RESEARCH ARTICLE

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Integrated Molecular Docking and Experimental Analysis of Ni(II) Proline Dithiocarbamate Cytotoxicity in MCF-7 Breast Cancer Cells

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Abstract

Objective: Chemotherapy is one of the most effective and widely used treatment types for breast cancer. The Ni(II) proline dithiocarbamate (Ni(II)ProDtc) complex has been synthesized as a potential anticancer agent with minimal systemic toxicity. The dithiocarbamate ligand, combined with the amino acid proline, holds promise as a radio chemotherapeutic target agent in tumors. The anticancer activity of a Ni(II) complex compound with a proline dithiocarbamate ligand was tested on the MCF-7 breast cancer cell line as part of a study on essential metal-based therapeutics. **Methods:** Molecular docking studies identified the active sites for the estradiol-estrogen receptor-α protein. The Ni(II)ProDtc complex was synthesized and characterized using melting point analysis, conductivity measurements, UV-Vis spectroscopy, and FT-IR spectroscopy. The cytotoxicity of the complex was evaluated in vitro using the MCF-7 breast cancer cell line. **Results:** The UV-Vis spectrum at 246 nm indicated the π→π* intraligand transition of the CS2 group, while FT-IR analysis revealed peaks at 364–457 cm^{-1} corresponding to the bonding between Ni and Sulfur (S) and Oxygen (O) from proline. Further, the UV-Vis spectrum displayed bands at 212 and 676 nm, and FT-IR data at 387–691 cm^{-1}, confirming the coordination of the Ni(II) atoms with sulfur, nitrogen, and oxygen in the isoleucine dithiocarbamate ligand. In vitro, cytotoxicity tests revealed that Ni(II)ProDtc induced cell death in the breast cancer cell line, showing significant morphological changes in MCF-7 cancer cells, with an IC_{50} value of 315.70 µg/mL. **Conclusion:** The Ni(II)ProDtc complex was successfully synthesized and demonstrates anticancer activity in MCF-7 breast cancer cells, indicating significant potential as an anticancer agent for breast cancer.

Keywords: Breast Cancer- chemotherapy- cytotoxicity- MCF-7 cells- Ni(II)- Proline- dithiocarbamate

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Introduction

Breast cancer, a type of malignancy that develops in the glandular tissue of the breast, is the most common cancer among women worldwide and a leading cause of cancer-related death [1]. In 2020, 2.3 million women were newly diagnosed with breast cancer, resulting in 685,000 fatalities globally. By the end of 2020, 7.8 million women who had been diagnosed with breast cancer within the preceding five years were still alive [2].

The primary treatments for cancer include surgery, radiotherapy, hormonal therapy, and chemotherapy. The U.S. Food and Drug Administration (FDA) authorized the use of cisplatin in 1978, following research dating back to 1965 that demonstrated its efficacy against a variety of cancer cells. Chemotherapy, including the use of cisplatin, constitutes a fundamental component of cancer treatments [3]. Cisplatin functions as a cytostatic agent by inhibiting DNA synthesis, leading to cancer cell death [4]. However, the use of cisplatin is associated with significant challenges, such as toxicity, resistance, and adverse effects on the kidneys, hearing, and digestive system [5].

To mitigate these issues, there is ongoing research into non-platinum-based chemotherapeutic agents that might offer effective cancer treatment with reduced side effects. Complex compounds, particularly those involving Group 10 metals (nickel (Ni), palladium (Pd), and platinum (Pt)), have garnered significant interest in recent years due to their potential for enhanced anticancer properties compared to cisplatin. In addition, these complex compounds can bind strongly to microbial cell DNA, inducing apoptosis in bacterial cells [6]. The manufacturing of such complex molecules can involve creating an essential metal complex compound with dithiocarbamate

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ligands bearing additional donor groups, such as oxygen and nitrogen from amino acids. The capacity of proline amino acids to selectively deliver cytotoxic agents into aggressive cancer cells is well-established [7]. The sulfur (S) group in dithiocarbamate facilitates robust and selective binding to metal ions, leading to the formation of organometallic complexes. Dithiocarbamates can form either monodentate or bidentate complexes with metals through coordination bonds, depending on the structure of the amine. Dithiocarbamate ligands can effectively and securely bind metals with varying oxidation states [8]. Notably, complex compounds containing Ni(II) metals have demonstrated significant antimicrobial properties [9]. Ni(II) is a soft Lewis acid intermediate that forms particularly strong bonds with sulfur donors (soft bases) [10]. These complexes have potential as radio-chemotherapeutic targeting agents in malignancies. Furthermore, dithiocarbamates are characterized by their low systemic toxicity, enhancing their suitability for therapeutic use [11].

