

# Homometallic Dinuclear Cu(II) and Zn(II) Complexes Derived from Salophen-type Ligand: Synthesis, Characterization and Anticancer Screening

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## ABSTRACT:

### Introduction:

A series of salophen-type Cu(II) and Zn(II) dinuclear metal complexes of a Schiff base derived from *o*-phenylenediamine were successfully synthesized, characterized and screened for their anticancer activity.

### Methods and Results:

All compounds were characterized physicochemical and spectral techniques namely elemental analysis (C, H, N), magnetic susceptibility (MSB), molar conductivity, thermal gravimetric analysis (TGA), infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy. The shifting of C=N, C-O phenolic and C-O methoxy peaks and the appearance of new peaks assignable to M-N and M-O in IR spectra of the complexes indicated the coordination of azomethine N, phenolic O and methoxy O donor atoms with metal centers. The disappearance of the hydroxyl peak in <sup>1</sup>H NMR spectra of the Zn(II) complex supported the involvement of phenolic O upon formation of the metal complex. The Cu(II) complex was paramagnetic with magnetic moment values of 1.97, close to the theoretical spin only magnetic moment,  $\mu_{so}$ , for Cu(II). The compounds were screened for anticancer activity against human colon cancer cells (HCT116). The Cu(II) complex revealed the highest activity with IC<sub>50</sub> value of  $21.17 \pm 0.76 \mu\text{M}$ .

### Conclusion:

The ligand coordinated as a hexadentate ligand through O and N donor atoms of phenolic, methoxy and azomethine groups. From anticancer screening, it was observed that Cu<sub>2</sub>(OVanOPD) complex exhibited the highest activity followed by OVanOPD ligand and Zn<sub>2</sub>(OVanOPD) complex.

**Keywords:** Schiff base; homometallic dinuclear; polydentate ligand; anticancer; colon cancer

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## 1. Introduction

Transition metal ions with Schiff base ligands have been reported to play an important role in biological applications. These ligands attracted the attention of chemists and biologists due to their wide range of

applications such as anticancer [1] antibacterial [2], antimalarial, antioxidant [3] and antifungal [4] agents. Among those ligands are Salophen-type Schiff bases, which are versatile ligands due to their facile preparation, ability to chelate metal ions through coordination with donor atoms.

In recent years, the number of people suffering from cancer has sharply increased and this disease is considered the leading cause of death worldwide [5], leaving humanity without any choice but to search for new treatment options and strategies.

The employment of small molecules as anticancer agents has great potential, a development pioneered by the discovery of a metal-based compound, cisplatin ( $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$ ), reported by Barnett Rosenberg in 1969. Unfortunately, the use of cisplatin was restricted due to serious side effects such as neurotoxicity and nephrotoxicity, as well as the lack of cell selectivity [6]. These drawbacks have prompted searches for alternative metal-based drugs in the fight against various types of cancer with fewer side effects and better cytotoxic properties [7].

The salophen-type Schiff base ligands derived from 2-hydroxy-3-methoxybenzaldehyde may act as the bidentate [8], tetradentate [9] and hexadentate [10] ligands, to construct mono-, bi- and polynuclear complexes likely due to the presence of azomethine N, phenolic O, and methoxy O donor atoms.

In this paper, we reported the synthesis and characterization of a salophen Schiff base ligand and its copper(II) and zinc(II) complexes containing hexadentate Schiff base ligand with O and N donor atoms. The Schiff base ligand and its complexes were characterized by elemental analysis, magnetic susceptibility, molar conductance, thermal gravimetric analysis, IR, and  $^1\text{H}$  NMR spectroscopy. The anticancer activity of the Schiff base and its metal complexes was studied via an MTT assay method against human colon cancer cell lines, HCT116.

## 2. Materials & Methods

### 2.1 Materials

The chemicals used in this investigation were of analytical grade. Ortho-vanillin (OVan), ortho-phenylenediamine (OPD), copper(II) acetate monohydrate and zinc(II) acetate dihydrate were purchased from Sigma Aldrich (St Louis, US). All

chemicals and solvents were used as purchased without further purification.

