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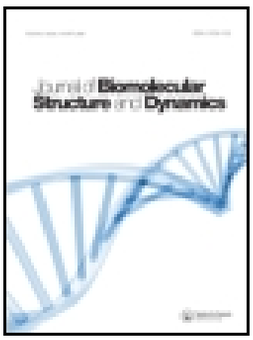

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Anticancer potential of Cu(II)prolinedithiocarbamate complex: design, synthesis, spectroscopy, molecular docking, molecular dynamic, ADMET, and in-vitro studies

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ABSTRACT

Breast cancer continues to be a major health issue for women all over the world. Cancer medications like cisplatin, which are widely used, still have negative side effects. The novel complex was created as a potential anticancer medication candidate that is both effective and safe, with few side effects. The Cu(II) complex using the prolinedithiocarbamate ligands was synthesized in situ. The Cu(II) complexes Characterization by UV-Vis, FT-IR spectroscopy and melting point determination, conductivity, and HOMO-LUMO were studied. Computational NMR spectrum analysis was performed. The interaction of Cu(II)prolineditiocarbamate complex with cancer cell target protein (MCF-7) was confirmed by molecular docking and molecular dynamic. The pharmacokinetic/ADMET properties were also performed on the complex. Results of the cytotoxic complex test against cancer cells (MCF-7) undergoing apoptosis with an IC50 value of 13.64 μg/mL showed high anticancer activity in MCF-7 cancer cells. The in-vivo data for Cu(II)prolineditiocarbamate complex was predicted using the Protox online tool with an LD50 value of 2500 mg/kg and belonging to the GHS toxicity class 5, which means the compound has a low acute toxicity effect. The Cu(II) prolineitiocarbamate complex may pave the way for the development of essential metal-based chemotherapy for the treatment of breast cancer.

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Cu(II); dithiocarbamate; in-vitro experimental; in-vivo predicted; ADMET

Introduction

Breast cancer treatment is multidisciplinary, involving surgery or surgery, chemotherapy, and radiation (Cardoso et al., 2009). Chemotherapy is currently a critical component of the breast cancer treatment paradigm (Gong et al., 2010). Platinum-derived compounds, such as cisplatin, are commonly used in chemotherapy. Cisplatin's success as an anticancer drug dates back to 1965, and its use was legalized by the American Food and Drug Administration (FDA) in 1978 proved effective for therapy against various types of cancer cells (Dorcier et al., 2006). Researchers are becoming increasingly interested in the production of metal complexes for various applications, particularly in the medical field. After the surprising discovery of the coordination molecule cisplatin, metal-based drugs have become a promising field of study in drug chemistry (Hadjiliadis & Sletten, 2009). The cisplatin complex is rectangular in shape, and has 2 labile chloride ligands and 2 inert ammonia ligands bonded to the central platinum(II) atom in a cis 5 configuration. Cisplatin was the first anticancer drug used in clinics and is still one of the most commonly used cancer drugs today (Dorcier et al., 2006). Platinum-based drugs are currently used to treat roughly half of all cancer patients. However, the drug cisplatin has some problems. Lack of selectivity, undesirable side effects, resistance and toxicity in the body are all factors driving the search for more effective and selective platinum-free therapies (Moussa & Wheate, 2018; Yang et al., 2014). Therefore, there is a need to combat or minimize the levels of free radicals found in the body, as well as anticancer therapy options with minimal or no side effects (Adeyemi et al., 2021).

The design of new therapeutic agents is critical for cancer drug development (Hong et al., 2014). One of the newest drug discovery methodologies for creating therapeutic compounds is the synthesis of metal complexes. Metal complexes

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have demonstrated antibacterial, antioxidant, anticancer, and antimalarial effects, among other biological features (Irfandi, Santi, et al., 2022; Prihantono et al., 2021). The ligand moiety's synergistic interplay with the central metal is often associated with this biological activity (Adeyemi & Onwudiwe, 2018). Metal-based anticancer drugs have made remarkable progress in avoiding the side effects of classical platinum therapy. Metal ions help adjust reactivity, and Many biochemical reactions require conformational changes and are catalytically active (Ferraro et al., 2022).

