RESEARCH ARTICLE

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Investigations of Ni(II)Cysteine-Tyrosine Dithiocarbamate Complex: Synthesis, Characterization, Molecular Docking, Molecular Dynamic, and Anticancer Activity on MCF-7 Breast Cancer Cell Line

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Abstract

Objective: Breast cancer ranks second in terms of the highest number of cancer deaths for women worldwide and is one of the leading causes of death from cancer in women. The drug that is often used for chemotherapy is cisplatin. However, cisplatin drugs have a number of problems, including lack of selectivity, unwanted side effects, resistance, and toxicity in the body. In this work, we investigated Ni(II) cysteine-tyrosine dithiocarbamate complex against breast cancer. **Methods:** Research on the new complex compound Ni(II) cysteine-tyrosine dithiocarbamate have several stages including synthesis, characterization, in-silico and in-vitro testing of MCF-7 cells for anticancer drugs. The synthesis involved reacting cysteine, CS2, KOH and tyrosine with Mn metal. The new complex compound Ni(II) cysteine-tyrosine dithiocarbamate has been synthesized, characterized, and tested in vitro MCF-7 cells for anticancer drugs. Characterization tests such as melting point, conductivity, SEM-EDS, UV Vis, XRD, and FT-IR spectroscopy have been carried out. **Result:** The synthesis yielded a 60,16%, conversion with a melting point of 216-218 oC and a conductivity value of 0.4 mS/cm. In vitro test results showed morphological changes (apoptosis) in MCF-7 cancer cells starting at a sample concentration of 250 µg/mL and an IC_{50} value of 618.40 µg/mL. Molecular docking study of Ni(II) cysteine-tyrosine dithiocarbamate complex identified with 4,4',4''-[(2R)-butane-1,1,2-triyl]triphenol - Estrogen α showing active site with acidic residue amino E323, M388, L387, G390 and I389. Hydrophobic and hydrophobic bonds are seen in Ni(II) cysteine-tyrosine dithiocarbamate - Estrogen α has a binding energy of -80.9429 kJ /mol. **Conclusion:** there were 5 residues responsible for maintaining the ligand binding stable. The compound had significant Hbond contact intensity, however, it was not strong enough to make a significant anticancer effect. Though the synthesized compound shows low bioactivity, this research is expected to give valuable insight into the effect of molecular structure on anticancer activity.

Keywords: Complex- MCF-7 cell lines- Breast Cancer- IC_{50}

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Introduction

Breast cancer is a type of cancer that occurs in the glandular tissue of the breast and is the number two killer disease in the world for women [1, 2]. Chemotherapy is one of the most widely used and effective cancer treatments [3]. The type of drug that is often used for chemotherapy is cisplatin [4]. However, cisplatin can exert toxicity and resistance effects as well as other disorders such as kidney, hearing, and digestive disorders [5]. The use of complex compounds as non-platinum-based chemotherapeutic agents can potentially act as anticancers

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and reduce the side effects they cause.

Researchers have studied many complex compounds as anticancers because the nature of their interactions with DNA can be easily predicted [6]. The use of dithiocarbamate ligands with the addition of additional donor groups such as oxygen and nitrogen contained in amino acids in the synthesis of complex compounds can increase anticancer activity [7-9]. The choice of the amino acid cysteine-tyrosine is generally recognized as the ability to safely deliver cytotoxic units into aggressive cancer cells [10, 11]. This compound can also be used as a radio chemotherapy-targeted agent in tumors. In addition, dithiocarbamate has low toxicity in the body [12].

Ni(II) metal can help overcome iron deficiency anemia and even overcome osteoporosis. Ni(II) metal is very important in development, digestion, reproduction, antioxidant defense, energy production, immune response, and regulation of neuron activity [13]. Complexes of essential metals that have potential anticancer activity Ni(II), Zn(II), Co(II), Cu(II), and other metals have been shown to outperform cis-platin based therapies with 200 enzymatic biochemical activities in the body in vitro and in vivo even at the clinical trial stage [14, 15]. Ni complexes with oxoaporphine derivatives have a very high cytotoxicity value against tumor cells [16]. The use of appropriate ligands can significantly increase the activity of complex compounds in inhibiting cancer cells. Ligands active in biological processes have attracted much attention to the design of potential antitumor agents [17, 6].

Dithiocarbamate complexes may be synthesized using metal ions from the transition group which are soft acids, because dithiocarbamate compounds have a special structure with a sulfur group (S-) which is a soft base with lone pairs that can bond monodentate and bidentate. The use of dithiocarbamate ligands with additional donor groups, from oxygen and nitrogen groups (such as cysteine) can increase the structural diversity of dithiocarbamate complexes and can affect the biological activity of the complex compounds [18]. Tyrosine is beneficial in regulating mood and stimulating the nervous system. In addition, tyrosine also functions to speed up metabolism and is useful in treating conditions characterized by symptoms of chronic fatigue. Tyrosine is also needed by our bodies for the production of various brain chemical compounds to carry out several functions such as regulating appetite, pain sensitivity, and the body's response to stress [19]. However, until now, there has been no research on the use of complex compounds Ni(II) with cysteine-tyrosine dithiocarbamate ligands and tests of their activity as an anticancer in the breast, so this research was conducted.

Materials and Methods

Experimental Design

Materials

All chemicals and reagents purchased are of professional quality (p.a). Nickel(II) chloride, cisplatin, tyrosine, cysteine, carbon disulfide (CS2), KOH, parafilm, aquabides, DMSO, KBr and Ethanol (95%) from the Central Laboratories of Hasanuddin University and Padjadjaran University Bandung, Indonesia.

Synthesis of Ni(II)cysteine-tyrosine ditiocarbamate

Synthesis of Ni(II) cysteine-tyrosinedithiocarbamate was carried out using the in situ method. In a 100 mL Erlenmeyer glass, 0.2805 g of KOH was added with aquabides and stirred until dissolved. Then 0.302 mL (5 mmol) of CS2 solution was added drop by drop at cold temperature. After that, 0.906 g (5 mmol) of tyrosine was added. Then add 0.6058 g (5 mmol) of cysteine. Next, 0.388 g (3 mmol) of NiCl2 was added which had been dissolved in 10 mL of ethanol. After that, stir using a magnetic stirrer for 30 minutes. Next, the precipitate formed is then filtered and placed in a desiccator until dry, then crystallized with a suitable solvent until pure crystals are obtained. The scheme of the synthesis of Ni(II) cysteine-tyrosinedithiocarbamate is shown in Figure 1.

Complex Characterization

Ni(II)cysteine-tyrosinedithiocarbamate complex compounds were characterized was determined, the synthesized complex compound was dissolved in ethanol, then the electrical conductivity of the solution was measured with a Lutron CD-4303 conductometer. The complex compound Ni(II) cysteine-tyrosinedithiocarbamate was inserted into a capillary tube and its melting point was determined using an Electrothermal IA 9100 melting point device.

UV-Vis absorption spectroscopy

The complex compound Ni(II) cysteine-tyrosinedithiocarbamate was dissolved in ethanol until a concentration of 100 ppm was obtained, then the electronic spectrum was measured with a UV-Vis spectrophotometer in the 200-1000 nm region.

