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Research Article

SYNTHESIS, CHARACTERIZATION AND CYTOTOXIC ACTIVITY OF Zn(II) CYSTEINE DITHIOCARBAMATE IN BREAST CANCER (MCF-7)

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ABSTRACT

To synthesize and characterize complex compound of Zn(II) with cysteine dithiocarbamate ligands and studies its cytotoxic activity in breast cancer (MCF-7). The complex of Zn(II) cysteine dithiocarbamate was prepared by "in situ method" and characterized by using Ultraviolet-Visible (UV-Vis) and Infra-Red (IR) spectroscopy, melting point and conductivity. The results of UV-Vis maximum spectrums of Zn(II)cysteine dithiocarbamate at 282 nm and 374 nm indicated that electronic transition $\pi \rightarrow \pi^*$ dan $n \rightarrow \pi^*$ of CS_2 and N=C=S. While the presence of IR spectra at the wavelength in the region of 397-534 cm^{-1} indicated that has been coordination occurred between Zn(II) with Sulphur (S), Nitrogen (N) and Oxygen(O) atoms from cysteine dithiocarbamate ligands. Complex characterization using UV-Vis and IR showed that complex Zn(II) cysteine dithiocarbamate compounds were successfully synthesized by the in-situ method. The results of the cytotoxicity assay of Zn(II) cysteine dithiocarbamate complex compounds in MCF-7 cells obtained IC_{50} values of Zn(II) complex = 98.60 µg/mL and cisplatin (IC_{50} = 200 µg/mL. These result can be seen that IC_{50} value of Zn(II) complex is lower than cisplatin so that Zn(II) complex has very good inhibitory activity against MCF-7 cancer cells compared to cisplatin and it can even cause apoptosis in cancer cells.

Keywords: Complexes; Cysteine; Dithiocarbamate; Apoptosis; Breast cancer; Chemotherapy.

INTRODUCTION

Breast cancer (MCF-7) is one of the highest lethal cancers in 7 countries, namely Indonesia, Japan, Malaysia, Philippines, Singapore, Sri Lanka and Taiwan [1]. Treatment of breast cancer is carried out in a multidisciplinary manner such as surgery, chemotherapy and radiation [2].

At present chemotherapy is a very important component in the paradigm of handling breast cancer [3]. Some drugs that are often used for chemotherapy are platinum derivative compounds, such as cisplatin, carboplatin, and oxaliplatin. Cisplatin is still the main choice in the treatment of cancer. However, cisplatin has very dangerous side effects, especially showing high toxicity in the body [4,5,6,7,8]. So that it needs effective and less toxic metal-based anticancer drugs [5]. The use of essential metals is interesting for researchers to develop metal-based anticancer drugs.

The use of appropriate ligands can significantly increase the activity of complex compounds in inhibiting cancer cells [9]. This study used a dithiocarbamate ligands. Dithiocarbamate compounds is a material that is very potential in the fields of agriculture, industry, and health. In the field of health, dithiocarbamate compounds can be character-based metal poisoning drugs that act as good chelating agents [10,11]. In addition, these compounds can also be used as radio chemotherapy target agents in tumors [12,13]. Dithiocarbamate compounds can be complexed mostly with metal ions from the transition element, because dithiocarbamate compounds have a very special structure where there are S groups that can donate electrons monodentate and bidentate [14].

The use of essential metal complexes with amine dithiocarbamate ligands is still lacking in scientific information either from journals or from other articles, so researchers will conduct a study of the anticancer activity of the Zn(II) complex with amine dithiocarbamate ligands.

MATERIAL AND METHODS

Materials

Zinc(II)sulfate, Cysteine, Ethanol (95%) methanol (95%), Acetone (95%), n-hexane (95%), Acetonitrile (95%), Carbon disulfide, Cisplatin, Roswell Park Memorial Institute Medium, and DMSO.

Synthesis of cysteine dithiocarbamate ligand

Cysteine 0.6133 gr (5 mmol) dissolved in 10 mL ethanol, followed by adding dropwise CS_2 0.3 mL (5 mmol) into 10 mL ethanol solution under conditions under 10^{O}C and stirring for 10 minutes.

Synthesis of Zn(II) with cysteine dithiocarbamate ligand

The cysteine dithiocarbamate ligand solution was added $ZnSO_4.7H_2O$ 0.8626 gr (3 mmol), which was dissolved in 10 mL ethanol and stirred for 30 minutes. Then the precipitate formed is then filtered and washed with ethanol and dried in a desiccator after recrystallization with the appropriate solvent, the mixture of acetonitrile and ethanol (1: 2.v / v), and the characterization of the product.

