RESEARCH ARTICLE

Editorial Process: Submission:09/15/2024 Acceptance:07/14/2025

Modeling of the Zn(II) Cysteine-Tyrosine dithiocarbamate Complex: Synthesis, Characterization, Molecular Docking and Anticancer Activity on MCF-7 Breast Cancer Cell Line

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Abstract

Objective: Cisplatin-based chemotherapy remains a widely used treatment for breast cancer, whether administered orally or intravenously. However, its clinical effectiveness is limited by poor selectivity, severe side effects, systemic toxicity, and the emergence of drug resistance. To overcome these limitations, this study investigates a novel molecular complex-Zn(II)-Cysteine-Tyrosine dithiocarbamate as a potential alternative with improved safety and efficacy in breast cancer therapy. **Methods:** The complex was synthesized via a reaction involving zinc metal, cysteine, carbon disulfide (CS_2), potassium hydroxide (KOH), and tyrosine. It underwent comprehensive physicochemical characterization using Fourier-transform infrared (FT-IR) spectroscopy, UV-Vis spectroscopy, scanning electron microscopy with energy-dispersive X-ray spectroscopy (SEM-EDS), X-ray diffraction (XRD), melting point analysis, and electrical conductivity measurements. The compound's anticancer activity was evaluated in vitro against MCF-7 breast cancer cells. In addition, molecular docking was performed to assess binding interactions with Estrogen Receptor α. **Results:** The synthesis achieved an 88.1% yield, with a melting point of 202–204°C and a conductivity of 0.4 mS/cm. In vitro analysis revealed morphological changes consistent with apoptosis at concentrations ≥250 µg/mL, and the IC_{50} value was determined to be 511.40 µg/mL. Molecular docking indicated strong binding affinity between the complex and Estrogen α, with a binding energy of -75.41 kJ/mol. Key amino acid residues involved in the interaction included Lys449, Phe495, Ile389, Ile514, Met388, Glu385, Leu387, and Gly390. Both hydrophobic interactions and hydrogen bonding contributed to the complex's structural stability. Conclusion: Although the Zn (II)–Cysteine–Tyrosine dithiocarbamate complex demonstrated limited cytotoxic activity, its strong binding interactions and molecular stability suggest potential for further structural optimization. These findings offer valuable insights into the relationship between molecular architecture and anticancer behavior, laying the groundwork for future therapeutic development.

Keywords: Complex- breast cancer- MCF-7 cell lines- IC_{50}

Asian Pac J Cancer Prev, **26 (7)**, 2369-2377

Introduction

Breast cancer is the leading cause of cancer-related cases among women globally, with its incidence rising steadily over the years [1]. In Indonesia, the disease also poses a significant challenge, affecting a large number of women and profoundly influencing various aspects of life, including their overall quality of life [2, 3]. Treatment approaches typically include surgery, radiation therapy, and systemic treatments tailored to cancer type, stage, and patient preferences. Kidney replacement therapy, however, complicates systemic treatment due to altered drug clearance and the necessity for regular dialysis sessions [4]. Cisplatin remains one of the most widely used chemotherapy drugs for treating breast cancer worldwide. Its strength lies in its multidimensional mechanism, particularly its ability to damage cancer cell DNA [5]. Nevertheless, cisplatin's effectiveness is often hindered by factors such as drug resistance, recurrence, poor prognosis, and adverse effects on healthy tissues [6].

This research investigates the Zn(II)Cysteine-Tyrosine dithiocarbamate complex as a promising alternative to cisplatin, an anticancer drug known for its effectiveness but associated with harmful side effects on other organs.

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The Zn(II)Cysteine-Tyrosine dithiocarbamate compound is anticipated to offer a more efficient approach to cancer treatment, minimizing adverse effects. By focusing on this molecular complex, the study seeks to mitigate the drawbacks of conventional chemotherapeutic drugs in breast cancer treatment.

Recent years have seen the development of numerous metal complexes as potent anticancer chemotherapy agents, leveraging innovative strategies that emphasize ligand frameworks and core metal ions [7]. These complexes show effectiveness against various cancers, including those resistant to traditional treatments. Their anticancer capabilities often stem from their ability to interact with DNA and other biomolecules, triggering cell death [8].

Zinc (Zn) performs numerous vital biological functions. Zn(II) ions contribute to the regulation of both intercellular communication and intracellular processes that are essential for maintaining normal physiological functions. This regulation occurs through the modulation of Zn-dependent proteins, such as transcription factors and enzymes, which are key players in critical cell signaling pathways responsible for proliferation, apoptosis, and antioxidant defense [9]. Furthermore, zinc exhibits anticancer properties due to its antioxidant capability, shielding cells from oxidative stress. It also influences cancer progression by supporting DNA repair, gene expression regulation, and the induction of apoptosis, or programmed cell death [10].

Dithiocarbamates have proven effective in mitigating the side effects associated with cisplatin, while also substantially boosting its anticancer efficacy [11]. These ligands feature acyl (NH-C=O) and thiolate (S, S) functional groups [12]. The reduced toxicity of dithiocarbamates is attributed to their unique molecular structure, which includes sulfur (S) and nitrogen (N) donor groups [13].

