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Screening the DNA interaction ability and antimicrobial activity of a few novel bioactive complexes tethering *N*-((2-aminophenyl)(phenyl)methylene)-4-nitroaniline

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ABSTRACT

Few novel transition metal complexes having *N*-((2-aminophenyl)(phenyl)methylene)-4-nitroaniline were synthesized and characterized by elemental analyses, IR, ^{1}H and ^{13}C NMR, electronic, EPR and mass spectra, conductivity and magnetic susceptibility measurements. All the metal complexes adopted square planar geometrical arrangements. The DNA-binding properties of the metal(II) complexes have been investigated by electronic absorption, fluorescence, CD spectra, cyclic voltammetry, differential pulse voltammogram and viscosity measurements. The results obtained indicate that these complexes bind to DNA *via* an intercalation binding mode. DNA cleavage activities indicate that the metal complexes exhibit greater activity than the ligand. The antimicrobial screening reveals that all the metal complexes exhibit better activity than the free ligand.

1. Introduction

Metal coordination compounds are promising as a new generation of anticancer drugs for effective oxidant therapy. Their anticancer activity may involve direct oxidative DNA damage and/or interference in the redox signaling pathways in cancer cells by novel mechanisms. Particularly, disturbances of the DNA structure induced by metal-based anticancer agents often correlate with anticancer activity. Hence, in designing a drug for the treatment of cancer, DNA is one of the most targeted molecules, which on denaturing can lead to apoptosis [1] and prevent the multiplication of the cancer cells. Cisplatin and its derivatives are such widely used anticancer drugs [2], functioning on the above said principle, which also cause several side effects such as anemia, diarrhea, alopecia, petechia, fatigue nephrotoxicity, emetogenesis, ototoxicity, and neurotoxicity. Consequently, bioinorganic chemists have started to focus their attention on designing DNA targeting metal complexes from bioactive ligands such as Schiff bases [3,4] as they are versatile organic blockers that have recently attracted great attention due to their preparative accessibilities, structural varieties and varied denticities. Schiff base transition metal complexes have suitable biometric properties that can mimic the structural features of the active sites, and they have been widely used in various areas such as biochemical reactions and biological regulators [5].

Among the Schiff base complexes reported, metal Schiff base complexes derived from benzophenone have been extensively studied [6–10]. On the other hand, the monocarboxylic acids are known to have a variety of pharmacological effects especially salicylic acid and its derivatives which have been shown to possess anti-inflammatory and antitumor activity [11]. The biologically active carboxylic acids often become more effective and desirable drugs upon coordinating with a suitable metal centre [12]. Moreover, most of the Schiff base transition metal complexes exhibit three noncovalent binding modes with double-helix DNA namely electrostatic interaction, groove binding and intercalative binding [13]. Among them, the most effective mode of the drugs targeted to DNA is intercalative binding, which is related to the antitumor activity of the compound [14,15].

Based on the above factors, we developed a new series of Cu(II), Ni(II), Co(II) and Zn(II) complexes containing *N*-((2-aminophenyl)(phenyl)methylene)-4-nitroaniline Schiff base ligand and salicylic acid (co-ligand). DNA binding modes of these complexes were evaluated using UV–vis absorption, fluorescence, CD spectra, viscosity measurements, cyclic voltammetry and differential pulse voltammogram. For the free ligand (**L**) and its metal complexes, *in vitro*

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antimicrobial activities have also been studied. In addition, the DNA cleavage activities of the complexes were also tested against pBR322 DNA using gel electrophoresis in the presence of H_2O_2.

2. Experimental protocol

The materials and methods, DNA binding, cleavage and antimicrobial procedures are given in the Supplementary file (S1).

