

IN-VITRO EVALUATION OF THE ANTICANCER ACTIVITY OF Cu(II)AMINA(CYSTEINE)DITHIOCARBAMATE

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ABSTRACT

The Complex of Cu(II)cysteinedithiocarbamate has been synthesized, it was prepared by the "in situ method" and characterized by using Ultraviolet-Visible (UV-Vis), Infra-Red (IR) spectroscopy, X-Ray Fluorescence (XRF) instruments. While melting point and conductivity also measured. The presence of UV-Vis maximum spectrums of Cu(II)cysteinedithiocarbamate at 296 nm and 436 nm indicated that electronic transition $\pi \rightarrow \pi^*$ dan $n \rightarrow \pi^*$ of CS₂ and N=C=S myotis. The presence of the wavelength in the region of 399-540 cm⁻¹ of IR spectra is indicated that has been coordination occurred between Cu(II) with Sulphur (S), Nitrogen (N), and Oxygen(O) atoms respectively from cysteinedithiocarbamate ligands. The XRF data confirm the presence of Cu and S in the new compound formed. The XRD spectrums also showed several hkl of CuO, CuS, and CuN indicating there is an interaction between Cu(II) with N, S, and O atoms. Cytotoxic test of Cu(II)cysteinedithiocarbamate complex has IC₅₀= 639,35 µg/mL which indicates that the complex can induce the morphological MCF-7 cancer cells changes towards apoptosis.

Keywords: Anticancer, Cu(II)Amina(cysteine)dithiocarbamate.

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INTRODUCTION

Nowadays, cisplatin is still the primary choice as an anticancer medicate since it has been demonstrated to be successful in treating different sorts of cancer and has been utilized in cancer chemotherapy for approximately 70% of all cancer patients. Be that as it may, cisplatin has exceptionally unsafe side impacts, especially showing tall harmfulness within the body, nephrotoxicity, neurotoxicity, and sedate resistance [1][2]. It is vital to utilize other metals that are less poisonous and have great potential as anticancer, with the utilize of fitting ligands to extend the natural action of complex compounds.

Dithiocarbamate complex has been reported in a large number of transition metal ions due to their unique structural characteristics and diverse applications. And it has been utilized extensively within the fields of analytical chemistry, agriculture, the pharmaceutical industry, and medicine[3][4]. The Dithiocarbamate complex has also been found to be widespread in ingredients and the science of separation and has the potential for use as a chemotherapy agent[5][6][7]. Dithiocarbamate compound has a very special structure in which there is an S group that can donate electrons in a monodentate or bidentate manner[8]. The utilize of dithiocarbamate ligands with additional donor groups, such as oxygen and nitrogen groups (such as amines), can increase the diversity of structures and influence the nature of the biological activity of complex compounds [9][10].

The Ligands active in biological processes have attracted more consideration towards the design of potential antitumor agents[11]. Nowadays, investigation of the use of essential

metal complexes with aminedithiocarbamate ligands is still ignorant, so the researchers will conduct an anticancer activity study of the Cu (II) complex with aminedithiocarbamate ligands. The complex was characterized by UV-Vis and IR and cytotoxic tests on breast cancer cells (MCF-7).

MATERIALS AND METHOD

Materials

Carbon disulfide 99.5% (Ajax Chemical Ltd), Cisplatin, Roswell Park Memorial Institute Medium, and DMSO (Central Laboratory of Padjadjaran University Bandung, Indonesia), copper(II) sulfate, Cysteine, Ethanol (95%) methanol (95%), Acetone (95%), n-hexane (95%), and Acetonitrile (95%) (Central Laboratory of Hasanuddin University, Indonesia).

Method

Synthesis of cysteinedithiocarbamate ligand

Amount of 0.6133 gr (5 mmol) cysteine were dissolved into 10 mL of ethanol, then added dropwise with 0.3 mL of CS₂ (5 mmol) into 10 mL ethanolic solutions (as Ligan, L) at temperatures below 10°C and stirred for 10 minutes Proposed reaction can be seen in (Figure 1).

