxybenzylidene)pyrazine-2-carboxamide, (HL) and 2,2' bipyridine, (L') were synthesized and characterized. The coordination of the Schiff base ligand and 2,2' bipyridine via azomethine N and naphthol O atoms and the two aromatic N atoms respectively with the divalent metal ions were corroborated by infrared and electronic spectral measurements. Electronic and infrared spectra data, electrolytic conductance values, room temperature magnetic moment and percentage metal measurements indicates that all the complexes were mononuclear, covalent, and octahedral and coordinated with the ligands in 1:1:1 molar ratio respectively. The *in-vitro* antibacterial results showed that the divalent heteroleptic metal complexes displayed moderate to good activities against screened microbes, proving their potentials as broad-spectrum antibacterial agents with the exception of Cu(II) and Ni(II) complexes that had no activity against *P. mirabilis*, *K. oxytoca* and *P. aeruginosa*.

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