Elemental analyses of carbon, hydrogen and nitrogen were performed on a Thermo Finnigan Flash EA 110 Elemental Analyzer. Molar conductance of the complexes was recorded in acetonitrile ( $1 \times 10^{-3}$  M) at room temperature using Mettler Toledo 730 Series conductivity meter, while magnetic measurements were performed on solid complexes using Sherwood Auto balance. Melting points were measured on a Stuart Melting Point SMP10 apparatus and thermal data were collected on a TA Instruments Q50 TGA under nitrogen atmosphere at the heating rate of  $10^\circ\text{C min}^{-1}$  from room temperature to 723 K. The IR spectra were recorded as KBr discs in the range of  $4000\text{--}400\text{ cm}^{-1}$  using Perkin-Elmer FTIR 1600 spectrometer, reported in  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR spectra were recorded on Bruker Avance 500 MHz NMR spectrometer. Chemical shifts ( $\delta$ ) were reported in ppm.

### 2.2 Synthesis of OVanOPD Ligand

OVan (4.5645 g; 30 mmol) and OPD (1.6221 g; 15 mmol) were dissolved in 20 mL of absolute ethanol and the mixture was subjected to reflux for half an hour (Figure 1). The orange precipitate formed was filtered off, washed with cold ethanol and air-dried before being kept in a vial and stored at room temperature.

### 2.3 Synthesis of Metal Complexes

Dinuclear  $\text{Cu}_2(\text{OVanOPD})$  complex was obtained by an insertion reaction between ligand OVanOPD (0.4514g; 1.2 mmol) with copper(II) acetate monohydrate (0.4792g; 2.4 mmol) (Figure 1). The ligand and metal salt were dissolved and refluxed for three hours in 25 mL of a 4:1 ratio of absolute ethanol: chloroform. The mixture was left to cool to room temperature and the brown precipitate obtained was filtered off, washed several times with cold ethanol, air-dried and stored in a desiccator over blue silica gel. The syntheses of the Zn(II) complex were carried out using the same protocol.

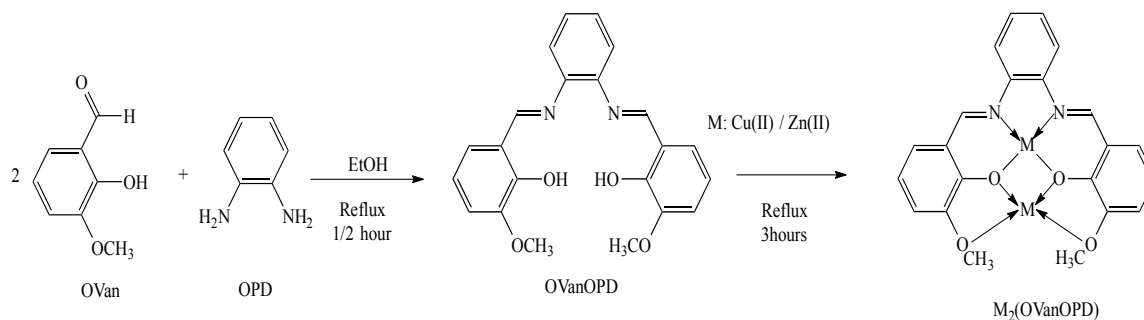


Figure 1. Synthesis of OVanOPD and its metal complexes

**Table 1.** The analytical and physical data of OVanOPD and complexes

Compounds	Molecular Formula (RMM)	Colour	Yield (%)	Melting Point (°C)	Elemental Percentages Found (Calculated)		
					C (%)	H (%)	N (%)
OVanOPD	C <sub>25</sub> H <sub>26</sub> N <sub>2</sub> O <sub>4</sub> (418.49)	Orange	91.53	168-170	69.90 (70.20)	5.36 (5.33)	7.20 (7.44)
Cu <sub>2</sub> (OVanOPD)	C <sub>22</sub> H <sub>18</sub> Cu <sub>2</sub> N <sub>2</sub> O <sub>4</sub> (501.49)	Brown	89.9	>300	53.69 (52.69)	4.47 (3.62)	5.63 (5.59)
Zn <sub>2</sub> (OVanOPD)	C <sub>22</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> Zn <sub>2</sub> (H <sub>2</sub> O) (523.17)	Brown	97.79	>300	50.51 (50.41)	4.48 (3.85)	5.13 (5.35)

