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Synthesis, characterization and anti-proliferative activity of Cd(II) complexes with NNN type pyrazole-based ligand and pseudohalide ligands as coligand

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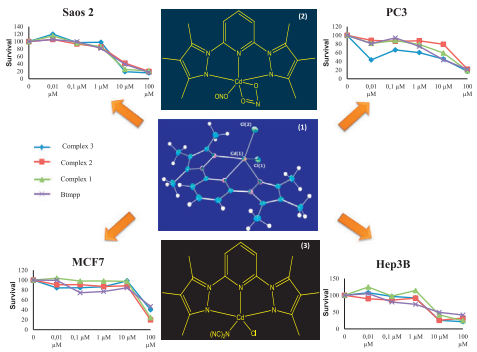
HIGHLIGHTS

- Cd(II) complexes of pyrazole based ligand with pseudohalides have been prepared.
- The complexes are characterized by different spectroscopic and thermal techniques.
- Compounds were tested for cytotoxic activity against the human carcinoma cell lines.
- MTT assay showed that complexes possess significant cytotoxic properties.

GRAPHICAL ABSTRACT



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ABSTRACT

Cd(II) complexes of tridentate nitrogen donor ligand, 2,6-bis(3,4,5-trimethylpyrazolyl)pyridine (btmpp), Cd(btmpp)X_2 (X:Cl, ONO or $N(CN)_2$) have been synthesized and characterized by elemental and spectral (FT-IR, ^{1}H NMR, ^{13}C NMR, UV–Vis) analyses, differential thermal analysis and single crystal X-ray diffraction studies. The molecular structure of reported complex **1**, revealed distorted square-pyramidal geometry around Cadmium. Complexes **1**–**3** and corresponding ligand were tested for cytotoxic activity against the human carcinoma cell lines HEP3B (hepatocellular carcinoma), PC3 (prostate adenocarcinoma), MCF7 (breast adenocarcinoma) and Saos2 (osteosarcoma). The results show that, complexes are more cytotoxic than the free ligand and complex **2** is the most cytotoxic complex for PC3.

Introduction

The classes of tridentate nitrogen donor ligands based on 2,6-bis(pyrazolyl)pyridine (pp) and 2,2′:6′,2″-terpyridine (terpy) systems are known for their rich coordination chemistry and have therefore been used widely in various area such as molecular biology. 2,6-bis(3,4,5-trimethyl-N-pyrazolyl)pyridine (btmpp) ligand belongs to the pp family and in contrast to the great number of studies concerning metal complexes with btmpp, very little is known about complexes of btmpp, although this class of ligands could offer unique features in terms of structural and physical properties [1]. Also, the geometry of the five-membered pyrazole ring was expected to provide interesting spectral properties to its

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metal complexes [2]. Transition metal complexes of pyrazole derivatives have been the subject of much recent notice because of their beneficial effects as anticancer agents [3]. Complexes of d^{10} metal ions, such as zinc(II) and cadmium(II) are interesting since they are involved in many biological processes [4]. Metal based chemotherapeutic drugs are in great interest of researchers specifically after success of cis-platin in cancer. Significant side effects and limitation in clinical use of cis-platin lead to scientists to search new potential anticancer compounds [5–7]. Although cadmium has been known as a toxic metal and is often associated with mercury and lead as one of the biologically harmful metal ions, cadmium(II) ion has recently found to serve catalytic center in carbonic anhydrase [4]. Moreover several studies have showed its cytotoxic effects against different tumor cell lines [8–10].

In this context, we have prepared a series of transition metal complexes of pp derivative ligand with pseudohalides and we wish to report the synthesis, structure, thermal properties and antiproliferative activities of them.

Experimental

Materials and instrumentation

All reagents and solvents were purchased from Aldrich and Fluka and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were obtained with DMSO-d_0 as solvent and internal TMS as Standard using a BrukerUltrashield Superconducting 400 MHz spectrometer at room temperature. The elemental analyses were carried out with the LECO, CHNS-932 analyzer. IR spectra were obtained by using IR grade KBr disks on a Perkin–Elmer 1600 series FTIR spectrophotometer in the range 4000–250 cm^{-1}. Electronic spectra were obtained using Perkin–Elmer Lambda 25 UV–Visible Spectrophotometer. The thermogravimetry/differential thermal analysis (TG/DTA) measurements were run on Perkin–Elmer Diamond instrument. In this study, thermogravimetric curves were obtained with a flow rate of carrier gas at 100 mL min^{-1} and the heating rate of 20 °C min^{-1} in nitrogen (3 bar) with the sample contained in a ceramic pan in the range 30–1200 °C.

Synthesis of ligand

2,6-bis(3,4,5-trimethyl-N-pyrazolyl)pyridine (btmpp) was prepared by heating 2,6-dichloropyridine and the sodium salt of 3,4,5-trimethyl-N-pyrazole in diglyme under reflux as described previously [11].

Synthesis of complexes

The synthetic pathway for complexes **1**–**3** is presented in Fig. 1.

[Cd(btmpp)Cl_2] (1)

Complex **1** was prepared by adding $CdCl_2{\cdot}H_2O$ (1 mmol, 0.201 g) in 10 mL of hot ethanol to the btmpp (1 mmol, 0.295 g) in 20 mL of hot methanol. This solution was heated to the boiling point and stirred for 15 min. After slow evaporation of the resulting solution at room temperature, colorless crystals were filtered off and dried in air.

[Cd(btmpp)$(ONO)_2$] (2)

Complex **2** was prepared by adding $CdCl_2{\cdot}H_2O$ (1 mmol, 0.201 g) in 10 mL of hot ethanol to the btmpp (1 mmol, 0.295 g) in 20 mL of hot methanol. After the resulting mixture was stirred for 10 min, $NaNO_2$ (2 mmol, 0.138 g) in 10 mL of aqueous solution was added to the mixture. This solution was heated to the boiling point and stirred for 15 min. After slow evaporation of the resulting solution at room temperature, colorless crystals were filtered off and dried in air.

[Cd(btmpp)(dca)Cl] (3)

Complex **3** was prepared in similar way to **2**, using $Na[N(CN)_2]$ (1 mmol, 0.089 g) instead of $NaNO_2$. Complete yield data of the complexes is available as Supplementary material.

Crystal structure determination

Diffraction measurements were made on a BrukerApexII kappa CCD diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at 100 K for compound **1**. The intensity data were integrated by using the APEXII program [12]. Absorption corrections were applied based on equivalent reflections using SADABS [13]. The structures were solved by direct methods and refined using full-matrix least-squares against F^2 using SHELXL [14]. All non-hydrogen atoms were assigned anisotropic displacement parameters and refined without positional constraints. Hydrogen atoms were included in idealized positions with isotropic displacement parameters constrained to 1.5 times the U_{equiv} of their attached carbon atoms for methyl hydrogens, and 1.2 times the U_{equiv} of their attached carbon atoms for all others. The H atoms of the water molecules were located in a difference Fourier map and refined isotropically. Distance restraints were also applied to the H atoms of the water molecules with a set value of 0.90 (1) Å. The absolute structure was determined on the basis of the Flack [15] parameter x = 0.01 (2). The Flack's parameter close to 0 is indicative of a non-centrosymmetric structure.

In vitro anti-proliferative activity

The human cancer cells (Hep3B, MCF7, PC3 and Saos2) were grown in DMEM medium supplemented with 10% fetal bovine serum (FBS) and 2 mM L-glutamine in an atmosphere of 5% CO_2 at 37 °C. Cell proliferation was evaluated by the MTT assay [16]. Briefly, tumor cells (500 μL, 125,000 cells/well) were plated in 24-well plates. All compounds were dissolved in dimethyl sulfoxide (DMSO) and diluted with the growth medium. DMSO final concentration was 1% and complexes final concentrations were ranged from 0.01 to 100 μM. After attachment to the culture surface, the cells were incubated with various concentrations of the compounds for 48 and 72 h. Following the drug treatment, the cells were fixed by adding 50 μL of MTT (5 mg/mL) per well and incubated for 4 h at 37 °C. Subsequently, the medium containing MTT was removed, and 500 μL of acidified isopropanol (0.04MHCl) added. Spectrophotometric absorbance of each sample was measured at 550 nm using a micro-plate reader (Bio-Tek, model powerwave XS). All cytotoxicity experiments were performed in two independent studies and quadruplicate points. The effects of tested complexes were denoted as percentage inhibition and calculated using the following equation:

$$\% \text{ Inhibition} = [1 - (T/C)] \times 100$$

where T is the mean absorbance of the treated cells and C the mean absorbance in the controls. The concentration required for 50% inhibition of cell viability (IC_{50}) was calculated using the concentration–percentage inhibition curves.

Results and discussion

Crystal structure description of 1

The crystallographic data, conditions used for the intensity data collection and some features of the complex **1** refinement are listed