FT-IR spectroscopic studies

FT-IR spectrum analysis of the complex compound Ni(II)cysteine-tyrosinedithiocarbamate made in pellet form with dry KBr, then measured with an FT-IR instrument in the wave number range of 340-4000 cm^{-1}.

Characterization with XRD

The crystal form was confirmed by an XRD-7000 Shimadzu Maxima -90° with intervals of 0.02°/step. Next, a diffractogram between the diffraction angle (2θ) and peak intensity (counts) was obtained.

Characterization with SEM

Analysis SEM JEOL JCM 6000plus to determine the morphology of the Ni(II)cysteine-tyrosinedithiocarbamate complex compound was placed on the surface of a block stage that had been attached with a carbon tip, then sprayed with air using an Electric Blower. Next, put the sample into the preparation box to be coated into the stage holder, then lock the stage holder bolts at each end of the side using an 'L' key and analyzed using a SEM (Scanning Electron Microscopy).

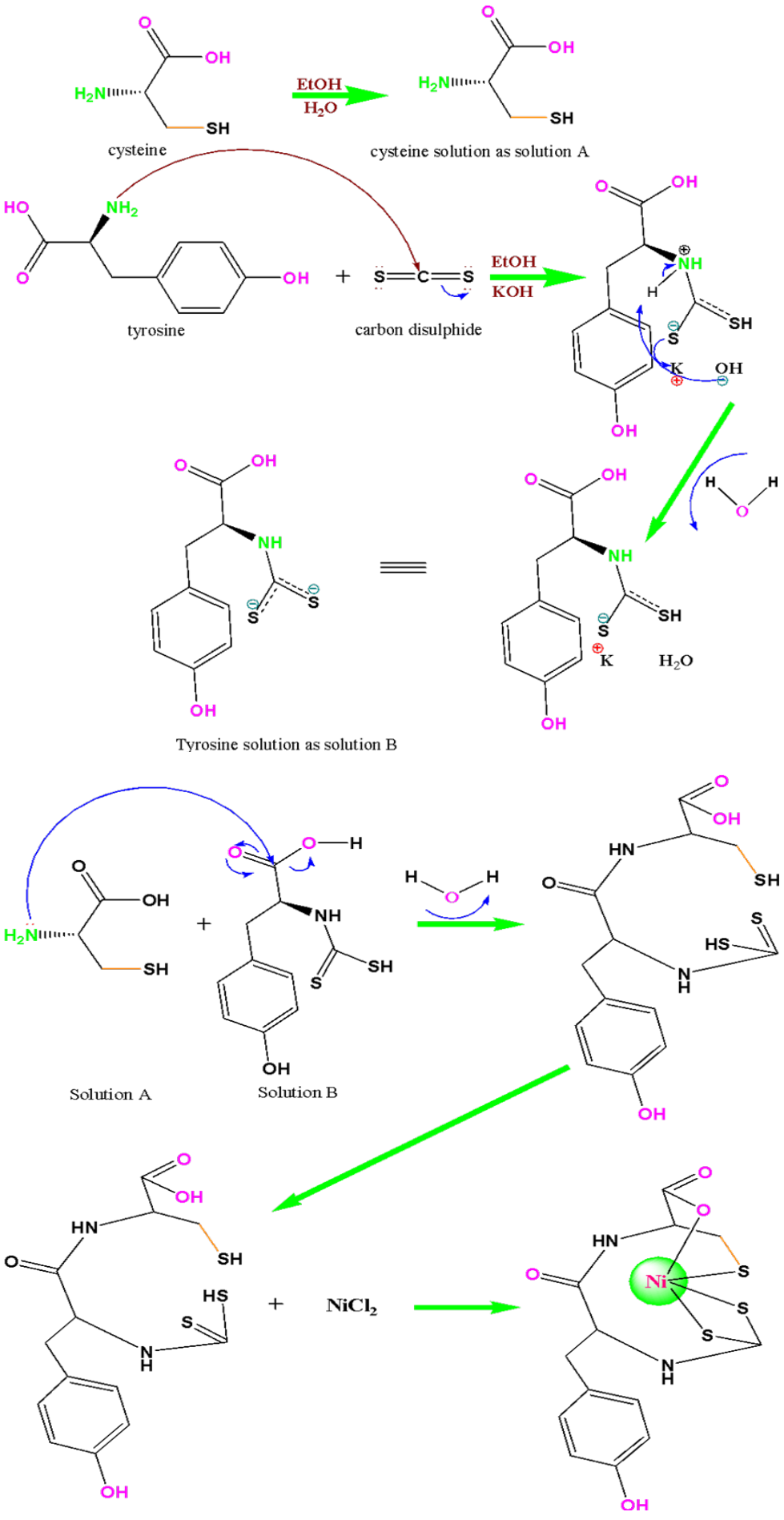

Figure 1. Synthesis Reaction of Ni(II)cysteine-Tyrosineditiocarbamate Complex

Characterization with SEM-EDS

Preparation of the Ni(II)cysteine-tyrosinedithiocarbamate complex compound is the same as the SEM analysis above, then continued with SEM-EDS by selecting a spot point on the sample. X-rays are emitted from the sample surface. These X-rays are detected with an EDS detector to provide information about the composition of the elements in the sample.

Anticancer activity test against breast cancer cells

The cell culture was put into 96 well plates and incubated (with a temperature of 37°C and a percentage of 5% CO_2 gas until it reached a percentage of 70% cell growth). The cells were then sampled and incubated (at 37°C for 48 hours with 5% CO_2 gas). Fill the cell with the blue presto working reagent. The Thermo Fisher Scientific Multimode Reader is used to measure absorbance.

Research Methods

Molecular Docking of Complex Compounds to Target Proteins of Breast Cancer Cells

Basic validation of the PLANTS proto

Protein and ref_ligand preparation was carried out using the YASARA software and preparation was carried out by removing unwanted ligand, covacctor and protein parts.

Ligand preparation was carried out using MarvinSketch at pH 7.4. The results are then saved as ligand_2D.mrv. Return to MarvinSketch and open the file ligand_2D.mrv, then search for various conformations of the ligand structure using the "*Conformers search*". The results are then stored as a ligand with file.mol2.

The results of the ligand and protein preparations were then docked using PLANTS. In addition to the input files in the form of protein.mol2 and ligand.mol2. The docking pose that gives the highest score is then estimated as an estimate of the original position of the ligand in the target protein structure. From these poses, RMSD (Root Mean Square Deviation) calculations are then performed using YASARA. The protocol is said to be valid if the docked pose gives an RMSD value of less than 2 Å (1 Å = 10-10 m) [20].

IR characterization

This analysis was carried out at wave numbers 4,000-300 cm^{-1} to determine the IR absorption peak of the Ni(II)cysteine-tyrosine editiocarbamate complex (Figure 3). The infrared absorption peak at wave number 3,205.69 cm-1 indicates the involvement of the O atom from the hydroxyl group attached to the aromatic group (Ar-OH) in the complex compound formed and the widening band at wave number 3,346.50 cm^{-1} indicates the -OH from ethanol or water [19, 24, 25]. The absorption peak of 1,591.27 cm^{-1} indicates the appearance of the C=N functional group. The presence of absorption at wave number 1,097.49 cm^{-1} indicates the dithiocarbamate ligand functional group C=S, and indicates the coordination of Ni metal bidentate with C=S. The absorption peak at wave number 379.98 cm^{-1} indicates the interaction of S atoms of complex compounds with Ni metal ions (M-S) and the new widening band has absorption peaks of 532.35 cm^{-1} and 576.72 cm^{-1} representing interactions between Ni metal with N atoms (M-N) and Ni metal with O (M-O) [26, 27]. FT-IR analysis of the synthesized complex compounds is shown in Table 1.

Table 1. FT-IR Spectrum Analysis Data of Ni(II) Cysteine-Tyrosineditiocarbamate Complex

Compound/functional group	Wavenumber (cm^{-1})
v(M-S)	379.98 s
v(M-O)	576.72 m
v(M-N)	532.35 s
v(C=S)	1097.49 m
v(C=N)	1591.27 s
v(O-H)	3205.69 s

s, strong; m, medium; w, weak

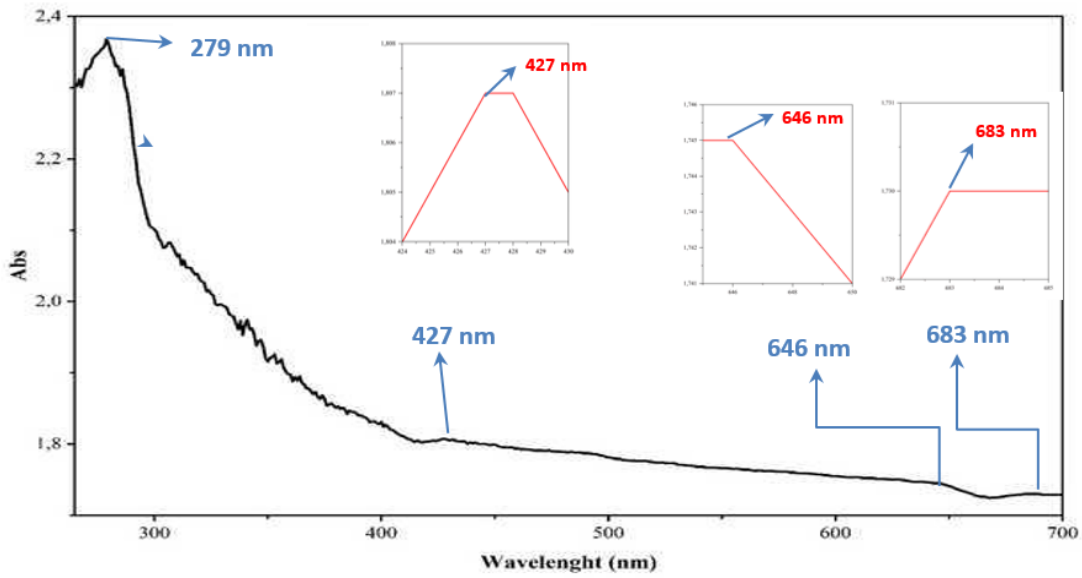

Figure 2. UV-Vis Spectrum of Ni(II)cysteine-tyrosineditiocarbamate Complex

XRD characterization

The characterization of the synthesis results by XRD aims to determine the crystal form of complex compounds. The difkogram resulting from the characterization of complex compounds shows the value of the Miller index which can determine the crystal structure (Figure 4). The results showed that the crystal structure of the Ni(II)cysteine-tyrosineditiocarbamate complex was face-centered cubic (FCC). The highest intensity diffraction angle (2θ) is 17.69; 20.07; 24.41; 28.17 44.10; and 64.43.

Results

The rendamen results obtained from the Ni(II) cysteine-tyrosineditiocarbamate complex showed that the complex compound had a high rendament of 60,16%, this indicated a strong coordination bond between the metal and the ligands. The strong bond between the metal and the ligands is also supported by the high melting point of 216-218°C, the high melting point indicates that the ligands are strongly bonded to the ligand and the measured conductivity value was 0.4 mS/cm, indicating that the Ni(II)cysteine-tyrosineditiocarbamate complex is a non-electrolyte compound.

Synthesis of Ni(II)cysteine-tyrosineditiocarbamate UV-Vis Characterization

The results of analysis of the Ni(II)cysteine-tyrosineditiocarbamate complex compound by UV-Vis spectroscopy showed 4 absorption bands consisting of the ultraviolet band (256-400 nm) and several other bands in the visible light area (427-682 nm). The Ni(II) cysteine-tyrosineditiocarbamate complex compound at band shift I was detected at a wavelength of 279-427 nm which is an intraligand transition from n to π* of the CS2 group. Complex compounds containing C=S groups show strong bands in the 250-320 region originating from the transitions π to π* and n to π*[21, 22]. In the dithiocarbamate complex, bands in the region of 310-400 nm indicate intraligan electronic transitions from n to π* from the N = C= S group. The appearance of various other bands at absorption of 400-427 nm indicates the presence of Charge Transfer (CT) transitions from L to M and M

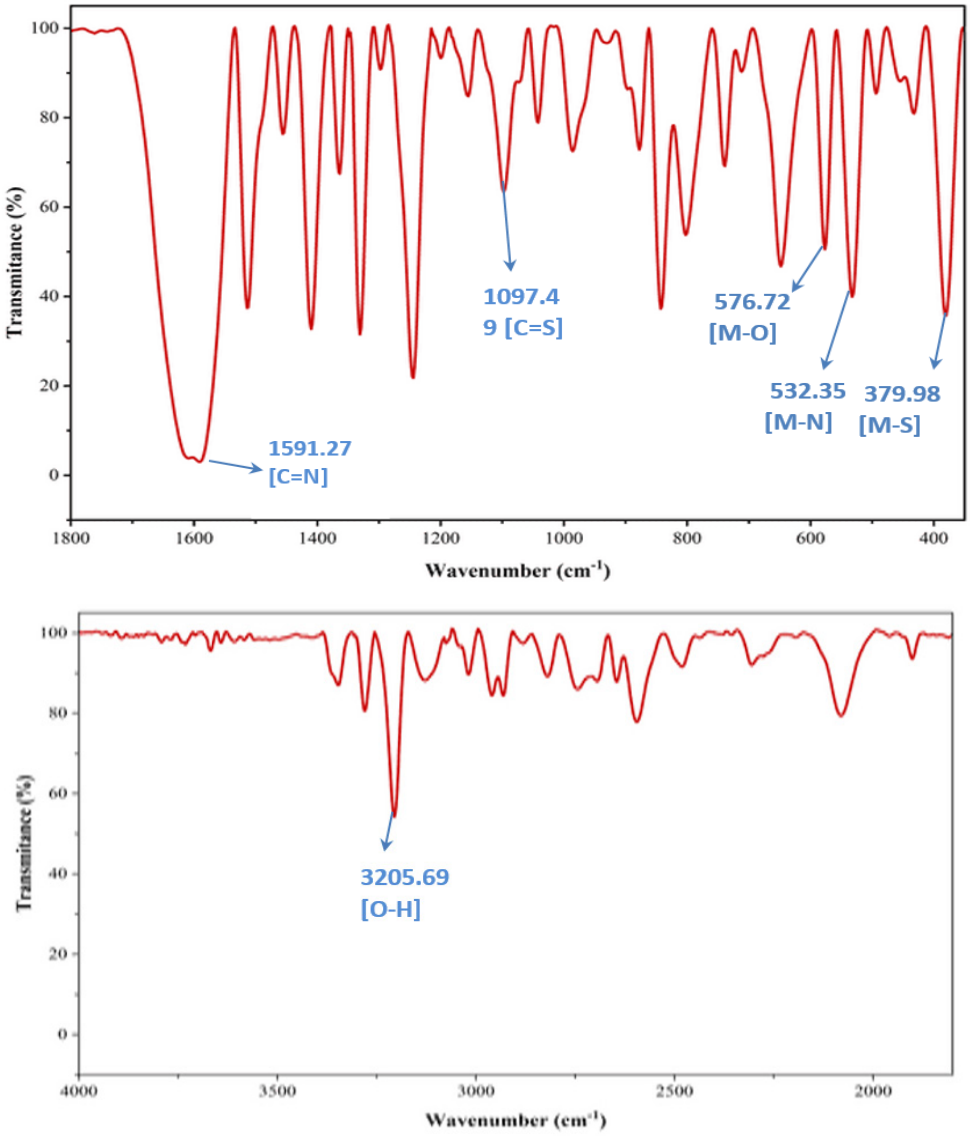

Figure 3. IR Spectrum of Ni(II)cysteine-tyrosine Ditiocarbamate Complex

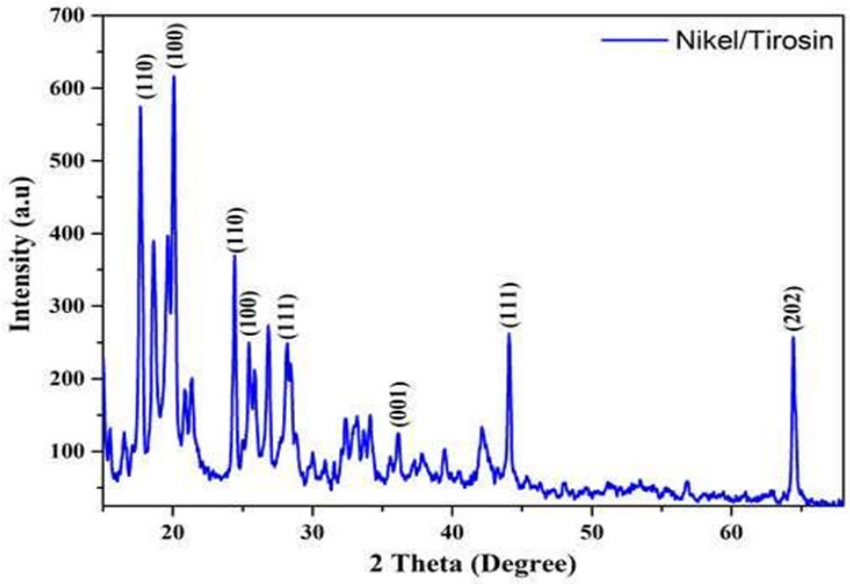

Figure 4. XRD Spectrum of Ni(II)cysteine-Tyrosineditiocarbamate Complex

Table 2. Docking Score of Complex

Complex	Score Docking
4,4',4"-[(2R)-butane-1,1,2-triyl]triphenol - Estrogen α (control +)	-103.936 kJ/mol.
Ni(II)Cystein-Tyrosine-Dithiocarbamate - Estrogen α	-80.9429 kJ/mol.

to L between the metal and the ligand. Then the presence of absorption in the region of 646-682 nm indicates that the complex has a larger conjugation system compared to the ligand and the presence of d orbital transitions from transition metals [23]. The resulting transition is from π to π* with a maximum wavelength of 279 nm. The illustration of this UV-Vis Characterization can be seen in Figure 2.

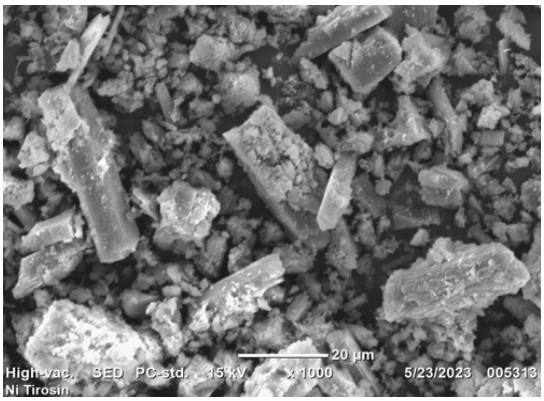

Figure 5. SEM Morphology of Ni(II)cysteine-Tyrosineditiocarbamate Complex

IR characterization

This analysis was carried out at wave numbers 4,000-300 cm^{-1} to determine the IR absorption peak of the Ni(II) cysteine-tyrosine editiocarbamate complex (Figure 3). The infrared absorption peak at wave number 3,205.69 cm-1 indicates the involvement of the O atom from the hydroxyl group attached to the aromatic group (Ar-OH) in the complex compound formed and the widening band at wave number 3,346.50 cm^{-1} indicates the -OH from ethanol or water [19, 24, 25]. The absorption peak of 1,591.27 cm^{-1} indicates the appearance of the C=N functional group. The presence of absorption at wave number 1,097.49 cm^{-1} indicates the dithiocarbamate ligand functional group C=S, and indicates the coordination of Ni metal bidentate with C=S. The absorption peak at wave number 379.98 cm^{-1} indicates the interaction of S atoms of complex compounds with Ni metal ions (M-S) and the new widening band has absorption peaks of 532.35 cm^{-1} and 576.72 cm^{-1} representing interactions between Ni metal with N atoms (M-N) and Ni metal with O (M-O) [26, 27]. FT-IR analysis of the synthesized complex compounds is shown in Table 1.

XRD characterization

The characterization of the synthesis results by XRD

Table 3. RMSD-Cα Values of the Complexes during MD Simulations

Complex	Min and Max (Å)	Average (Å) ± Std
Estrogen α	0.43-2.12	1.75 ± 0.20
4,4',4"-[(2R)-butane-1,1,2-triyl]triphenol-Estrogen α	0.68-3.21	2.58 ± 0.37
Ni(II)cysteine-tyrosine-dithiocarbamate-Estrogen α	0.67-3.35	2.78 ± 0.27

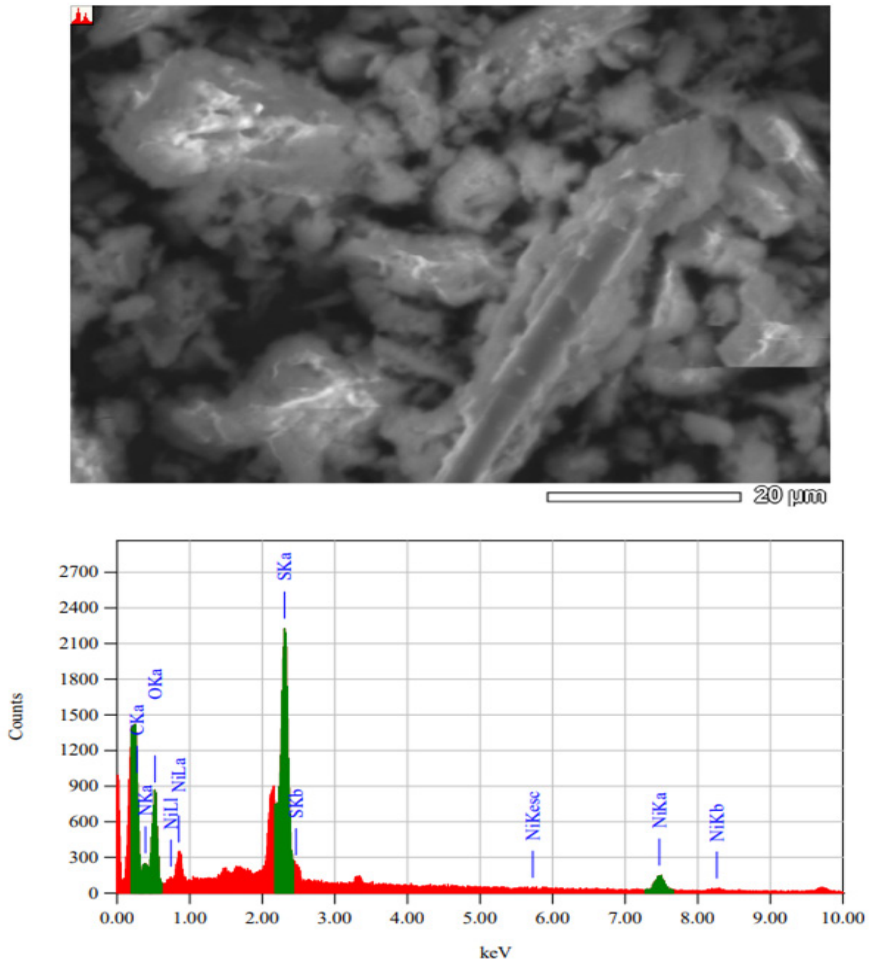

Figure 6. Morphology and SEM-EDS of Ni(II)cysteine-Tyrosineditiocarbamate Complex

aims to determine the crystal form of complex compounds. The difkogram resulting from the characterization of complex compounds shows the value of the Miller index which can determine the crystal structure (Figure 4). The results showed that the crystal structure of the Ni(II)cysteine-tyrosineditiocarbamate complex was face-centered cubic (FCC). The highest intensity diffraction angle (2θ) is 17.69; 20.07; 24.41; 28.17 44.10;

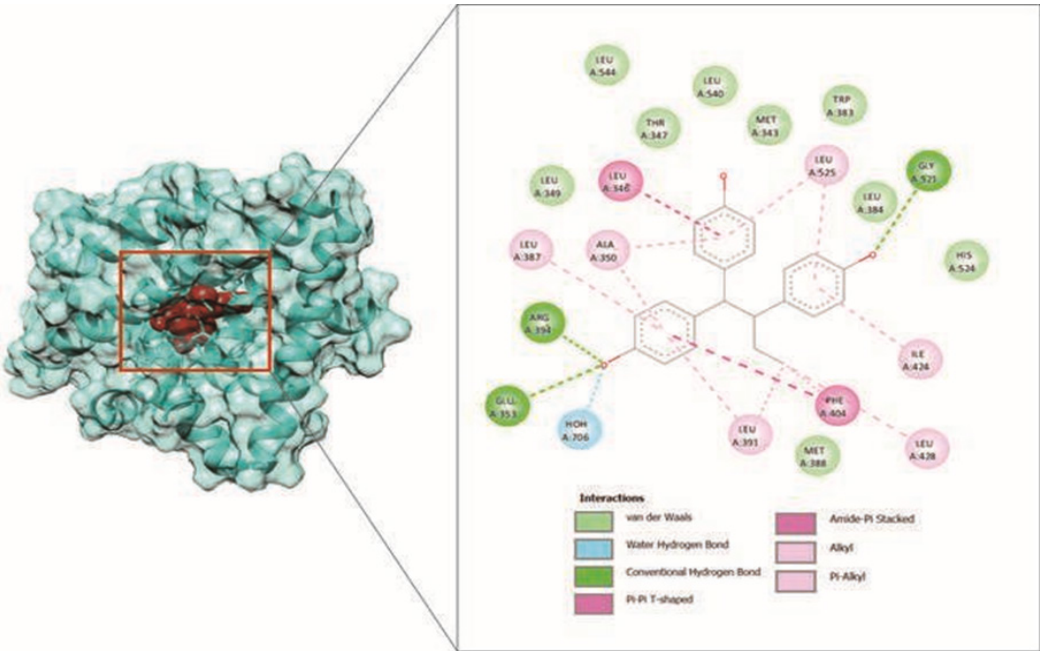

Figure 7. Docking Visualization of 4,4',4"-[(2R)-butane-1,1,2-triyl]triphenol (control +) against Estrogen Receptor α

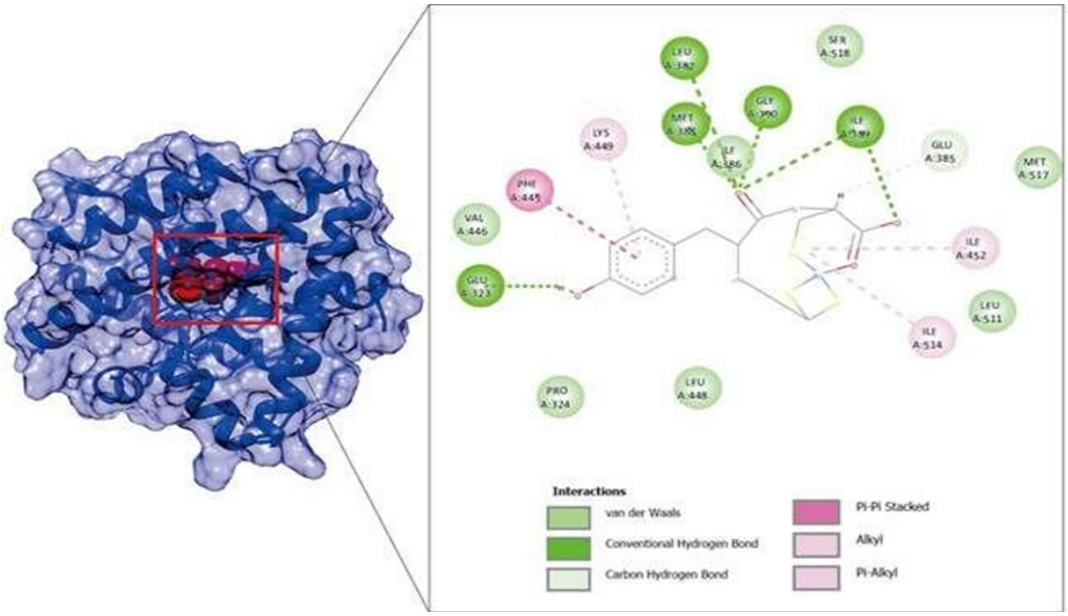

Figure 8. Docking Visualization of Ni(II)cysteine-tyrosine-dithiocarbamate against Estrogen Receptor α

and 64.43.