**Table 2.** Magnetic susceptibility and molar conductivity value of complexes.

Compound	Molar conductivity, $\Lambda_m$ ( $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$ )	Effective Magnetic moment, $\mu_{\text{eff}}$ (B.M.)	Suggested Geometry
Cu <sub>2</sub> (OVanOPD)	0.23	1.97	Tetrahedral/Square planar
Zn <sub>2</sub> (OVanOPD)	0.26	0.00	-

## 2.4 Cytotoxicity Assay

### 2.4.1 Cell culture

Roswell Park Memorial Institute, RPMI 1640 Medium w/ 25mM HEPES & L-Glutamine, Biowest supplemented with 10% heat-inactivated fetal bovine serum (FBS) (PAA Laboratories), and 1% penicillin/streptomycin, Sigma Aldrich, (St. Louis, US) were used to grow the human colorectal carcinoma cell line, HCT116 (ATCC<sup>®</sup> CCL-247<sup>™</sup>). Cultures were maintained in a humidified incubator at 37 °C in an atmosphere of 5% CO<sub>2</sub>.

### 2.4.2 MTT assay

The methylthiazolyldiphenyl-tetrazolium bromide (MTT) assay was measured according to the procedure described by [11] with some modification. HCT116 cells were plated at 7,000 cells per well and allowed to incubate at 37 °C for 24 hours. Schiff base OvanOPD and its metal complexes were subjected to serial dilutions before being added to each well. The cells were treated with the compounds at concentrations ranging between 0.01-100  $\mu\text{M}$  and incubated at 37 °C for 72 hours.

The cytotoxicity of the compounds was assessed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide, Sigma Aldrich. Briefly, 50  $\mu\text{L}$  of 0.06 mol/L MTT solution (Sigma) was added to each well and plates were incubated at 37 °C for 4 hours. All solutions were aspirated and the formazan crystals were dissolved in DMSO (Merck). Cell viability was evident by the transformation of tetrazolium salt MTT to formazan (colored) by mitochondrial dehydrogenases and the plate was read at 450 nm. Data generated were used to plot a dose-response curve from which the concentration of compounds required to kill 50% of the cell population (IC<sub>50</sub>) was determined.

## 3. Results

The analytical data of OVanOPD and complexes are tabulated in Table 1. The experimental and calculated C, H, and N percentage compositions

were in close accord, indicating that the expected compounds have been obtained. Analytical data suggested a ratio of 2:1 for metal:ligand for the dinuclear OVanOPD complexes. The melting points of the ligands were much lower than those of the metal complexes, as expected, mostly due to the larger molecular size of the complexes and the presence of stronger dative covalent bonds in the latter.

### 3.1. Magnetic Susceptibility and Molar Conductivity

The Cu<sub>2</sub>(OVanOPD) complex revealed a magnetic moment of 1.97 B.M. (Table 2), close to the theoretical spin only magnetic moment,  $\mu_{\text{so}}$ , a value of 1 unpaired electron of 1.73 B.M. This is in agreement with Cu(II)  $d^9$  configuration. Zn<sub>2</sub>(OVanOPD) complex has 0 magnetic moment values,  $\mu_{\text{so}}$ , indicating the absence of unpaired electrons, corresponding to Zn(II)  $d^{10}$  configuration. The experimental molar conductivity data of ligand and metal complexes were low, revealing their non-electrolytic nature (Table 2), much lower than the conductivity value of 40  $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$  expected for a mono-electrolytic species [12].

