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Synthesis, Characterization, Biological Evaluation, DFT and Molecular Docking sStudies of (Z)-2-((2-bromo-4-chlorophenyl)imino)methyl)-4-chlorophenol and its Co(II), Ni(II), Cu(II), and Zn(II) Complexes

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¹H and ¹³C NMR spectra

NMR spectroscopy is one of the important tools used for the elucidation and authentication of molecular structures and provides information regarding the chemical environment and interaction of atoms within a given molecule. To ascertain the formation of the compounds, NMR spectroscopy was used. The spectra of HL, and its NiL₂ and ZnL₂ are presented in (Figs S6-7, S21-22, and S35-36), respectively. However, due to the paramagnetic nature Co(II) and Cu(II) complexes, their ¹H and ¹³C{H}NMR spectra could not be obtained. Hence, other characterization methods were used to validate their structures.

The ¹H NMR spectrum of the ligand (Fig. S6), displayed characteristic peaks for aromatic protons at 7.03-7.90 ppm, which accounted for all protons in the compound. The signal for azomethine proton was observed as a single peak at 8.94 ppm [1]. Similarly, the phenolic (OH) proton appeared as a single peak downfield at 12.72 ppm [2, 3]. The appearance of the phenolic proton in the downfield region relative to the azomethine proton is due to the oxygen atoms electron withdrawing effect, which causes a decrease in the electron density around the proton's nucleus, resulting in the deshielding of the proton's nucleus by moving downfield. The ¹³C{H}NMR of the ligand (Fig. S7), is characterized by peaks at 158.8 and 163.3 ppm from the

azomethine carbon and aromatic carbon directly linked to the hydroxyl group, respectively [4, 5]. The signals of these carbon peaks appeared in the downfield region of the spectrum as the result of a deshielding effect arising from electronegative nitrogen and nitrogen and oxygen atoms, respectively. Similarly, the signals for carbons atoms of the aromatic ring were observed at 118.7-145.1 ppm and it accounted for all the carbon atoms within the ligand. After complexation, the signal for the phenolic proton which appeared at 12.72 ppm in the ligand, disappear on the spectra of NiL₂ and ZnL₂ complexes (Figs S21 and S35). This is due to deprotonation and subsequent chelation of the ligand to the metal via oxygen atom of the phenolic group [6, 7]. The azomethine protons signals were spotted at 8.55 ppm and 8.73 ppm on the spectra of NiL₂ and ZnL₂ complexes, respectively (Figs S21 and S35). These peaks moved upfield in the spectra of the complexes compared to the 8.94 ppm in the free ligand due to the decrees in electron density on the nitrogen atom arising from coordination to the metal center, leading to the formation of metal to nitrogen (M-L) bond [6, 7]. In addition, the aromatic protons shifted to 7.66-6.10 ppm and 7.76-6.57 ppm in the spectra of NiL₂ and ZnL₂, respectively. These shifts are due the molecular vibration resulting to the formation of the complexes [7]. The summary of this data is presented in Table 3.

IR spectra

The vibrational stretching frequencies associated with the functional groups in the ligand and the complexes were studied in the range of 4000-400 cm⁻¹ of infrared spectrum. The spectra are presented in (Figs S8, S14, S23, S29, and S37), respectively. Some selected vibrational stretching frequencies with their band assignment are given in Table S1. The spectrum of the ligand (Fig. S8), showed a weak broad band at 3018 cm⁻¹ which is due to v(O-H) stretching vibrations [8]. The appearance of this stretching vibration as weak band is due intramolecular

hydrogen bonding between the hydrogen atom of the phenolic group with the azomethine nitrogen (Fig. S1).



