SYNTHESIS AND ANTI-CANCER ACTIVITY OF COPPER(II) COMPLEX WITH 2, 4, 5-TRIPHENYL-1H-IMIDAZOLE LIGAND

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SYNTHESIS AND ANTI-CANCER ACTIVITY OF COPPER(II) COMPLEX WITH 2, 4, 5-TRIPHENYL-1*H*-IMIDAZOLE LIGAND

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ABSTRACT : The ligand 2,4,5-triphenyl-1*H*-imidazole (L) has been used to synthesize copper(II) complex, $[Cu(L)_2(H_2O)_2].Cl_2$. The complex is well characterized from various spectral and physical meausrements. Complex synthesis resulted in obtaining a green, light crystalline solid. The maximum absorbance, at 529 nm, indicated bonding had occurred within the metal-ligand that is Cu-N in region 422.38 cm^{-1}. Cytotoxicity was tested for in complex compounds made by the method of (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (MTT). The value of cytotoxicity activity (CC_{50}) of complex compounds against T74D and HeLa cells was 8.78 µg/ml, 14.46 µg/ml, respectively, indicating promising anticancer activity. The complex enhanced growth inhibition; the cells exhibited better anticancer activities in both the T74D and HeLa cell lines. Despite potent *in vitro* activity, this complex compound exhibited a cytotoxicity against the normal Vero cells at an effective concentration.

Key words : Copper(II), 2,4,5-triphenyl-1H-imidazole, complex compound, anticancer, T74D cells, HeLa cells.

INTRODUCTION

Complex compounds are made up of a central metal ion with one or more ligands contributing their lone pair to the central metal ion. Complex compounds continue to be developed for use in the field of medicine. Some that have been successfully synthesized show good applications in the field of medical chemistry, especially those that bind to organic compounds.

Cis-platin, a complex compound used as the first anticancer drug, experienced rapid development in the 1960s. However, platinum-based complexes cause side effects at certain doses and provide drug resistance during the therapeutic process (Santini *et al*, 2013). Awareness of this triggered the development and discovery of new complex compounds based on non-platinum, with the hope of improving pharmacological properties, reducing side effects, and targeting specific drugs (Qiao *et al*, 2011). Examples of transition metals used in the synthesis of anticancer complex compounds include Co (II), Ni (II), Cu (II), Pd (II), Ru (II) and Pt (II) (Budzisz *et al*, 2009; Ali *et al*, 2011).

Metal Cu(II) is an essential element and plays an important role in the biological system of the human body (Linder and Maryam, 1996) as a constituent of redox enzymes and hemocyanin (Huheey *et al*, 1993). Cu metal has an atomic number 29 with an electron configuration of [Ar] $4s^2$ $3d^9$. Importantly, it has an empty orbital that can function as an electron pair acceptor of ligands. Based on these characteristics, Cu(II) metal is expected to have good anticancer activity capabilities, in the use of a ligand complexing metal. Research done by Devereux *et al* (2007), studied complexes synthesized from Cu(II) metal ions with ligands 2-(42 -thiazolyl) benzimidazole and 2-(2-pyridyl) benzimidazole. Tests performed on liver cancer cells (Hepatocellular carcinoma) showed a complex of Cu(II) metal ions with an IC_{50} value of 200 ìM had the best cytotoxicity. Compounds with IC_{50} values are classified as anticancer compounds with low toxicity (Meyer *et al*, 1982).

Research has shown the effectiveness of Imidazole-based complex compounds and their derivatives against cancer. Devereux (2004) synthesized imidazole-based complex compounds which were shown to have activity against SK-MEL-31 skin cancer cells and CAL-27 tongue cancer cells. Imidazole-based compounds also show

cytotoxic effects on Hep-G2 liver cancer cells as well as on A-498 colon cancer (Devereux *et al*, 2007), MCF-7 breast cancer, HeLa cervical cancer and HL-60 blood cancer (Bhat *et al*, 2011).