Previous research has demonstrated that metal complexes featuring dithiocarbamate ligands exhibit noteworthy anticancer activity. Five innovative complexes—Fe(II), Co(II), Ni(II), Cu(II), and Zn(II)—derived from N-cyclohexyl N-(3,4-dimethoxy benzyl) dithiocarbamate ligands have displayed exceptional cytotoxicity results [9]. Additionally, findings from Saiyed et al. (2024) highlight that Ni(II) and Zn(II) complexes containing 4,7-diphenyl-1,10-phenanthroline and N-methyl or ethyl-N-phenyl dithiocarbamate exhibit moderate to strong anti-inflammatory properties in comparison to diclofenac, a controlled medication. This suggests the potential of these compounds—specifically [Zn(L1)2L3]—as effective anticancer agents, emphasizing the need for further evaluation via clinical trials, encompassing in silico, in vitro, and in vivo testing.

Materials and Methods

Experimental Design

Materials

All the chemicals and reagents used in this study were of professional analytical grade (p.a.). The compounds utilized, sourced from the Central Laboratories of Hasanuddin University and Padjadjaran University in Bandung, Indonesia, include zinc(II) chloride, cisplatin, tyrosine, cysteine, carbon disulfide (CS2), potassium hydroxide (KOH), parafilm, aquabides, dimethyl sulfoxide (DMSO), potassium bromide (KBr), and 95% ethanol.

Synthesis of Zn(II)cysteine-tyrosine ditiocarbamate complex

The Zn(II) cysteine-tyrosine dithiocarbamate complex was synthesized using an in situ technique. The process began by dissolving 0.2805 g of KOH in aquabides within a 100 mL Erlenmeyer flask with gentle swirling. At a low temperature, 0.302 mL (5 mmol) of CS2 solution was gradually added dropwise. Subsequently, 0.906 g (5 mmol) of tyrosine was incorporated, followed by 0.6058 g (5 mmol) of cysteine. To this mixture, a solution of 0.622 g (3 mmol) of $ZnCl_2$ dissolved in 10 mL of ethanol was added. The reaction mixture was stirred with a magnetic stirrer for 30 minutes.

Afterward, the product was filtered and dried in a desiccator. The resulting precipitate was crystallized using a suitable solvent to obtain pure crystals of the Zn(II) cysteine-tyrosine dithiocarbamate complex. Figure 1 illustrates the synthesis scheme for this compound.

Complex Characterization

The Zn(II) cysteine-tyrosine dithiocarbamate complexes were synthesized and analyzed for their properties. After dissolving the compounds in ethanol, the electrical conductivity of the solution was measured using a Lutron CD-4303 conductometer. Additionally, the melting point of the Zn(II) cysteine-tyrosine dithiocarbamate complex was determined by placing the compound in a capillary tube and using an Electrothermal IA 9100 melting point apparatus for precise measurement.

UV-Vis absorption spectroscopy

The Zn(II) cysteine-tyrosine dithiocarbamate complex was dissolved in ethanol at a concentration of 100 ppm, and its electronic spectrum was analyzed within the wavelength range of 200–1000 nm. This analysis was conducted using a UV–Vis spectrophotometer to evaluate the compound's spectral characteristics.

FT-IR spectroscopic studies

The Zn(II) cysteine-tyrosine dithiocarbamate complex was formed into a pellet with dry potassium bromide (KBr) and subsequently analyzed using an FT-IR spectrometer. The analysis covered the wave number range of 340–40,00 cm^{-1} to identify the compound's functional groups and molecular characteristics.

Characterization with XRD

The crystal structure of the Zn(II) cysteine-tyrosine dithiocarbamate complex was analyzed using an XRD-7,000 Shimadzu Maxima -90° diffractometer. The analysis was conducted with a step size of 0.02°/step, generating a diffractogram that correlates peak intensity (counts) with the diffraction angle (2θ). This technique provided insights into the crystalline nature and phase composition of the compound.