Figure. S1: Intramolecular hydrogen bonding in the ligand

The stretching vibration due to v(C=N) group was observed at 1618 cm⁻¹ as a strong and sharp band [2]. The other stretching bands observed at 1463, 1092, and 760 cm⁻¹ are due to the vibrations of v(C-N), v(C-Cl), and v(C-Br), respectively. The spectra of the complexes (Figs. S14, S23, S29, and S37) show the absence of peak due to v(O-H) stretching. The disappearance of this peak in the spectra of the complexes is because of chelation of the ligand to the metal ions through oxygen atom after deprotonation and affirmed the result of the NMR study. The stretching vibration frequency due C=N appeared at 1600-1652 cm⁻¹ region of the spectra of the complexes, compared to 1618 cm⁻¹ in the ligand. This further affirmed the participation of nitrogen atom in the coordination. This result, also, supported the observation made on the NMR study. Similarly, marked shifts were observed in the other stretching bands and this could be due to the vibration of the molecule arising from the complexation. New stretching bands were also observed between 537-524 cm⁻¹ and 468-423 cm⁻¹ in the spectra of the complexes which are assignable to v(M-O) and v(M-N) vibration, respectively [2]. This justified the coordination through (OH) and (C=N), groups.

Compound	OH	C=N	C-N	C-Cl	C-Br	M-O	M-N
HL	3018	1618	1363	1092	760	-	-
CoL ₂	-	1600	1355	1044	789	524	423
NiL ₂	-	1635	1342	1023	784	524	455
CuL ₂	-	1612	1352	1074	823	554	428
ZnL_2	-	1652	1320	1079	754	537	468

Table S1: Some selected vibrational mode (cm⁻¹) of the compounds

UV-Vis spectra

The electronic absorption study was performed using a 10^{-3} M sample solution in dimethyl sulfoxide. The spectrum of ligand (Fig. S9) displayed two distinct bands at 259 and 361 nm, which are due the aromatic moiety and azomethine group, and can be assigned to the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, respectively [9]. Similarly, the spectra of CoL₂, NiL₂, CuL₂, and ZnL₂ complexes (Figs. S15, S24, S30, and S38) revealed three absorption bands each in the range of 237-268 nm, 283-355 nm, and 401-474 nm, which correspond to the $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, and ligand-to-metal charge transfer (LMCT) transitions, respectively [10-12]. The decrease in absorption associated with the azomethine group is caused by a decrease in electron density on the nitrogen atom because of its participation in coordination with a metal ion *via* the lone pair of electrons. Furthermore, all the complexes' formation was justified by the appearance of a new absorption band in the visible region of the spectra.

PXRD and SEM-EDX studies

Several attempts to isolate the crystals of CoL_2 and ZnL_2 suitable for single crystal X-ray diffraction (SCXRD) data collection were futile. To further elucidate their structure and examine their chemical composition, powder X-ray diffraction (PXRD), scanning electron microscopy

(SEM), and energy dispersive X-ray (EDX) analyses were performed. The diffractogram and spectra are presented in (Figs. S11-12, S17-19, S26-27, S32-33, and S39-41) for HL, CoL₂, NIL₂, CuL₂, and ZnL₂, respectively.

The XRD diffraction patterns for the CoL₂ and ZnL₂ complexes were obtained in the $2\Theta = 0.90$ ° range, and the diffractogram are shown in Fig. S2. The complexes' diffraction pattern exhibits several reflections with peaks that are clearly defined and sharply crystalline, ranging from 0 to 60 °, proving that the compounds are crystalline [13]. The average crystallite size (d_{XRD}) of the complexes was also determined using Scherers' formula [14], with the result revealing that CoL₂ has an average crystallite size of 79 nm and ZnL₂ has an average crystallite size of 72 nm. Similarly, the diffractogram of ZnL₂ showed sharp peak peaks compared to CoL₂ diffractogram. This indicates that ZnL₂ has a higher crystallinity than CoL₂[15].