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. Melting point was measured with Electrothermal IA 9100, and conductivity was measured with conductometer.

The Cytotoxic Assay of MCF-7 Breast Cancer Cells

The MCF-7 cell cultures were placed into 96 well plates and then incubated at 37°C and 5% of CO_2 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% CO_2 gas). To facilitate reading of absorbance, it was adding a presto blue work reagents onto the cell. Absorbance measured by using Multimode Reader.

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

Compound	λ Maximum (nm)	Electronic Transition
Zn(II)CysDtc	282	π→π*
	374	n→π*

CysDtc = Cysteine Dithiocarbamate

Table 2. IR data of Zn(II) cysteine dithiocarbamate

Compound	v(C=N)	v(C=S)	v(M-S)	v(M-O)	v(M-N)
Zn(II)CysDtc	1624 s	1126 m	397 w	420 w	534 w

s = strong; m = medium; w = weak

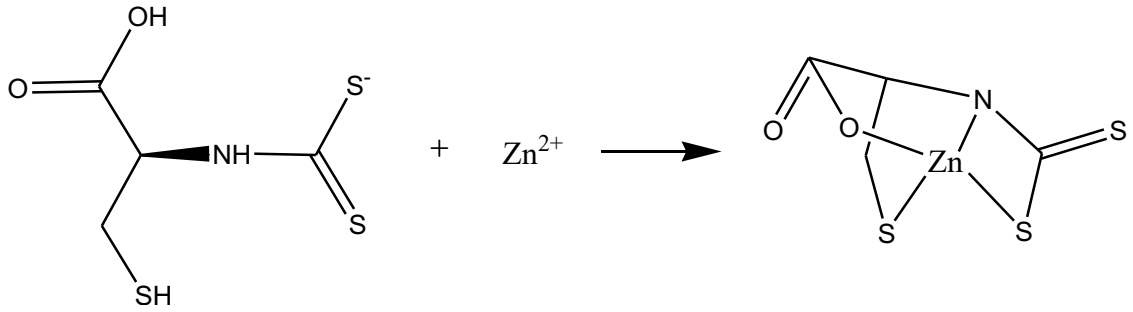

Figure 1. Synthesis reaction of Zn(II) cysteine dithiocarbamate

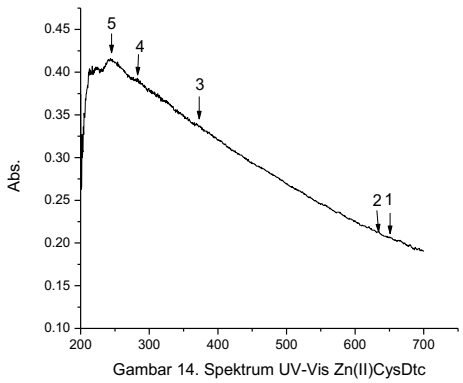

Figure 2. UV-Vis Spectrum of Zn(II) cysteine dithiocarbamate

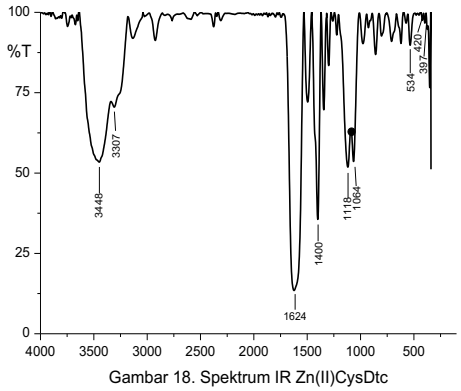

Figure 3. IR Spectrum of Zn(II) cysteine dithiocarbamate

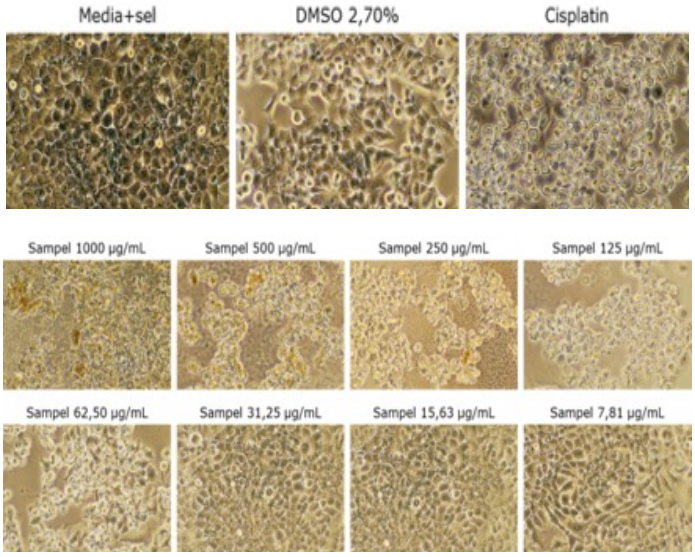

Figure 4. Apoptosis of MCF-7 cells induced by Zn(II) cysteine dithiocarbamate.