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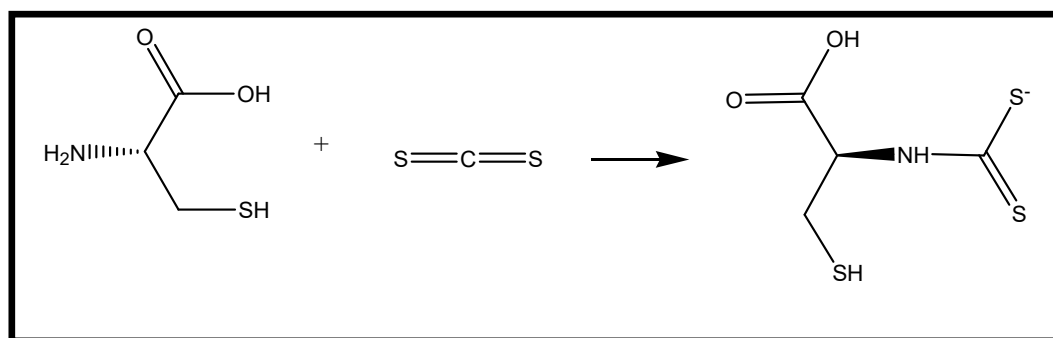


Figure 1. Synthesis reaction of cysteinedithiocarbamate ligand

Synthesis of Cu(II) with cysteinedithiocarbamate ligand

A solution of cysteinedithiocarbamate ligand added to an ethanolic solution of 0,7320gr (3 mmol) CuSO_4 , which is dissolved in 10 mL ethanol. It was stirred for 30 minutes. The precipitate formed then filtered and washed with ethanol and dried within the desiccator after recrystallized with the appropriate solvent, a mixture of acetonitrile and ethanol

(1:2.v/v), and then characterized of the product, and the reaction expressed in (Figure 2).

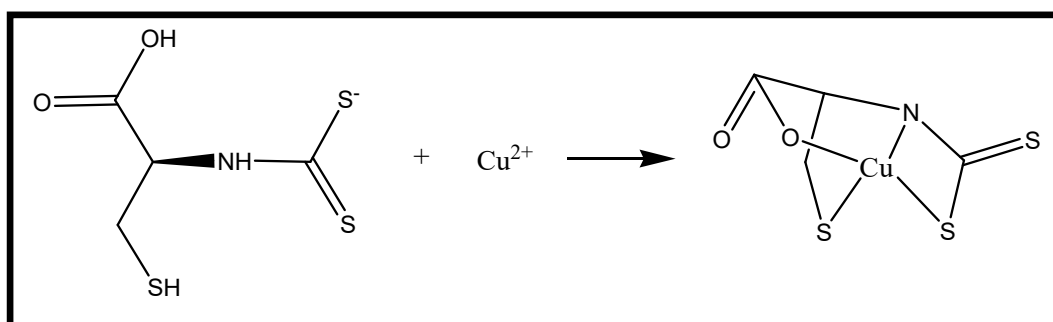


Figure 2. Synthesis reaction of Cu(II) Cysteinedithiocarbamate

Characterization of Complex

The electronic spectra obtaining by using UV-Vis Jenway 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 Cu and O, N, and S were confirmed by XRD. The presence of Cu and Sulphur confirmed by the XRF instrument. The melting point was measured with Electrothermal IA 9100, and conductivity was measured with a conductometer.

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 CO_2 gas until the percentage of cell growth reaches more than 70%. Next cells were treated with dithiocarbamate complexes and then incubated (for 24 hours at 37°C and 5% CO_2 gas). To facilitate the reading of absorbance, it was adding a presto blue work reagents onto the cell. Absorbance measured by using Multimode Reader.