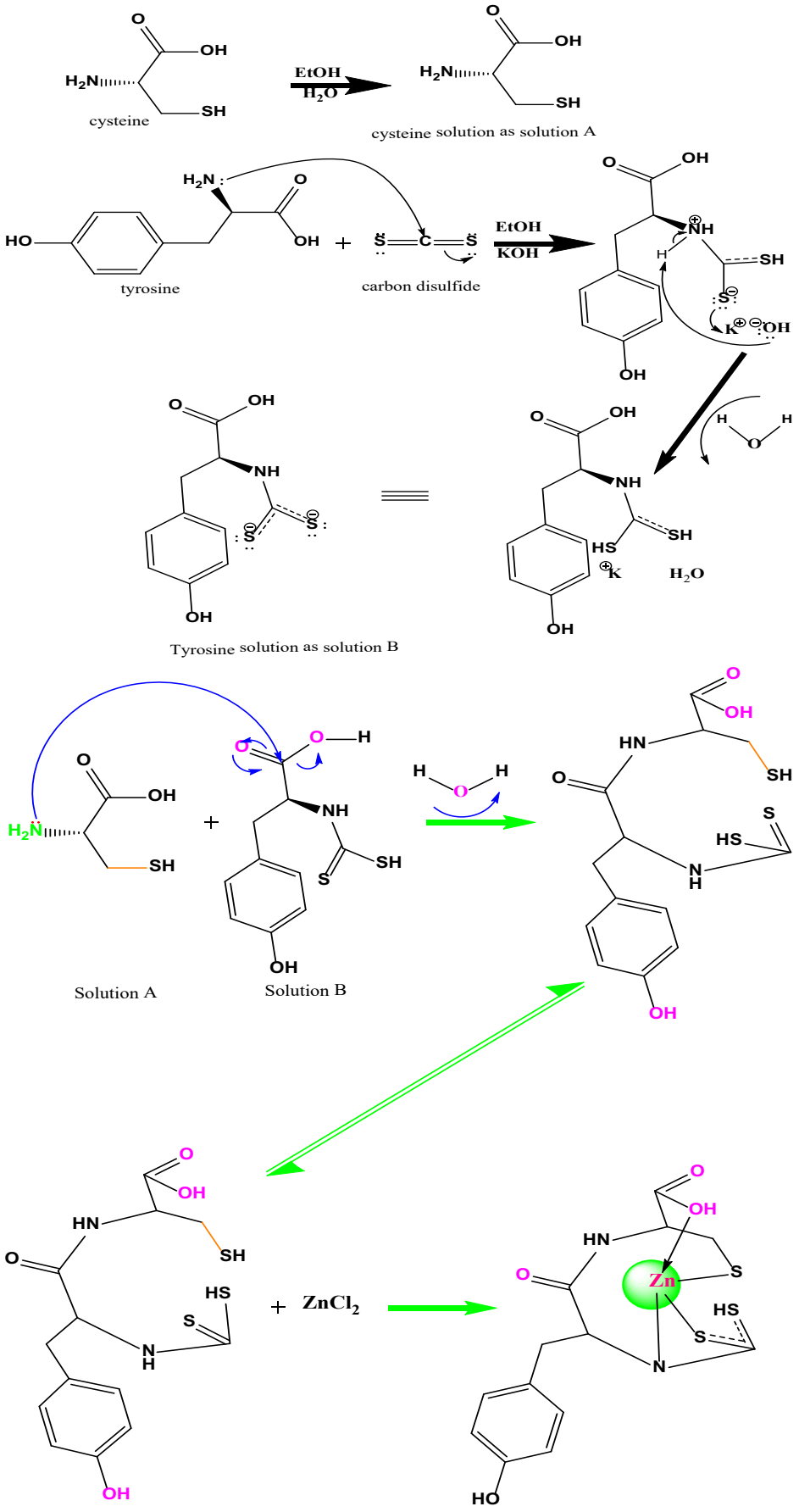

Figure 1. Synthesis Reaction of Zn(II)Cysteine-Tyrosine Dithiocarbamate Complex

Characterization with SEM

To analyze the morphology of the Zn(II) cysteine-tyrosine dithiocarbamate complex, a JEOL JCM 6000plus Scanning Electron Microscope (SEM) was employed. The compound sample was first mounted onto the surface of a block stage with a carbon tip using an electric blower. The sample was then placed inside the preparation box for coating and secured into the stage holder. The bolts at both sides of the stage holder were locked using an "L" key to ensure stability during the examination. Finally, the SEM was utilized to assess and capture detailed morphological data of the complex.

Characterization with SEM-EDS

The Zn(II) cysteine-tyrosine dithiocarbamate complex was prepared following the same method outlined in the SEM procedure. SEM-EDS analysis was conducted by selecting specific spot points on the sample surface. During this process, X-rays emitted from the sample's surface were detected using an EDS detector, which then analyzed these emissions to determine the elemental composition of the sample. This approach provided insights into both the morphology and the chemical makeup of the compound.

Anticancer activity test against breast cancer cells

The cell culture was prepared by placing it into 96-well plates and incubating at 37°C with 5% CO_2 gas until the growth reached approximately 70%. Following this, the cells underwent further cultivation for 48 hours under the same conditions of 37°C with 5% CO_2 gas. Subsequently, the blue Presto working reagent was added to the cells, enabling measurements to be carried out using a Thermo Fisher Scientific Multimode Reader to assess the sorbent.

Research Methods

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

Basic validation of the PLANTS proto

Protein and reference ligand preparations were conducted using YASARA software, where unwanted ligands, cofactors, and protein sections were removed for refinement. Ligand preparation was carried out at pH 7.4 using MarvinSketch, and the resulting file was saved as ligand_2D.mrv. The ligand_2D.mrv file was reopened in MarvinSketch to perform a "Conformers search," generating various structural conformations of the ligand. These conformations were then saved in a ligand.mol2 file.

The prepared ligand and protein files were subsequently docked using PLANTS software, utilizing protein.mol2 and ligand.mol2 input files. Docking determined the initial position of the ligand in the target protein structure, with the docking pose achieving the highest score identified. YASARA was used to calculate the Root Mean Square Deviation (RMSD) of the docked position, ensuring validity if the RMSD value was less than 2 Å (1 Å = 10^{-10} m) [14].

Results

The synthesis yielded a high efficiency of 88.1%, accompanied by a melting point range of 202–204 °C and a conductivity value of 0.4 mS/cm, reflecting the stability and successful formation of the Zn(II) cysteine-tyrosine dithiocarbamate complex. The in vitro findings demonstrated promising anticancer activity, with morphological changes indicating apoptosis in MCF-7 cancer cells at a concentration of 250 µg/mL and an IC_{50} value of 511.40 µg/mL, which is noteworthy.

The molecular docking studies shed light on the complex's interaction with the target molecule, 4,4',4''-[(2R)-butane-1,1,2-triyl]triphenol - Estrogen α. Identification of the active site involving amino acid residues Lys449, Phe495, Ile389, Ile514, Met388, Glu385, Leu387, Gly390, and Glu385 further emphasizes the specificity of its binding. Additionally, the hydrophobic interactions and calculated bond energy of -75.4095 kJ/mol suggest a stable and potentially effective therapeutic complex.

UV-Vis Characterization

The UV-Vis spectroscopy analysis of the Zn(II) cysteine-tyrosine dithiocarbamate complex identified four distinct absorption bands. These include bands in the visible light spectrum (578–683 nm) and the ultraviolet region (280–389 nm). In the shift I band (280–389 nm), the complex displayed an intraligand transition corresponding to the CS2 group transitioning from n to π. Strong transitions from π to π and n to π* were observed in the 250–320 nm range in compounds containing C=S groups [15].