RESULTS AND DISCUSSION

The results of the complex synthesis of Zn(II) cysteine dithiocarbamate was 48% with the melting point obtained 280ºC-282ºC and conductivity values 0.08 mS/cm.

UV-Vis characterization

The results of characterization with UV-Vis **(Figure 2)**, in water solvents for complex Zn(II) cysteine dithiocarbamate compounds obtained in band 1 show absorption bands at wavelength 282 nm which are intraligand 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 [15]. The shift in the II band which is an intraligand transition $n \rightarrow \pi^*$ from the group N=C=S at wavelengths 374 nm is indicated by complex compounds.

IR characterization

Dithiocarbamate complex compounds, for v(C-N) lies in the wave number between single bonds (1350-1250)cm^{-1} and double bonds (1690-1640)cm^{-1}, so the bond is written as v(C=N). Furthermore, for C-S uptake it is written as v(C=S), with the number of wavelengths being between double bond wavenumbers C=S (1050-1200)cm^{-1} and single bonds C-S (550-800)cm^{-1} [16]. To ascertain the existence of bonds between metals and ligands was observed in far infrared absorption (400-100)cm^{-1}, namely the presence of sulfur metal bond strain from dithiocarbamate ligands and metal bonds with nitrogen from bipyridyl or f phenanthroline ligands [17].

Infra red absorption peak at wavenumber 397 cm^{-1} indicates the interaction of S atoms with Zn metal ions. The absorption peak at wavenumber 420 cm^{-1} indicates the interaction of O atoms of complex compounds with Zn metal ions. The absorption peak at wave number 534 cm^{-1} indicates the interaction of N atoms of complex compounds with each Zn metal ion. The appearance of absorption at wavenumber 1126 cm^{-1} shows double absorption peak which indicates monodentate coordination between groups (C=S) with Zn metal ions. Then there is a strong absorption at the wavenumber 1624 cm^{-1} which indicates that it is derived from the amine group (C=N). Results of the spectrum of complex compounds that have been synthesized, **Figure 3**.

Cytotoxic Test on MCF-7 Cancer Cells

The results of the cytotoxicity test of Zn (II) cysteine dithiocarbamate complex compounds in MCF-7 cells obtained IC_{50} values of complexes Zn = 98.60 µg/mL and cisplatin (IC_{50} = 200 µg/mL. These results can be seen that the IC_{50} value of Zn complex is lower than that of cispatin, so that this complex has more ability than cisplatin in inducing morphological changes in cancer cells and causing apoptosis in cancer cells **(Figure 4).**

The target of a metal complex is DNA itself which can bind adenine and guanine in a double-helix DNA. The bond that occurs is covalent bonds with DNA. Metal ions from complex compounds can connect the two strands to form intra-strand cross-links, bonding to two DNA strands in a double helix. This intra-strand cross bond prevents cell breakdown through the mitosis process so that the tumor stops growing. Then the tumor cell becomes rigid which is induced by crosslinking on metal ions so that it cannot be recognized and DNA cannot be repaired. As a result, the cells experience death and the tumor will degenerate. In addition, planar molecules and most hydrophobics can enter the inside of the helix, with the process of intercalating between base pairs in a noncovalent manner. Metallodrugs not only bind covalently to DNA but also in a noncovalent way through an intercalation process [18].

CONCLUSION

Complex characterization using UV-Vis and IR showed that complex Zn(II)cysteine dithiocarbamate compounds were successfully synthesized by the in-situ method. The IC_{50} value of the Zn complex is lower than cisplatin, which indicates that the Zn(II) complex has very good inhibitory activity against cancer cells. Even, Zn(II) complex induces cancer cell apoptosis.