Preparation of Media, Positive Control and Cysteinedithiocarbamate complex

Roswell Park Memorial Institute Medium (RPMI) liquid culture media prepared by mixing 10% Fetal Bovine Serum (FBS) and 50 $\mu\text{L}/50\text{mL}$ antibiotics. In this test the positive control used is Cisplatin. However cysteinedithiocarbamate complex dissolved in the non-toxic solvent, namely DMSO in certain

concentrations as stock. TheThe antiproliferation assay work solution was used PrestoBlue™ Cell Viability Reagent.

Preparation of MCF-7 Cells

The MCF-7 cells have been confluent at 70%, and discharged onto a media dish, were cells rinse twice with 1 mL Phosphate Buffered Saline (PBS). 1 ml of Trypsin-EDTA solutions it was added on the dish, and then incubated for 5 minutes. The cell layers were dispersed (under the cell inverted microscope it would appear to be floating. The cells moving into a tube containing growth media and it centrifuged at 3000 rpm for 5 minutes. Supernatant removed, then pellets dissolved into a tube containing media.

Seeding cells into 96 well plates

Cell count and viability (with trypan blue exclusion), and cell resuspend with the final cell density of 170,000 cells/mL in the media. (17,000 cells/well) Prepared 10 μL of trypan blue in a sterile microtube. 10 μL of cell suspension added to the trypan blue solution and homogenized. Cleaned the hemacytometer and the lid slips using 70% ethanol then dried. Using a pipette, 10 μL of trypan blue cell solution is slowly inserted into one of the chambers/chambers. Calculated the number of healthy cells and determine the number of cells (viable) per mL. Seeding/cell culture into 96 well plates, then incubated for 24 hours (or until min. 70% confluent cells) at 37 °C and 5% CO_2 gas

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Cell treatment with positive sample / positive control / negative control

Eight 1.5 mL microtubes were prepared, then each microtube was labeled the appropriate dilution concentration, then the sample stock was diluted to eight concentration variants using a media solvent. 96 well plates were released which contained cells from the incubator. Labeled on the plate along the left margin for which row will be treated by the standard and which row will be given the sample. Then discard the media from each well. Using a micropipette, 100 μ L of each sample was transferred and the cisplatin positive control of the microtube into each of the corresponding wells on the 96 well plates containing the cell. Then re-incubate for 24 hours.

Provision of Presto Blue reagents and absorbance measurements

Squandered Media at each well. Arranged 9 mL of media on the tube which included 1 mL of "Presto Blue TM Cell Viability Reagent" (10 μ L of reagent for 90 μ L media), then inserted 100 μ L of the mixture into each well microplate then incubated for 1-2 hours until discoloration showed up when entering the living cell, PrestoBlue[®] reagent will be reduced from the resazurin blue compound without intrinsic fluorescent value, becoming a red and highly fluent resorufin compound. The

conversion of values is proportional to the number of cells that are metabolically active and therefore can be measured quantitatively. absorbance, absorbance spectrum is used for resazurin and resorufin). Then the absorbance is measured at a wavelength of 570 nm (reference: 600 nm) using a multimode reader.

RESULT AND DISCUSSION

The yield of synthesis complex Cu(II) Cysteinedithiocarbamate was 62.92% with melting points obtained 182°C-184°C and the conductivity value of 0.04 mS/cm.

