



# Synthesis, spectroscopic characterization and antimicrobial activity of binuclear metal complexes of a new asymmetrical Schiff base ligand: DNA binding affinity of copper(II) complexes



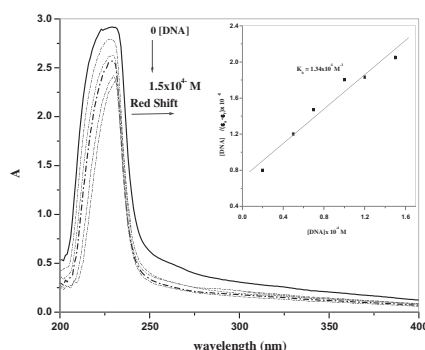
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## HIGHLIGHTS

- A new dicompartmental Schiff base was synthesized and characterized.
- Binuclear complexes were synthesized and characterized.
- The ligand and its complexes showed antibacterial and antifungal activities.
- The DNA-binding properties of copper complexes were investigated.

## GRAPHICAL ABSTRACT



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## ABSTRACT

The 1:1 condensation of *o*-acetoacetylphenol and 1,2-diaminopropane under condition of high dilution gives the mono-condensed Schiff base, (*E*)-3-(1-aminopropan-2-ylimino)-1-(2-hydroxyphenyl)butan-1-one. The mono-condensed Schiff base has been used for further condensation with isatin to obtain the new asymmetrical dicompartmental Schiff base ligand, (*E*)-3-(2-((*E*)-4-(2-hydroxyphenyl)-4-oxobutan-2-ylideneamino)propylimino)indolin-2-one ( $H_3L$ ) with a  $N_2O_3$  donor set. Reactions of the ligand with metal salts give a series of new binuclear complexes. The ligand and its metal complexes were characterized by elemental analyses, IR,  $^1H$  and  $^{13}C$  NMR, electronic, ESR and mass spectra, conductivity and magnetic susceptibility measurements as well as thermal analyses. The analytical and spectroscopic tools showed that the complexes can be formulated as:  $[(HL)(VO)_2(SO_4)(H_2O)] \cdot 4H_2O$ ,  $[(HL)Fe_2Cl_4(H_2O)_3] \cdot EtOH$ ,  $[(HL)Fe_2(ox)Cl_2(H_2O)_3] \cdot 2H_2O$ ,  $[(L)M_2(OAc)(H_2O)_m] \cdot nH_2O$ ;  $M = Co, Ni$  or  $Cu$ ,  $m = 4, 0$  and  $n = 2, 3$ ,  $[(HL)Cu_2Cl]Cl \cdot 6H_2O$  and  $[(L)(UO_2)_2(OAc)(H_2O)_3] \cdot 6H_2O$ . The metal complexes exhibited octahedral geometrical arrangements except copper complexes that exhibited tetrahedral geometries and uranyl complex in which the metal ion is octa-coordinated. The Schiff base and its metal complexes were evaluated for antimicrobial activity against Gram positive bacteria (*Staphylococcus aureus*), Gram negative bacteria (*Escherichia coli*) and fungi (*Candida albicans* and *Aspergillus flavus*). The ligand and some of its complexes were found to be biologically active. The DNA-binding properties of the copper complexes (**6** and **7**) have been investigated by electronic absorption, fluorescence and viscosity measurements. The results obtained indicate that these complexes bind to DNA via an intercalation binding mode with an intrinsic binding constant,  $K_b$  of  $1.34 \times 10^4$  and  $2.5 \times 10^4 M^{-1}$ , respectively.

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## Introduction

For decades, coordination chemistry of Schiff base ligands has been the subject of great interest. This interest comes from the fact that their metal complexes have found various applications in antimicrobial, antifungal and antitumor agents [1], catalysis [2] and several other applications.

Isatin is a versatile lead molecule for designing potential bioactive agents and its derivatives were reported to possess a broad spectrum of antiviral activities [3]. Schiff bases of isatin are known to possess a wide range of pharmacological properties that include antibacterial, antifungal [4,5], anticonvulsant [6] and anti-HIV [7] activities.

The term “dinucleating ligands” was first introduced in 1970 by Robson [8] to describe the class of polydentate chelating ligands which able to bind simultaneously two metal ions. A large number of such ligands have been designed, and their coordination compounds have been thoroughly investigated. Among many different types of dinucleating ligands, the phenol-based compartmental ligands attracted particularly wide attention of scientists. The term “compartmental” was introduced to indicate a ligand containing two adjacent, but dissimilar coordinating sites [9]. Particular interest in this type of ligands resulted from the recent recognition of the asymmetric nature of a number of bimetallic biosites [10].

Deoxyribonucleic acid, DNA, is a molecule of great biological significance since it contains all the genetic information for cellular function. Studies of the interaction between transition metal complexes and DNA have been pursued in recent years [11]. DNA provides a range of binding sites and binding modes for covalent and non-covalent interactions, including intercalation, groove bindings, electrostatic forces and hydrogen bonds, with metal complexes. Interest in the fashion of metal complex binding to DNA has been motivated not only by a desire to understand the basics of these interaction modes but also by the development of metal complexes into anti-inflammatory, antifungi, antibacteria or anticancer reagents. Hence, much of the attention has been targeted on the design of metal-based complexes, particularly copper(II) complexes, which can bind and cleave DNA [12].