We evaluated the anticancer activity of a Ni(II) complex compound with a proline dithiocarbamate ligand on the MCF-7 breast cancer cell line as a part of our investigation into essential metal-based therapeutics. Our synthetic strategy employed proline amino acid and carbon disulfide as a scaffold for our complex. This approach aimed to optimize the therapeutic properties and safety of the compound, including enhanced cellular uptake, increased water solubility, and improved selectivity and specificity at the molecular level while reducing toxicity.

Materials and Methods

Materials and Characterization Analysis

Ni(II) sulfate (NiSO4), carbon disulfide (99.5%, Ajax Chemical Ltd), proline, cisplatin, Roswell Park Memorial Institute Medium (RPMI), dimethyl sulfoxide (DMSO), ethanol (95%), acetone (95%), and acetonitrile (95%) were sourced from Hasanuddin University Central Laboratory, Indonesia.

The melting point of the Ni(II) proline dithiocarbamate (Ni(II)ProDtc) complex was measured with an Electrothermal IA 9100 apparatus. Conductivity was assessed with a Lutron CD-4303 conductometer (Coopersburg, Pennsylvania, USA). The Fourier-transform infrared (FT-IR) spectrum was recorded using a SHIMADZU FT-IR Spectrophotometer with a wavelength range of 300–4000 cm^{-1}. Ultraviolet-visible (UV-Vis) spectra were obtained using a Jenway UV-Vis spectrophotometer over the range of 200–700 nm.

Ni(II) Complex Synthesis with Proline Dithiocarbamate Ligand

In a 100 mL Erlenmeyer glass, 3 mmol of NiSO4 was dissolved in 10 mL of 95% ethanol (Solution 1). In a separate 100 mL Erlenmeyer flask, 5 mmol of proline was dissolved in 10 mL of 95% ethanol. To this solution, 0.302 mL (5 mmol) of carbon disulfide was slowly added at a temperature of -18 °C and agitated for 30 minutes (solution 2). Solution 1 was then added dropwise to Solution 2 while stirring continuously with a magnetic stirrer for 30 minutes. The resulting precipitate was filtered, dried in a desiccator, and crystallized using a suitable solvent to obtain pure crystals, which were subsequently characterized and described (Figure 1).

Breast Cancer Cell (MCF-7) Cytotoxicity Test

Cells were seeded into a 96-well plate and incubated at 37°C with 5% CO2 until a confluency of approximately 70% was achieved. The stock solution of Ni(II)ProDtc was diluted to eight concentrations ranging from 2.34 to 300 µg/mL in eight 1.5 mL microtiter plates, each labeled with respective concentrations. Cells were then removed from the incubator, labeled, and the media was aspirated from each well. Using a micropipette, 100 µl of each drug concentration, as well as cisplatin used as the positive control, were added to the corresponding wells of the 96-well plate, and cells were cultured for 48 hours. After incubation, cell viability was assessed using 10 µL of the PrestoBlue™ Cell Viability Reagent per 90 µl of media. The solution was added to each well, and the plate was incubated for 1–2 hours until a color change was observed.

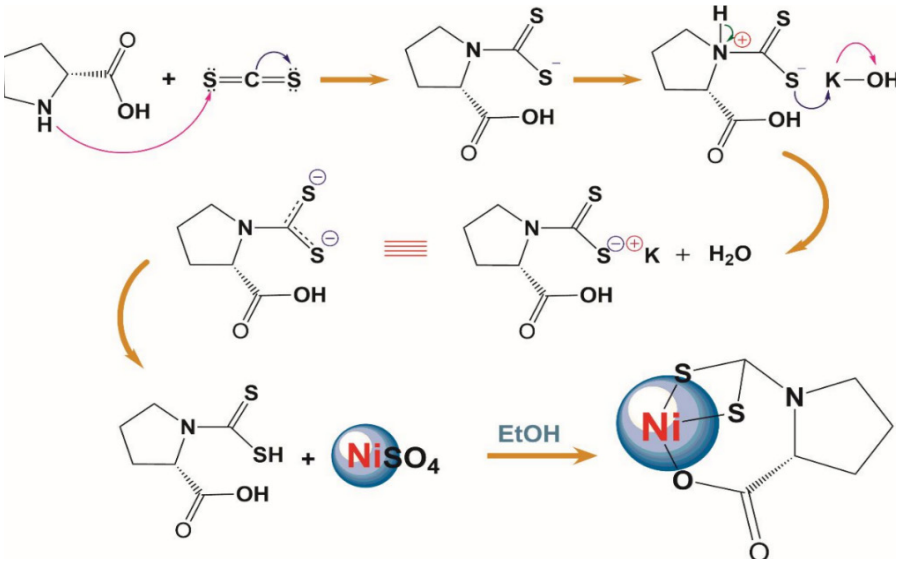

Figure 1. The Ni(II) Proline Dithiocarbamate Synthesis Process.

The number of metabolically active cells is proportional to the colorimetric change, which was quantified by measuring absorbance. Absorbance was measured using resazurin and resorufin absorbance spectra at a wavelength of 570 nm using a multimode reader.

Characterization of Ni(II)ProDtc Molecular Docking Ligand and Protein Structure Modelling

The web application MolView (https://molview.org/) was used to model Ni(II)ProDtc complex molecules. The estrogen receptor-α protein (PDB ID 1A52) [12] was obtained from the Protein Data Bank database and imported into Molegro Virtual Docker version 5 [13,14]. The protein's 3D structure was visualized by identifying the active site using a molecular van der Waals surface with a maximum of 5 binding cavities. The active site of the estrogen receptor-α protein was located at coordinates X = 106.14 Å, Y = 13.93 Å, Z = 96.58 Å, with a radius of 10 Å [15].

Docking Simulation

Docking simulations were performed using Molegro Virtual Docker version 5.0, with the grid defined for the docking area. The docking parameters included: Score Function = Moldock Score [Grid]; Grid resolution = 0.30; Algorithm = MolDock SE; Number of Runs = 10; Maximum iterations = 1500; Maximum population size = 50; Pose generation energy threshold = 100; Tries = 10–30; Simplex evolution max steps = 300; Neighbor distance factor = 1.00; Multiple poses, number of poses = 5; Energy threshold = 0.00; Cluster similar poses RMSD threshold = 1. The binding energy of the ligand-protein complex was calculated from the sum of the MolDock Score, Moldock Grid Score, and Rerank score [12]. Bond energies, expressed in kJ/mol, represent the average of five ligand-protein complex binding models. Docking results were visualized in both 3D and 2D using Discovery Studio version 21.1.1 [16].

Results

The yield of the synthesized Ni(II)ProDtc complex was 21.90%. The melting point, ranging from 226–228, suggests that the Ni(II)ProDtc complex is pure. The conductivity measurement of 0.02 mS/cm indicates that the compound is a non-electrolyte.

Molecular Docking Studies

The 3D structure of the Ni(II) complex reveals interactions with the active site residues ARG394, LEU387, ALA350, and PHE404 (Figure 2; Table 1). The hydrophobic interaction profile of the Ni(II) complex indicates a high degree of hydrophobicity. The complex forms a total of 4 hydrophobic interactions with the estrogen receptor-α protein. Additionally, the hydrogen bond profile of the Ni(II) complex shows the presence of both hydrogen donors and acceptors, with a total of two hydrogen bonds.

UV-Vis Spectral Analysis

UV-Vis analysis of the Ni(II)ProDtc complex revealed an absorption band in the range of 212–248 nm,

Table 1. Interaction between Ni(II) Complexes and Estrogen Receptor-α Protein

Compound	Binding Energy (kJ/mol)	Interaction	Distance (Å)	Category	Bond Types
Ni(II)ProDtc	-215.4	A:ARG394:NH2 - :10:O1	301,534	Hydrogen Bond	Conventional Hydrogen Bond
		:10:O2 - A:LEU387:O	31,861	Hydrogen Bond	Conventional Hydrogen Bond
		A:ALA350 - :10	421,868	Hydrophobic	Alkyl
		:10 - A:LEU346	467,225	Hydrophobic	Alkyl
		:10 - A:LEU349	513,734	Hydrophobic	Alkyl
		A:PHE404 - :10	473,581	Hydrophobic	Pi-Alkyl

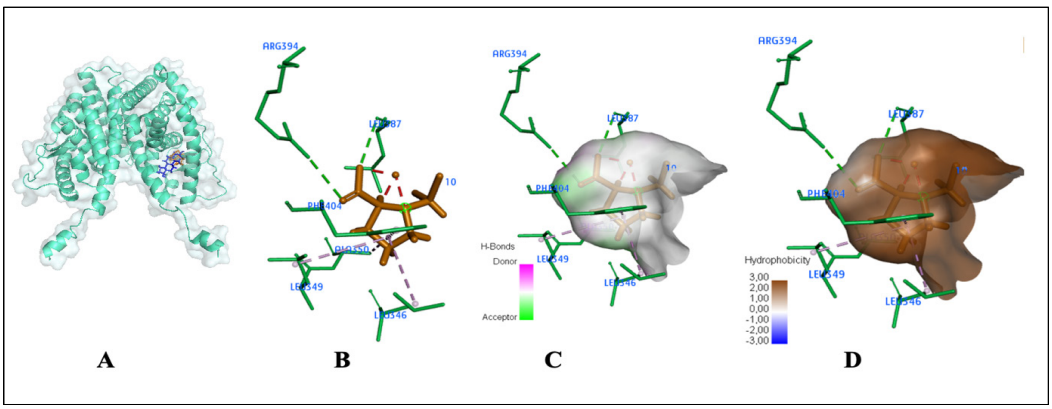

Figure 2. Interaction between Ni(II) Complexes and the Estrogen Receptor-α Protein. Docking simulations were performed using Molegro Virtual Docker version 5.0. (A) 3D structure of the Ni(II) complex and the estrogen receptor-α protein. (B) Superimposed compound–protein complex. (C) Hydrogen bond profile, with pink indicating hydrogen donors and green indicating hydrogen acceptors. (D) Hydrophobicity profile, with blue indicating low hydrophobicity and brown indicating high hydrophobicity.

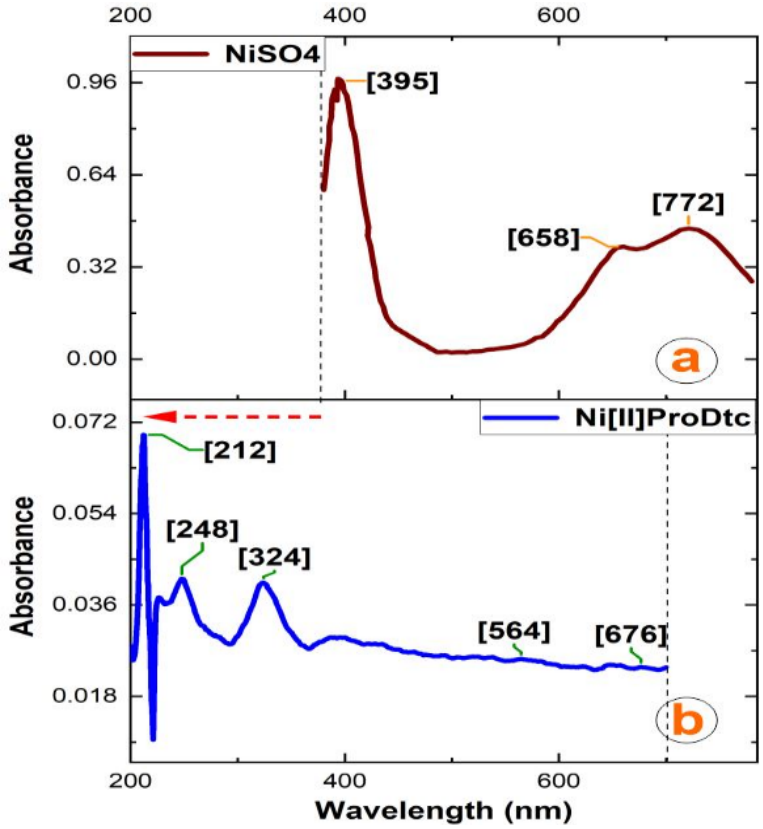

Figure 3. Ni(II) Proline Dithiocarbamate UV-Vis Spectral Analysis

corresponding to the π →π * intraligand transition of the CS2 group (Figure 3).