Several other complex compounds have been reported in terms of their potential as anticancer. Sheldrick et al. reported monoiridium and di-iridium polypyridyl have potential as anticancer with ligand modification around the iridium center (Hong et al., 2014). Several palladium complexes were significantly higher than cisplatin in the treatment of human breast and cervical cancer cells (Kumar et al., 2017). In addition, the central metal of complex compounds which has also been reported for its potential as anticancer is ruthenium which has been proven to be very good in the laboratory, but on a practical scale it still needs to be studied further considering that this metal is less common in living things and is toxic (Mudasir et al., 2010). So it is necessary to use other metals that are less toxic or without side effects, such as Cu metal. Researchers are interested in the use of essential metals conduct research related to the use of complex compounds as anticancer. This is based on several previous studies.

Copper is very important in enzymatic reactions especially as an electron donor (Zoroddu et al., 2019). Studies on the activity of heavy metal chelating factors for their anti-influenza effects RNA-dependent RNA-polymerase (RdRp), revealed surprising and promising results. Like chelating Cu(II) and Zn(II), it can inhibit proper RdRp folding (Prosser et al., 2018). Appropriate use of ligands can increase complex compounds' biological activity (Ritacco et al., 2015). Ligands that are active in biological processes have sparked a lot of interest in the development of potential antitumor agents (Kamaludin et al., 2013). Amino acids contribute significantly to the biological activity of platinum and palladium-based antitumor agents (Rau et al., 1998). The addition of new donor groups to the ligand framework could facilitate increased bioavailability of potential Pd(II) chemotherapy, due to its strong binding to biomolecules (Radisavljevic et al., 2018).

Dithiocarbamate is a chemical that chelates metals and has a number of uses in medicine ((Irfandi, Raya et al., 2022; Irfandi, Riswandi et al., 2022). Infections caused by bacteria and fungi, perhaps AIDS, and most recently cancer have all been treated with it. Due to their extreme toxicity, current chemotherapeutic medicines have a relatively limited ability to eradicate tumors. In order to minimize toxicity while maximizing the possibility of being a desirable therapeutic agent, numerous scientists have joined the quest for new targeted medicines (Boschi et al., 2017, 2019; Daniela, 2012; Malaguarnera et al., 2003; Schreck et al., 1992). In order to target malignancies with radiotherapy and chemotherapy, dithiocarbamate molecules can be utilized (Feng et al., 2011; Ferlay et al., 2015; Khan et al., 2016). One of the beneficial metal chelating antioxidants are dithiocarbamate molecules and their derivatives (Nabipour et al., 2010). It has been demonstrated that the dithiocarbamate complex can inhibit cell growth (Hassan & Zayed, 2014; Prihantono et al., 2020). The dithiocarbamate complex is renowned for its exceptional structure and has several biological applications (Peter et al., 2021). Several findings on the antifungal, antibacterial, anticancer, and apoptosis-inducing properties of dithiocarbamate metal complexes with mixed ligands were validated by a recent literature review. Now that dithiocarbamate has been developed for some of the metals, they can be used as radiopharmaceuticals and as parts of diagnostic kits for medical purposes (Askari et al., 2019; Kalia et al., 2009). The biological action of dithiocarbamates metal has been demonstrated to be promising (Yi et al., 2019). Dithiocarbamate compounds have a unique structure due to the presence of a S group that can supply monomeric electrons and bind to them (Rogachev et al., 1999). Because dithiocarbamate compounds have a distinctive structure composed of sulfur groups (S-), which are soft bases with lone pairs of electrons that can bond monodentate and bidentate, the majority of the time, dithiocarbamate complexes are synthesized using metal ions from transition groups, which are soft acids. Increased structural variety of dithiocarbamate complexes and changes in the biological activity of the complex molecules can result from the usage of dithiocarbamate ligands with additional donor groups derived from oxygen and nitrogen groups (amines) (Ferreira et al., 2015).

We evaluated anticancer (molecular docking and in vitro studies of the Cu(II) complex with the proline dithiocarbamte ligand on the breast cancer cell line (MCF-7) as a part of our study interest in necessary metal-based medications. A synthetic strategy involving the amino acid proline and carbon disulfide as a scaffold for our complex.Thus this complex will exhibit the desired therapeutic properties for more potent and safer drugs delivery, namely better cellular uptake, increased water solubility, selectivity and specificity towards targets at the molecular and molecular levels reduce toxicity.

