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Journal of Physics: Conference Series

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In vitro antibacterial and anticancer activity of Zn(II)Valinedithiocarbamate complexes

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Abstrack. A new complex of Zn(II) that contain amino acid valine and dithiocarbamate ligands were synthesized and characterized by using Ultraviolet Visible (UV-Vis), Infra Red (IR) spectroscopy, X-Ray Fluoroscence (XRF), X-Ray Diffraction (XRD), melting point and molar conductance. The complex was prepared by "in situ method" and showed that complexes are successfully synthesis. The invitro cytotoxic complexes compound was examined againts MCF-7 (breast cancer) using cis-Pt drug as a control positive and the complexes exhibit very strong invitro cytotoxic againts MCF-7 based on IC_{50} data is 639,35 μg/mL which indicates that the complex can induce the morphological MCF-7 cancer cells changes towards apoptosis. Complexes compound were evaluated as their antibacterial agents activity against of *mycobacterium tuberculosa* H37RV using LJ method and results show these complexes are potential as anti-tuberculosis agents. Therefore this complexes compounds can be use to new drugs compound in the treatment againts of MCF-7 and tuberculosis.

1. Introduction

Cisplatin, carboplatin and oxaliplatin are widely used commercial platinum(II) based metallo-drugs which have been used effectively for the treatment of cancers [1-3]. Howefer, the effectivitas of cispaltin has been frequently limited is is mainly hampered due to some side effects such as neurotoxicity, ototoxicity, nausea, anemia, myelotoxicity [4] development of resistances exhibited by cancer cell lines [5]. Therefore non platinum metallic like Zn compounds have been synthesized and with the use of appropriate ligands to increase the biological activity of complex compounds and evaluated for their potential as anticancer activity with much lower toxicity and fewer side effects against a wide panel of cancer cell lines.

Dithiocarbamates and their metal complexes have invited much research attention due to their diverse applications and interesting biological, structural, magnetic, electrochemical and thermal properties [6][7][8]. Some metal complexes of DTC used in medical applications like in health care for the management of alcoholism [9], also dithiocarbamates have been applied to prevent arthrosclerosis [10]. Their anti-microbial activity, anti-inflammatory, anti-cancer and metal transport in membranes have been reported [11][12] and also been found to be widespread in ingredients and the science of separation, and has the potential for use as chemotherapy [13][14][15]. In terms of aspects of bioactivity and the application of dithiocarbamate we report in this paper the In vitro antibacterial and anticancer activity of Zn(II)Valinedithiocarbamate complexes. The complex was characterized by UV-Vis and IR and cytotoxic tests on breast cancer cells (MCF-7) and tuberculosis.

2. Experimental

2.1. Materials

CS_2 99.5% (Ajax Chemical Ltd), Cisplatin, Roswell Park Memorial Institute Medium, DMSO, Zink(II)clorida, valine PA, Ethanol (95%) methanol (95%), Acetone (95%), n-hexane (95%), and Acetonitrile (95%) (Central Laboratory of Hasanuddin University, Indonesia).

2.2. Synthesis of valinedithiocarbamate ligand

0.58 gr (5 mmol) valine was dissolved in the 10 mL ethanol, then added dropwise with 0.3 mL of CS_2 (5 mmol) into 10 mL ethanolic solutions at temperatures below 10^{O}C and stirred for 10 minutes.

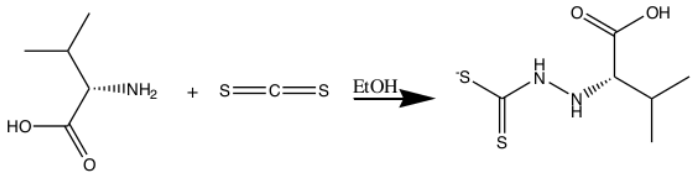

Figure 1. Synthesis reaction of valinedithiocarbamate ligand

2.3. Synthesis of Zn(II) with valinedithiocarbamate ligand

The corresponding ligand of valinedithiocarbamate added to an ethanolic solutions of 0,40gr (3 mmol) $ZnCl_2$, wich is dissolved in 10 mL ethanol. It was stirred for 30 minute. It was sentrifuged and washed with distilled water several times and then characterized of product (**Figure 2).**

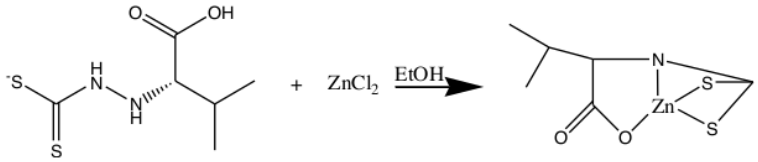

Figure 2. Synthesis reaction of Zn(II) Valinedithiocarbamate

2.4. Characterization of Complex

The electronic spectra obtaining by using UV-Vis Jenwey spectrophotometer 200-1100 nm and Infrared spectra perform by using Infra red SHIMADZU spectrophotometer, in 4000-300 cm^{-1} range of frequency. While the interaction between Zn and O, N and S were confirmed by XRD. The presence of Zn and Sulphur confirmed by XRF instrument. Melting point was measured with Electrothermal IA 9100, and conductivity was measured with conductometer.