SEM characterization

Characterization used SEM with 1,000 times magnification to determine the surface shape of the Ni(II)cysteine-tyrosineditiocarbamate complex formed, showing a cubic crystal shape and several impurities with inhomogeneous shapes (Figure 5).

SEM-EDS characterization

Based on the results of the SEM-EDS analysis (Figure 6), the composition of the compounds in the spectrum results was obtained. SEM-EDS results show that the sample consists mostly of Ni, C, O, N and S. The EDS spectrum of Ni(II)cysteine-tyrosineeditiocarbamate complex displays peaks of Ni 24.96%, C 8.88%, O 12.11%, N 2.27% and S 51.33%, showing a large percentage of sulfur derived from the amino acids cysteine and CS2.

Molecular Docking of Complex on Estrogen α

Molecular docking study in this research was used to learn the inhibitory mechanism of our drug candidate. Ni(II)Cystein-Tyrosine-Dithiocarbamate has lower binding affinity than 4,4',4''-[(2R)-butane-1,1,2-triyl] tripheno (Table 1). There are some crucial binding modes initiating that strong binding in 4,4',4''-[(2R)-butane-1,1,2-triyl]triphenol including H-bond interaction and amide-π stacked in R394, Q353, G521, L346 and F404 to maintain the ligand binding stable (Figure 7). If compared to Ni(II)Cystein-Tyrosine-Dithiocarbamate, the

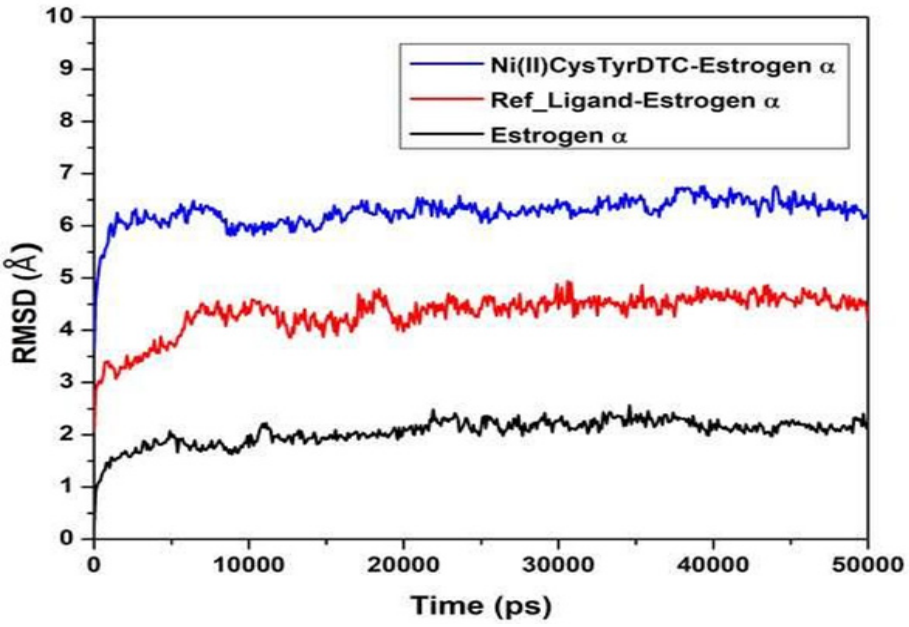

Figure 9. Comparison of RMSD values between Ni(II)CysTyrDTC – Estrogen α, Ref_Ligand – Estrogen α, and Estrogen α

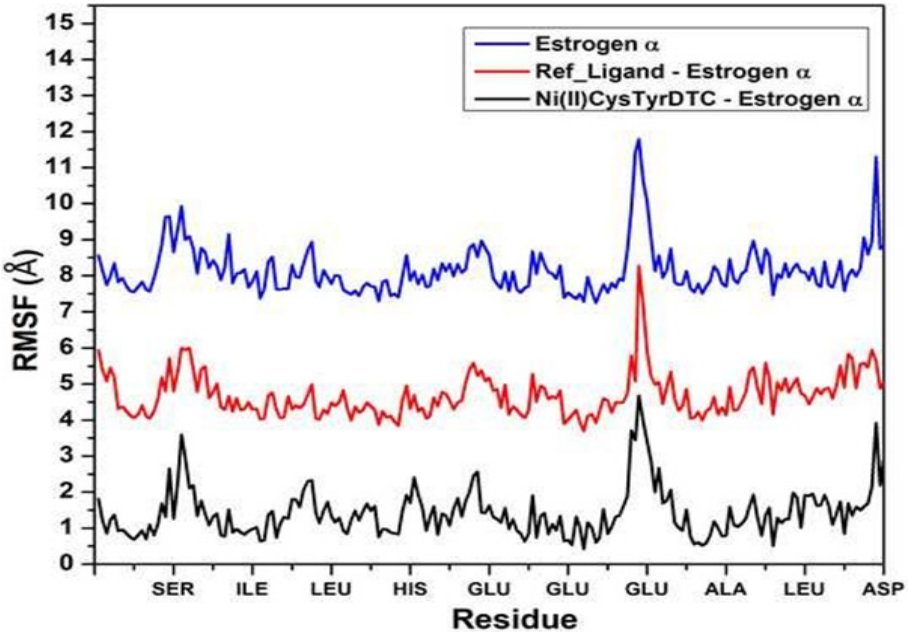

Figure 10. Comparison of RMSF values between Ni(II)CysTyrDTC – Estrogen α, Ref_Ligand – Estrogen α, and Estrogen α

binding appearing, control, sustains in the whole surface of ligand. The most favorable binding in Ni(II)cysteine-tyrosine-dithiocarbamate appears in carbonyl and oxygen group (Figure 8). There are some residues involved in its binding mode such as E323, M388, L387, G390 and I389. These hydrogen bond interactions can initiate the binding stability between the candidate and estrogen α [28]. The docking scores of the complex compounds that have been synthesized can be seen in Table 2.

Molecular Dynamic of Complex on Estrogen α

Molecular dynamics simulation is used to study the response of estrogen α to the studied drug during interval time. This study examined the molecular flexibility, structural behavior, and stability of estrogen α with Ni(II) CysTyrDTC through 50 ns of simulation. The RMSD-Cα values of complex compounds during MD simulations can be seen in Table 3.

Furthermore, we analyzed root mean square fluctuation (RMSF) to describe the individual residue fluctuation of estrogen α during simulation. Inhibition decreases the atomic dynamic movement of estrogen α in its regulatory pathway [7].

To understand the stability of the complex, this study also examined the number of hydrogen bonds during simulation. These hydrogen bonds have the essential role to maintain the strong affinity between the ligand and protein.

