RESEARCH ARTICLE

Editorial Process: Submission:05/08/2024 Acceptance:09/19/2024

Design, Synthesis and Characterization of Mn(II)Cysteine-Tyrosine Dithiocarbamate Complex for against the Cancer on MCF-7 Breast Cancer Cell Line

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Abstract

Objective: Breast cancer is the most frequently diagnosed cancer and the second cause of death worldwide. The drug often used for chemotherapy is cisplatin. However, the drug cisplatin has a number of problems, including lack of selectivity, undesirable side effects, resistance, and toxicity in the body. So research is carried out on new drug compounds with low toxicity by designing in silico with molecular docking. **Methods:** Mn(II) Cysteine-Tyrosine dithiocarbamate is a new complex molecule whose research involves several steps, such as in-silico molecular docking testing with target proteins, ADMET then synthesis, characterization and in-vitro MCF-7 cells for anticancer drugs. The synthesis process involves the reaction of manganese metal with tyrosine, cysteine, CS2 and KOH. Characterization tests have been carried out including FT-IR spectroscopy, SEM-EDS, UV Vis, conductivity, melting point and XRD. **Result:** Confirm the structure of the compound using UV Vis, obtained orbitals π to π* and n to π* in the group N = C = S is represented by the absorption at 400 nm and 600 nm, FT-IR with the results obtained by the functional groups O-H, N-H, C =N and C=S. In vitro test results showed morphological changes (apoptosis) in MCF-7 cancer cells starting from 250 µg/mL and an IC_{50} value of 416.90 µg/mL. Molecular docking studies of the Mn(II)Cysteine-Tyrosine dithiocarbamate complex were identified with 4,4',4''-[(2R)-butane-1,1,2-triyl]triphenol - Estrogen α which showed an active site with amino acid residues GLU323, GLU385, VAL446, ILE514, TRP360, LYS449, MET388, MET357, PHE445, VAL392 and ILE389. Hydrophobic and hydrophobic bonds are seen in Mn(II)Cysteine-Tyrosine dithiocarbamate - Estrogen α has a bond energy of -77.5372 kJ/mol. **Conclusion:** Despite having a high H-bond interaction intensity, the chemical does not have a powerful enough anticancer impact. Despite the produced compound's low bioactivity, this study should offer important new understandings into how molecular structure affects anticancer activity.

Keywords: molecular docking- Complex- MCF-7 cell lines- IC_{50}- Mn(II)Cysteine-Tyrosine dithiocarbamate

Asian Pac J Cancer Prev, **25 (9)**, 3251-3261

Introduction

Breast cancer is the most common type of cancer suffered by women besides skin cancer and is the second cause of death after lung cancer. Breast cancer in the United States is ranked first (32%) and deaths due to this type of cancer reach 18% [1] In efforts to treat breast cancer, various methods such as surgery, radiotherapy, chemotherapy, hormone therapy, and therapy that targets biological targets can be used alone or in combination to increase their effectiveness [2]. In particular, the compound cisplatin has attracted attention in recent research on breast cancer treatment [3]. Cisplatin, also known as cisplatinum or cis-diaminedichloroplatinum (II), is a commonly used chemotherapy drug [4]. Its success in deferring negative effects in cancer patients has been well documented, mainly due to its ability to bind interdependently with DNA purine bases [5]. Its use is often aimed at treating ovarian cancer, although it is important to remember that high doses can cause serious side effects [6]. One of the noteworthy side effects of Cisplatin is severe kidney damage, allergic reactions, decreased immunity to infections, digestive tract disorders, bleeding, and risk of hearing loss [4]. Kidney damage can include acute kidney injury or injury to the tubules, which can result in electrolyte imbalances. Kidney damage can

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include acute kidney injury or injury to the tubules, which can result in electrolyte imbalance [7], prompting the search for efficient and selective non-platinum drugs [8].

After the historical success of compounds such as cisplatin, metal-based complexes carry promising potential, which has not yet been fully explored [9]. Metal complexes, consisting of a central metal atom or ion bound to a ligand, show promising applications in various fields, including anticancer therapy [10]. Bidentate ligands, such as cysteine and tyrosine, which are involved in metal complexes, have been shown to have significant pharmacological activities, including as anticancer, antiproliferative, and anti-inflammatory agents [11]. The advantage of metal-based complexes lies not only in their anticancer properties, but also in their ability to modify enzymatic activity, metabolism and molecular signals in cells [12].

In this case, Mn(II)Cysteine-Tyrosine dithiocarbamate Complex, the central metal ion is Mn(II) and the ligands are cysteine, tyrosine, and dithiocarbamate. Amino acids such as cysteine have a key role in forming metal complexes, and tyrosine with its phenolic functional groups can contribute to efficient interactions [13,14].

In addition, Manganese (Mn), as one of the main bio-metals, plays a crucial role in the process of forming connective tissue, bone formation, and blood clotting factors in the body. Recent discoveries reveal that manganese-based synthetic compounds exhibit promising antibacterial and antifungal properties [15].