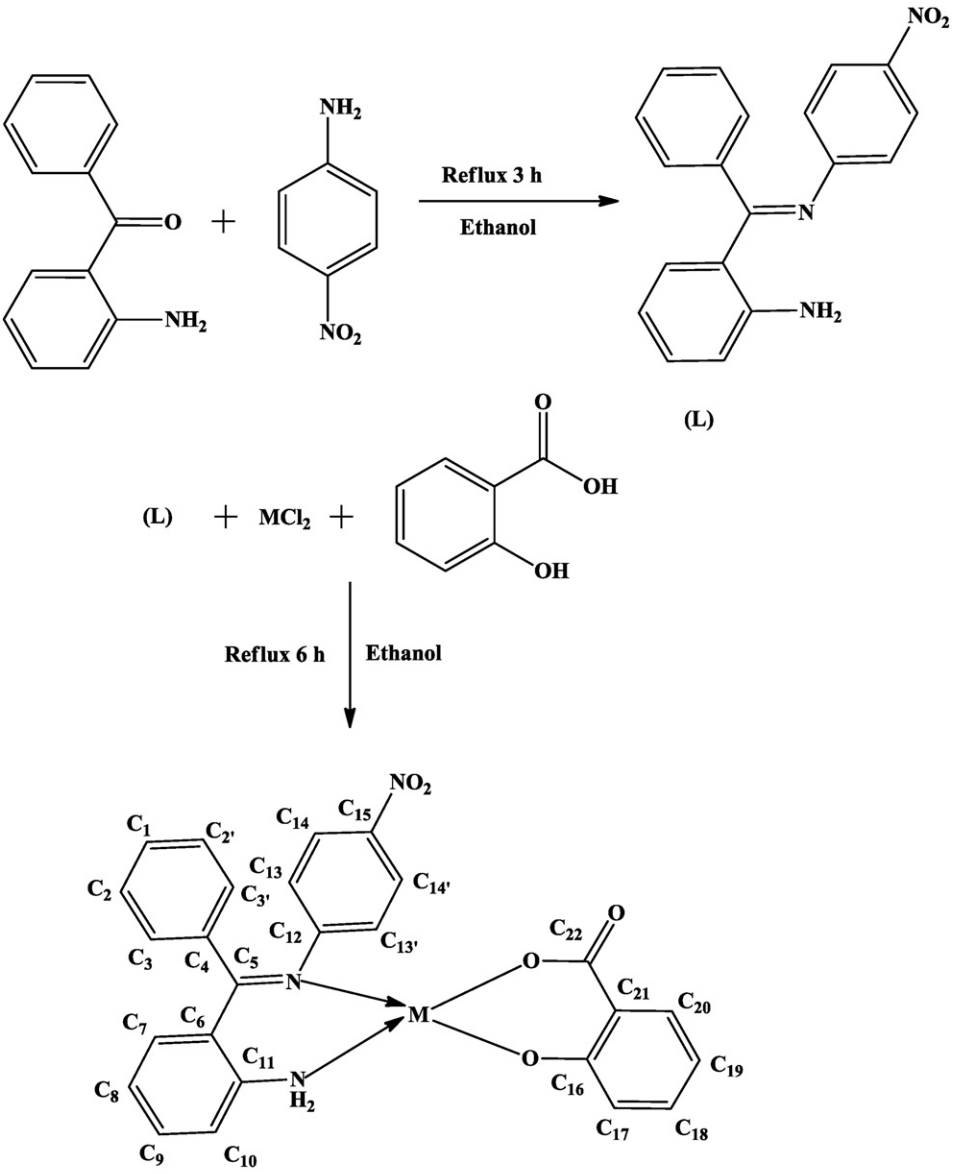
2.1. Preparation of Schiff base ligand (L)

The Schiff base ligand (**L**), *N*-((2-aminophenyl)(phenyl)methylene)-4-nitroaniline was synthesized by refluxing equimolar quantities (1 mM) of (2-aminophenyl)(phenyl)methanone (0.317 g, 10 mL) with *p*-nitroaniline (0.138 g, 10 mL) in ethanol (Scheme 1). The mixture was stirred for 4 h under reflux and the reaction was monitored through TLC. After completion of reaction, the mixture was reduced to half of its original volume by using water bath and kept aside at room temperature. On standing, a brown crystalline product was obtained, filtered by *vacuum* filtration, washed several times with water and diethyl ether. The brown crystal of **L** was recrystallized from ethyl alcohol and finally dried *in vacuo* over anhydrous $CaCl_2$.

[**L**], Yield: 82% Anal. Calc. for $C_{19}H_{15}N_3O_2$: C, 71.9; H, 4.7; N, 13.2%; Found C, 71.1; H, 4.5; N, 12.9%. IR data (KBr, cm^{-1}); 1589 ν(C═N), 3419 $_{asy}(-NH_2)$, 3336 $_{sy}(-NH_2)$. ^{1}H NMR (δ, ppm): 6.6–7.7 (aromatic) (m); 6.2 ($-NH_2$) (s). ^{13}C NMR (δ, ppm):128.4–137.2 (C_1 to C_4, C_7 and C_9), 175.8 (C_5), 116.7 (C_6), 127.8 (C_8), 117.8 (C_{10}), 151.3 (C_{11}), 158.5 (C_{12}), 124.4 (C_{13}), 126.7 (C_{14}), 147.8 (C_{15}). UV–vis, (DMF, cm^{-1}); 32,213, 33,609. MS *m/z* (%): 318 $[M+1]^+$.

2.2. Preparation of mixed ligand metal complexes

10 mL ethanolic solution of Schiff base ligand of *N*-((2-aminophenyl) (phenyl)methylene)-4-nitroaniline (**L**) (0.317 g, 1 mM) was added dropwise to an ethanolic solution (10 mL) of appropriate metal(II) chloride salts (1 mM) and stirred for 2–4 h. To this solution, 10 mL hot ethanolic solution of salicylic acid (SA) (0.138 g, 1 mM)



Scheme 1. Synthesis of Schiff base ligand and its mixed ligand metal complexes.