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Synthesis, anticancer activity and molecular docking study of Schiff base complexes containing thiazole moiety

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ABSTRACT

A Schiff base ligand **1** was prepared from condensation of salicyaldehyde with 2-amino-4-phenyl-5-methyl thiazole. The ligand forms complexes with Co^{II}, Ni^{II}, Cu^{II}, and Zn^{II} in good yield. The synthesized compounds were characterized by elemental analysis, magnetic susceptibility, molar conductance, infrared spectra, ^{1}H and ^{13}C NMR, mass, electronic absorption and ESR spectroscopy. The anticancer activity of the synthesized compounds was studied against different human tumor cell lines: breast cancer MCF-7, liver cancer HepG2, lung carcinoma A549 and colorectal cancer HCT116 in comparison with the activity of doxorubicin as a reference drug. The study showed that Zn^{II} complex showed potent inhibition against human TRK in the four cell lines (HepG2, MCF7, A549, HCT116) by the ratio 80, 70, 61 and 64% respectively as compared to the inhibition in the untreated cells. Moreover, the molecular docking into TRK (PDB: 1t46) was done for the optimization of the aforementioned compounds as potential TRK inhibitors.

1. Introduction

The chemistry of the Schiff base ligands and their metal complexes has expanded enormously and encompasses a vast area of organometallic compounds and various aspects of bioinorganic chemistry (Abu-Diefa and Mohamed, 2015). Schiff base ligands are considered "privileged ligands" because they are mainly prepared by condensation between aldehydes and primary amines (Chang et al., 2016). These ligands are able to coordinate many different metals and to stabilize them in various oxidation states (Ejidike and Ajibade, 2015). They are used also as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilizers (Menati et al.,

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2013). Large numbers of Schiff bases have also been shown to exhibit a broad range of biological activities, including anti-tumor, anti-bacterial, fungicidal and anticarcinogenic properties (Nagesh et al., 2015; Salehi et al., 2015; Shukla et al., 2013; Zaltariov et al., 2015; Zayed and Zayed, 2015). Metal complexes of Schiff bases with heterocyclic compounds also find applications as potential drugs, (Andersen, 1999; Konstantinović et al., 2003) due to the presence of multifunctional groups (Chohan et al., 2004; Joseyphus et al., 2006; Vashi and Naik, 2004; Venugopala and Jayashree, 2003). The excessive attention of synthesizing determined broad range of N and S chelating ligands as thiazole molecule have attracted significant interest. This is because thiazoles have a great pharmacological activity. Besides these atoms play an important role in the coordination of metals at the active sites of various metal biomolecules that have a therapeutic activity or serving as study models for metallo-enzymes (Chen et al., 2012; Venkatraman et al., 2010; Yenilmez et al., 2013). Thiazoles are very important building blocks in medicinal chemistry and can be found in numerous natural products (e.g. epothilone) and biologically important compounds including the anticancer drug dasatinib, antiviral clinical candidate TMC435350 and anti-diabetic drug candidate MB06322 (Dang et al., 2008; Doggrell, 2005; Erion et al., 2005; Lin et al., 2009). Recently, thiazoles found application in drug development for the treatment of allergies (Brzezińska et al., 2003), hypertension (Mishra et al., 2015), inflammation (Sharma et al., 1998), schizophrenia (Jaen et al., 1990), bacterial (Suzuki et al., 1994), HIV infections (Bell et al., 1995), hypnotics (Ergenc et al., 1999), as fibrinogen receptor antagonist with antithrombotic activity (Badorc et al., 1997) and as new inhibitors of bacterial DNA gyrase B (Rudolph et al., 2001).

Following all these observations and as a part of our continuing research on the coordination chemistry of multidentate ligands (Abd-Elzaher, 2004a, 2004b; Abd-Elzaher et al., 2005, 2006, 2010, 2012a, 2012b; Fouda et al., 2008a, 2008b), we report here the preparation and characterization of a Schiff base ligand derived from condensation of salicyaldehyde with 2-amino-4-phenyl-5-methyl thiazole. The study has been extended to synthesize Cu^{II}, Co^{II}, Ni^{II} and Zn^{II} complexes with the prepared ligand. All the prepared complexes have been characterized by IR, ^{1}H and ^{13}C NMR, mass spectra, ESR, UV–Vis, in addition to elemental analysis, molar conductivity and magnetic susceptibility.