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REFERENCES

1. P. Hertz, RZ, McDonald M, and Phitman S. The Burden of Cancer in Asia. 2nd ed. USA: Pfizer Fact; 2008. p. 2.
2. Cardoso F, Bedard, PL, Winer EP, Pagani O, Senkus-Konefka E, Fallowfield, LJ, et al. International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. Journal of the National Cancer Institute 2009; 101:1174-1181. (11/3/2019)
3. Gong C, Yao H, Liu Q, Chen J, Shi J, Su F, & Song E. Markers of tumor-initiating cells predict chemoresistance in breast cancer. PLoS One 2010; 5(12): e15630. (11/3/2019)
4. Dorcier A, Han AW, Bolano S, Gonsalvi L, Juillerat-Jeannerat L, Laurenczy G, et al. In Vitro Evaluation of Rhodium and Osmium RAPTA Analogues: The Case for Organometallic Anticancer Drugs Not Based on Ruthenium. Organometallic 2006; 25: 4090-4096. (11/3/2019)
5. Qiao X, Ying MZ, Zhi XC, Xue F, Wen ZY, Yuan XJ. Study on potential antitumor mechanism of a novel Schiff Base copper(II) complex: Synthesis, crystal structure, DNA binding, cytotoxicity and apoptosis induction activity. Journal of Inorganic Biochemistry 2011; 105: 728–737. (11/3/2019)
6. Prasad PR, Mukhopadhyay S, Shikha SR, Sharma V, Mobin S, and Shankar PD. Anticancer Activity of Iridium(III) Complexes Based on a pyrazole-Appended Quinoline-Based BODIPY. Inorg. Chem. ACS 2017; 56: 12232-12247. (12/3/2019)
7. Salim SA , and Kettunen M. Platinum Group Antitumor Chemistry: Design and development of New Anticancer Drugs Complementary to Cisplatin. Current Medical Chemistry 2006; 13: 1337-1357. (12/3/2019)
8. Bruijnincx P, and Sandler P. New trends for metal complexes with anticancer activity. Current Opinion In Chemical Biology 2008; 12: 197-206. (12/3/2019)
9. Ferreira I, De lima G, Paniago E, Pinheiro C, Wardell J, and Wardel S. Study of metal dithiocarbamate complexes, Part V. Metal complexes of $[S_2CN(CH_2(OMe)_2]$: a standard dimeric zinc dithiocarbamate structural motive, a rare cadmium dithiocarbamate coordination polymer, and a hydrated sodium dithiocarbamate complex, with a$[Na_2O_2]$ core and chain. Inorganica Chimica Acta 2015; 11: 1-9. (13/3/2019)
10. Ritacco I, Russo N and Sicilia E. DFT Investigation of the Mechanism og Action of Organoiridium(III) Complexes As Anticancer Agents. ACS. Inor.Chem 2015; 30: A-J. (13/3/2019)
11. Awang N, and Baba I. Diorganotin(IV) Alkylcyclohexyl ditiocarbamate Compounds; Synthesis, Characterization and Biological Activities. Sains Malaysiana 2012; 41(8): 977–982. (14/3/2019)
12. Aruna K, Drishty S, Anupam M, Madhaya M, Shrmila B, Kannchan K. [99mTc]-labeling of colchine [99mTc(CO)3(H2O)3]+. Bioorganic and Medicinal Chem 2006; 14: 793-799. (14/3/2019)
13. Raya I, Baba I, Yamin BM. New mixed ligan complexes of samarium(III) with dithiocarbamate and 1,10-phenantroline. Malaysia Journal of Analitycal Sciences 2006; 10(1): 93-98. (14/3/2019)
14. Rogachev I, Gusis V, Gusis A, Cortina JL, Gressel J, and Warshawsky A. Spectrofotometric Determination Of Copper Complexation Properties Of New Amphifilic Dithiocarbamates. React.Funct. Polym 1999; 42(3): 243-254. (14/3/2019)
15. Bookhari A, Hill JO, and Magee RJ. Nickel(II) and copper(II) complexes of monoethanol and diethanoldithiocarbamic acid. journal of nuclear Inorganic Chemistry 1974; 36: 1253-1257. (14/3/2019)
16. Bernal C, Neves EA, and Cavalheiro TG. Differences in thermal decomposition of Ag(I), Mn(II), F(II), and Fe(III) complexes of cyclic dithiocarbamate. Thermocemica Acta 2001; 370(1-2): 49-55. (13/3/2019)
17. Wang B, Ma HZ, and Shi QZ. Chiral lanthanide (III) complexes of sulphur-nitrogen-oxygen ligand derived from aminothiourea and sodium D-camphor-β-sulfonate. Inor. Chem Commun 2001; 4: 409-412. (14/3/2019)
18. Mjos KD, and Orvig C. Metallodrugs in Medicinal Inorganic Chemistry. Chem.Rev 2014; 114(8): 4540-4563. (14/3/2019)

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