Nitrogen atoms function as donor electron pairs with metals to form complex compounds. Their effectiveness against cancer is linked to their interactions with DNA. Other nitrogen atoms contained in the complex can interact non-covalently, such as hydrogen bonding with base pairs (in major grooves and minor DNA) (El-Boraey, 2012). The positive charge of metals is also involved in electrostatic interactions with negative charges on the sugar-phosphate groups found in the DNA backbone (Chauhan and Farukh, 2006).

Therefore, complex compounds of Cu(II) metal ion synthesized with 2,4,5-triphenyl-1*H*-imidazole ligand in this study were tested for anticancer activity by MTT method {3-(4,5-dimethyltiazole-2-il)-2,5-diphenyl-tetrazolium bromide} *in vitro* assay against breast cancer cell (T74D cells) and cervical cancer cells (HeLa cells).

MATERIALS AND METHODS

Material

The materials used in this study were copper(II) chloride dihydrate ($CuCl_2.2H_2O$) (Merck 99.0%), N,N-dimethylformamide (DMF) (Merck 99.8%), dimethyl sulfoxide (DMSO) (Merck 99.8%), 2,4,5-triphenyl-1H-imidazole (Sigma-Aldrich 90%), methanol (Sigma-Aldrich 98%), breast cancer cells T74D (CVCL_0553), Cervical cancer cells HeLa (HeLa ATCC® CCL-2™), RPMI 1640 Medium (Gibco), Phospate-buffered saline 1X (PBS 1X) (Gibco) and Thiazoyl blue tetrazolium bromide (MTT) (Bio Basic).

Synthesis and characterization of complex compounds

A 1:2 mole ratio of metal and ligand Copper(II) chloride dihydrate and 2,4,5-triphenyl-1*H*-imidazole used to synthesize compounds was added to DMF and observed. The resulting complex solution was then put into a vial, distilled for 30 minutes and then heated at 120°C for 3 hours. The mixture was then cooled to room temperature in a vial covered with aluminum foil punctured with several small holes and left for 7 days to form solids. Daily washes with methanol was performed to remove any impurities contained in the mixture. The formed solid was then decanted and dried. Character observations were taken by UV-Vis Spectrophotometer, FTIR Spectroscopy and Thermal Gravimetric Analyzer (TGA).

Anticancer activity

Cancer cells with a density of 5×10^3 cells/well were distributed into 96 well plates, and incubated for 24 hours at a 37°C CO_2 to attach. The medium was then replaced with fresh complete medium containing either DMSO 0.1% (control) or complex compounds at concentrations of 50; 25; 12.5; 6.25; 3.13 and 1.56 µg/ml, and incubated for 20 hours (37°C/CO_2). 100 µl RPMI containing MTT reagent was then added to each well and the plates incubated for an additional 4 hours. Living cells react with MTT to form formazan crystals (Mosmann 1983). After 4 hours, the medium containing MTT was discarded and 50 µl DMSO solution was added to dissolve the formazan crystals, homogenized on top of shaker for 10 minutes and then read with a Microplate reader at a wavelength of 595 nm.

Statistical analysis

Microsoft Excel 2010 for Windows was used to determine the Cytotoxicity concentration 50 (CC_{50}) values of the complex compounds, analyzed unpaired t-test, and standard deviation.

RESULTS AND DISCUSSION

Synthesis and characterization of complex compounds

The complex compounds obtained as previously described were analyzed by microscopy. The results of a microscope photo at 10x magnification show that the solid obtained is in the form of a needle, as shown in Fig. 1. The yield of Cu (II)-2,4,5-triphenyl-1*H*-imidazole complex obtained was 72.127%.

The maximum wavelengths of the 2,4,5-triphenyl-1*H*-imidazole ligand and the Cu(II)-2,4,5-triphenyl-1*H*-imidazole complex are 243 nm and 529 nm, respectively. The increase in maximum wavelength change was due to d-d electron transitions, resulting in a metal charge transfer from the metal to the ligand (Ligand Metal Charge Transfer) (LMCT). This data also supports the research of Pramanik *et al* (2010), which showed that the maximum wavelength of the Cu(II)-aryl azo imidazole complex metal shifts towards a greater wavelength as compared to 2,4,5-triphenyl-1H-imidazole ligands.

