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Synthesis, spectroscopic studies, antimicrobial activities and antitumor of a new monodentate V-shaped Schiff base and its transition metal complexes

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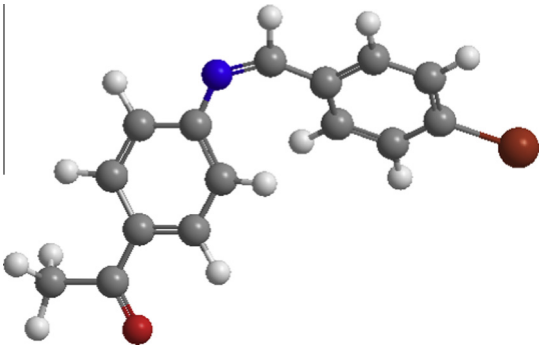
HIGHLIGHTS

- Synthesis and characterization of a V-shaped monodentate Schiff base ligand (L).
- Synthesis and spectroscopic studies of some transition metal complexes with L.
- Biological activity of L and complexes against bacteria and fungus were screened.
- Cytotoxicity of L and complexes were checked as antitumor agents.

GRAPHICAL ABSTRACT

A V-shaped Schiff base, (*E*)-1-(4-((4-bromo-benzylidene)amino)phenyl)ethanone, was obtained from reaction of 4-aminoacetophenone and 4-bromobenzaldehyde. Some transition metal derivatives were also synthesized from the corresponding metal species with the base. The biological activities and cytotoxicity of ligand and metal complexes were screened.



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ABSTRACT

Reaction of 4-aminoacetophenone and 4-bromobenzaldehyde in ethanol resulted in the formation of the monodentate V-shaped Schiff base (*E*)-1-(4-((4-bromo-benzylidene)amino)phenyl)ethanone (L). Interaction of L with different di- and trivalent metal ions revealed disubstituted derivatives. The ligand and its complexes were characterized by elemental analysis, mass, IR and NMR spectrometry. Biological activities of the ligand and complexes against the *Escherchia coli* and *Staphylococcus aureus* bacterias, and the two fungus *Aspergillus flavus* and *Candida albicans* were screened. The cytotoxicity of the compounds were checked as antitumor agents on liver carcinoma cell line (HepG2). They exhibited *in vitro* broad range of antitumor activities towards the cell line; the $[ZnL_2(H_2O)_2](NO_3)_2$ complex was stronger antitumor towards HepG2 cell line as well as two breast cancer cell lines (MCF7 and T47D) relative to *cis*-platin.

Introduction

A large number of Schiff bases and their complexes have been investigated for their interesting and important properties, such

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as their ability to reversibly bind oxygen [1,2], catalytic activity in the hydrogenation of olefines [3–5], photochromic properties [6,7] and complexing ability towards some toxic metals [8–10]. Furthermore, Schiff bases and their transition metal complexes showed promising applications in biological activity and biological modeling applications [11–15]. For example, importance in designing new macrocyclic Schiff base ligands arises mainly from their use as models for protein-metal binding sites in a substantial array of metalloproteins in biological systems, such as the synthetic ionophores, models for the magnetic exchange phenomena, therapeutic reagents in chelate therapy for treatment of metal intoxication and the cyclic antibiotics that retain their antibiotic actions to specific metal complexation [16–18]. On the other hand, transition metal complexes play a vital role in antitumor therapy. Complexes especially those of platinum have been investigated in preclinical as well as in clinical studies. The best known platinum(II) drugs approved worldwide, *cis*-platin or carboplatin, are used in nearly 50% of all cancer therapies. Due to their severe toxicity, their high activity is not always satisfactory and side effects are frequently encountered. Therefore, ongoing efforts are aiming to identify novel metal-based substances with less toxicity and new mechanisms of action [19–21].

Recently, we have reported the synthesis and spectroscopic studies of some transition metal complexes with unusual Schiff base. The cytotoxicity of the $[PtL(Cl)_2]$ complex, a *cis*-platin analogous, was checked as an antitumor agent on two breast cancer cell lines (MCF7 and T47D) and human liver carcinoma cell line (HepG2) [11]. Also, interactions of Pt(II) and Pd(II) with some heterocyclic ligands with nitrogen donors gave some binary and ternary complexes. Some of the reported platinum complexes exhibits promising signs as they acted as strong antitumor agents [22]. The ultimate aim of this article is to synthesize and characterize some transition metal derivatives with a V-shaped Schiff base ligand, which is expected to have higher antitumor activity. These complexes may display more tolerable toxicological profiles and overcome resistance in many tumor types.