Manganese complexes involving various ligands show significant application potential, especially as carriers in antitumor and antimicrobial therapy [16]. Ligand selection is the key to successful synthesis of metal complex compounds, or what are known as coordination compounds [17]. Recent advances in the field of bioinorganic chemistry allow the design of biologically relevant metal compounds with the use of well-tailored ligands, such as metal dithiocarbamate (DTC) conjugates [17]. Dithiocarbamate functions as a ligand that forms a complex with dual chelating properties, known as bidentate [18]. In its negative bidentate nature, dithiocarbamate coordinates through its sulfur atom with various metal ions [19]. Several studies have shown that dithiocarbamate complexes exhibit significant antimicrobial activity against pathogenic bacterial species [20]. The results of anticancer activity tests on Mn(II) and Pt(II) compounds showed higher IC_{50} values compared to the anti-cancer drug cisplatin, namely 31.5 ± 3.8 and 25.5 ± 4.4 μM respectively. compared to 8.6 ± 0.3 μM [21].

This study aims to explore the potential of Mn(II) Cysteine-Tyrosine dithiocarbamate Complex as a new drug candidate for breast cancer. The approach used is to design this compound in silico using molecular docking techniques. This approach aims to support the discovery and development of new therapeutic agents with the hope of providing innovative solutions in the field of medicine [22]. By optimizing the 3D compound structure and docking it with ERs (estrogen receptors) proteins, we hope to produce compounds with high effectiveness and low toxicity. After obtaining the optimized compound, the next stage includes purity testing through spectroscopic analysis such as UV Vis, FT-IR, XRD, and SEM EDS to confirm the expected molecular structure.

Materials and Methods

Experimental Design

Materials

Mangan(II) chloride, Cisplatin, tyrosine, cysteine, carbon disulfide (CS_2), KOH, DMSO, parafilm, aquabides, ethanol p.a.

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.

ADMET Properties Calculation

All of the ligands were converted into smiles format using the Open Babel program [23], and then submitted to the pkCSM web server one by one .Calculate the ADMET properties by choosing the ADMET menu. pkCSM program provided the data including the result of the Lipinski rule of five calculations and adsorption, distribution, metabolism, excretion and toxicity data for each ligand.

Synthesis of Mn(II)cysteine-tyrosineditiocarbamate

A CS_2 solution of 0.302 mL (5 mmol) drop by drop at cold temperature was added to a potassium hydroxide solution of 0.2805 g (5 mmol) which had been dissolved in distilled water in a 100 mL Erlenmeyer glass. After that, 0.906 g (5 mmol) of tyrosine was added which had been dissolved in 10 mL of ethanol, then stirred. Then add 0.6058 g (5 mmol) of cysteine which has been dissolved in 10 mL ethanol, then stir. Next, 0.591 g (3 mmol) of $MnCl_2$ 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 filtered and placed in a desiccator until dry, then crystallized with a suitable solvent until pure crystals are obtained.

Complex Characterization

UV-Vis absorption spectroscopy

After dissolving the complex chemical Zn(II) cysteine-tyrosine dithiocarbamate in ethanol to a concentration of 100 ppm, the electronic spectrum in the 200–1000 nm

range was examined using a UV–Vis spectrophotometer.

FT-IR spectroscopic studies

Zn(II) cysteine-tyrosine dithiocarbamate complex, which was prepared as a pellet using dry KBr and analyzed using an FT-IR spectrometer in the wave number range of 340–4000 cm^{-1}.

Characterization with XRD

An XRD-7000 Shimadzu Maxima -90° with steps of 0.02°/step verified the crystal's shape. The diffractogram between peak intensity (counts) and the diffraction angle (2θ) was then obtained.

Characterization with SEM

Examination SEM Using an electric blower, JEOL JCM 6000plus was put on the surface of a block stage that had a carbon tip attached in order to study the morphology of the N Zn(II) cysteine-tyrosine dithiocarbamate complex compound. Proceed to place the sample inside the preparation box for coating into the stage holder. Next, use a 'L' key to lock the stage holder bolts at each end of the side, and use a SEM (Scanning Electron Microscopy) to assess the results.

Characterization with SEM-EDS

The Zn(II) cysteine-tyrosine dithiocarbamate complex molecule is prepared in the same way as described in the SEM analysis above, and SEM-EDS is then performed by choosing a spot point on the sample. The surface of the sample emits X-rays. An EDS detector picks up on these X-rays and uses it to determine the elemental composition of the sample.

Anticancer activity test against breast cancer cells

After being placed onto 96-well plates, the cell culture was incubated at 37°C with 5% CO_2 gas until it attained a growth percentage of 70%. After that, the cells were taken and cultured for 48 hours at 37°C with 5% CO_2 gas. Pour the blue presto working reagent into the cell. Sorbent is measured using a Thermo Fisher Scientific Multimode Reader.

Research Methods

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

Basic validation of the PLANTS proto

Using the YASARA software, protein and ref_ligand preparation was completed by deleting unnecessary protein, covacctor, and ligand portions.