In the 310–400 nm range, the electronic transitions within the ligand (from n to π) were associated with the N=C=S group. Additional absorption bands between 400 and 427 nm indicated Charge Transfer (CT) transitions between the ligand (L) and the metal (M), both from L to M and M to L. Furthermore, the complex exhibited a broader conjugation system than the ligand alone, as evidenced by absorbance in the 646–682 nm range, corresponding to transition metal d orbital transitions (Annuar, 1974). The maximum wavelength of the resultant transition, attributed to π to π, was found at 280 nm. Figure 2 illustrates the UV-Vis characterization results, visually detailing these

Table 1. FT-IR Spectrum Analysis Data of Zn(II) Cysteine-Tyrosine Dithiocarbamate Complex

Compound/functional group	Wavenumber (cm^{-1})
v (M-S)	378,04 m
v (M-O)	433,98 w
v (M-N)	532,35 m
v (C=S)	1097,49 m
v (C=O)	1608,63 s
v (C-N)	1330,88 m
v (N-H)	3232,99 w
v (O-H)	3454,50 w
v (C-N)	1330,88 m

s, strong; m, medium; w, weak

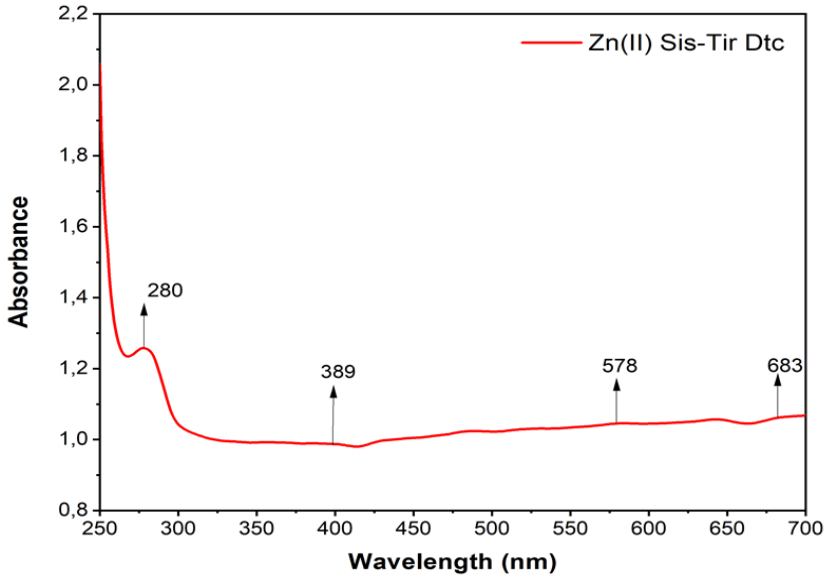

Figure 2. UV-Vis Spectrum of Zn(II)Cysteine-Tyrosine Dithiocarbamate Complex

observations.

IR characterization

The infrared absorption peaks of the Zn(II) cysteine-tyrosine dithiocarbamate complex were investigated across the wave number range of 4,000–300 cm^{-1} (Figure 3). A broad band observed at 3454.50 cm^{-1} indicates the presence of -OH groups, likely contributed by ethanol or water. Additionally, an absorption peak at 3,205.69 cm^{-1} suggests the involvement of the oxygen atom from the hydroxyl group (-OH) linked to the aromatic ring (Ar-OH) within the structure of the complex compound [16-18].

The FT-IR analysis of the Zn(II) cysteine-tyrosine dithiocarbamate complex revealed important functional group interactions. Peaks at 1,330.88 cm^{-1} and 1,608.63 cm^{-1} confirm the presence of the C-N and C=O functional groups, respectively. The absorption at 1,097.49 cm^{-1} highlights the coordination of Zn metal in a bidentate manner with the C=S group, which corresponds to the dithiocarbamate ligand's functional group.

Further, new broad absorption bands at 532.35 cm^{-1} and 433.98 cm^{-1} indicate interactions between the Zn metal and nitrogen atoms (M-N) and Zn metal and oxygen atoms (M-O), respectively. Additionally, an absorption peak at 378.04 cm^{-1} signifies interactions between sulfur atoms in the compound and Zn metal ions (M-S). These findings detail the comprehensive bonding environment within the complex.

XRD characterization

The X-ray diffraction (XRD) analysis of the synthesized Zn(II) cysteine-tyrosine dithiocarbamate complex