Breast cancer cell line (MCF-7) cytotoxicity of the Ni(II) cysteine-tyrosine-dithiocarbamate complex

Figure 13 also shows the results of recording Ni(II)

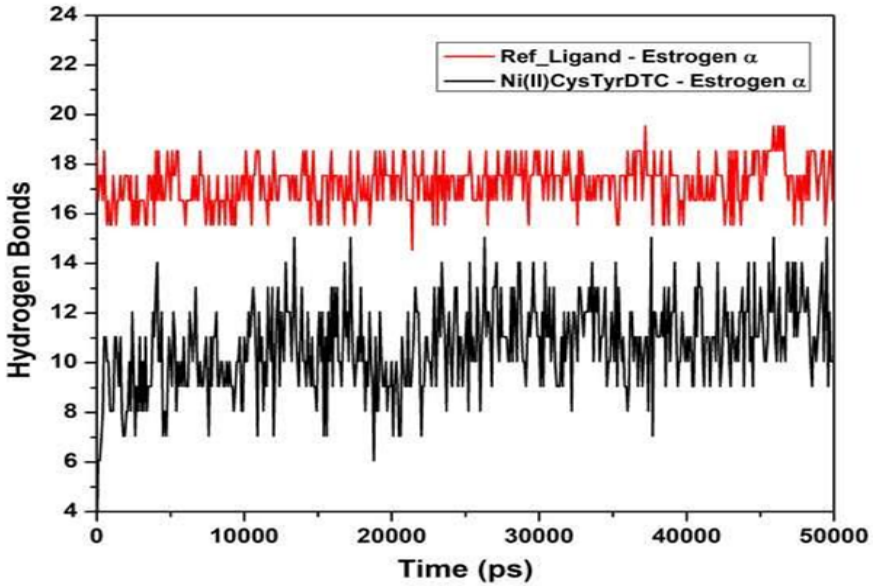

Figure 11. Number of Hydrogen Bonds of the Complex during Simulation

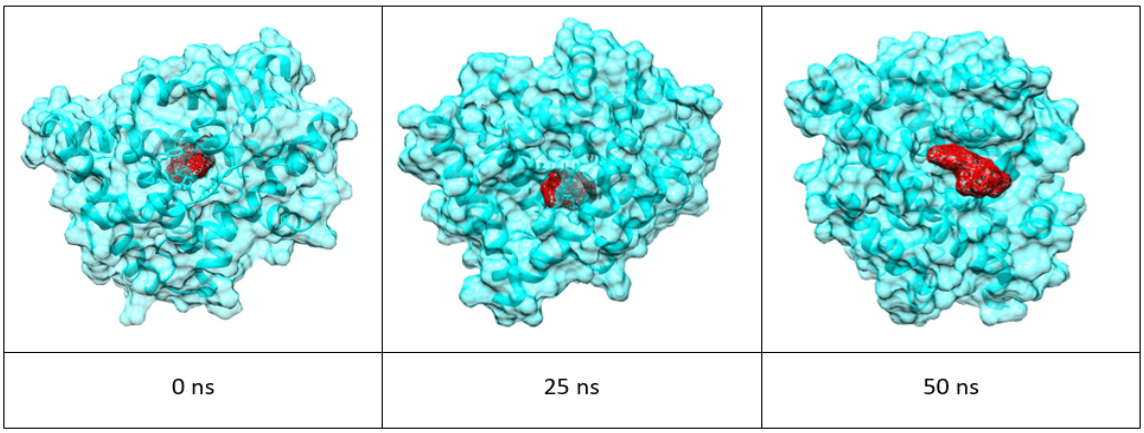

Figure 12. 3D Visualization of the Complex in the Interval Period of 0 ns, 25 ns, and 50 ns

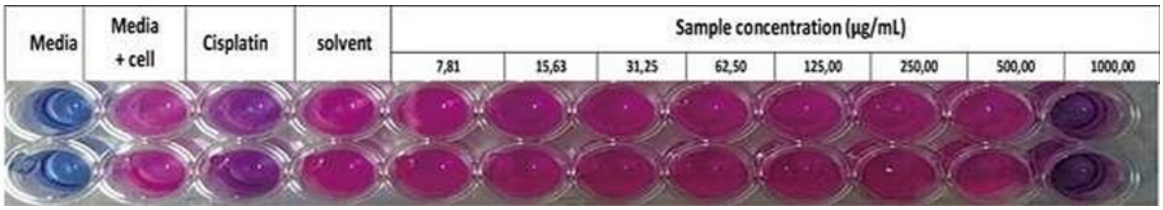

Figure 13. Well Plate Documentation of Ni(II)cysteine-tyrosineditiocarbamate Results on MCF-7 cells

cysteine-tyrosine dithiocarbamate plates, comparison of cell concentrations of medium + MCF-7, cisplatin samples, and the results of recording Ni(II)cysteine-tyrosine dithiocarbamate wells.

The cytotoxicity of the produced Ni(II)cysteine-tyrosinedithiocarbamate complex against breast cancer cells (MCF-7) was examined in vitro and contrasted with cisplatin's anticancer properties. The MTS method (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl))-2H-tetrazolium was used to investigate the cytotoxicity of the Ni(II)cysteine-tyrosinedithiocarbamate complex. One of the most popular methods to measure cytotoxicity and cell growth is the MTS test [29].

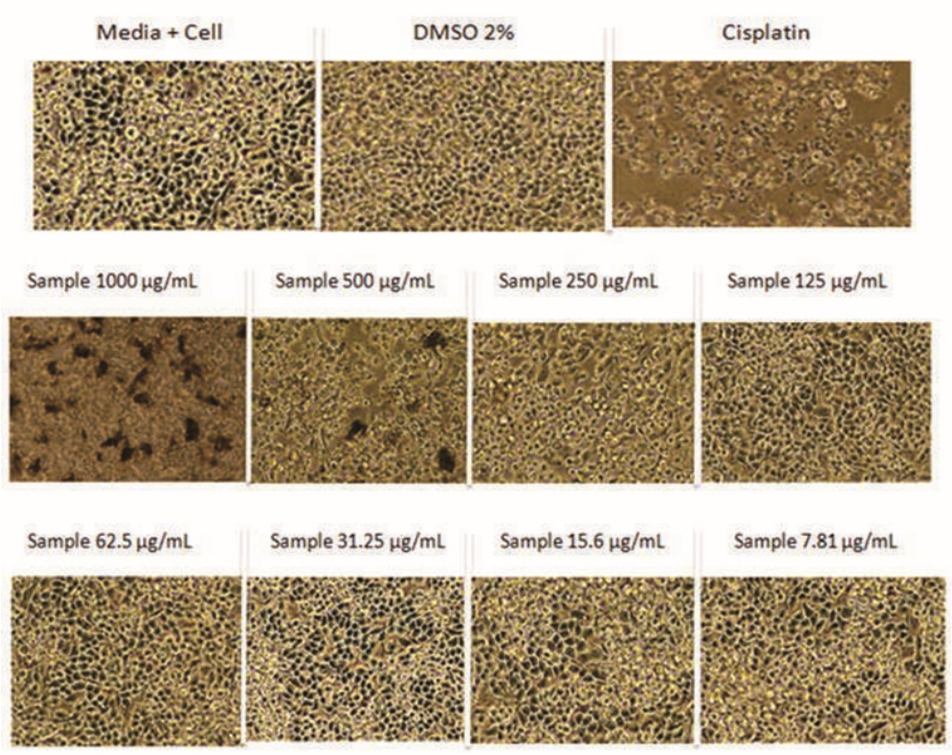

Figure 14. MCF-7 Cell Apoptosis Induced by Ni(II)cysteine-tyrosinedithiocarbamate