The particle morphology and chemical composition of the ligand were investigated using SEM and EDX analyses, and it was compared to the CoL_2 and ZnL_2 complexes. Figs.S3-4 show SEM images and EDX spectra of HL, CoL_2 , and ZnL_2 . The ligand's particle morphology consists of well-arranged block-like structures in various forms. However, the particle morphology of CoL_2 and ZnL_2 revealed a fine rod-like array of various sizes and shapes scattered across it, indicating the complexes' crystalline nature. This difference in particle morphology between the ligand and

the complexes is indicative of the formation of new material (the complex). The chemical composition of CoL_2 and ZnL_2 were further examined using EDX. The spectra of the complexes show peaks of elements C, N, Cl, Br, O, Co, and Zn, which account for the presence of the elements in the compounds quantitatively and supported their proposed structures.



Figure S3: SEM images of HL (A), CoL_2 (B), and ZnL_2 (C)



Figure S4: EDX spectra of CoL_2 (A) and ZnL_2 (B)

Thermal study

The thermal properties of the free ligand and its complexes were evaluated using thermogravimetric analysis (TGA) in a nitrogen environment from room temperature to 800 °C, and the combined thermogravimetric curve is shown in Fig. S5, and individual thermogravimetric curves are shown in (Figs. S10, S16, S25, and S31), respectively. The curves show that the ligand was stable from 0 to 200 °C and decomposed in a single stage at 220 °C, representing 96.6% molecule decomposition. The thermal behavior of the complexes shows some similarity. Their thermogravimetric curves showed two stages of decomposition. They were all stable from 0 to 220 °C, with the first decomposition stage occurring between 230 and 300 °C and the formation of air-stable residual metal oxides occurring between 310 and 450 °C. The two stages represent the decomposition of the ligand molecules. Overall, the complexes show a clear increase in thermal stability when compared to the ligand.



Figure S5: Thermogravimetric curve of the ligand and its complexes



Figure S8: FTIR of spectrum HL





Figure S11: SEM image of HL



Figure S14: FTIR of spectrum CoL₂









Figure S19: EDX spectra of CoL₂



Figure S21: ¹H NMR spectrum of NiL₂ (500 MHz, DMSO-d₆)



Figure S22: ¹³C NMR spectrum of NiL₂ (125 MHz, DMSO-d₆)









Figure S27: EDX spectra of NiL₂



Figure S28: HRMS spectrum of NiL₂





Figure S30: UV-Vis spectrum of CuL₂







Figure S32: SEM image of CuL₂



Figure S33: EDX spectra of CuL₂



Figure S34: Mass spectrum of CuL₂



Figure S37: FTIR spectrum of ZnL₂



Figure S38: UV-Vis spectrum of ZnL₂



Figure S39: PXRD spectrum of ZnL₂







Figure S41: EDX spectra of ZnL₂



Figure S42: Mass spectrum of ZnL₂

















(v)









(y)





(aa)

(bb)



(cc)















di



(ii)

(jj)



(kk)

(11)













(pp)





(rr)





Ethered

(ss)

(tt)

















(zz)











(ddd)





(fff)

di



(ggg)

(hhh)



(iii)

(jjj)





(111)







di



(000)

Figure S43: Two-dimensional fingerprint plots for the free ligand (HL) (a-v), CuL2 (w-tt) and NiL2 (uu-000)

Table S2: Interaction energies between the atoms within the interaction topology network for

HL

Interaction Energies (kJ/mol) R is the distance between molecular centroids (mean atomic position) in ${\rm \AA}.$

Total	energies, only	reported fo	r two bench	marked ene	ergy models,	are the sum of the
four e	energy comport	nents, scaled	appropriate	ely (see the	e scale factor	table below)

N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
2	-x, y+1/2, -z+1/2	9.37	B3LYP/6-31G(d,p)	-11.0	-2.1	-21.3	18.6	-20.2
2	x, y, z	14.37	B3LYP/6-31G(d,p)	5.6	-0.1	-4.0	0.0	2.4
2	-x, y+1/2, -z+1/2	10.56	B3LYP/6-31G(d,p)	-3.7	-0.9	-11.2	7.7	-9.6
2	x, y, z	3.91	B3LYP/6-31G(d,p)	-3.9	-1.5	-74.7	42.8	-43.8
1	-х, -у, -z	9.82	B3LYP/6-31G(d,p)	-4.3	-0.4	-14.9	13.2	-9.6
1	-x, -y, -z	8.15	B3LYP/6-31G(d,p)	-1.4	-1.2	-19.7	7.9	-14.6
2	x, y, z	14.89	B3LYP/6-31G(d,p)	2.9	-0.1	-4.0	0.0	-0.5
1	-х, -у, -z	9.47	B3LYP/6-31G(d,p)	-4.8	-0.2	-12.9	9.5	-10.6
1	-x, -y, -z	9.50	B3LYP/6-31G(d,p)	-13.0	-2.2	-11.3	15.3	-15.8

Scale factors for benchmarked energy models See Mackenzie et al. IUCrJ (2017)

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

Table S3: Interaction energies between the atoms within the interaction topology network for CuL2

Interaction Energies (kJ/mol) R is the distance between molecular centroids (mean atomic position) in Å.

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
2	x, y, z	13.64	B3LYP/DGDZVP	0.0	-0.8	0.0	0.0	-0.6
4	-x, y+1/2, -z+1/2	11.67	B3LYP/DGDZVP	-15.7	-1.0	-27.5	37.6	-18.1
4	-x, y+1/2, -z+1/2	8.04	B3LYP/DGDZVP	-51.3	-6.5	-82.8	86.7	-77.6
2	x, y, z	10.77	B3LYP/DGDZVP	7.9	-5.2	-32.0	23.1	-9.1

Scale factors for benchmarked energy models

See Mackenzie et al. IUCrJ (2017)

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

Table S4: Interaction energies between the atoms within the interaction topology network for NiL2

Interaction Energies (kJ/mol)

R is the distance between molecular centroids (mean atomic position) in Å.

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
4	-x, y+1/2, -z+1/2	11.47	B3LYP/DGDZVP	-13.5	-0.7	-29.2	39.4	-15.9
2	x, y, z	13.69	B3LYP/DGDZVP	-5.3	-0.5	-17.0	0.0	-20.8
2	x, y, z	9.97	B3LYP/DGDZVP	-3.5	-0.1	-9.6	8.7	-6.7
4	-x, y+1/2, -z+1/2	8.09	B3LYP/DGDZVP	-38.2	-4.1	-81.7	88.3	-60.0
2	x, y, z	10.36	B3LYP/DGDZVP	4.3	-3.2	-31.7	21.4	-12.2

Scale factors for benchmarked energy models

See Mackenzie et al. IUCrJ (2017)

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Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618



Figure S44: Representative culture plates for the *in vitro* studies showing the zone inhibitions



Figure S45: Representative of the 96 well plates for the MIC studies

Compound	HOMO	LUMO	ΔΕ	Ionization	Electron	Electronegativity	Hardness	Softness	Electrophilicity	Nucleophilicity	Chemical
	(eV)	(eV)	(eV)	Potential	Affinity	(χ)	(η)	(δ)	index (ω)	index (N)	Potential (µ)
				(eV)	(EA)			(1×10 ⁻²)			(eV)
L2	-7.73	-1.32	6.41	7.54	0.289	3.91	7.25	1.38	1.06	3.04	-3.91
CoL2	-7.18	-1.38	5.80	-	-	1.34	-	0	0	1.94	-1.34
CuL2	-7.21	-1.45	5.77	-	-	2.33	-	0	0	1.96	-2.33
NiL2	-7.17	-1.36	5.81	6.67	1.27	3.97	5.40	1.85	1.46	3.62	-3.97
ZnL2	-7.09	-1.43	5.66	6.87	1.01	3.94	5.86	1.71	1.32	3.42	-3.94

 Table S5: Comparisons of the energies for highest occupied molecular orbitals, lowest unoccupied molecular orbitals, energy gaps and Ionization Potentials for the compounds



Figure 46: The highest occupied and lowest unoccupied molecular orbitals of the compound

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