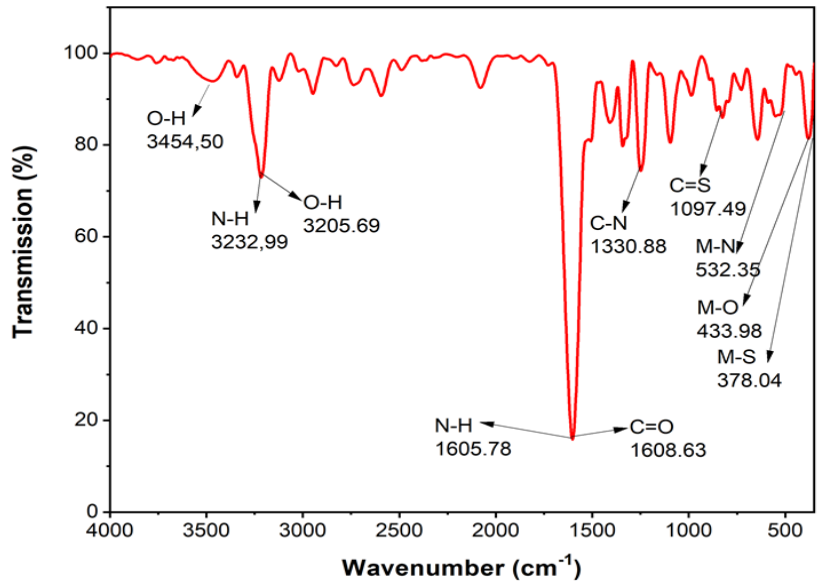

Figure 3. IR Spectrum of Zn(II)Cysteine-Tyrosine Dithiocarbamate Complex=

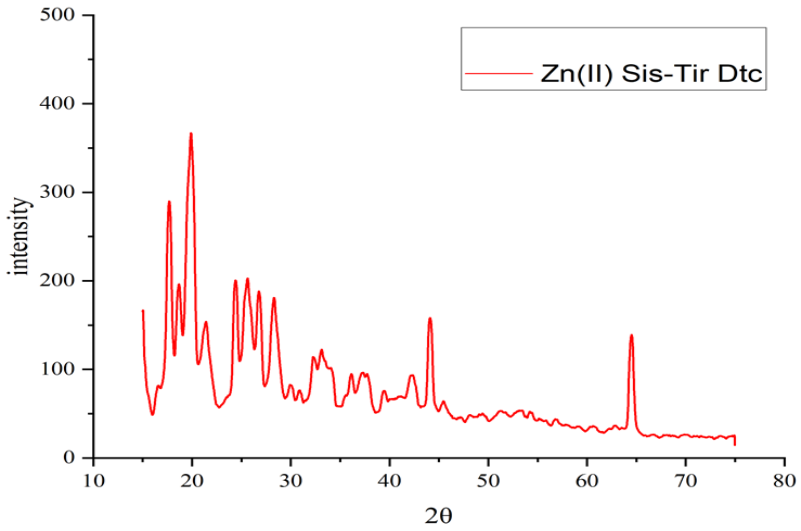

Figure 4. XRD Spectrum of Zn(II)Cysteine-Tyrosine Dithiocarbamate Complex

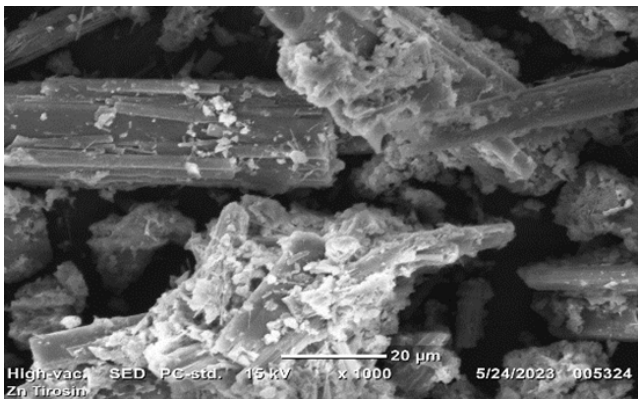

Figure 5. SEM Morphology of Zn(II)Cysteine-Tyrosine Dithiocarbamate Complex

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.
Zn(II)Cysteine-Tyrosine dithiocarbamate - Estrogen α	-75.4095 kJ/mol.

revealed important insights into its crystal structure. The Miller index values derived from the diffractogram provide valuable estimations of the crystalline form of the complex (Figure 4). The results confirmed that the complex exhibits a face-centered cubic (FCC) crystal structure. The diffraction angles corresponding to the highest intensities (2θ) were observed at 19.80°, 17.66°, and 24.37°, highlighting key structural characteristics (Figure 5).

The SEM-EDS analysis provided detailed insights into the elemental composition of the Zn(II) cysteine-tyrosine dithiocarbamate complex (Supplementary Figure 1). The spectrum results revealed that the sample primarily consists of zinc (Zn), carbon (C), oxygen (O), nitrogen (N), and sulfur (S). Specifically, the EDS spectrum showed the following percentages: Zn at 38.11%, C at 8.27%, O at 11.25%, N at 2.48%, and S at 39.88%. The high sulfur content highlights its significant contribution from cysteine amino acids and CS_2, underscoring its structural importance in the complex.

Molecular Docking of Complex on Estrogen α

Molecular docking studies were conducted to investigate the inhibitory mechanisms of potential drug candidates, comparing the binding affinities of Zn(II) cysteine-tyrosine dithiocarbamate and 4,4',4''-[(2R)-butane-1,1,2-triyl]triphenol (Table 1). The study showed that Zn(II) cysteine-tyrosine dithiocarbamate demonstrated a lower binding affinity compared to 4,4',4''-[(2R)-butane-1,1,2-triyl]triphenol. Strong binding in 4,4',4''-[(2R)-butane-1,1,2-triyl]triphenol was attributed to crucial binding modes, such as hydrogen bond interactions and amide-π stacking involving residues R394, Q353, G521, L346, and F404, ensuring stable ligand binding (Supplementary Figure 2).

For the Zn(II) cysteine-tyrosine dithiocarbamate complex, the most favorable binding interactions

were observed at the carbonyl and oxygen groups (Supplementary Figure 3). Amino acid residues Lys449, Phe495, Ile389, Ile514, Met388, Glu385, Leu387, Gly390, and Glu385 played key roles in stabilizing the binding modes. These hydrogen bond interactions contribute to the stability of the complex's binding with estrogen α [19] (Table 2).