At a pH of 7.4, ligand preparation was done with MarvinSketch. Next, the outcomes are stored as ligand_2D.mrv. Go back to MarvinSketch, open the ligand_2D.mrv file, and use the "Conformers search" to look for different ligand structural conformations. After that, the outcomes are saved as a ligand in file.mol2.

The PLANTS program was then used to dock the outcomes of the ligand and protein preparations. Additionally to the protein.mol2 and ligand.mol2 input files. The initial position of the ligand in the target protein structure is then determined using the docking pose that yields the greatest score. YASARA is then used to calculate the Root Mean Square Deviation, or RMSD, from these positions. If the docked position yields an RMSD value of less than 2 Å (1 Å = 10-10 m), the technique is considered valid.

Results

The rendamen results obtained from the Mn(II) cysteine-tyrosine ditiocarbamate complex showed that the complex compound had a high rendament of 66,08%, 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 204-206 °C, the high melting point indicates that the ligands are strongly bonded to the ligand and the measured conductivity value was 0.3 mS/cm, indicating that the Mn(II)cysteine-tyrosine ditiocarbamate complex is a non-electrolyte compound.

Molecular Docking of Complex on Estrogen α

One effective strategy for predicting the correct binding mode and the interaction region is to use the molecular simulation method. Molecular docking may be used to model the form of a molecule's binding with target DNA [24, 25] (Table 1, Figure 1, 2).

ADMET Properties

The result of ADMET properties calculate in the pkCSM web server is present in Table 2.

The structure of the Mn(II) Cysteine-Tyrosine Dithiocarbamate complex compound that has been synthesized is related to the HSAB concept, where the Mn(II) ion which is classified as Hard Acids will be more interested in forming bonds with Hard Bases, as in [RCOO]-, ROH, and RNH2 groups of the Cysteine-Tyrosine Dithiocarbamate ligand in forming complex compound bonds (Figure 3).

UV-Vis Characterization

The technique of electronic absorption spectroscopy holds great significance in examining the DNA binding mechanism of metal complexes [2]. When a compound binds to DNA through intercalation, the coupling π orbital is partially filled by electrons, resulting in hypochromism. Bathchromism is also visible in UV absorption spectroscopy [26] Conversely, the bathochromism is produced when the ligand's π* orbital intercalates with the DNA base pairs' π orbitals. It

Table 1. Docking Score of Complex

Complex	Score Docking
4,4',4"-[(2R)-butane-1,1,2-triyl]triphenol - Estrogen α (control +)	-103.936 kJ/mol.
Mn(II)Cystein-Tyrosine-Dithiocarbamate - Estrogen α	-77.5372 kJ/mol.

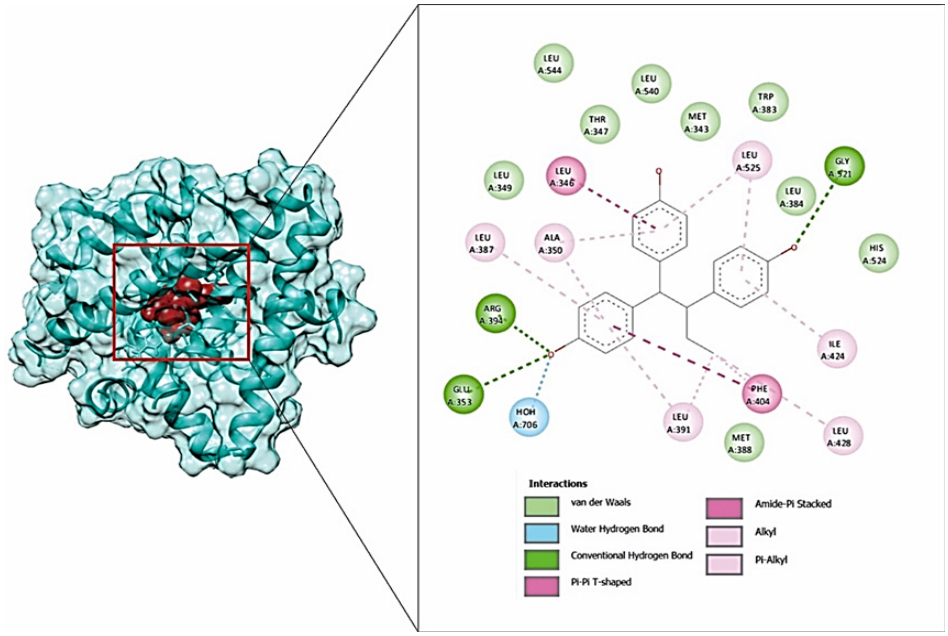


Figure 1. Docking Visualization of 4,4',4"-[(2R)-butane-1,1,2-triyl]triphenol (control +) against Estrogen Receptor α

appears to be widely acknowledged that the degree of hypochromism in the ultraviolet spectrum corresponds to the intensity of intercalative interaction [27, 28]. The π-π* transition is represented by the wave number with the greatest absorption band in the 285 nm band (Mishra 2). The electron transition from orbital n to π* in the group N = C = S is represented by the absorption at 400 nm and 600 nm [29, 30] (Figure 4).