FTIR spectroscopy was used to determine the existence of functional groups in the complex as well as new bonds formed between the metal and the ligand. New peaks appeared at wave number 422.38 cm^{-1}. This is consistent with the research of Gomathi et al. (2014) that showed new peaks indicating metal bonds and ligands (Cu-N) appearing at wave number 453 cm^{-1} while bonds of metal ions with H_2O ligands appeared at absorption peaks of 534.25 cm^{-1}, indicating the presence of Cu-O vibrations.

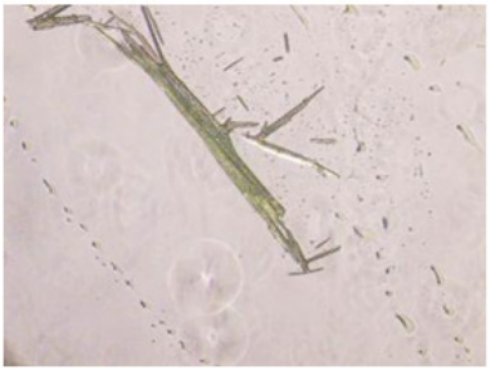

Fig. 1 : Cu(II)-2,4,5-triphenyl-1 *H*-imidazole Complex Compound under Microscope 10X.

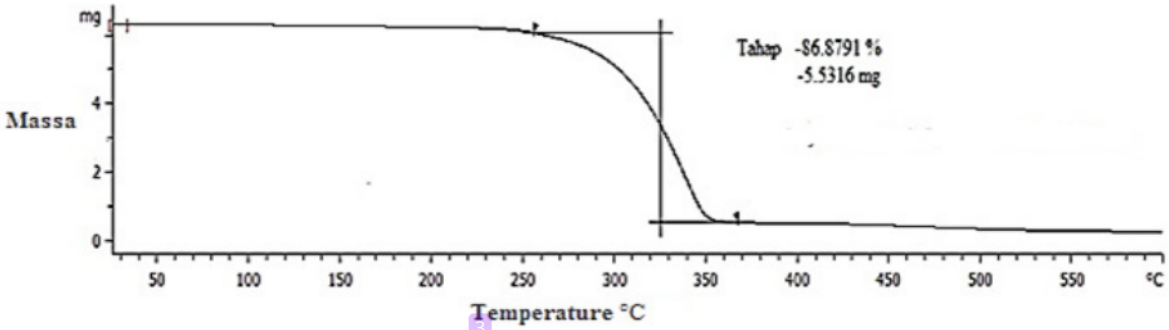

Fig. 2 : TGA Curve of Cu(II)-2,4,5-triphenyl-1*H*-imidazole complex compound.

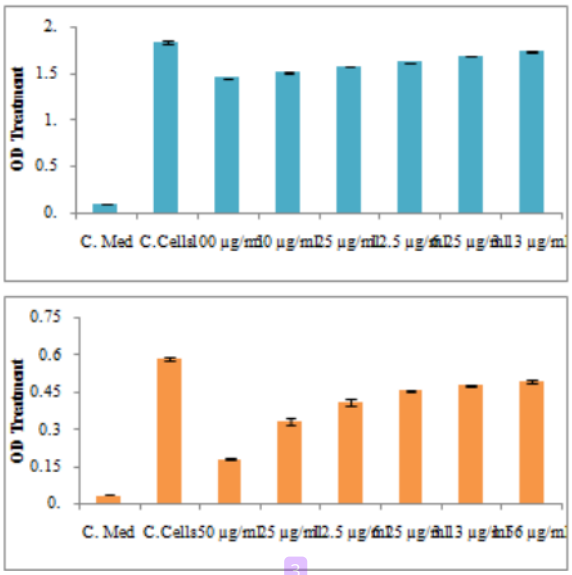

Fig. 3 : MTT Test Curve of Cu(II)-2,4,5-triphenyl-1*H*-imidazole Complex compound; HeLa cervical cancer cells shown in light blue; T74D breast cancer cells in orange.