Breast cancer cell line (MCF-7) cytotoxicity of the Zn(II) Cysteine-Tyrosine dithiocarbamate complex

In this study, an in vitro cytotoxicity test was conducted to evaluate the effectiveness of the Zn(II) cysteine-tyrosine dithiocarbamate complex against MCF-7 breast cancer cells, comparing its results to cisplatin, a widely used anticancer drug. The experimental setup included analyzing Zn(II) cysteine-tyrosine dithiocarbamate plates, recording comparisons between cell concentrations in medium + MCF-7, cisplatin samples, and wells containing the complex. The tests were carried out over 48 hours, with concentrations ranging from 7.81 µg/mL to 1,000 µg/mL. Supplementary Figure 5 highlights the recorded outcomes and visual comparisons.

In this study, the cytotoxic properties of the synthesized Zn(II) cysteine-tyrosine dithiocarbamate complex were evaluated against MCF-7 breast cancer cells in vitro, with comparisons made to cisplatin's well-documented anticancer activity. The investigation employed the MTS assay method (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl))-2H-tetrazolium, one of the most widely used techniques for measuring cytotoxicity and cell proliferation. This approach provided quantitative insights into the compound's potential therapeutic efficacy and its impact on breast cancer cells [20].

Discussion

The study successfully modeled, synthesized, and characterized the Zn(II) complex with cysteine-tyrosine dithiocarbamate ligands, achieving a high synthesis yield of 88.1%. Notably, the band gap energy of these semiconductor complexes suggests they can release radicals that effectively penetrate cancer cell membranes.

In vitro cytotoxicity testing against MCF-7 breast cancer cells categorized the activity of the Zn(II) complex as moderate. Moreover, in silico molecular docking studies indicated that the Zn(II) cysteine-tyrosine dithiocarbamate complex could inhibit MCF-7 growth by interacting with Protein 4,4',4''-[(2R)-butane-1,1,2-triyl] triphenol - Estrogen α. The active binding site, involving residues Lys449, Phe495, Ile389, Ile514, Met388, Glu385, Leu387, Gly390, and Glu385, demonstrated a binding energy of -75.4095 kJ/mol. This interaction may influence the DNA methylation process, potentially preventing cancer cell proliferation. These findings highlight the Zn(II) complex as a promising candidate for future breast cancer therapies, warranting further investigation and development.

The cytotoxicity evaluation revealed that Zn(II) cysteine-tyrosine dithiocarbamate has an IC_{50} value of 511.40 µg/mL, while cisplatin demonstrates a much lower IC_{50} value of 53.48 µg/mL, indicating a stronger anticancer potency for cisplatin. As depicted in Supplementary Figure 4, the apoptotic phase of MCF-7 breast cancer cells was analyzed in response to both Zn(II) cysteine-tyrosine dithiocarbamate and cisplatin. Interestingly, no cell death was detected within the sample concentration range of 7.81 to 62.5 µg/mL for the Zn(II) complex. However, apoptosis began to manifest at higher concentrations, specifically within the range of 125 to 1,000 µg/mL.

The comparison of cytotoxicity test results revealed that the IC_{50} value of the Zn(II) cysteine-tyrosine dithiocarbamate complex is higher than that of cisplatin, indicating lower potency against cancer cells. However, the safety of the raw chemicals used in the synthesis suggests that the Zn(II) complex might exhibit minimal adverse effects on normal cells, making it a potential candidate for further research and development in anticancer treatments.

The Zn(II) cysteine-tyrosine dithiocarbamate complex falls within the moderate cytotoxicity category, as its cytotoxicity aligns with the range of 100–1,000 µg/mL, as defined for cytotoxic complexes [21]. The metal's bioactivity in the MCF-7 cell line highlights its anticancer potential, with approximately 40% of metal ions in cells known to function as active anticancer agents [22].

Enhancing the selection of ligands can further improve the therapeutic properties of such complexes [23]. Dithiocarbamate complexes, along with other sulfur-containing ligands, have gained significant attention as Zn-based chemotherapeutic agents [24]. These sulfur donor ligands are generally compatible with biological systems and exhibit versatility, impacting proteins involved in oxidative stress, transcription, degradation, and apoptosis. Such properties make them highly valuable in cancer treatment [25-27].

Furthermore, certain dithiocarbamate complexes act as proteasome inhibitors, which adds another promising avenue for their use in anticancer therapies. These findings reinforce the potential of Zn(II) cysteine-tyrosine dithiocarbamate and similar complexes as future candidates in cancer research and treatment [28, 29].

To summarize, the Zn(II) cysteine-tyrosine dithiocarbamate complex with its cysteine-tyrosine-dithiocarbamate ligand was successfully synthesized and characterized. Its demonstrated anticancer activity against MCF-7 breast cancer cells highlights its potential as a therapeutic agent.

The UV-Vis spectrum analysis confirmed the presence of the C=S functional group, with the transition from π to π* observed at wavelengths of 280–389 nm. Additional absorption bands between 400 and 427 nm pointed to Charge Transfer (CT) transitions occurring between the metal and ligand (L→M and M→L). Furthermore, absorbance within the 646–682 nm range indicated a more extensive conjugation system in the complex compared to the ligand alone, along with transitions involving the metal's d orbitals. The primary transition with a maximum wavelength of 280 nm corresponds to π→π*, emphasizing the complex's structural and electronic attributes [30].

This study provided comprehensive insights into

the characteristics and anticancer potential of the Zn(II) cysteine-tyrosine dithiocarbamate complex. The FT-IR characterization confirmed key functional groups, with absorption peaks at 1097.49 cm^{-1} (C=S) and 1330.88 cm^{-1} (C-N). Additional peaks at 378.04 cm^{-1}, 433.98 cm^{-1}, and 532.35 cm^{-1} highlighted interactions between sulfur (S), oxygen (O), and nitrogen (N) atoms in the complex with Zn metal ions.