Experimental

Synthesis of Cu(II) complex compounds with prolinedithiocarbamate ligand

3 mmol of CuCl2 was added in a 100 mL Erlenmeyer glass, dissolved with 10 mL of ethanol (solution 1). 5 mmol of Proline was added in 100 mL Erlenmeyer, then dissolved with 10 mL of ethanol. Furthermore, 5 mmol of CS2 solution was added slowly at a cold temperature, then stirred for 60 minutes (solution 2). In solution (2), solution (1) was added slowly while stirring with a magnetic stirrer for thirty minutes. Furthermore, the precipitate is filtered and dried in a desiccator before being crystallized with a suitable solvent to obtain pure crystals, which are then analyzed and characterized. The schematic for the synthesis of the Cu(II)Prolinedithiocarbamate complex is shown in Figure 1. The prolinediocarbamate ligand was previously created by adding KOH catalyst to make it neutrally charged. The H^+ attached to the iminium ion would then be drawn to the OH base, converting it to a water molecule, while K^+ would

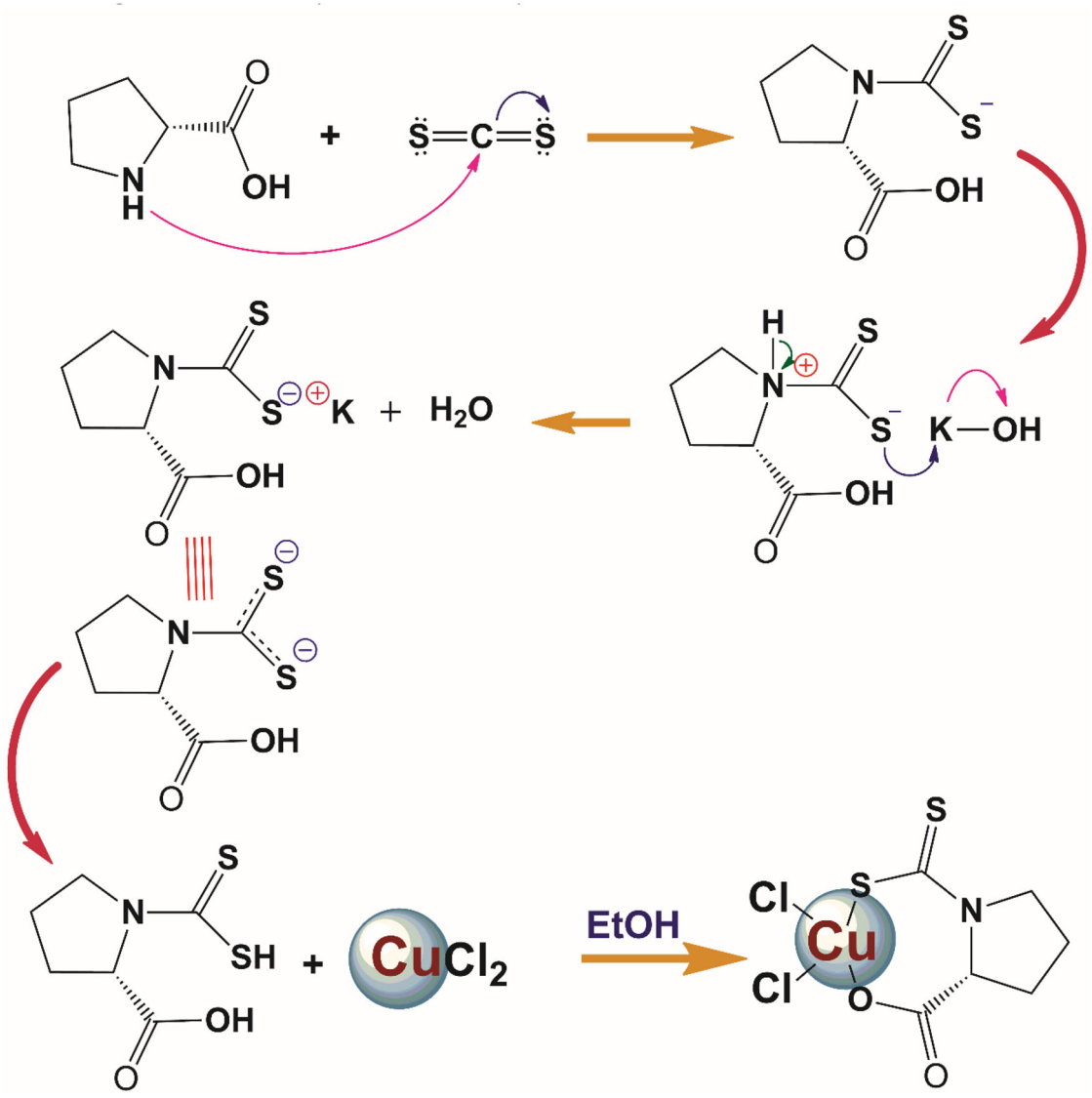

Figure 1. Schematic of Synthesis of Cu(II)Prolinedithiocarbamate Complex.

interact with the sulfide. Then used a $CuCl_2$ precursor to react with the Cu metal. The ultimate complex molecule Cu(II)Prolineditiocarbamate is produced when the disulfide group experiences electron resonance, which easily separates the apparent interaction between K^+ ions and sulfide ions. A conductometer was utilized to assess the conductivity, and an Electrothermal IA-9100 was used to calculate the melting point of the synthesized material Cu complex. The Shimadzu model FTIR instrument was used to obtain infrared spectroscopic data of the Cu complex. The wave numbers used were 340 to 4000 cm^{-1}. UV-Vis absorption is used in complex compounds, in complex compounds, to identify the bond between the ligand and the metal as the central atom. Jenwey UV-Vis measurements in the 200–1100 nm wavelength range. An investigation of the computational NMR spectra was also carried out.

Molecular docking simulation

The canonical smile compound CuProDT (O = C1O[Cu]SC(=S)N2CCCC12) was modeled with the molview webserver (https://molview.org/). The synthetic compound CuProDT was interacted with the protein NUDT (nucleotide-metabolizing enzymes), and the cisplatin (PubChem CID 5460033) was used as a control. The NUDT5 protein structure has been downloaded to the protein data bank (PDB) database with the PDB access number ID 5NWH. The NUDT5 protein's 3 D structure was created by importing Molegro Virtual Docker 5 (MVD version 5.0) and predicted the active site with molecular surface van der Waals parameters maximum 5 (Bitencourt-Ferreira & de Azevedo, 2019). The synthetic compound CuProDT interacted with the NUDT5 protein on the protein grid X= −5.22; Y = −11.19; Z = −29.73; Radius 11. Bond energy is obtained by adding Moldock score, Moldock Grid score, and rerank score. Docking results were analyzed with Pymol 2.2 and Discovery Studio 21.1.1 were both available.

Molecular dynamic simulation

Molecular dynamics simulation was carried out using the YASARA Dynamics program. Molecular dynamics is a method

to study macromolecules' dynamic behavior at the molecular and atomic levels (Ebrahimi et al., 2021). Molecular dynamics simulation is used to determine the dynamic stability and effectiveness of single and complex proteins interactions with ligands in each unit of time (Krieger & Vriend, 2015). Before the simulation process began, preparation was carried out by setting the temperature to 310 K or 37 °C, which was the physiological temperature. Then the level of NaCl or physiological salt used was 0.9%, representing the physiological condition to maintain the viability of the sample. While, the pH treatment was set pH 7.4 indicating the body's physiological pH. The running process was executed with the macro md_run.mcr. Running time used was 1000 ps (1 ns) with snapshot storage every 10 ps. The simulation was carried out using the AMBER14 forcefield type because it is one of the available forcefields in the YASARA Dynamics program and is commonly used for simulating biological materials (Zhang et al., 2003). After the running process, the results were analyzed by running the macro md_analyze.mcr and obtaining the output of potential energy, RMSD, and RMSF.

ADMET (absorbtion, distribution, metabolism, excretion, toxicology) screening of Cu(II)prolinedithiocarbamate

Physicochemical properties, pharmacokinetic profiles and toxicity profile of Cu(II)Prolinedithiocarbamate was determined by subjecting it to adsorption, distribution, metabolism, excretion and toxicity test using swissADME (http://www.swissadme.ch) and Pro-Tox II online servers (https://tox-new.charite.de/protox_II) (Daina et al., 2017; Pires et al., 2015).

Prediction of Cu(II)prolinedithiocarbamate complex toxicity

To predict the toxicity (LD50) orally in rodents of the Cu(II)Prolinedithiocarbamate complex the Protox online tool (http://tox.charite.de/tox/) was used for compound toxicity classification based on the Globally Harmonized System (GHS) (Ruswanto et al., 2017).

Cytotoxic test of Cu(II)prolinedithiocarbamate complex against breast cancer cell line (MCF-7)

In vitro anticancer activity testing of complex compounds with breast cancer cells (MCF-7) was performed. Cell cultures were planted in 96 well plates and incubated (at 37 °C and 5% CO2 gas until cell growth reached 70%). Cells were collected and incubated for 24 hours at 37 °C with 5% CO2. Fill the cell with presto blue working reagent. Multimode Reader for measuring absorbance.

Result

Analysis of physicochemical properties of Cu(II)prolineditiocarbamate complexes

The Cu(II)Prolineditiocarbamate complex was synthesized successfully, and the yield was high 19.33%. The resulting yield

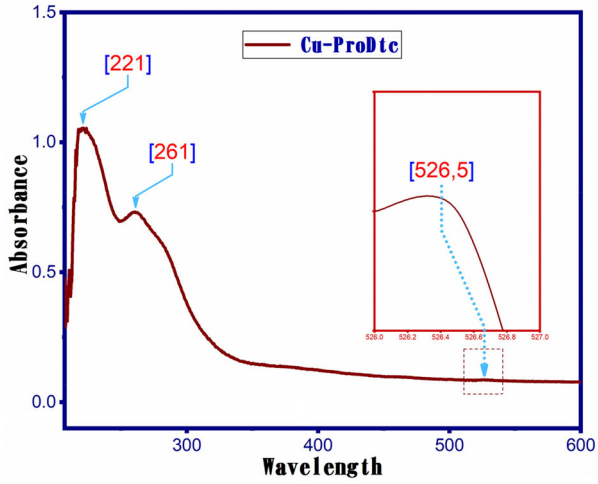

Figure 2. Cu(II)ProlineDithiocarbamate complex UV-Vis spectrum.

reflects the strength of the coordination bond formed between the metal and the ligand in the formation of a complex, and it can also indicate the stability of a complex compound. The melting point of the complex is 248–250 °C. Value of the melting point is determined by the type of metal ion and its ligand. The larger the metal ion's size and charge, the weaker the bonds with the ligands and the lower the melting point. A high melting point, however, indicates a tight connection between the central ion and its ligand. Above 200 °C, it was discovered that the Cu(II) complex was extremely pure and stable. Because of its conductivity of 0.02 mS/c, the compound cannot be an electrolyte. The proline's electron-rich structure assaults the carbon disulfide's carbocation throughout their reaction. The proline nitrogen atom forms a connection with carbon disulfide using a single pair of electrons. An unstable iminium ion is created after binding. By including a base, the iminium ion is stabilized. The base utilized is KOH. While the K + interacts with the sulfide, the H^+ coupled to the iminium ion is drawn to the OH base and remains as a water molecule. When an electronic resonance develops in the disulfide group, the apparent contact between K^+ and sulfide ions is easily disturbed. As $CuCl_2$ is added to the ethanol, a complex molecule called Cu(II)Proline dithiocarbamate will be created as the reaction's end result.

UV-VIS spectrometer characterization

Figure 2 absorption band at 221 nm, which is the domestic transition $\pi \rightarrow \pi^*$ of the CS2 group impacted by the hyper-effect. conjugate of the R group on the nitrogen atom, can be seen in the UV-Vis characterization data for complex compounds in aqueous solvents. related. 45. is in the absorbance range of 250–300 nm. Band shift II, or intrinsic $n \rightarrow \pi^*$ transition of the N = C= S group at 261–392 nm, is a property of complex molecules.

Analysis using FT-IR

The infrared absorption maxima around 364 cm^{-1} indicates the interaction of the cation group (CS) with the Cu metal

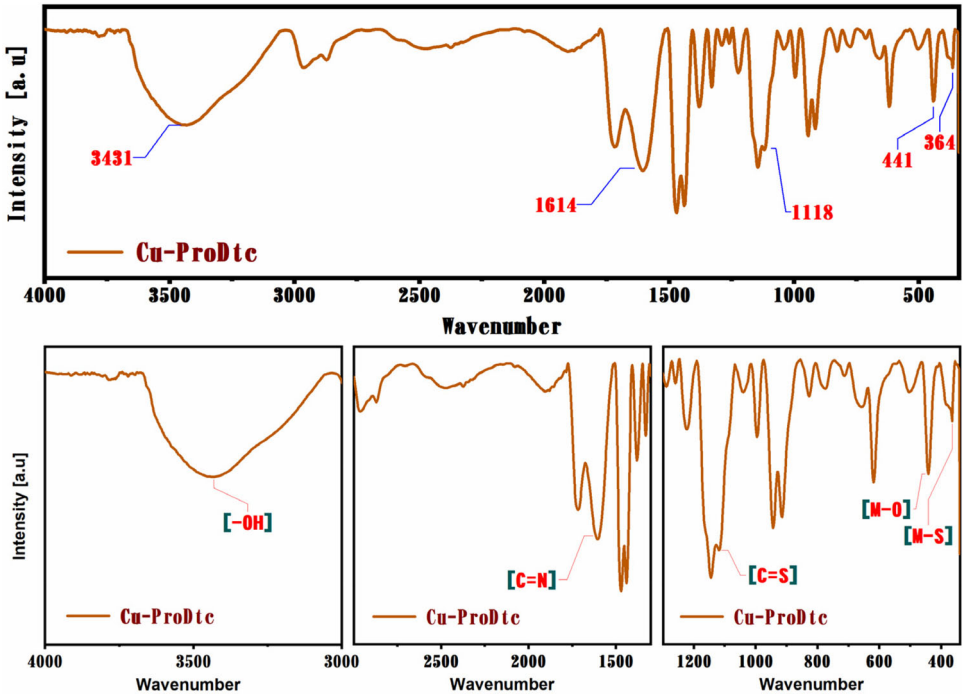

Figure 3. Cu(II)ProlineDithiocarbamate complex IR spectrum.

ions. An absorption peak with a mass number of 441 cm^{-1} represents the interaction of the complex's O atom with Cu metal ions. The emergence of absorption at a wave number of 1118 cm^{-1} indicates the presence of a C = S functional group from the dithiocarbamate ligand. Then, at wave number 1614 cm^{-1}, there is a significant absorption, indicating that it is from the C = N group (Raya et al., 2006). The emergence of a single broad absorption peak in the mid-wavelength region 3431 cm-1 indicates the presence of a hydroxy functional group (-OH) from water- or ethanol-based solvents (Santi et al., 2020). The infrared absorption of Cu metal complex compounds with proline dithiocarbamate ligands typically reveals the characteristics of the produced complex compounds. The challenging chemical Cu(II)Proline Dithiocarbamate has therefore been successfully synthesized. The IR spectra of the two produced complex compounds are shown in Figure 3 as findings.

Using the H-NMR and C-NMR spectrum computations illustrated in Figure 4, the hydrogen and carbon skeletons of the Cu(II)Prolinedithiocarbamate complex were determined. It can be inferred that the ligand and the metal have formed the -O-Cu bond because there isn't a broad singlet proton signal from the OH carboxylic acid group in the region above 10 ppm. The region of 1.95, 1.70; 1.64, 1.54 ppm is where the methylene proton signal from the dithiocarbamate moiety's N-proline group resonates. The 2.8, 2.7 ppm area contained the hydrogen signal from the –CH–N group (Shaheen et al., 2018). At a change of 202.8 ppm, the carbon from the C = S group resonates (Sharma et al., 2009). The nitrogen-attached carbon atom of the cyclopentane ring similarly resonates at a downward shift of 70.8 ppm. The deshielding of the nitrogen atoms is what causes the downward shift. Both the cyclopentane carbon and the carbon atom linked to the carboxylic group have resonances at 52.2 ppm and 178.2 ppm, respectively. The signal at 23.8, 27.9 ppm is attributed to an additional carbon atom from the cyclopentane ring (Kumar & Nath, 2018). Based on the results of the characterization of the structure of complex compounds so that the geometry of the complex compound is predicted, namely square planar.