The aim of the present work is to synthesize a new asymmetric dicompartmental Schiff base ligand, H<sub>3</sub>L, and its metal complexes with vanadyl(II), iron(III), cobalt(II), nickel(II), copper(II) and uranyl(II) ions. The structures of the ligand and its metal complexes were characterized by elemental and thermal analyses, IR, <sup>1</sup>H and <sup>13</sup>C NMR, electronic, ESR and mass spectra as well as conductivity and magnetic susceptibility measurements at room temperature. The antimicrobial activity of the ligand and its complexes was screened against selected kinds of bacteria and fungi. The interaction between the Cu(II) complexes of the Schiff-base and HS-DNA was investigated by electronic absorption, fluorescence and viscosity measurements.

## Experimental

### Reagents and materials

CuCl<sub>2</sub>·2H<sub>2</sub>O, FeCl<sub>3</sub>·6H<sub>2</sub>O, Cu(OAc)<sub>2</sub>·H<sub>2</sub>O, Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O, Co(OAc)<sub>2</sub>·4H<sub>2</sub>O, UO<sub>2</sub>(OAc)<sub>2</sub>·2H<sub>2</sub>O, VOSO<sub>4</sub>·H<sub>2</sub>O, oxalic acid, ethylacetate, sodium metal, *o*-hydroxyacetophenone, 1,2-diaminopropane and isatin were either BDH or Merck chemicals. *o*-Acetoacetylphenol was prepared following the literature procedure [13]. Organic solvents (ethanol, methanol, chloroform, diethylether, dimethylformamide (DMF) and dimethylsulfoxide (DMSO)) were spectroscopic grade and used without further purification.

### Synthesis of the ligand

*o*-Acetoacetylphenol and the half-unit ligand were prepared according to Ref. [13]. The new Schiff base (*E*)-3-(2-((*E*)-4-(2-hydroxyphenyl)-4-oxobutan-2-ylideneamino)propylimino)indolin-2-one (H<sub>3</sub>L) was prepared by condensation of the half-unit ligand (*E*)-3-(1-aminopropan-2-ylimino)-1-(2-hydroxyphenyl)butan-1-one dissolved in CHCl<sub>3</sub> with isatin. A pale brown precipitate is formed upon cooling the solution slowly to room temperature and the precipitate was filtrated off, washed with ethanol then diethyl ether and finally air-dried. The analytical and physical data of the ligand and its metal complexes are listed in Table 1. Scheme S1 (Supplementary material) represents the synthetic outline of the asymmetric Schiff base ligand.

### Synthesis of the metal complexes

A hot 20 mL ethanolic solution of the metal salt of VO<sup>2+</sup>, Fe(III), Co(II), Ni(II), Cu(II) and UO<sub>2</sub><sup>2+</sup> was gradually added to the solution of the ligand (30 mL) in 1:1 or 1:2 (L:M) molar ratio and the solution was refluxed for 3 h on a water bath during which the solid complex precipitated. The precipitate was filtered off, washed with ethanol then diethyl ether and finally air-dried. The uranyl complex was prepared in methanol as uranyl acetate is more soluble in methanol. The vanadyl complex was prepared in least amount of bidistilled water as VOSO<sub>4</sub>·H<sub>2</sub>O is soluble in water. The following detailed preparations are given as examples and the other complexes were obtained similarly.

#### [(HL)Fe<sub>2</sub>Cl<sub>4</sub>(H<sub>2</sub>O)<sub>3</sub>]·EtOH, **2**

To 0.5 g (1.38 mmol) of the ligand suspended in 25 mL ethanol, was added 0.746 g (2.76 mmol) of FeCl<sub>3</sub>·6H<sub>2</sub>O dissolved in 20 mL ethanol with stirring. The reaction mixture was refluxed for 3 h on a water bath. The precipitate was filtered off, washed with ethanol then ether and finally air-dried. Yield: 0.716 g (72.8%).

#### [(HL)Fe<sub>2</sub>(ox)Cl<sub>2</sub>(H<sub>2</sub>O)<sub>3</sub>]·2H<sub>2</sub>O, **3**

To 0.5 g (1.38 mmol) of the ligand suspended in 25 mL ethanol, was added 0.746 g (2.76 mmol) of FeCl<sub>3</sub>·6H<sub>2</sub>O dissolved in 20 mL ethanol with stirring. The reaction mixture was refluxed for 0.5 h then an aqueous solution of 0.174 g (1.38 mmol) of oxalic acid was added and the resulting mixture was refluxed for 3 h on a water bath. The precipitate was filtered off, washed with water, ethanol then ether and finally air-dried. Yield: 0.755 g (76.0%).

### Analytical and physical measurements

Microanalyses of carbon, hydrogen, nitrogen, chlorine and sulfur were carried out on Vario El Elementar apparatus at the National Research Centre, Dokki, Giza, Egypt. Analyses of the metals followed decomposition of their complexes with concentrated nitric acid. The resultant solution was diluted with bidistilled water and filtered. The solution was then neutralized with aqueous ammonia solution (except iron(III) complexes) and the metal ions titrated with EDTA [14]. The uranium content of the uranyl complex was determined by igniting a definite mass of the complex at ≈1000 °C and weighing the residue as U<sub>2</sub>O<sub>3</sub>. IR spectra were recorded using KBr discs on FT IR Nicolet IS10 spectrometer. Electronic spectra were recorded as solutions in DMF or Nujol mulls on a Jasco UV-Vis spectrophotometer model V-550 UV-Vis. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at room temperature by using a Bruker WP 200 SY spectrometer. Dimethylsulfoxide, DMSO-d<sub>6</sub>, was used as a solvent and tetramethylsilane (TMS) as an internal reference. The spectra were extended from 0 to 18 ppm. The chemical shifts (δ) are given down field relative to TMS. D<sub>2</sub>O was added to every sample to test for the deuteration of the samples. ESR

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