2.5. The Cytotoxic Assay of MCF-7Breast Cancer Cells

The MCF-7 cell cultures were placed into 96 well plates and then incubated at 37°C and 5% of CO2 gas until the percentage of cell growth reaches to 70%. Next cells were treated with dithiocarbamate complexes and then incubated (for 24 hours at 37°C and 5% CO2 gas). To facilitate reading of absorbance, it was adding a presto blue work reagents onto the cell. Absorbance measured by using Multimode Reader.

3. Result And Discussion

The yield of synthesis complex Zn(II) valinedithiocarbamate was 42.12% with melting points obtained 268°C-270°C and the conductivity value of 0.135 mS/cm.

3.1. UV-Vis characterization

The electronic spectra of dithiocarbamates (table 1) obtained in band 1 show absorption bands at wavelength 235-296 nm which are intraligant transitions $\pi \rightarrow \pi^*$ from CS_2 groups which are influenced

by the presence of the R group hyperconjugation to nitrogen atoms in the absorption area of 250-300 nm [16]. Results of UV-Vis spectrum of complex compounds that have been synthesized, **Figure 3**.

Table 1. UV-Vis data of Zn(II)valinedithiocarbamate

Compound	λ maximum (nm)	Electronic Transition
ZnValDtc	238	0,316

ValDtc = ValineDithiocarbamate

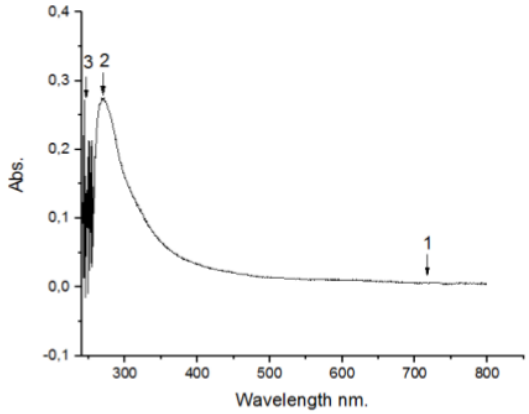

Figure 3. UV-Vis Spectrum of Zn(II)ValDtc

3.2. IR characterization

Dithiocarbamate compounds can be identified *via* the presence of certain absorbance peaks primarily vibrational ν(C-N) and ν(C-S). In the infrared spectra of dithiocarbamate compounds, the region 1480–1550 cm-1 is primarily associated with the R2N–CS2 'thioureide' band which defines the carbon-nitrogen bond order between a single bond at 1250–1350 cm-1 and a double bond at 1640–1690 cm-1 [17]. To ensure the existence of bonds between metals and ligands was observed in far infrared absorption (400-100)cm^{-1} [18].

The infra red absorption peak at wave number 376 cm^{-1} indicates interaction between groups (C=S) with Zn metal ions. The absorption peak at wave number 472 cm^{-1} indicates the interaction of O atoms of complex compounds with Zn metal ions. The absorption peak at wave number 543 cm^{-1} indicates the interaction of N atoms of complex compounds with each Zn metal ion. The appearance of absorption at wave number 1031 cm^{-1} shows double absorption peak which indicates monodentate coordination between groups (C=S) with Zn metal ions. There is a strong absorption at the wave number 1500 cm^{-1} which indicates that it is derived from the amine group (C=N). The important IR and far bands of dithiocarbamate complexes are depicted in table 2 figure 4.

Table 2. IR data of Zn(II)valinedithiocarbamate

Compund	**ν(C=N)**	**ν(C=S)**	**ν(M-S)**	**ν(M-O)**	**ν(M-N)**
Zn(II)ValDtc	1500s	1031m	376m	472w	543w

s = strong; m = medium; w = weak

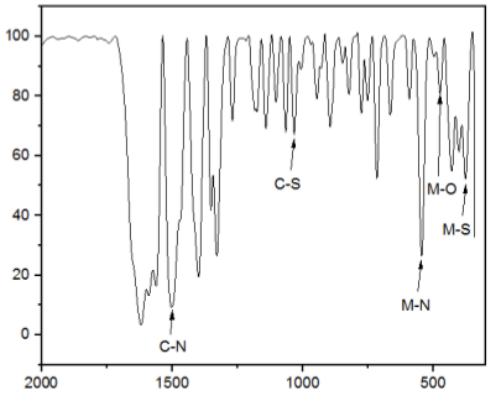

Figure 4. IR Spectrum Zn(II)ValDtc

3.3. XRF Characterization

The results of the elemental analysis of complex compounds using XRF obtained by Zn was 38.27% and sulfur was 4.11%.