IR characterization

The two primary bond types found in dithiocarbamate molecules are C=N and C=S, which may be distinguished from one another using the infrared absorption peaks (3 Morizzi dkk, 2001). The dithiocarbamate complex has a single bond group, v (C - N), at wave numbers between 1330.88 cm^{-1} and 1608.63 cm^{-1}. In the meantime, wave numbers 1097.49 cm^{-1} are where the C = S bond group is found [4]. Moreover, the links that develop between sulfur or nitrogen and metals can be observed through far-infrared absorption in the 400–100 cm^{-1} wave number range, indicating the connections between the ligands and the metals [31]. (Figure 5, Table 3)

XRD characterization

The pattern in the diffractogram obtained from X-Ray Diffraction (XRD) depicts the crystallinity of a complex compound showing the growth of a sharp crystal lattice in the diffractogram in the angle area 2θ 17° 44° and 65° which forms orthorhombic crystals. This crystal growth is caused by coordinating bonds of ligands and metals in

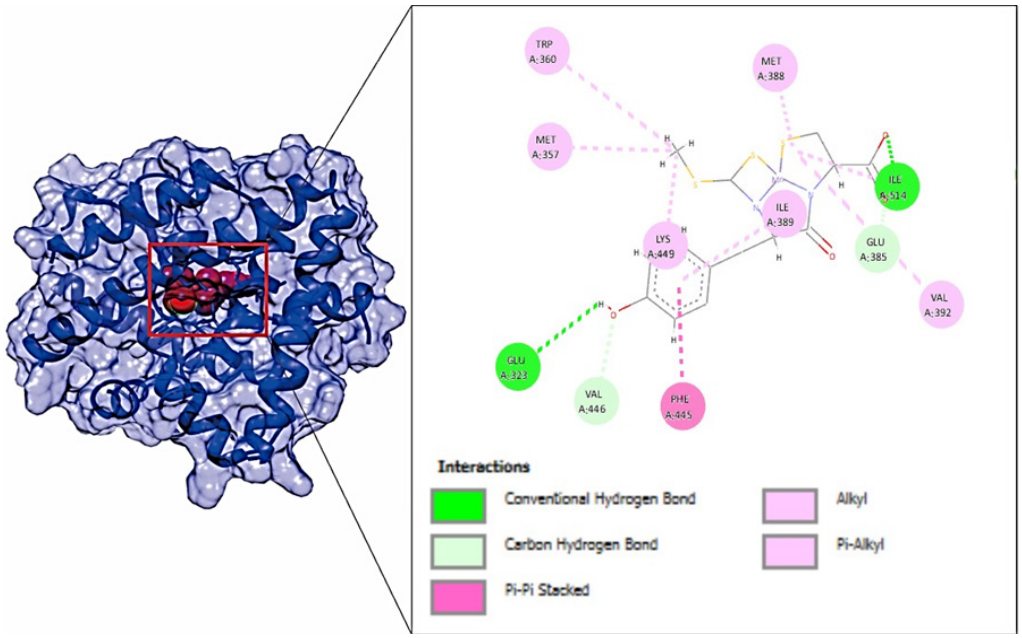


Figure 2. Docking Visualization of Mn(II)cysteine-tyrosine-dithiocarbamate against Estrogen Receptor α