### 3.2. Infrared Spectroscopy

The important IR bands in ligand and complexes are listed in Table 3. The spectra of the ligand showed a strong peak at 1612  $\text{cm}^{-1}$  corresponding to  $\nu(\text{C}=\text{N})$ , as similarly reported by [13, 14]. Upon complexation, this band was shifted either to lower or higher wave numbers attributed to the bonding of azomethine N to the metal center, in accord with the reports by [15,16]. It is expected that coordination of nitrogen to the metal center through a dative covalent bonding would reduce the electron density in the azomethine bond, weakening it, thus lowering the (C=N) frequency. In the case of  $\nu(\text{C}=\text{N})$ , shifting to higher frequencies, could be tentatively explained by the possible occurrence of  $\pi$  back-bonding from the metal to the nitrogen, strengthening the azomethine bond and increasing the frequency [17].

**Table 3.** The IR analytical data for ligand and complexes.

Compound	Frequency (cm <sup>-1</sup> )				
	$\nu(\text{C}=\text{N})$	$\nu(\text{C}-\text{O})$ Phenolic	$\nu(\text{C}-\text{O})$ Methoxy	$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{O})$
OVanOPD	1612	1248	1205	-	-
Cu <sub>2</sub> (OVanOPD)	1610	1242	1194	535	482
Zn <sub>2</sub> (OVanOPD)	1613	1237	1192	507	462

The shifting of about 8-10 cm<sup>-1</sup> of C-O phenolic and C-O methoxy stretching vibrations to a lower frequency in the spectra of metal complexes was indicative of coordination of metal center through phenolic and methoxy O atoms. The involvement of azomethine N, phenolic O and methoxy O in complexation were supported by the presence of new weak peaks in the region 507-535 cm<sup>-1</sup> and 458-482 cm<sup>-1</sup>, in the spectra of complexes attributed to  $\nu(\text{M}-\text{N})$  and  $\nu(\text{M}-\text{O})$  vibrations, respectively, as reported by Lu (2006) [18]. These peaks were absent in the spectrum of the free ligand.

### 3.3. <sup>1</sup>H NMR Spectroscopy

The <sup>1</sup>H NMR data for OVanOPD and Zn<sub>2</sub>(OVanOPD) were tabulated in Table 4. The spectra of the OVanOPD show a singlet peak at the chemical shift of 11.20 ppm corresponding to the hydroxyl proton. This signal was absent in Zn<sub>2</sub>(OVanOPD) spectra indicating the deprotonation of phenolic proton and involvement of phenolic O in coordination with the metal center, as it

was reported by [18-20].

The azomethine proton of the ligand appeared at 9.93 ppm and this peak was observed to be shifted to lower chemical shifts in the Zn(II) complex inferring shielding by the metal centre bonded through azomethine nitrogen atom via donation of lone pair of electrons to the metal center, an observation similarly reported by [21, 22]. The multiplets at the range 6.47-7.90 ppm in ligand and complex spectrum were assigned to aromatic protons. Two types of aromatic protons were detected i.e. the ones that are ortho (one carbon apart) to each other, having a coupling constant value of 6-10 Hz, and the ones that are meta to each other (two carbon apart), having a coupling constant value of 1-3 Hz. As expected, there were no para (three carbons apart) protons detected in the molecules as no coupling constant with the value of 0-1 Hz were recorded.

The spectra of ligand and complex showed a singlet with an integration equivalent to three hydrogens at 3.93 and 3.77 ppm, respectively, corresponding to the methoxy protons.

**Table 4.** The <sup>1</sup>H NMR data of OVanOPD and Zn<sub>2</sub>(OVanOPD).

Assignments	Chemical shift, (ppm)							
	C <sup>1</sup> -OH	N=C <sup>8</sup> -H	C <sup>3</sup> -H (Ar.)	C <sup>4</sup> -H (Ar.)	C <sup>5</sup> -H (Ar.)	C <sup>10</sup> -H (Ar.)	C <sup>11</sup> -H (Ar.)	C <sup>2</sup> -OCH <sub>3</sub>
OVanOPD	11.20(s)	9.93(s)	7.29(s)	7.20(dd)	7.13(dd)	6.98(t)	-	3.93(s)
Coupling constant, J, (Hz)	-	-	-	7.8, 1.4	8.0, 1.4	7.9	-	-
Number of proton	1	1	1	1	1	1	1	3
Zn <sub>2</sub> (OVanOPD)	-	9.01(s)	7.90(dd)	7.39(dd)	7.05(d)	6.88(d)	6.47(t)	3.77(s)
Coupling constant, J, (Hz)	-	-	5.9, 3.5	6.0, 3.3	8.1	7.5	7.7	-
Number of proton	-	1	1	1	1	1	1	3