TGA analysis in this study was carried out to provide specific information from complexes decomposing during heating. Thermogravimetric analysis of Cu(II)-2,4,5-triphenyl-1*H*-imidazole complex was carried out at 25-600°C with a complex sample weight of 6.3670 mg. The complex TGA curve of Fig. 2 shows that there is one stage of decomposition in the complex. A weight reduction of 86.8791% occurred at 255.33 - 355.83°C indicating a complex decomposition consisting of 2 2,4,5-triphenyl-1*H*-imidazole ligand molecules, 2 H_2O molecules and 1 Cl_2 molecule. This resulted in accordance with the theoretical weight in that the weight reduction of 86.8791% seen is the decomposition $(C_{21}H_{16}N_2)_2(H_2O)_2C_{l2}$). Residues of 13.1209% can be predicted to be Cu, as demonstrated by the research of Kukovec *et al* (2012), which showed that CuO is the final residue of the [Cu(6-hydroxyphicholine)$_2$(3-picolinate)$_2$] complex.

Cancer fighting activity

In this research, a cytotoxicity test was done by MTT method (3-(4,5-dimethyltiazole-2-yl)2,5-diphenyltetrazolium bromide) using T74D breast cancer cells and HeLa cervical cancer cells and based on the MTT test curve of the Cu(II)-2,4,5-triphenyl-1*H*-imidazole complex as shown in Figure 3. Based on these calculations, the CC_{50} values obtained for Cu(II)-2,4,5-triphenyl-1H-imidazole complex was 8.78 ìg/ml for T74D breast cancer cells and 14.46 ìg/ml for HeLa cervical cancer cells, with P>0.05. The compound added to Vero cells exhibited cytotoxic effects at CC_{50} = 44.74 µg/ml (Sucipto *et al*, 2018). 1% DMSO (negative control) did not show any cytotoxic effects against Vero cells.

One of the derivatives of the imidazole compound, 2-aryl-4-benzoyl-imidazole, showed effectiveness against cancer in skin cells A375, B16-F1, WM164, LNCaP, PC-3, Du 145, and PPC-1 with CC_{50} values amounting to 0.16; 0.12; 0.10; 0.15; 0.29; 0.20 and 0.13 ìM (Chen *et al*, 2010). The compounds with these CC_{50} values are classified as highly toxic to cancer (Meyer *et al*, 1982). This is consistent with the research of Ali *et al* (2013) which showed that a CuL complex (L = 3-(1,3-

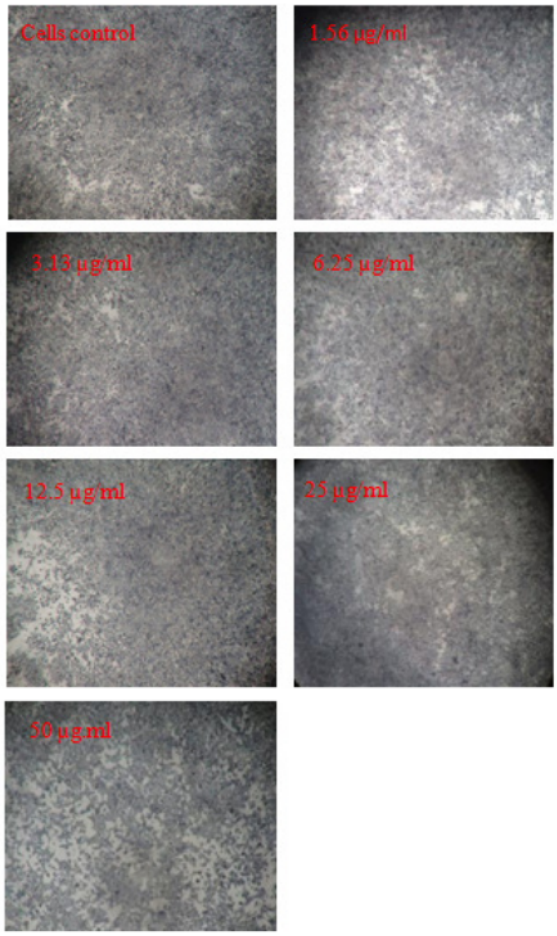

Fig. 4 : T74D Breast cancer cells following treatment with Cu(II)-2,4,5-triphenyl-1*H*-imidazole complex compound