UV-Vis characterization

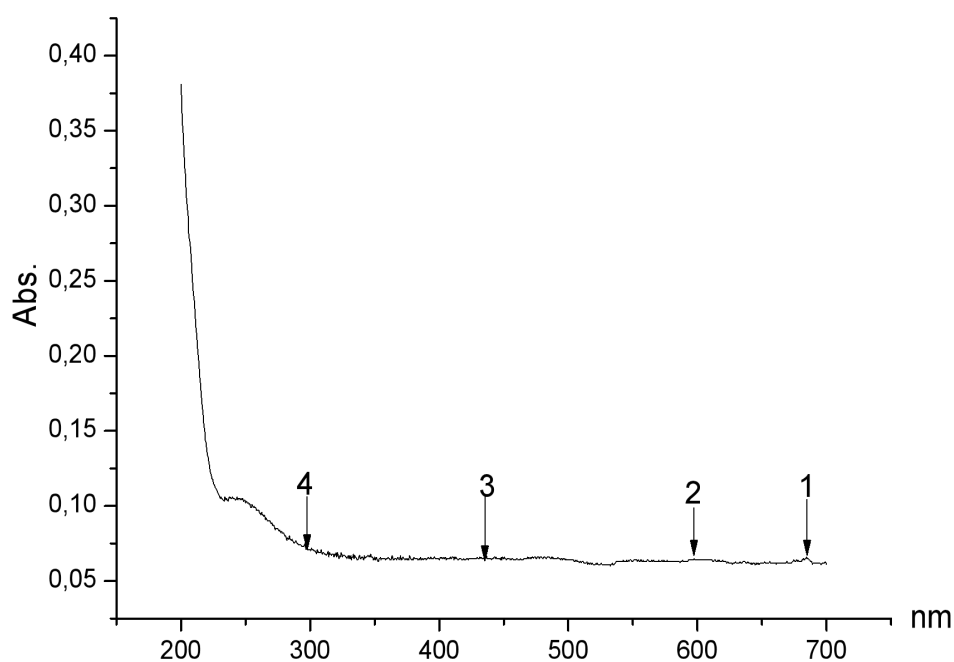
Based on **Table 1**, the results of characterization with UV-Vis in water solvents for Cu(II)cysteinedithiocarbamate compound obtained in band 1 show absorption bands at wavelength 245-296 nm which are intraligand transitions $\pi \rightarrow \pi^*$ from CS₂ groups which are influenced by the presence of the R group hyperconjugation to nitrogen atoms in the absorption area of 250-300 nm [12]. The shift in the II band which is an intraligand transition $n \rightarrow \pi^*$ from the group N=C=S at wavelengths 341-436 nm is indicated by complex compounds. Results of the UV-Vis spectrum of complex compounds that have been synthesized, Figure 3.

Table 1. UV-Vis data of Cu(II)cysteinedithiocarbamate

Compound	λ maximum (nm)	Electronic Transition
	296	$\pi \rightarrow \pi^*$
Cu(II)CysDtc	436	$n \rightarrow \pi^*$

CysDtc = CysteineDithiocarbamate

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Scheme 3. UV-Vis Spectrum of Cu(II)CysDtc

Figure 3. UV-Vis Spectrum of Cu(II)CysDtc

IR Characterization

Dithiocarbamate compounds contain two main types of bonds, namely C=N and C=S which are identified from infrared peak absorption [13]. The absorption peak $\nu(\text{C-S})$ has two types of coordination, monodentate and bidentate. A single absorption peak $\nu(\text{C-S})$ signifies coordination in a bidentate manner, while a double absorption peak signifies monodentate coordination[14].

Dithiocarbamate complex compound, for $\nu(\text{C-N})$, shows in wavenumber between single bonds (1350-1250) cm^{-1} and double bonds (1690-1640) cm^{-1} , so the bond is written as $\nu(\text{C=N})$. Furthermore, for C-S uptake it is written as $\nu(\text{C=S})$, with the number of wavelengths being between double bond wave numbers C=S (1050-1200) cm^{-1} and single bonds C-S (550-800) cm^{-1} [15]. To ensure 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 phenanthroline ligands [16].