Discussion

The conformational change of estrogen α was evaluated from the root mean square deviation (RMSD). Figure 9 illustrates the pattern of native protein, ligand control-estrogen α, and Ni(II)CysTyrDTC-estrogen α which aims to compare the effect of ligand binding in protein during the interval period. The overall pattern of the ligands almost similar with native protein, in the beginning simulation they increase and remain constant until the end of simulation. Additionally, at initial of 20 ns, the graph shows some fluctuation that indicates protein structure change due to ligand binding, then remained stable with little fluctuation. This conformational change is important as we designed a ligand as an inhibitor.

As shown in Figure 10, the plot of native protein, ligand standard, and Ni(II)CysTyrDTC are almost similar, suggesting the same pattern. As confirmed by RMSD value, in the beginning of simulation, the ligands contributed to inhibitory effect in the protein. This was strengthened by RMSF result revealed that SER and GLU might be the two residues having more influence in the conformational change of estrogen α due to ligand binding. Figure 11 shows the number of hydrogen bonds of the complex during the interval time. The figure reveals that Ni(II)cysteine-tyrosine-dithiocarbamate has potency to stabilize the complex. The intensity of hydrogen bond contact occurring during simulation (Figure 11) of our candidate is around 17 and the control around 11. This indicates how well the studied compounds interact with estrogen α to interfere the protein activity [30]. The significant H-bond contacts shown by our candidate explain the reason why this compound has potential as estrogen α inhibitor.

To understand the conformational change of protein during the interval period, Figure 12 presents the 3D visualization of the ligands-protein complex in 0 ns, 25 ns, and 50 ns. It illustrates that there is a conformational change of protein due to ligand binding in the binding site of protein. However, the ligands remained in the binding pocket until the end of simulation which might correlated to the high number of hydrogen bonds contribution of Ni(II)cysteine-tyrosine dithiocarbamate towards Estrogen α.

Ni(II)cysteine-tyrosine dithiocarbamate has an IC_{50} of 618.40 µg/mL, while cisplatin has an IC_{50} of 53.48 µg/mL. According to the number and type of inhibitors, Figure 14 shows the apoptotic phase of MCF-7 cells in response to cisplatin and Ni(II)cysteine-tyrosine dithiocarbamate complexes. In addition, no cell death was observed in the sample concentration range of 7.81 to 125 µg/ml. Apoptosis begins in the range of 250 to 1000 µg/mL.

The cytotoxicity value of the Ni(II)cysteine-tyrosinedithiocarbamate complex was found to be lower than that of cisplatin, according to test results of the IC_{50} value of the two compounds. Because the raw chemicals employed are safe for the body, it is envisaged that the Ni(II)cysteine-tyrosineeditiocarbamate complex will only have minor negative effects on normal cells.

High cytotoxicity is defined as 1-100 g/mL, moderate as 100-1000 g/mL, and mild as 1000 g/mL for cytotoxic complexes [31]. This justifies classifying the Ni(II) cysteine-tyrosinedithiocarbamate combination as moderately cytotoxic. The bioactivity of the metal reveals that the complex possesses characteristics in the MCF-7 cell line. About 40% of the metal ions found inside of cells are thought to be active anticancer agents [32]. Additionally, careful and adequate ligand selection can improve the complexes' active characteristics [6]. Dithiocarbamate complexes and other sulfur-containing ligands have been investigated as Zn metal-based chemotherapeutic drugs [33]. Sulfur donor ligands from the dithiocarbamate molecule are suited for and compatible with the majority of biological systems. Dithiocarbamates have been found to have the ability to change crucial proteins involved in a variety of biological processes, including oxidative stress, transcription, degradation, and apoptosis. This makes them very useful in the battle against cancer [8, 34, 9]. The ability of some of its complexes to act as proteasome inhibitors has also been discovered, and these may be employed to treat cancer [35, 36].

In conclusion, the Ni(II) complex compound with a cysteine-tyrosine-dithiocarbamate ligand has been successfully synthesized and characterized and its anticancer activity shows that the Ni(II)cysteine-tyrosine-dithiocarbamate complex has potential as an anti-breast cancer agent (MCF-7). This can be seen in the FT-IR characterization results at an absorption of 1097.49 cm-1 which indicates the presence of the C=S functional group, and 1591.27 cm-1 which indicates the presence of the C=N functional group. A C=S functional group exists in the UV-Vis spectrum supported by $\pi \rightarrow \pi^*$ at a wavelength of 279-427 nm. The results of research using XRD characterization show that the crystal structure of the Ni(II) cysteine-tyrosinedithiocarbamate complex is in the form of a face-centered cube (FCC). Characterization using SEM 1,000 times shows a cubic crystal shape and several impurities with inhomogeneous shapes. The EDS spectrum of the Ni(II)cysteine-tyrosinedithiocarbamate complex displays peaks of Ni 24.96%, C 8.88%, O 12.11%, N 2.27% and S 51.33%, indicating a large percentage of sulfur originating from acid. amino cysteine and CS2. Based on the results of in vitro tests, morphological changes (apoptosis) in MCF-7 cancer cells began at a sample concentration of 250 µg/mL and the IC_{50} value was 618.40 µg/mL. This shows that the Ni(II) cysteine-tyrosinedithiocarbamate complex compound has potential as an anti-breast cancer agent, supported by the molecular docking study of the Ni(II) cysteine-tyrosine dithiocarbamate complex identified with 4,4',4''-[(2R)-butane- 1,1,2-triyl]triphenol - Estrogen α exhibits an active site with amino acid residues E323, M388, L387, G390 and I389. Hydrophobic and hydrophobic bonds are seen in Ni(II) cysteine-tyrosine dithiocarbamate - Estrogen α has a binding energy of -80.9429 kJ /mol.

Author Contribution Statement

Eka Pratiwi, Indah Raya, and Hasnah Natsir: Conceptualization, Methodology, Supervision; Rizal Irfandi, Paulina Taba, Rugaiyah Arfah, and Herlina

Rasyid: Conceptualization, Methodology, Investigation, Writing–original draft; Yusafir Hala and Syahruddin Kasim: in vitro test analysis of breast cancer: Andi Besse Khaerunnisa and Baso Ilham: molecular docking; Dewi Luthfiana and Yosua Tanzil: molecular dynamic; Maulida Mazaya : Writing – review & editing, Validation.

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Ethical Declaration

Both humans and animals are not used as research participants in this study.

Conflict of Interest

The authors declare that none of the work reported in this study could have been influenced by any known competing financial interests or personal relationships.

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