XRD characterization revealed the complex's face-centered cubic (FCC) crystal structure. SEM analysis at 1,000x magnification displayed a cubic crystal shape along with some impurities of irregular shapes. The EDS spectrum confirmed the elemental composition, with significant percentages of Zn (38.11%), C (8.27%), O (11.25%), N (2.48%), and S (39.88%), emphasizing the substantial contribution of sulfur from cysteine amino acids and CS_2.

In vitro cytotoxicity tests demonstrated morphological changes (apoptosis) in MCF-7 breast cancer cells starting at a concentration of 125 µg/mL, with an IC50 value of 511.40 µg/mL, categorizing the complex as moderately cytotoxic. These findings align with the in silico study results, which showed a binding energy of -75.4095 kJ/mol. Together, the in vitro and in silico results underscore the potential of this complex as a future anti-breast cancer agent.

Author Contribution Statement

Eka Pratiwi and Indah Raya: Conceptualization, Methodology, Supervision; Eka Pratiwi, Indah Raya, Eka Anggraeni Odja, Rizal Irfandi, Andi Besse Khaerunisa, Andi Muhammad Anshar, Bulkis Musa, Fredryk W. Mandey, Erna Mayasari: Methodology, Investigation and Writing–original draft; Andi Adillah Nur Syafirah4 :in vitro test analysis of breast cancer; Rizal Irfandi and Eka Pratiwi: molecular docking: Writing – review & editing, Validation.

Acknowledgements

General

It's wonderful to see such collaboration and support contributing to this research. A big acknowledgment to the Central Laboratory for Inorganic, Organic Research, Integrated Chemistry Laboratory, Science Research and Development Laboratory at Hasanuddin University Makassar, Indonesia, and the Central Laboratory of Pajajaran University for their valuable assistance.

Additionally, the funding and endorsement from the Directorate of Research, Technology, and Community Service of the Ministry of Education and Culture of Indonesia, under Main Contract 050/E5/PG.02.00.PL/2024 and Derived Contract 02035/UN4.22.2/PT.01.03/2024, were vital in enabling this work.

This research stands as a testament to the power of collaboration across institutions and organizations—such contributions truly advance scientific inquiry.

Ethical Declaration

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

Conflict of Interest

All Author declare there is no of conflict interested

References

1. Cuthrell KM, Tzenios N. Breast cancer: updated and deep insights. International Research Journal of Oncology. 2023;6(1):104-18.
2. Pancakarsa EP, Soemitro MP, Budianto A, Abdurahman M, Rizki KA, Azhar Y, Gaol DL. Analysis of Risk Factors for Psychological Stress in Breast Cancer Patients: Observational Study in West Java, Indonesia. BioSci Med J Biomed Transl Res. 2024;8(7):4648-56. https://doi.org/10.37275/bsm.v8i7.1037.
3. Sukarno A, Dewi R, Kurnia MP, Kalalo S. Quality of life determinants among breast cancer women undergoing treatment in indonesia: A cross-sectional study. Indian J Palliat Care. 2024;30(3):215-21. https://doi.org/10.25259/ijpc_344_2023.
4. Khan S, Araji G, Yetiskul E, Keesari PR, Haddadin F, Khamis Z, et al. Systemic oncological therapy in breast cancer patients on dialysis. World J Clin Oncol. 2024;15(6):730-44. https://doi.org/10.5306/wjco.v15.i6.730.
5. Zoń A, Bednarek I. Cisplatin in ovarian cancer treatment-known limitations in therapy force new solutions. Int J Mol Sci. 2023;24(8). https://doi.org/10.3390/ijms24087585.
6. Li Q, Chen S, Wang X, Cai J, Huang H, Tang S, et al. Cisplatin-based combination therapy for enhanced cancer treatment. Curr Drug Targets. 2024;25(7):473-91. https://doi.org/10.2174/0113894501294182240401060343.
7. Arjmand F, Tabassum S, Khan HY. Biochemical Mechanistic Pathway of Cell Death Induced by Metal-Based Chemotherapeutic Agents. In F Arjmand, S Tabassum, & H. Y. Khan (Eds.), Advances and Prospects of 3-d Metal-Based Anticancer Drug Candidates. Springer Nature Singapore. 2024; 30: 169-2-2. https://doi.org/10.1007/978-981-97-0146-9_7.
8. Sara A, Alireza A, Samad K. Riding the metal wave: A review of the latest developments in metal-based anticancer agents. Coord Chem Rev. 2024;501:215579. https://doi.org/10.1016/j.ccr.2023.215579.
9. Costa MI, Sarmento-Ribeiro AB, Gonçalves AC. Zinc: From biological functions to therapeutic potential. Int J Mol Sci. 2023;24(5):4822. https://doi.org/10.3390/ijms24054822.
10. Matuszczak M, Kiljańczyk A, Marciniak W, Derkacz R, Stempa K, Baszuk P, et al. Zinc and its antioxidant properties: The potential use of blood zinc levels as a marker of cancer risk in brca1 mutation carriers. Antioxidants (Basel). 2024;13(5). https://doi.org/10.3390/antiox13050609.
11. Ahmad, S. Advances in anticancer applications of platinum(II) complexes of dithiocarbamates. Med Chem Res. 2024;33:1133-56. https://doi.org/10.1007/s00044-024-03257-5.
12. Hussain U, Muhammad N, Ghulam M, Amir W, Maria Betania de Freitas M, Muhammad S, et al. Dithiocarbamate ligands as heavy metal expectorants from aqueous solutions. J Taibah Univ Sci. 2023;17(1):2214750. https://doi.org/10.1080/16583655.2023.2214750.
13. Arabpour shiraz Z, Sohrabi N, Eslami Moghadam M, Oftadeh M. Molecular docking and spectroscopic study of bovine serum albumin interaction with new anticancer Pt complex with isopentyl dithiocarbamate ligand. Nucleosides Nucleotides Nucleic Acids. 2024;43(1):65-85. https://doi.org/10.1080/15257770.2023.2233576.
14. Istyastono E. Docking studies of curcumin as a potential lead compound to develop novel dipeptydyl peptidase-4