Experimental

Reagents

4-Aminoacetophenone, 4-bromobenzaldehyde and the transition metal salts were purchased from Aldrich. All the solvents were of analytical reagent grade and were purified by standard methods.

Instruments

IR measurements (KBr pellets) were carried out on a Unicam–Mattson 1000 FT-IR spectrometer. NMR measurements were performed on a Spectrospin–Bruker 300 MHz spectrometer. Samples were dissolved in $(CD_3)_2SO$ and TMS was used as an internal reference. Thermogravimetric analysis measurements were carried out under N_2 atmosphere at a heating rate of 10 °C/min using a Shimadzu DT-50 thermal instrument. Elemental analyses were performed on Perkin–Elmer 2400 CHN elemental analyzer. Mass spectrometry measurements of the solid complexes (70 eV, EI) were carried out on a Finnigan MAT SSQ 7000 spectrometer. Conductivity measurements were made on a YSE conductance meter model 32. Samples of concentration *ca.* 1×10^{-3}–1×10^{-6} M in DMSO were used for the measurements. Magnetic measurements of the complexes in the solid state (Gouy method) were recorded on a Sherwood magnetic susceptibility balance. The computational details for the geometrical optimization and theoretical calculations of the ligand were performed as reported previously [9].

Preparation of the Schiff base (L)

A solution of 4-aminoacetophenone and 4-bromobenzaldehyde in absolute ethanol with molar ratio 1:1 were mixed together and heated to reflux for ½ h. The reaction mixture was then cooled and the formed white precipitate was isolated by filtration. The crude was recrystallized from hot ethanol to give white fine crystals. The compound was left to dry under vacuum for several hours (yield 92%).

Preparation of complexes

A mixture of metal ion salt and (*E*)-1-(4-((4-bromobenzylidene)-amino)phenyl)ethanone ligand (1:2 molar ratio) in about 30 cm^3 aqueous ethanol was heated to reflux with stirring for *ca.* 1 h. The reaction mixture was cooled and solid complex was separated by slow evaporation. The isolated complex was recrystallized from hot ethanol. Table 1 gives the color, yield, elemental analysis and mass spectrometry data for the complexes.

Biological activity

In vitro antibacterial and antifungal activity of the ligand and the synthesized complexes were tested against the two bacteria: *Escherchia coli* as Gram-negative bacteria and *Staphylococcus aureus* as Gram-positive bacteria, and the two fungus: *Aspergillus flavus* and *Candida albicans*. The tests were carried out using paper disk diffusion method. The nutrient agar medium (peptone, beef extract, NaCl and agar–agar) and 5 mm diameter paper disks of Whatman No. 1 were used. The test compound was dissolved in DMSO in 0.1–0.4% concentrations. The paper disks was soaked in different solutions of the compound, dried and placed in the Petri plates (9 cm diameter) previously seeded with the test organisms. The plates were incubated for 24–30 h at 27 ± 1 °C and the inhibition zones (mm) were measured around each disk. As the organism grows, except in the region where the concentration of antibacterial agent was above the minimum inhibitory concentration and a zone of inhibition was seen. The size of the inhibition zone depends upon the culture medium, incubation conditions, rate of diffusion and the concentration of the antibacterial agent. Comparison of the obtained data was carried out with the two standards: tetracycline antibacterial agent and Amphotericin B antifungal agent.

Cytotoxicity determination

Human liver carcinoma cell line (HepG2) was used for *in vitro* screening experiments for the ligand and all the tested complexes. In addition, two breast cancer cell lines (MCF7 and T47D) were used for *in vitro* screening experiments for the zinc complex. The cancer cells were obtained frozen in liquid nitrogen (−180 °C) from the American Type Culture Collection. The tumor cell lines were maintained in the National Cancer Institute, Cairo, Egypt, by serial sub-culturing. Cell culture cytotoxicity assays were carried out as described in literature [23]. RPMI-1640 medium (Sigma Chemical Co., St. Louis, Mo, and USA) was used for culturing and maintenance of the human tumor cell lines. Cells were seeded in 96-well microliter plates at a concentration of 5×10^4–10^5 cell/well in a fresh medium and left to attach to the plates for 24 h. Growth inhibition of cells was calculated spectrophotometrically using a standard method with the protein-binding dye sulforhodamine B (SRB) [24]. The optical density (OD) of each well was measured at 564 nm with an ELIZA microplate reader (Meter Tech. Σ 960, USA). The sensitivity of the human tumor cell lines to thymoquinone was determined by the SRB assay. The percentage of cell survival was calculated as follows: