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Preparation, Characterization and Anti-Cancer Activity of a New Bis[(Z)-N-(naphthalene-1-yl methylene) aceto hydrazide] Mn(II) Complex

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ABSTRACT

Metal-hydrazide of the ligand Bis[(Z)-N-(naphthalene-1-yl methylene) aceto hydrazide] that was abbreviated as NNMAH. It was synthesized and identified and was prepared by the reaction of Bis [(E)-N-(3-nitrobenzylidene) isonicotino hydrazide] and $Mn(NO_3)_2$ in hexane with Diethyl ether. Characterization of the ligand and its complex were made by microanalyses, FT-IR, ^{1}HNMR and UV–Visible spectroscopies. The biological property such as antitumor of this complex was studied. This new complex showed excellent anti-tumor activity against two kind of cancer cells that are K562 (human chronic myeloid leukemia) cells and Jurkat (human T lymphocyte carcinoma) cells.

Key words: Manganese (II), Bis[(Z)-N-(naphthalene-1-yl methylene) aceto hydrazide], Praparation, Anti-cancer activity, K562.

INTRODUCTION

Metal- hydrazides are used as homogeneous catalysts in a variety of oxidation reactions. Kinetic study of hydrazides metalation is indispensable in order to understand in vivo metal. Incorporation processes leading to the formation of natural metalo hydrazides. Generally, hydrazides are synthesized in a metal-free form and metal ions are subsequently inserted in the processes catalyzed by enzymes [1].

Manganese is an essential trace nutrient in all forms of life. The classes of enzymes that have manganese cofactors are very broad, and include oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases, lectins, and integrins. The reverse tranascriptases of many retroviruses (though not lentiviruses such as HIV) contain manganese. The best-known manganese-containing polypeptides may be arginase, the diphteria toxin [2].

Synthetic metalo hydrazides are suitable sensitizers for photodynamic therapy of cancer [3]. From these points of view, it is interesting to study different types of transition metal complexes of these biologically active ligands. The hydrazides are a class of naturally occurring macro cyclic compounds, which play a very important role in the metabolism of living organisms. Presently, there is a growing interest in the coordination chemistry of structurally modified bio ligands [4]. Particular attention has been given to hydrazides as the highly sensitive chromogenic reagents for spectrophotometric determination of several metal ions based on the use of the so-called Soret band at 400 - 500 nm [5-8]. These have been extensively studied due to their biological importance as well as analytical applications. The photodynamic therapy of cancer (PDT) is used a combination of photosensitize drug and light giving rise to reactive oxygen species in the tumor environment, leading to tumor death .In recent years, several papers have

been published on the mechanism and kinetics of metal ions incorporation into the hydrazides nucleus[9-10]. Metallo hydrazides have been extensively studied for many years because of their biological and catalytic functions[11]. Several spectroscopic techniques such as EPR, NMR and Mossbauer spectroscopy have been used to directly probe the metal centers in metallo hydrazides systems[12]. In this paper, the synthesis, characterization and anti-tumor properties of a number of the first row transition metal complexes with one of the above ligands have been studied.

EXPERIMENTAL

Material and Method

$Mn(NO_3)_2$, DMF, were either Merck chemicals and were used without further purification. Organic solvents were reagent grade. Electronic spectra were recorded by Cam spec UV–Visible spectrophotometer model Wpa bio Wave S2 100. The IR spectra were recorded using FT-IR Bruker Tensor 27 spectrometer. ^{1}H-NMR was recorded on a Bruker AVANCE DRX 500 spectrometer at 500 MHz respectively. All the chemical shifts are quoted in ppm using the high-frequency positive convention; ^{1}H NMR spectra was referenced to external $CDCl_3$. The percent composition of elements was obtained from the Micro analytical Laboratories, Department of Chemistry, OIRC, Tehran.

Cell culture

The human chronic myeloid leukemia: K562 cell line and the human T lymphocyte carcinoma: Jurkat cell line, used for treatment with the drugs, was provided. K562 and Jurkat cells were grown at 37 °C in an atmosphere containing 5% CO2, with RPMI-1640 MEDIUM HEPES Modification with L-glutamine and 25mm HEPES (SIGMA-ALDRICH CHEMIE GmbH) supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Gibco), 2.7% sodium bicarbonate and 500 mg/L ampicillin.

Preparation and characterization of complex

(0.426 g, 2.0mmol) Bis[(Z)-N-(naphthalene-1-yl methylene) aceto hydrazide] was taken to the container (50ml) including a magnet and methanol (20ml) after solving the color of ligand solution became light yellow. $Mn(NO_3)_2.4H_2O$ (0.251g, 1.0mmol) was added to the previous solution. The whole solution was mixed at the room temperature. Finally the yellow compound was precipitated, separated and washed with hexane and diethyl ether. Elemental analysis of $[Mn(C_{13}H_{11}N_2O)_2]^{2+}$ Found, (%):C: 73.46, H: 5.65, N: 13.22. Calculated, (%): C: 73.56, H: 5.76, N: 13.39%: FTIR absorptions (ν, cm^{-1} KBr): 1673 ν (C-N), 3079 ν (C-H), 1388 ν (C=O), 524 ν (Mn-N), 427 ν (Mn-O). UV- Vis (MeCN): $\lambda_{1=}$ 259 nm, λ_2= 309 nm, λ_3= 320 nm, λ_4= 336 nm (Fig. 1 and 2).

In Vitro Activities

NNMAH ligand and $[Mn(C_{13}H_{11}N_2O)_2]^{2+}$ compound were assayed for cytotoxicity in vitro against K562 (human chronic myeloid leukemia) cells and Jurkat (human T lymphocyte carcinoma) cells. The two cell lines were provided by the Pasteur Institute Laboratory of natural and Biomimetic in Iran. The procedure for cytotoxicity studies was similar to that reported earlier. Briefly, in order to calculate the concentration of each drug that produces a 50% inhibition of cell growth (IC_{50}), 190 mL of cell suspension (5×10^4 cell/mL) were exposed to various concentrations of ligand and complexes dissolved in sterile DMSO. The final concentration of DMSO in the growth medium was 2% (v/v) or lower, concentrations without effect on cell replication. After incubation periods 72h for all cell lines, the cell concentrations were determined both in control and in drug-treated cultures. All experiments were carried out in six times and series (Figure 4).

RESULTS AND DISCUSSION

Preparation for Ligand (NCBAH) and Mn (II) complex

The reaction of Mn (II) salt with the ligand, NNMAH, results in the formation of [ML] for M= Mn (II). The structure of the complex was shown (Fig. 3). The Manganese (II) complex was characterized by several techniques using FT-IR, electronic spectra and molar conductance measurements. The molar conductance measurements reveal the presence of 1:2 electrolytic nature complexes. This complex is quite stable and could be stored without any appreciable change. This is insoluble in solvents, such as benzene, hexane, diethyl ether, toluene

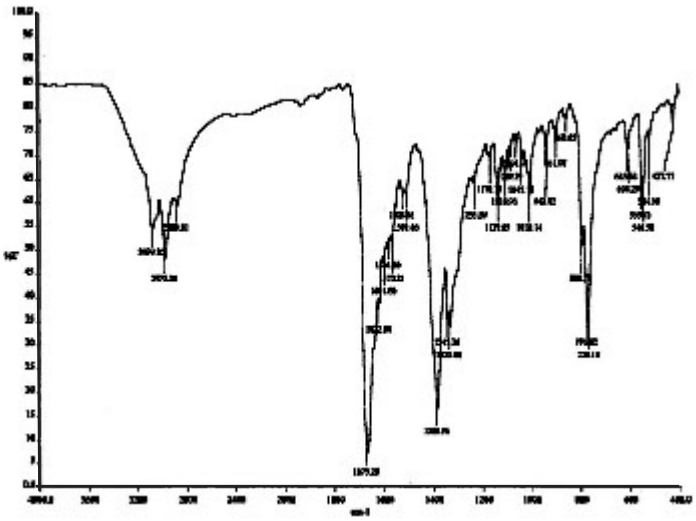

Fig. 1: The FT-IR spectrum of the $[Mn(C_{13}H_{11}N_2O)_2]^{2+}$ complex (Frequencies in cm^{-1})

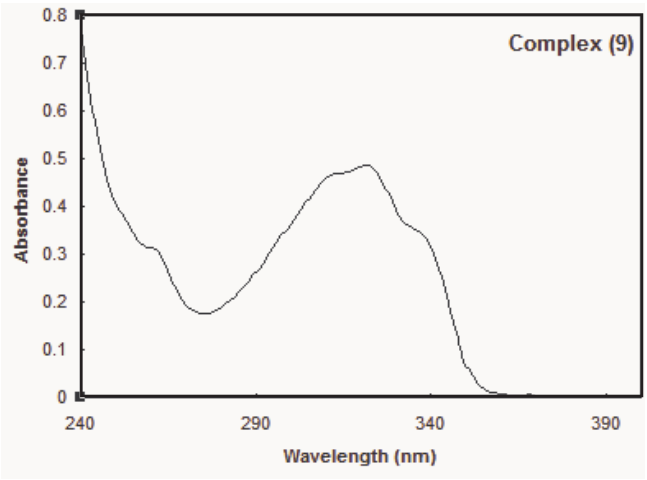

Fig. 2: The UV/Visible spectrum of the $[Mn(C_{13}H_{11}N_2O)_2]^{2+}$ complex

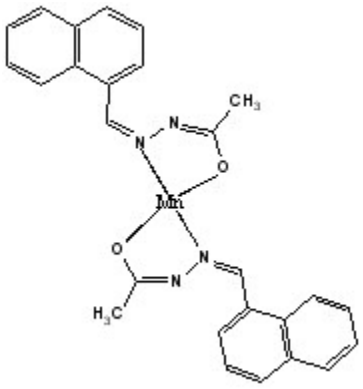

Fig. 3: The Structure of $[Mn(C_{13}H_{11}N_2O)_2]^{2+}$ complex

and dichloromethane. The structure was characterized by elemental analysis, ^{1}H-NMR and IR. The spectral data of the complex has good relationship with the literature data.

The coordination chemistry of transition metals with ligands from the hydrazide family has been of interest due to different bonding modes shown by these ligands with both electron rich and electron poor metal. Manganese containing ligands are known to form stable complexes with transition metal ions.

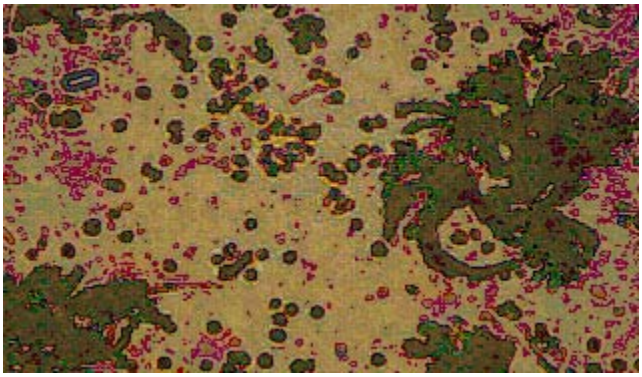

Fig. 4: Tumor cell after 72h with $[Mn(C_{13}H_{11}N_2O)_2]^{2+}$ compound

Cytotoxicity studies

NNMAH ligand and $[Mn(C_{13}H_{11}N_2O)_2]^{2+}$ compound have been tested against two human cancer cell lines: K562 and Jurkat. The IC_{50} cytotoxicity values of the complex was compared to those found for the starting organic bases as well as for some of the anti-cancer agents used nowadays that are cisplatin and oxaplatin compounds. The general method used for testing on anti-tumor properties of these compounds is the standard testing method that has been previously described in greater detail in some papers and abbreviated in following:

The incubation lasted 72 h and at the end of this period IC_{90} and IC_{50} of the dead cells and live cells was measured by Trypan blue (Fig. 4).

CONCLUSION

It is clear from the above discussion that NNMAH, $[Mn(C_{13}H_{11}N_2O)_2]^{2+}$ compound offer a new outlook for chemotherapy. The results of antitumor activity show that the metal complex exhibits anti-tumor properties and it is important to note that it shows enhanced inhibitory activity compared to the parent ligand. The mechanism by which this complex acts as antitumor agents is apoptosis. It has also been proposed that concentration plays a vital role in increasing the degree of inhabitation.

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