inhibitors. Indo J of Chem. 2009;9:132-36. https://doi.org/10.22146/ijc.21574.
15. Mishra AK, Manav N, Kaushik NK. Organotin(iv) complexes of thiohydrazones: Synthesis, characterization and antifungal study. Spectrochim Acta A Mol Biomol Spectrosc. 2005;61(13-14):3097-101. https://doi.org/10.1016/j.saa.2004.11.035.
16. Şakıyan İ, Özdemir R, Öğütcü H. Synthesis, characterization, and antimicrobial activities of new N-(2-hydroxy-1-naphthalidene)-amino acid (L-Tyrosine, L-Arginine, and L-Lysine) Schiff bases and their manganese (III) complexes. Syn and React in Inor. 2014;44(3):417-23.
17. Ghorbanloo M, Jaworska M, Paluch P, Li GD, Zhou LJ. Synthesis, characterization, and catalytic activity for thioanisole oxidation of homogeneous and heterogeneous binuclear manganese(ii) complexes with amino acid-based ligands. Transit Met Chem. 2013;38(5):511-21. https://doi.org/10.1007/s11243-013-9718-4.
18. Jeyaprakash D, Jeyaprakash B, Sutha S. Synthesis, structural elucidation, microbial, antioxidant and nuclease activities of some novel divalent m(ii) complexes derived from 5-fluorouracil and l-tyrosine. J Saudi Chem Soc. 2017;21:S67-S76. https://doi.org/10.1016/j.jscs.2013.10.007.
19. Fusani L, Palmer DS, Somers DO, Wall ID. Exploring ligand stability in protein crystal structures using binding pose metadynamics. J Chem Inf Model. 2020;60(3):1528-39. https://doi.org/10.1021/acs.jcim.9b00843.
20. Wang Y, Nguyen DT, Yang G, Anesi J, Chai Z, Charchar F, et al. An improved 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2h-tetrazolium proliferation assay to overcome the interference of hydralazine. Assay Drug Dev Technol. 2020;18(8):379-84. https://doi.org/10.1089/adt.2020.1004.
21. Prayong P, Barusrux S, Weerapreeyakul N. Cytotoxic activity screening of some indigenous thai plants. Fitoterapia. 2008;79(7-8):598-601. https://doi.org/10.1016/j.fitote.2008.06.007.
22. Kontoghiorghes GJ, Kontoghiorghe CN. Iron and chelation in biochemistry and medicine: New approaches to controlling iron metabolism and treating related diseases. Cells. 2020;9(6). https://doi.org/10.3390/cells9061456.
23. Ritacco I, Russo N, Sicilia E. Dft investigation of the mechanism of action of organoiridium(iii) complexes as anticancer agents. Inorg Chem. 2015;54(22):10801-10. https://doi.org/10.1021/acs.inorgchem.5b01832.
24. Inyang OK, Omotuyi OI, Ogunleye AJ, Eniafe GO, Adewumi B, Metibemu DS. Molecular interaction and inhibitory potential of polyphenol on DNA repair pathway in small cell lung cancer: A computational study. J Anal Pharm Res. 2017;6(3):00178.
25. Irfandi R, Raya I, Ahmad A, Fudholi A, Santi S, Puspa Azalea W, et al. Anticancer potential of cu(ii)prolinedithiocarbamate complex: Design, synthesis, spectroscopy, molecular docking, molecular dynamic, admet, and in-vitro studies. J Biomol Struct Dyn. 2023;41(22):12938-50. https://doi.org/10.1080/07391102.2023.2169764.
26. Irfandi R, Santi S, Raya I, Ahmad A, Fudholi A, Sari DR. Study of new Zn (II) Prolinedithiocarbamate as a potential agent for breast cancer: Characterization and molecular docking. J Mol Struct. 2022;1252:132101.https://doi.org/10.1016/j.molstruc.2021.132101.
27. Prihantono, Irfandi R, Raya I, Warsinggih. Potential anticancer activity of mn (ii) complexes containing arginine dithiocarbamate ligand on mcf-7 breast cancer cell lines. Ann Med Surg (Lond). 2020;60:396-402. https://doi.org/10.1016/j.amsu.2020.11.018.
28. Nair RR, Blake P, Grigorenko AN, Novoselov KS, Booth TJ, Stauber T, et al. Fine structure constant defines visual transparency of graphene. Science. 2008;320(5881):1308. https://doi.org/10.1126/science.1156965.
29. Wang B, Ma HZ, Shi QZ. Chiral lanthanide(III) complexes of sulphur–nitrogen–oxygen ligand derived from aminothiourea and sodium D-camphor-β-sulfonate. Inorg Chem Commun. 2001;4(8):409-12. https://doi.org/10.1016/S1387-7003(01)00223-4.
30. Bookhari A, Hill JO, Magee RJ. Nickel(ii) and copper(ii) complexes of mono-ethanol and di-ethanol-dithiocarbamic acid. J Inorg Nucl Chem. 1974;36(6):1253-7. https://doi.org/10.1016/0022-1902(74)80060-6.