Infrared Characterization

IR spectroscopy of the Ni(II)ProDtc complex provides insights into the complex's properties. The IR spectra confirm the successful synthesis of the Ni(II)ProDtc complex (Figure 4).

Breast Cancer Cell Cytotoxicity Assay

In vitro cytotoxicity testing of the Ni(II)ProDtc complex was conducted on MCF-7 breast cancer cells. Cisplatin, a well-known and effective drug against breast cancer cells, was used as a comparative standard. The complex was tested over 48 hours at doses ranging from 7.81 µg/mL to 1000 µg/mL. The Ni(II)ProDtc complex exhibited an IC_{50} value of 315.70 µg/mL, with an R2 value

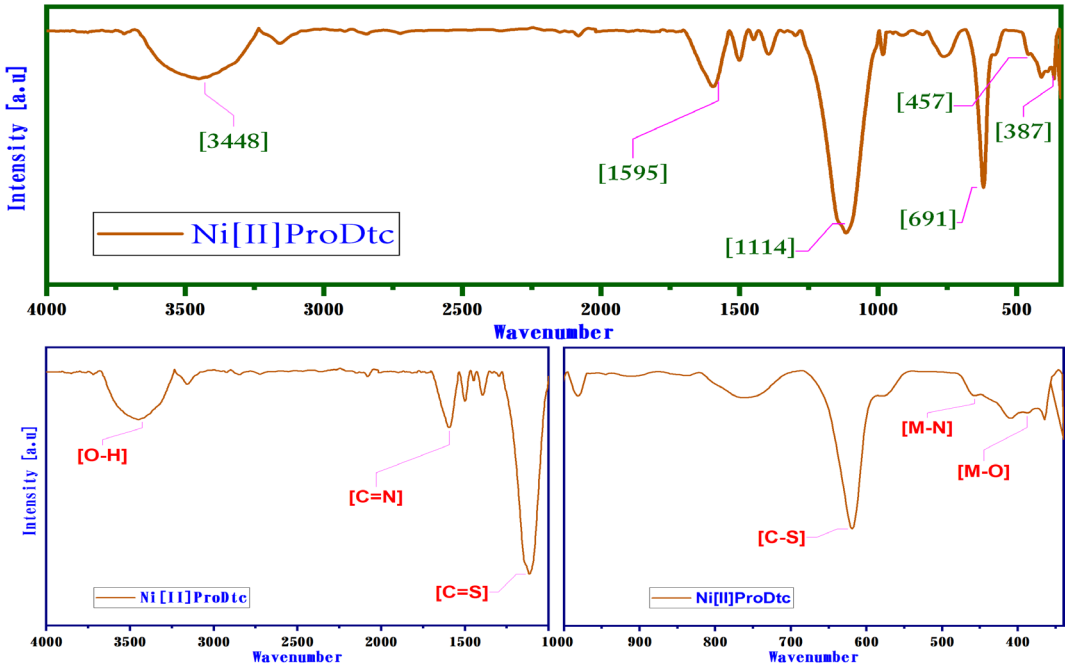

Figure 4. Ni(II) Proline Dithiocarbamate Infrared Characterization

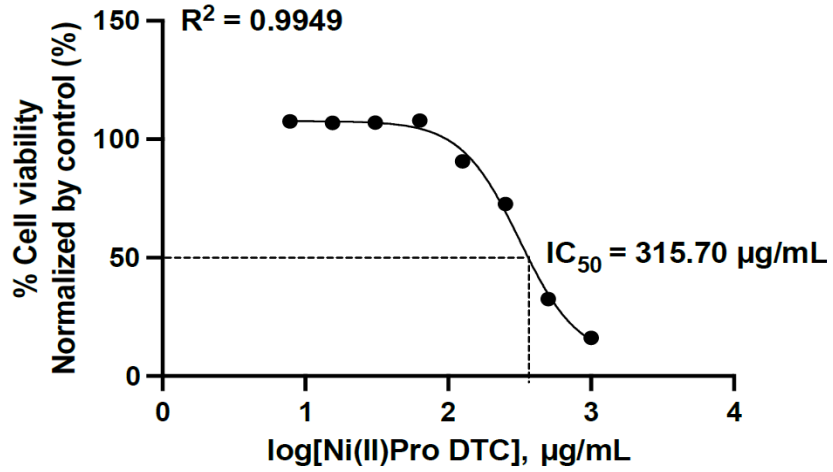

Figure 5. Ni(II) Proline Dithiocarbamate Cytotoxicity Curve in MCF-7 Cells.