3.4. XRD Characterization

Diffraction peaks from figure 5, obtained 3 polycrystalline phases namely Zink monosulfide (ZnS), Zink monoxide (ZnO) and Zink cyanide ($Zn(CN)_2$). Value of 2θ 26.97°; 28.03°; 34,55°; 45,54°; 47,59°; and 56.03°, with hkl values of 100; 101; 013; 011; 110; and 201 were identified as hexagonal Zink monosulfide (ZnS) structures based on standard X-ray diffraction powder patterns (pdf 96-901-3410 files) and similar results were reported by Soltani [19]. X-ray diffraction peaks with a value of 2θ 24.88°; 30.99°; 36,35°; 37.50°; 44,13°; 47,54°; 56,61°; and 62,92°. The value of hkl respectively, which is 130; 210; 230; 103; 222; 301; 180; and 400, identified as a monoclinic structure of Zink monoxide (ZnO) based on the standard X-ray powder diffraction pattern (pdf file 96-220-0783) and supported from data reported by Raoufi [20]. Then the X-ray diffraction peak with a value of 2θ 21.30°; 30.06°; 37,33°; and 43.42°, with hkl values of 101; 020; 121; and 202 were identified as cubic zinc cyanide ($Zn(CN)_2$) structures based on standard X-ray powder diffraction patterns (pdf 96-722-2768 files) and were supported based on data reported by Trapalis [21].

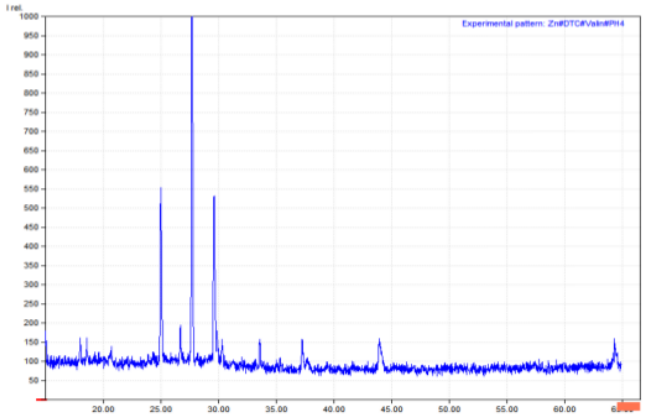

Figure 5. XRD Zn(II)ValDtc

3.5 *Antibacterial activity*

The antibacterial activity of the complexes is presented in table 3 with LJ method. The results of these studies revealed that metals complexes showed an effective in the inhibition of *Mycobacterium tuberculosa*. Biological activity of the previous compounds in inhibition of bacterial growth could be by the inhibition of the bacterial cell wall synthesis by bounding to the precursor of the cell wall [22]

Table 3. Population *M. Tuberculosis* For Complexes

Compound	Concentration (ppm)	Population M.Tb complex
Zn(II)ValineDtc	0, 2	-
	0, 4	-
	0, 6	-

Figure 6. Antibacterial test result against *M. tuberculosis* $ZnVal_1$ Complexes 0,002; $ZnVal_2$ Complexes 0,004; $ZnVal_3$ Complexes 0,006

3.6. Cytotoxic Test on MCF-7 Cancer Cells

Cytotoxicity test of Zn(II)valinedithiocarbamate complex compounds on MCF-7 line cells obtained IC_{50} showed a correlation between Znvaline complex (IC_{50} = 210.27 μg/mL) and cisplatin (IC_{50} = 470 μg/mL). Therefor this complex can induce morphological changes in cancer cells and cause apoptosis in cancer cells. [23]. Figure 6 is result cell undergo apoptosis.

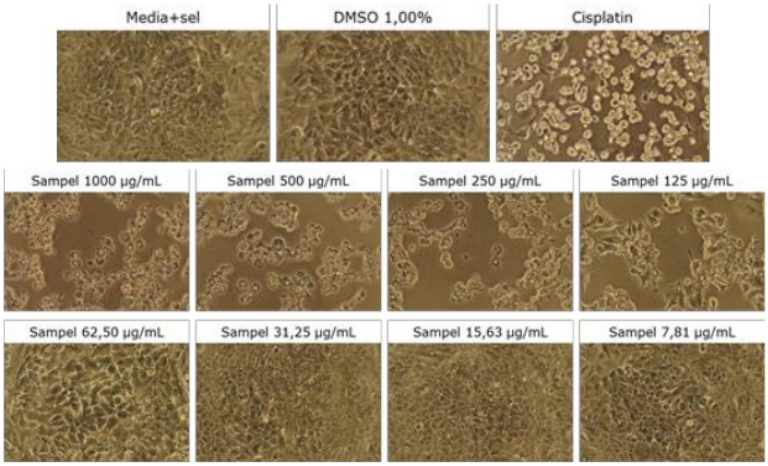

Figure 7. Apoptosis of MCF-7 cells induced by Zn(II)ValDtc

4. Conclusion

The dithiocarbamate complex were found active to against *mycobacterium tuberculosa*. In vitro study, the complex showed good activity at 210.27 μg/mL inhibit the MCF-7 cancer, so that cancer cells undergo apoptosis.

Acknowledgements

We would like to thank was supported financially by the Education Fund Management Institute (LPDP), we are grateful to Inorganic Research Center Laboratory of Hasanuddin University, Makassar, Indonesia for supporting this research, especially to Ms. Haslinda, Ms. Kartini, Mr.Sugeng, Mr. Rony and Mr. Markus who participated of this research.

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