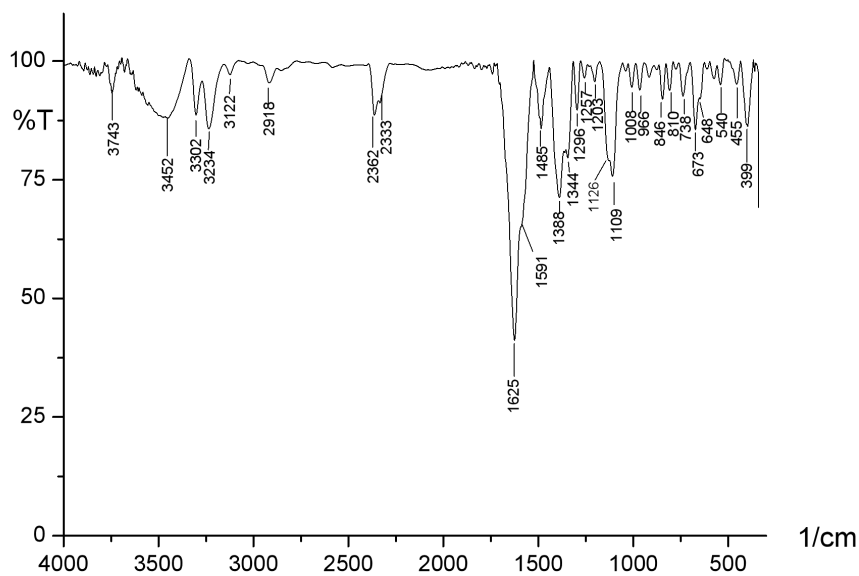
Based on Table 2, the infrared absorption peak at wave number 399 cm^{-1} indicates interaction between groups (C=S) with Cu metal ions. The absorption peak at wave number 455 cm^{-1} indicates the interaction of O atoms of complex compounds with Cu metal ions. The absorption peak at wave number 540 cm^{-1} indicates the interaction of N atoms of complex compounds with each Cu metal ion. The appearance of absorption at wave number 1109 cm^{-1} shows a double absorption peak which indicates monodentate coordination between groups (C=S) with Cu metal ions. Then there is a strong absorption at the wave number 1625 cm^{-1} which indicates that it is derived from the amine group (C=N). Infrared uptake of Cu complex metal compounds with cysteindithiocarbamate ligands generally shows the characteristics of complex compounds that have been synthesized. Results of the IR spectrum of complex compounds that have been synthesized shows in Figure 4.

Table 2. IR data of Cu(II)cysteinedithiocarbamate complex

Compound	$\nu(\text{C=N})$	$\nu(\text{C=S})$	$\nu(\text{M-S})$	$\nu(\text{M-O})$	$\nu(\text{M-N})$
Cu(II)CysDtc	1625 s	1109 m	399 m	455 w	540 w

s = strong; m = medium; w = weak

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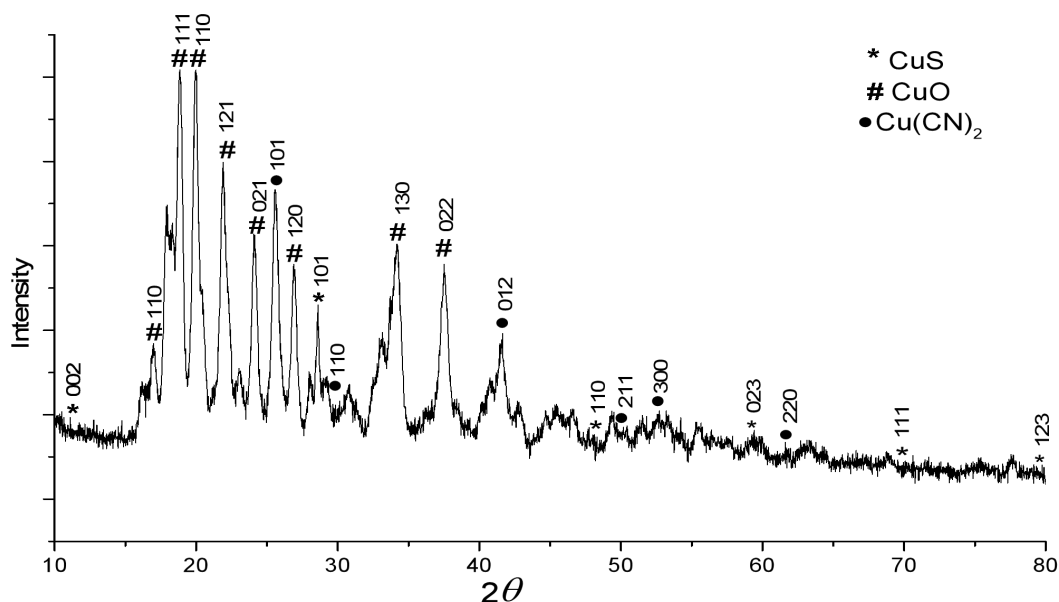
Scheme 4. IR Spectrum Cu(II)CysDtc

Figure 4. IR Spectrum Cu(II)CysDtc

XRF Characterization

The results of the elemental analysis of complex compounds using XRF obtained by copper was 41.01% and sulfur was 57.76%.

XRD Characterization



Scheme 5. XRD spectrum Cu(II)CysDtc

Figure 5. XRD Spectrum of Cu(II)CysteineDithiocarbamate complex

The results of XRD diffraction analysis of Cu (II) carried out using Match! 2 software, which obtained 3 Cysteindithiocarbamate complex compounds (Figure 5) were

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polycrystalline phases namely copper monosulfide (CuS), copper monoxide (CuO) and copper cyanide (Cu(CN)₂).

X-ray diffraction peaks with a value of 2θ 10.72°; 27.82°; 48.25°; 58.97°; 69.67° and 79.55° and the value of hkl respectively is 002; 101; 110; 023; 111 and 123, identified as hexagonal structures of copper monosulfide (CuS) based on X-ray diffraction powder pattern standards (PDF files 96-900-8370) and similar results reported by Song et al., 2017 [17]. X-ray diffraction peaks with a value of 2θ 15.77°; 18.23°; 19.38°; 21.98°; 23.85°; 27.61°; 33.38° and 36.84° and hkl values respectively, namely 110; 111; 110; 121; 021; 120; 130 and 022, identified as triclinic structures of copper monoxide (CuO) based on the X-ray diffraction powder pattern standard (PDF file 96-900-3893) and supported from data reported by Zhenzhen et al., 2015 [18]. Then X-ray diffraction peaks with a value of 2θ 25.07°; 29.56°; 41.15°; 49.54°; 52.45° and 61.43° with their respective hkl values of 101; 110; 012; 211; 300 and 220 were identified as trigonal structures of copper cyanide (Cu(CN)₂) based on the X-ray diffraction powder pattern standard (PDF file 110-900-0001) and supported based on data reported by Pereira, et al., 2003 [19].

Cytotoxic Test on MCF-7 Cancer Cells

Results cytotoxicity test of Cu(II)cysteindithiocarbamate complex compounds on MCF-7 line cells obtained IC₅₀ values showed a strong correlation between Cu complex (IC₅₀ = 639.35 µg/mL) and cisplatin (IC₅₀ = 470 µg/mL). So that this complex can induce morphological changes in cancer cells and cause apoptosis in cancer cells.

The mechanism of complex compounds against cancer cells was the complex compounds that binding to N(7) in guanine in double-helical DNA (Figure 7). The bonding that occurs is covalent bonds with DNA. Metal ions can connect the two strands to form intra-strand cross-links, bind to two strands of DNA in a double helix. This intra-strand cross bond prevents cell breakdown through the mitosis process so that the tumor stops growing. The tumor cells become rigid which is induced by crosslinking on metal ions so that it cannot be recognized and DNA cannot be repaired[20]. Finally, cells undergo apoptosis, the result evaluations shown in (Figure 6).

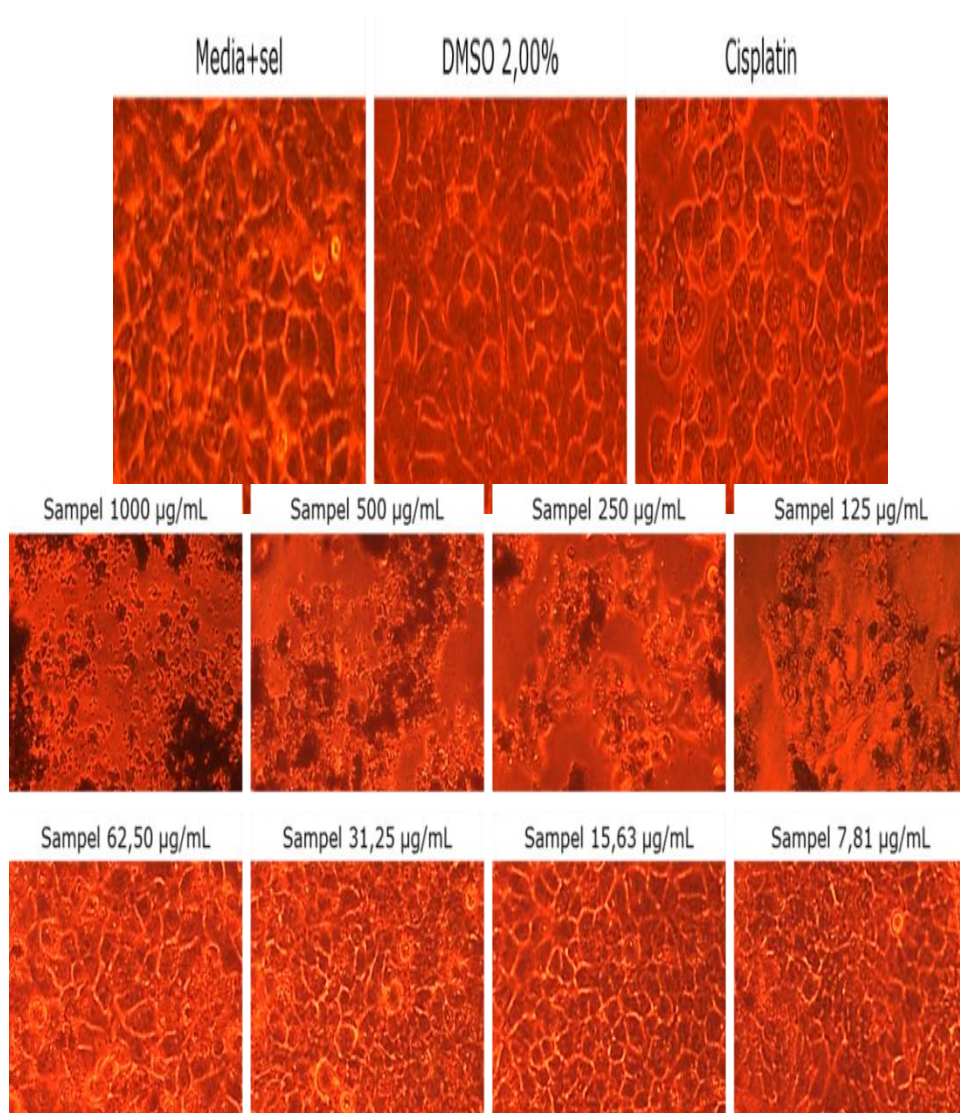


Figure 6. Apoptosis of MCF-7 cells induced by Cu(II)CysteineDithiocarbamate complex