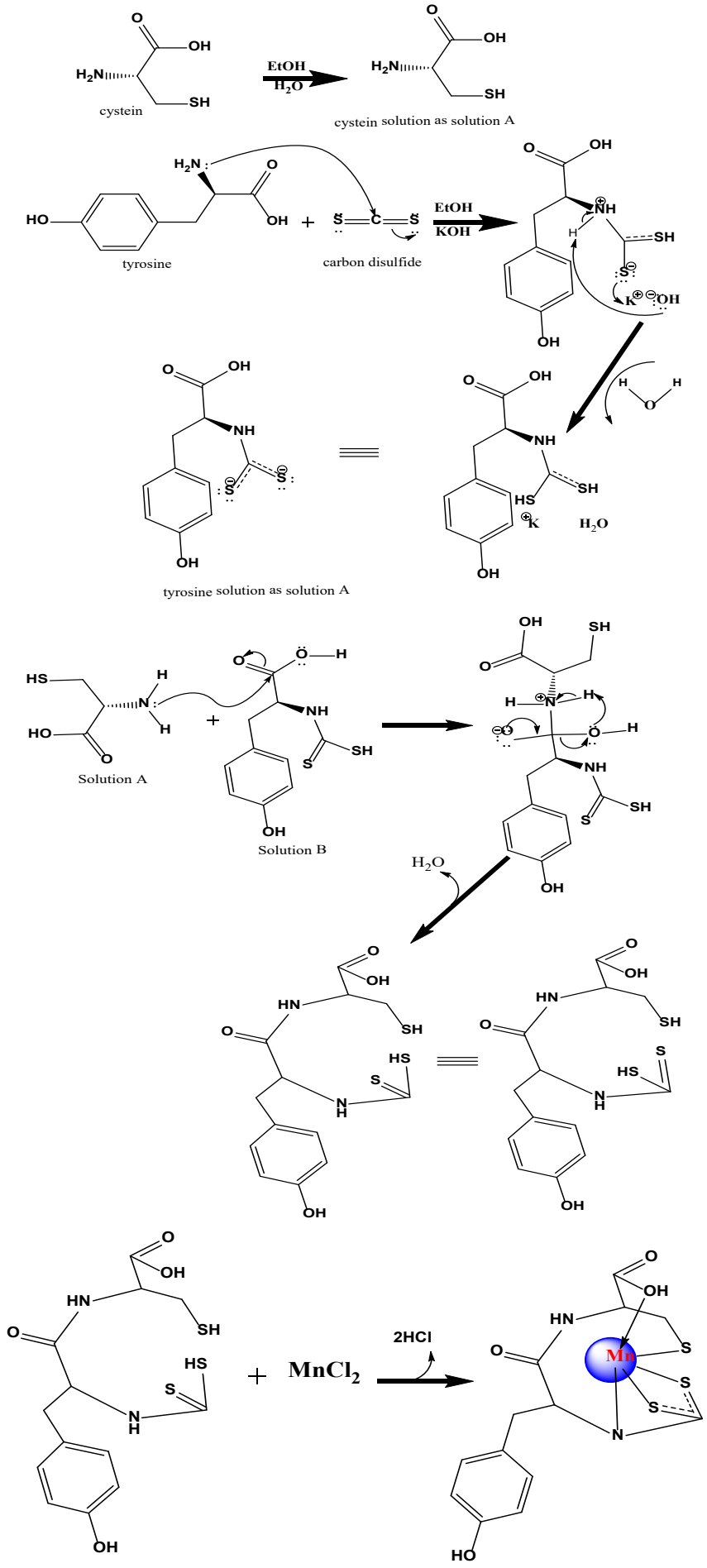


Figure 3. Synthesis Reaction of Mn(II)cysteine-tyrosineditiocarbamate Complex Compound

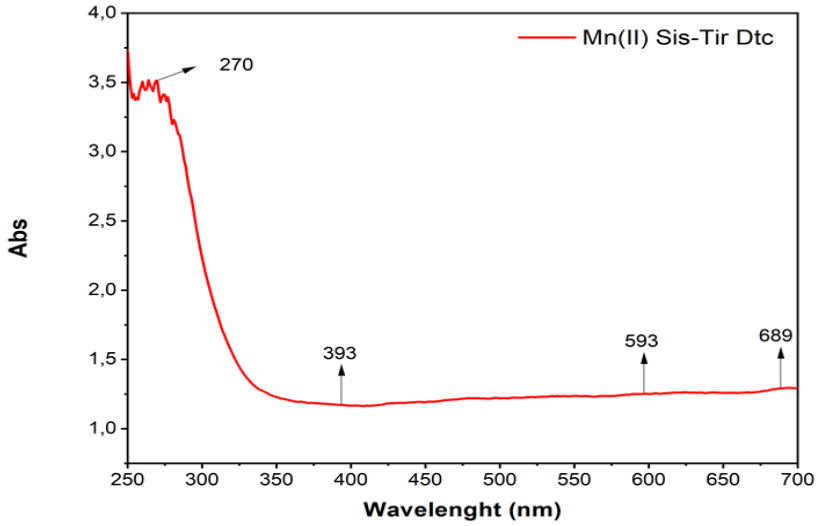


Figure 4. UV-Vis Spectrum of Mn(II)cysteine-tyrosine Ditiocarbamate Complex

Table 2. ADMET Properties of Complex Mn Sis-Tir Dtc

ADMET	Characteristic	Mn Sis-Tir Dtc
	Solubility in water	-3.509
	Caco-2 Cell Permeability	0.171
	Intestinal absorption (human)	76.841
Absorption	Skin Permeability	-3.887
Distribution	VDss (human)	-0.321
	Unbound fractions (human)	0.351
	BBB Permeability	-1.088
	CNS Permeability	-3.545
Metabolism	CYP2D6 Substrate	No
	CYP3A4 Substrate	No
	CYP2C9 inhibitior	No
	CYP2D6 inhibitior	No
	CYP3A4 inhibitior	No
	Total Clearance	-0.055
Excretion	Renal OCT2 Substrate	No
Toxicity	AMES Toxicity	No
	Tolerated dose (human)	-0.377
	hERG I inhibitor	No
	hERG II inhibitors	No
	Oral rat acute toxicity (LD50)	2.961
	Hepatotoxicity	No
	Skin Sensitization	No
	T.Pyriformis toxicity	0.421
	Small fish toxicity	2.56

the formation of complex compounds. The crystallinity of the complex compound is strengthened by the synthesis results which are physically visible in the form of a yellowish white solid (Figure 6).

SEM characterization

With 1000X magnification it shows what looks like a chunk of orthorhombic crystal with a size of 20 µm.