In the same direction and in continuing effort to find more potent and selective anticancer compounds, herein, anticancer activity of the prepared compounds was carried out against four different human tumor cell lines including breast cancer cell line MCF-7, liver cancer cell line HepG2, lung carcinoma A549 and colorectal cancer HCT116 that may act through tyrosine kinase (TRK) inhibition. Molecular Docking has been done to evaluate the binding affinity of the Ni and Zn complexes to TRK.

2. Experimental

2.1. Materials and methods

All chemicals were obtained from Merck. Elemental analyses were determined at the micro analytical center, Cairo University. IR spectra were recorded in the 4000-400 cm^{-1} on a spectrometer (Jasco FTIR- 6100 Japan), using KBr pellets. ^{1}H and ^{13}C NMR were recorded on a Bruker DPX 300, δ values relative to the deuterated DMSO. Mass spectra: Jeol JMS-700 using FAB technique with a 3-nitrobenzyl alcohol NBA matrix. Magnetic susceptibilities were measured at 20 °C by the Gouy method at the Faculty of Science, Cairo University. The molar conductance measurements were measured in solution of the metal complexes in DMF (10^{-3}) using Metrohem 660 conductivity meter. Electronic absorptions were recorded on a automatic spectrophotometer (PG Instruments ltd., +80 + UV–Vis) in DMSO. ESR measurements were made at approximately 298K with a Bruker E500, X-band spectrometers operating at a frequency of 9.5 GHz at National Institute for Standards, Giza.

2.2. Synthesis of the Schiff base ligand $C_{17}H_{14}N_2OS$ (1) and metal complexes (2–5)

2-amino-4-phenyl-5-methyl thiazole (1 mmol, 2.95 g) dissolved in about 20 mL absolute ethanol was added slowly to a magnetically stirred solution of salicyladehyde (1 mmol, 1.22 g), in the presence of few drops of glacial acetic acid. The mixture was refluxed for four hours. Then the solution was concentrated to its half volume then cooled; n-hexane was added to the reaction mixture drop wise until a product began to precipitate. The formed product was filtered off, washed several times with n-hexane, and recrystallized from ethanol. The different complexes were prepared by addition of 1 mmol of $CoCl_2.6H_2O$, $NiCl_2.6H_2O$, $CuCl_2.2H_2O$ and $ZnCl_2$, dissolved in about 20 mL ethanol, into a solution of the ligand (2 mmol in 20 mL ethanol). The mixture was refluxed for three hours, then the solution was concentrated. The obtained solid products were filtered, washed twice with cold n-hexane and dried.

2.3. Anticancer activity

2.3.1. Chemicals

Fetal bovine serum (FBS) and L-glutamine were obtained from Gibco Invitrogen Company (Scotland, UK). Dulbecco's modified Eagle's medium (DMEM) was provided from Cambrex (New Jersey, USA). Dimethyl sulfoxide (DMSO), doxorubicin, penicillin, and streptomycin were obtained from Sigma Chemical Company (Saint Louis, MO, USA). Human tyrosine kinase (TRK) ELISA kit was purchase from Glory Science Co., Ltd (Del Rio, TX 78840, USA).

2.3.2. Cell lines and culturing

Anticancer activity screening for the tested compounds utilizing 4 different human tumor cell lines including breast cancer cell line MCF-7, liver cancer cell line HepG2, lung carcinoma A549 and colorectal cancer HCT116 were obtained from the American Type Culture Collection (Rockville, MD, USA) through LGC Standards GmbH, Wesel, Germany. The tumor cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat inactivated fetal calf serum (GIBCO), penicillin (100 UmL^{-1}) and streptomycin (100 μgmL^{-1}) at 37 °C in humidified atmosphere containing 5% CO_2. Cells at a concentration of 0.50×10^6 were grown in a 25 cm^2 flask in 5 mL of complete culture medium.