Note: Ar.=Aromatic, s=singlet, d=doublet, dd=doublet of doublet, t=triplet

**Table 5.** The decomposition temperature and the percentage weight loss of complexes.

Compounds	Molecular formula	Decomposition temperature (°C)	Weight loss (%)		Lost species
			Found	Calculated	
Zn <sub>2</sub> (OVanOPD)	C <sub>22</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> Zn <sub>2</sub> (H <sub>2</sub> O)	36-80	3.4	3.44	One lattice water molecule

### 3.4. Thermogravimetric Analysis

The thermogravimetric analysis (TGA) was carried out for the  $Zn_2(OVanOPD)$  metal complex to determine the presence and the nature bonding of water molecules in the complex. Generally, two types of water molecules are associated with the complex, either as lattice water or coordinated water molecules. The lattice water was lost at lower temperatures below 150 °C whereas the coordinated water molecule was lost at higher temperatures above 150 °C as reported by [23]. The decomposition temperature and the percentage weight loss of complex are listed in Table 5. The thermogram of  $Zn_2(OVanOPD)$  is displayed in Figure 2.

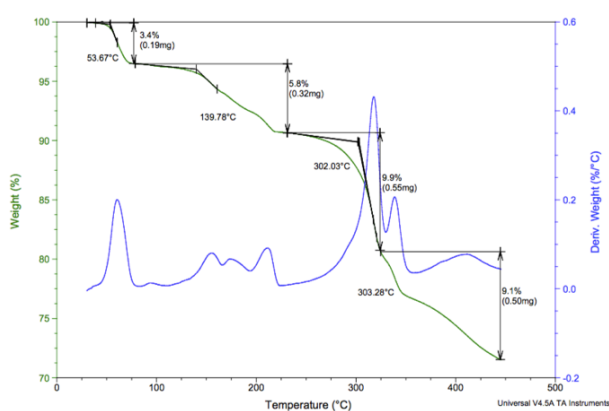


Figure 2. Thermogram of  $Zn_2(OVanOPD)$

## 4. Discussion and Conclusion

The ligand and its corresponding metal complexes were screened for their cytotoxic activity against human colon cancer (HCT116) by MTT assay method using DMSO as a negative control. The  $IC_{50}$  of  $OVanOPD$  and its complexes, from which their respective  $IC_{50}$  and the results were tabulated in Table 6. It was observed that  $Cu_2(OVanOPD)$  complex exhibited the highest activity followed by  $OVanOPD$  ligand and  $Zn_2(OVanOPD)$  complex. All compounds except  $Zn_2(OVanOPD)$  showed better activity than the standard drug, carboplatin ( $IC_{50} > 100\mu M$ ). Zn(II) complex exhibited the lowest anticancer activity, likely due to the low solubility of the complex in DMSO.

In summary, the Schiff base ligand and its copper(II), cobalt(II) and zinc(II) complexes were successfully synthesized and characterized using microanalysis, TGA, IR, and  $^1H$  NMR spectroscopy. The elemental analysis data of the complexes revealed that the compounds have a molar ratio of 2:1 metal to ligand stoichiometry. The ligand coordinated as a hexadentate ligand through O and N donor atoms of phenolic, methoxy and azomethine groups. The copper complex is

paramagnetic with a magnetic moment value 1.97. On the other hand, the zinc complex is diamagnetic. From anticancer screening, it was observed that  $Cu_2(OVanOPD)$  complex exhibited the highest activity followed by  $OVanOPD$  ligand and  $Zn_2(OVanOPD)$  complex.

Table 6.  $IC_{50}$  values of ligand and complexes.

Compounds	$OVanOPD$	$Cu_2(OVanOPD)$	$Zn_2(OVanOPD)$
$IC_{50}$ , $\mu M$	$29.40 \pm 5.90$	$21.17 \pm 0.76$	$> 100$

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## Conflict of interest

There is no conflict of interest.

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