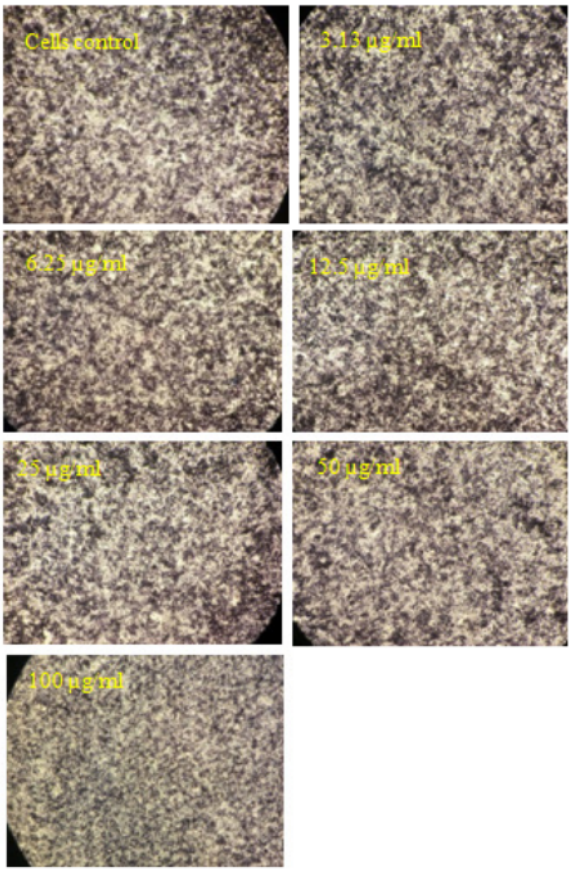

Fig. 5 : HeLa Cervical cancer cells following Treatment with Cu(II)-2,4,5-triphenyl-1*H*-imidazole complex compound.

dioxoisoindolin-2-yl)-2,6-dioxopiperidine-1-carbodithioate) killed more cancer cells than free ligands. The CC_{50} yield of Cu(II)-2,4,5-triphenyl-1*H*-imidazole complex in this study was smaller than what was showen by Deverux *et al* (2007), where the MTT test was carried out on the $[Cu(TBZH)_2(BZA)]$-(BZA).0.5TBZH.H_2O complex at 32 µM.

Fig. 4 shows that with higher concentrations of Cu(II)-2,4,5-triphenyl-1*H*-imidazole complex compounds, more T74D Breast Cancer Cells die and Fig. 5 for HeLa cervical cancer cells). In high concentrations, the compound is toxic, which can kill or inhibit cell growth.

A strong oxidative can cause cell death in more than one way: passive cell death, such as necrosis caused by the disruption of osmotic balance and apoptosis, such as active cell death caused by caspases (Tardito *el al*, 2009). Based on previous research, active cell death is characterized by cytoplasmic vacuolation, largely in the endoplasmic reticulum and by the absence of caspases (cysteine proteases). The copper charge can cause direct cell inactivation between metal-protein interactions. The enzymatic activity of caspases is regulated by oxidative modification of cysteine residues and is inhibited by disulfiram thereby forming a direct relationship between sulfur protein and drugs (Sperandio *et al*, 2000).

In conclusion, this study demonstrated that Cu(II)-2,4,5-triphenyl-1H-imidazole complex compounds exhibited significant cancer cell fighting properties. The application of complex compound was found to be more reactive in T74D breast cancer cells than with HeLa cervical cancer cells. The mechanisms of how a complex compound exerts is anticancer effects are not known.

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