Figure 7, in the presence of Mn(II)cysteine-tyrosine dithiocarbamate complex shows an orthorhombic surface morphology with the appearance of sulfur and oxygen peaks with the highest presentation as well as the appearance of adsorbed Mn metal peaks to increase the stability of the complex compound. The interaction of elements C 26.24%, N 5.35%, O 23.59%, S 31.38% and Mn 13.44% in the Mn(II) cysteine-tyrosine dithiocarbamate complex will form a strong coordination bond which confirms the results obtained in the gravimetric studies [32, 33, 34].

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

Apoptosis is the most common occurring gene-controlled process that plays a critical role in tissue homeostasis and elimination of unwanted cells without affecting normal/ unaffected cells [35] (Figure 8, 9).

It has been possible to synthesise and characterise Mn (II) metal complexes using the cysteine-tyrosine dithiocarbamate ligand. Additionally, it demonstrates the interaction of the Mn (II) atom with the cysteine-tyrosine dithiocarbamate ligand's sulphur (S), nitrogen (N), and oxygen (O). Depending on the Mn (II) complex's concentration, this complex can impede the growth of cancer cells. Mn (II) cysteine-tyrosine dithiocarbamate exhibits good inhibitory effect against MCF-7 cancer cells, as indicated by its IC_{50} value [36].

Discussion

Molecular docking study in this research was used to learn the inhibitory mechanism of our drug candidate.

Table 3. The Wavelength of Mn(II) Cysteine-tyrosine Dithiocarbamate

Compound	v(M-S) cm^{-1}	v(M-O) cm^{-1}	v(M-N) cm^{-1}	v(C=S) cm^{-1}	v(C-N) cm^{-1}	v(NH_2) cm^{-1}	v(O-H) cm^{-1}
Mn(II) Cysteine-tyrosine dithiocarbamate	379.97 s	432.05 w	532.35 m	1097.49 m	1330.88 m	1593.2 s	3205.69 m

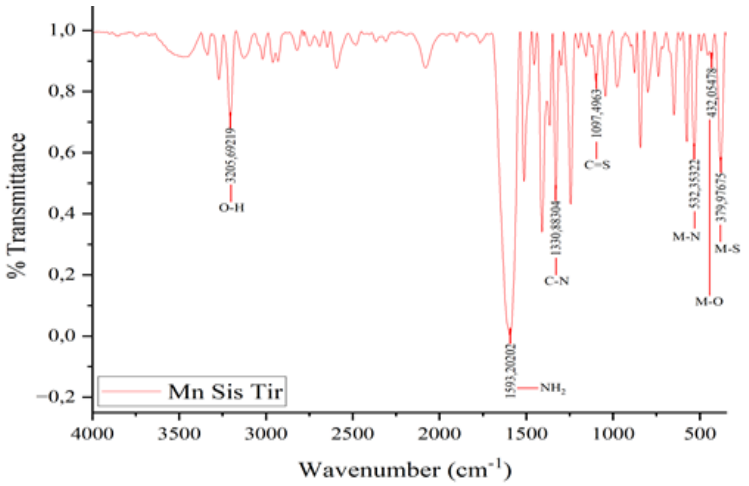


Figure 5. IR Spectrum of Mn(II)cysteine-tyrosine Ditiocarbamate Complex

Mn(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 1). If compared to Mn(II)Cystein-Tyrosine-Dithiocarbamate, the binding appearing, control, sustains in the whole surface of ligand. The most favorable binding in Mn(II)cysteine-tyrosine-dithiocarbamate appears in carbonyl and oxygen group (Figure 2). There are some residues involved in its binding mode such as GLU323, GLU385, VAL446, ILE514, TRP360, LYS449, MET388, MET357, PHE445, VAL392 dan ILE389These hydrogen bond interactions can initiate the binding stability between the candidate and estrogen α

In adsorption parameters, fulfil all the parameters except $CaCO_2$ permeability. This parameter describes the cell line of human epithelial colorectal adenocarcinoma cells and is considered to have a high $CaCO_2$ permeability higher than 0.9. The distribution parameters of ligands are demonstrated by some of parameters. The volume of distribution (VDss) describes the total dose of a drug and considers having a low value (log VDss < -0.15) [23]. Metabolism parameters show that the designed compound cannot act as a substrate or inhibitor of CYP enzymes, so it can be predicted that the action of the drug compound will be more efficient with good selectivity. These two are the main ones responsible for the metabolism process in Cytochrome P450. Renal Organic Cation Transporter 2 (OCT2) is a parameter that describes the disposition and clearance of the drug.The compound has a low total clearance value so that the amount of compound accumulation in the body is high and does not pass through the Renal OCT2 substrate. In toxicity tests, a design has non-mutagenic potential based on AMES toxicity results. and has no side effects and is not toxic to the body

Figure 4 displays the UV-Vis spectrum of the Mn(II) cysteine-tyrosine ditiocarbamate complex compound. It displays four absorption bands, including multiple bands in the visible light spectrum and the ultraviolet band (285 nm and 337 nm). The π-π* transition is represented by the wave number with the greatest absorption band in the 285 nm band (Mishra 2). The electron transition