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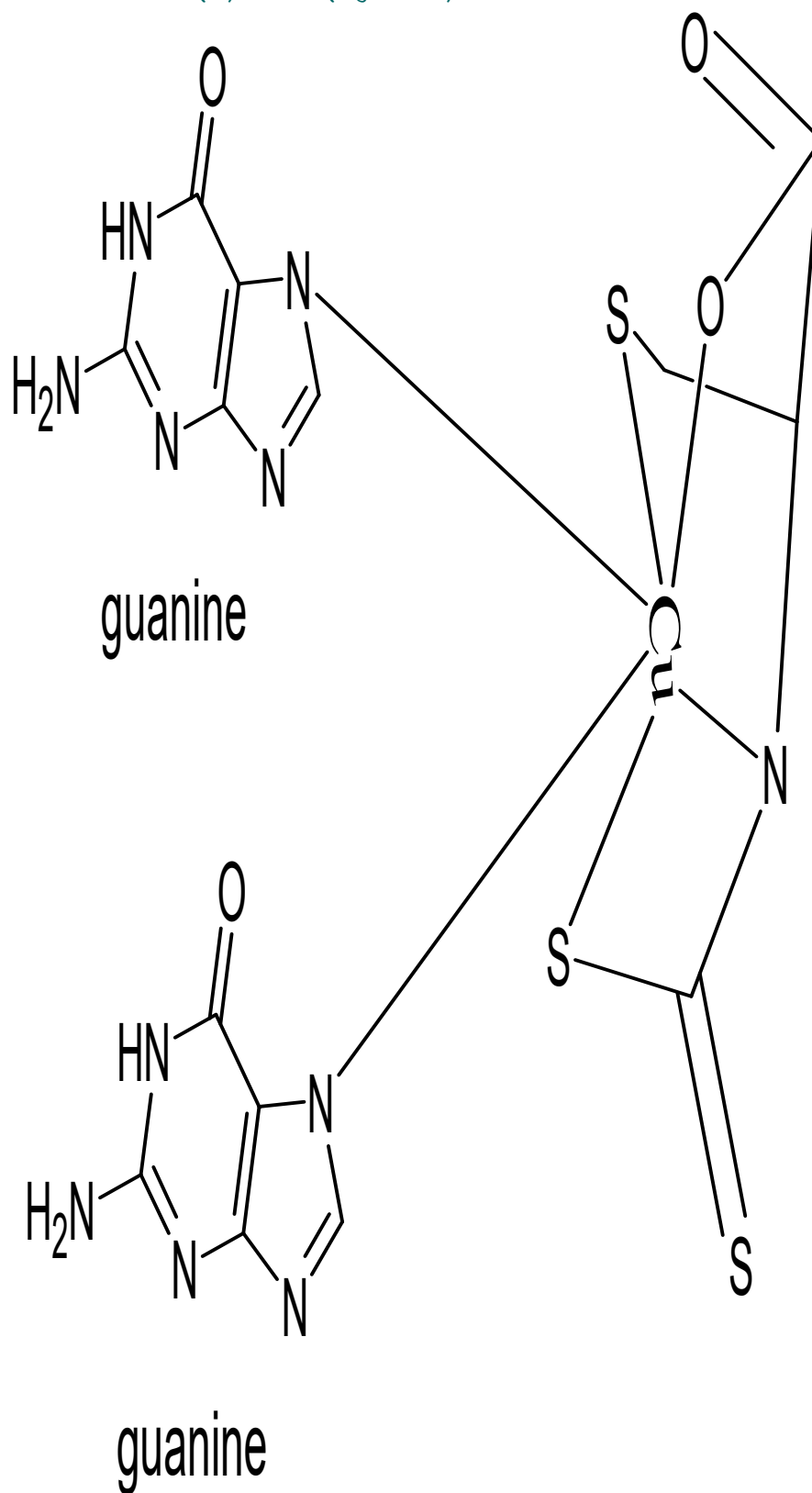


Figure 7. Proposed reaction of Cu(II) Cysteine dithiocarbamate complex to N(7) of guanine

CONCLUSION

The Complex of Cu(II)Cysteindithiocarbamate were successfully synthesized and the toxicity test result showed potential as anti-cancer agent for breast cancer (MCF-7).

CONFLICTS OF INTEREST

There is no conflict of interest with this research

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