Table 2. IC_{50} Values of Ni(II) Proline Dithiocarbamate Complexes and Cisplatin

Chemical Compounds	IC_{50} (µg/mL)
Ni(II)ProDtc	315.70
Cisplatin	53:48:00

of 0.9949 (Figure 5), while cisplatin has an IC_{50} of 53.48 µg/mL (Table 2). Figure 6 depicts the initiation of cell death in MCF-7 cells treated with Ni(II)ProDtc. Apoptosis in MCF-7 cells was observed starting at a concentration of 31.25 µg/mL. These results suggest that the Ni(II)ProDtc complex exhibits significant activity against cancer cells, similar to cisplatin.

Discussion

The interaction of Ni and estradiol complexes with the estrogen receptor-α protein results in a binding energy of -215.4 kJ/mol. The relatively low binding energy indicates that both complexes may effectively inhibit the activity of the estrogen receptor-α protein. A stronger binding interaction with the estrogen receptor-α protein suggests greater stability and a higher affinity of the complex for the receptor [17,18]. Therefore, the Ni(II) complex is predicted to exhibit a strong binding affinity for the estrogen receptor-α protein, which may abrogate the receptor's downstream signaling pathways. This inhibition mechanism is likely occurring through conformational changes in the receptor, which may interfere with the proliferative processes of breast cancer cells [19].

UV-Vis analysis of the Ni(II)ProDtc complex in band I revealed an absorption band at 212–248 nm, attributable to the $\pi \rightarrow \pi^*$ transition associated with the hyperconjugation effects of the R group on the nitrogen atom, which is found in the absorbance band of 324 nm [6,20]. The complex

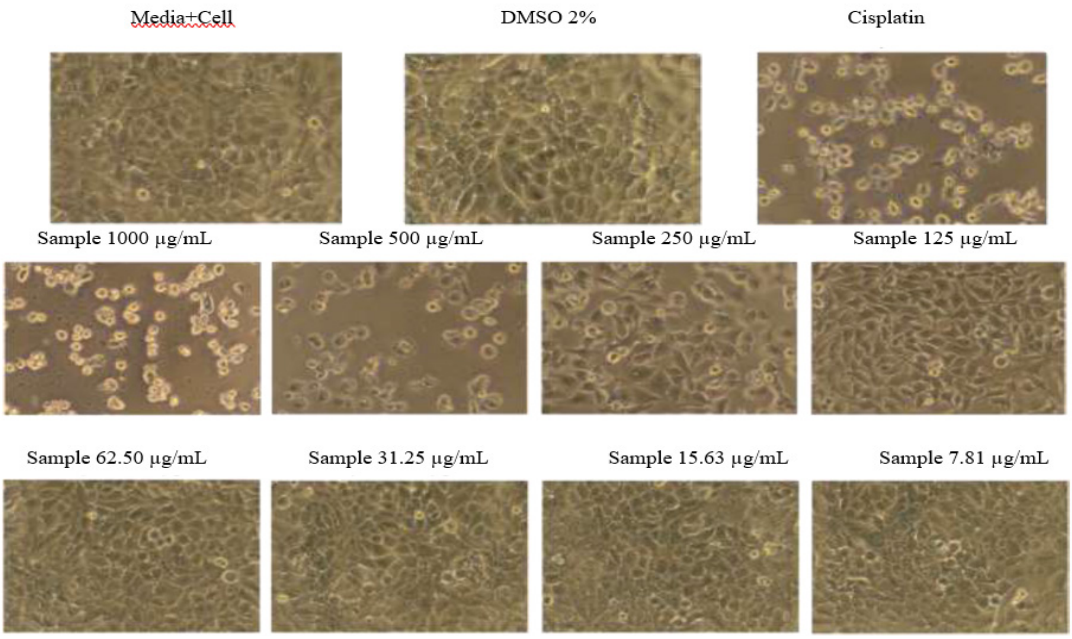

Figure 6. Apoptosis Mediated by Ni(II) Proline Dithiocarbamate in MCF-7 Cells.