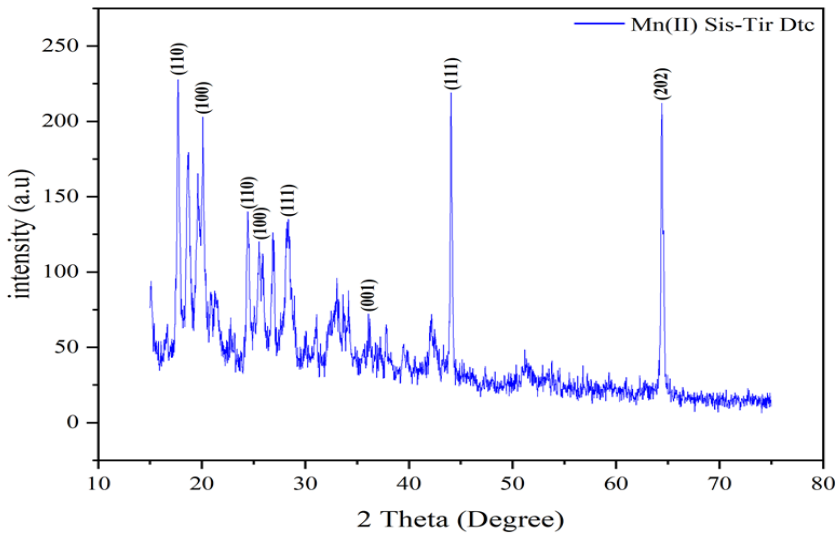
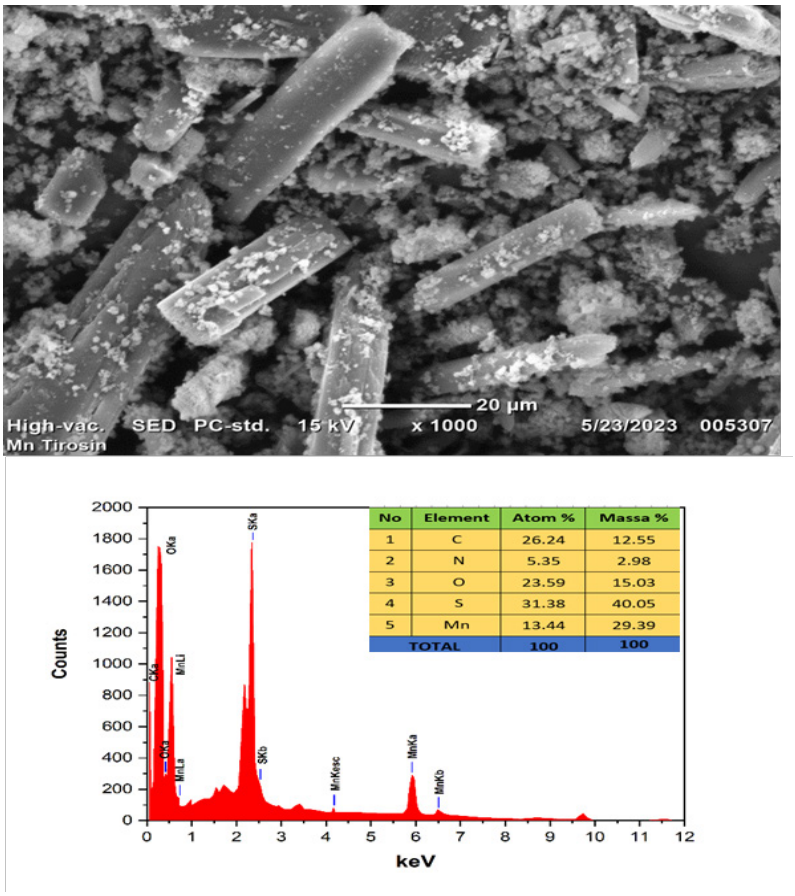


Figure 6. XRD Spectrum of Mn(II)cysteine-tyrosine Ditiocarbamate Complex



No	Element	Atom %	Massa %
1	C	26.24	12.55
2	N	5.35	2.98
3	O	23.59	15.03
4	S	31.38	40.05
5	Mn	13.44	29.39
TOTAL		100	100

Figure 7. Morphology and SEM-EDS of Mn(II)cysteine-tyrosine Ditiocarbamate Complex

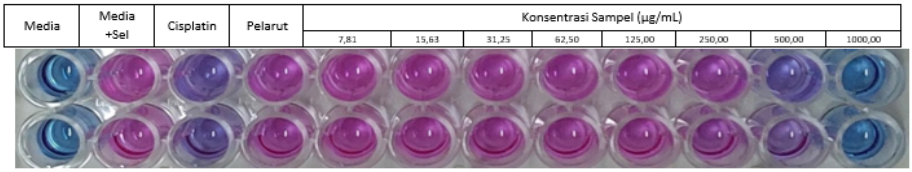


Figure 8. Well Plate Documentation of Mn(II)cysteine-tyrosine Ditiocarbamate Results on MCF-7 Cells