also exhibits a shift in band II, indicative of the n → π* intraligand transition of the N=C=S group, occurring at 411 nm. Furthermore, the complex demonstrates a larger conjugation system than the ligand, with band III appearing at 676 nm in the UV-Vis absorption spectrum of the complex [21].

The FT-IR study aims to identify the bound functional groups in the synthesized complex and the nature of the chemical bonds with metals and ligands [22]. The wavenumber range used for this analysis was 4000–300 cm^{-1}. The interaction that occurs between the C=S group and the Ni metal is indicated by the IR radiation absorption peak at 387 cm^{-1}. The interaction of Oxygen with the Ni metal ions is indicated by its absorption peak at 387 cm^{-1} (Figure 4). Additionally, the absorption peak at 457 cm^{-1} reflects the interaction between the nitrogen atom in the complex and Ni metal ions [23]. The occurrence of an absorbance peak at 1114 cm^{-1} confirms the presence of the dithiocarbamate ligand's C=S functional group [24,25]. The presence of a C=N group is revealed by a peak at 1595 cm^{-1} [26].

In this study, the in vitro cytotoxicity of the Ni(II) ProDtc complex was compared with results from in silico molecular docking studies. The in vitro tests demonstrated that the complex effectively inhibits the growth of MCF-7 cells. The in silico molecular docking studies revealed that the Ni(II)ProDtc complex interacts with the estrogen receptor-α protein at active sites ARG394, LEU387, ALA350, and PHE404. The binding involves hydrogen bonds and hydrophobic interactions, potentially disrupting the proliferation of breast cancer cells.

According to a previous study by Eka Pratiwi et al. that examined Ni(II) complex activity on breast cancer cells, the Ni(II)cysteine-tyrosinedithiocarbamate complex exhibited lower cytotoxicity compared to cisplatin, as indicated by the IC_{50} values of the two compounds [27]. Given that the raw materials used in the synthesis of the complex are considered safe for biological systems, it is anticipated that the Ni(II)cysteine-tyrosinedithiocarbamate complex will have minimal adverse effects on normal cells [27]. Although the bioactivity of the produced molecule is modest, this study provides valuable insights into the effects of molecular structure on anticancer activity.

Based on the results of our study, given that the efficacy and safety of Ni(II)ProDtc in patients have not been directly evaluated, definitive conclusions cannot be drawn. While this study provides preliminary data from in vitro tests on MCF-7 cells, additional in vivo studies and eventual clinical trials are necessary to assess the effectiveness of the complex in breast cancer patients. Furthermore, while the current study focuses on breast cancer cells, the potential of Ni(II)ProDtc against other types of cancer cells, as well as adverse cytotoxicity against healthy cells, remain underexplored and require further investigation.

In summary, the Ni(II)ProDtc complex was synthesized in situ by reacting proline with carbon disulfide (CS2) in ethanol. The cytotoxicity assay conducted with MCF-7 cancer cells yielded an IC_{50} value of 315.70 µg/mL, suggesting that Ni(II)ProDtc holds significant potential for the treatment of breast cancer.

Author Contribution Statement

Pri: Conceptualization, Resources, Methodology, Writing – original draft, Software. IR: Project administration, Supervision, Formal analysis. SJ: Writing – review & editing, Investigation, Data curation, Methodology, Software, Resources. SS: Validation, Visualization. KP: Data curation, Methodology, Software. SAS: Data curation, Methodology, Software, Resources. NS: Data curation, Methodology, Software, Resources. MF: Data curation, Methodology, Software.

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Ethics approval

The study was approved by the Research Ethics Committee of the Faculty of Medicine Universitas Hasanuddin, Makassar, Indonesia, number: 253/UN4.6.4.5.31/PP36/2023,), with protocol number UH23040210, on April 26, 2023.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

The data that support the findings of this study are available from the corresponding author (PRI) upon reasonable request.

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