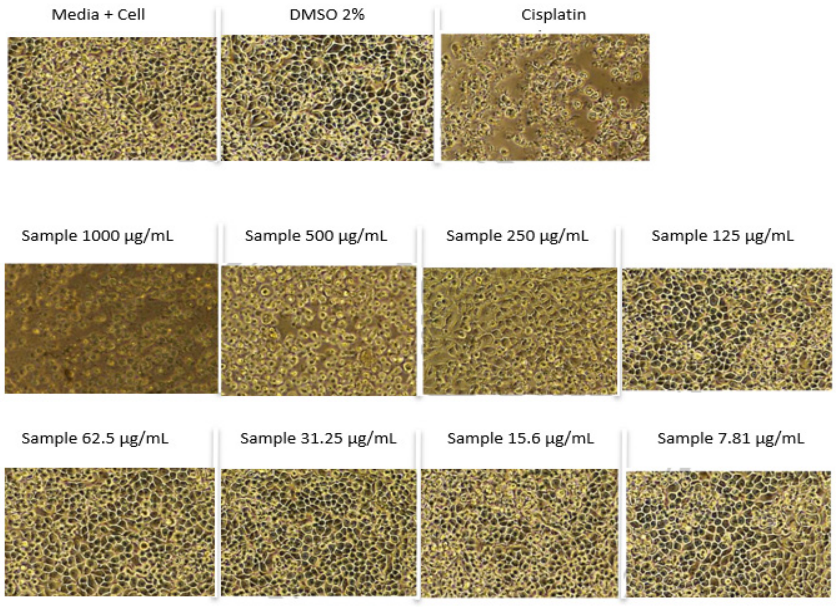


Figure 9. MCF-7 Cell Apoptosis Induced by Mn(II)cysteine-tyrosine Dithiocarbamate

from orbital n to π* in the group N = C = S is represented by the absorption at 400 nm and 600 nm. Additionally, as shown in Table 3, the resultant spectrum clearly identifies the metal coordination bonds with ligands. The interactions between the S group and the Mn bond were then found at wave number 379.97 cm^{-1}, followed by the O atom at 432.05 cm^{-1} and the N atom at 532.35 cm^{-1}. Further more, Figure 5 shows the FT-IR spectrum of the complex compound, with each compound having a specific absorption in the infrared spectrum dependent on the metal and ligands. XRD Mn(II)cysteine-tyrosine ditiocarbamate complex compound showing the growth of a sharp crystal lattice in the diffractogram in the angle area 2θ 17° 44° and 65° which forms orthorhombic crystals. SEM-EDS The interaction of elements C 26.24%, N 5.35%, O 23.59%, S 31.38% and Mn 13.44% in the Mn(II) cysteine-tyrosine dithiocarbamate complex will form a strong coordination bond which confirms the results obtained in the gravimetric studies

Actually, the Mn Mn (II) arginine dithiocarbamate complex can suppress the growth of MCF-7 cancer cells by causing cancer cells to undergo apoptosis in vitro in a concentration-dependent manner [37]. The Mn (II) arginine dithiocarbamate complex may therefore have application as a cancer medication. Finding a single solvent to use for the Mn complex's crystallisation stage is a hurdle faced in this study. Instead, acetonitrile and ethanol are used as a double solvent to tackle the problem.

Based on the HSAB principle, Mn complexes exhibit strong coordination with DNA. Another essential metal that decreases toxicity and changes into a bioactive element in the human body is magnesium. Additionally, the arginindithiocarbamate ligand, which was used as a scaffold in the complex synthesis, increased the cytotoxicity of the Mn(II) complex and allowed the ligand to intercalate into the DNA gap [38, 39]. Furthermore, metal complexes have the ability to intercalate, or enter, into the gaps created by the base pairs of the DNA double helix. However, most of these reactions occur in complexes containing planar aromatic heterocyclic ligands [40].

DNA can form noncovalent or covalent bonds with metal complexes. Regarding exterior binding, or electrostatic contact, the first non-covalent interaction is of the most basic kind. The negatively charged DNA outer skeleton and the metal complex interact in this way. In addition to van der Waals forces, hydrogen bonds, and the hydrophobic effect, groove bonding is another type of interaction [41].

The Mn(II) complex's IC_{50} value, which ranges from 100 to 1000 μg/mL, indicates that it is moderately cytotoxic based on the cytotoxic sample IC_{50} standard [42, 43]. Further investigation is necessary to fully understand the anti-cancer properties of the cysteine-tyrosine dithiocarbamate essential metal complex, as well as its long-term stability and durability.

Author Contribution Statement

Rugaiyah A. Arfah, Eka Pratiwi, Indah Raya, and Hasnah Natsir: Conceptualization, Methodology, Supervision; Muh. Alfliadi, Paulina Taba, and Herlina Rasyid: Conceptualization, Methodology, Investigation, Writing–original draft; in vitro test analysis of breast cancer: Rizal Irfandi, Andi Besse Khaerunnisa: molecular docking: Sulistiani Jarre: Writing – review & editing, Validation.

Acknowledgements

General

Many thank to the Laboratory for Inorganic, Organic Research, Integrated Chemistry Laboratory, Science Research and Development Laboratory, Hasanuddin University Makassar, Indonesia, and also the Central Laboratory of Pajajaran University for supporting this research.

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.

Ethical Declaration

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

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