Band gap energy of Cu(II)prolineditihiocarbamate complex

Because the HOMO symbolizes electron donor capacity while the LUMO stands for electron acceptor capacity, the limited molecular orbital (FMO) made composed of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) plays a significant role in chemical reactions (Khemalapure et al., 2019). It is possible to identify molecular electronic transitions, molecular charge distribution, and intramolecular charge transfer using HOMO and LUMO. The energy levels of HOMO and LUMO can also be utilized to determine a molecule's electrical characteristics (Santi et al., 2020). EHOMO = −8.109 eV, ELUMO = −7.593 eV, and energy gap Eg = 0.516 eV were determined for the Cu(II)Prolinedithiocarbamate complex (Figure 5). The HSAB (hard acids and bases) theory states that while hard bases have atoms or compounds with a high HOMO energy, strong acids have atoms or compounds with a high LUMO energy. Proline's amine group and dithiocarbamate's thiol group serve as the boundary bases, contributing to the low HOMO energy value, while metallic copper is present in the boundary acid group, contributing to the low LUMO energy value.

Table 1 shows the mass percentages of elements such as N, S, O, and Cu in this complex. Quantitative estimation of these elements showed that the concentrations of S, O and Cu were significantly higher (except N in the 1.99% dialysis complex)

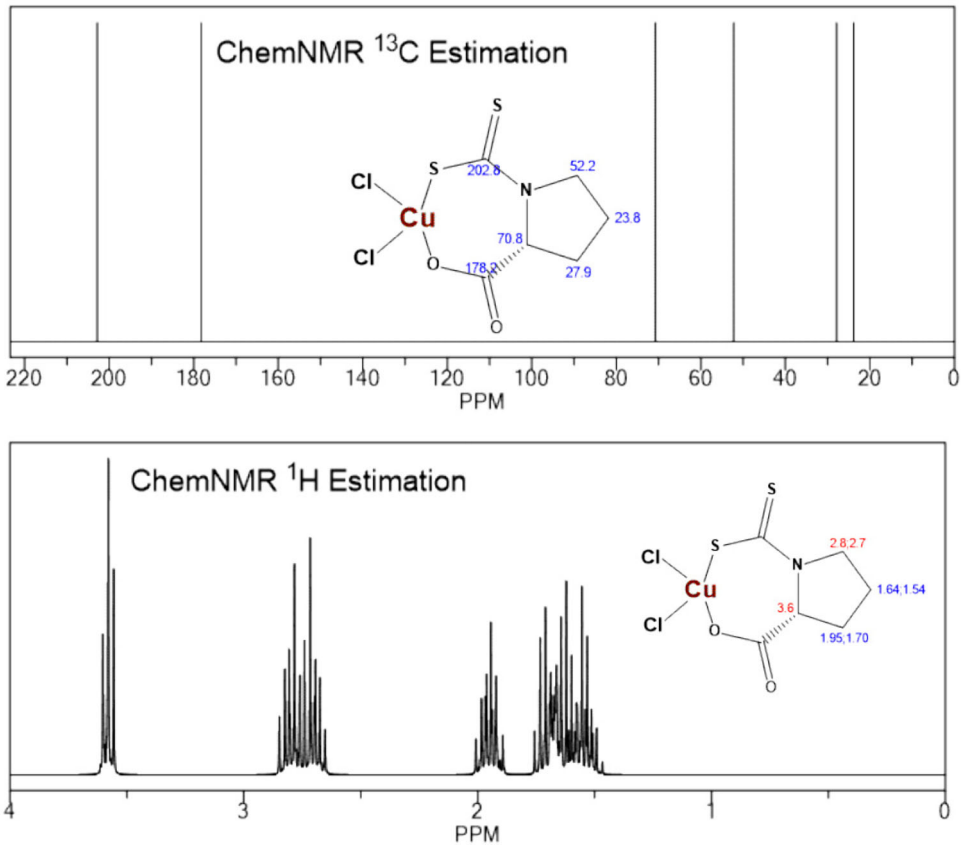

Figure 4. Computational C NMR and H NMR spectra of the Cu(II)Prolinedtihiocarbamate complex.

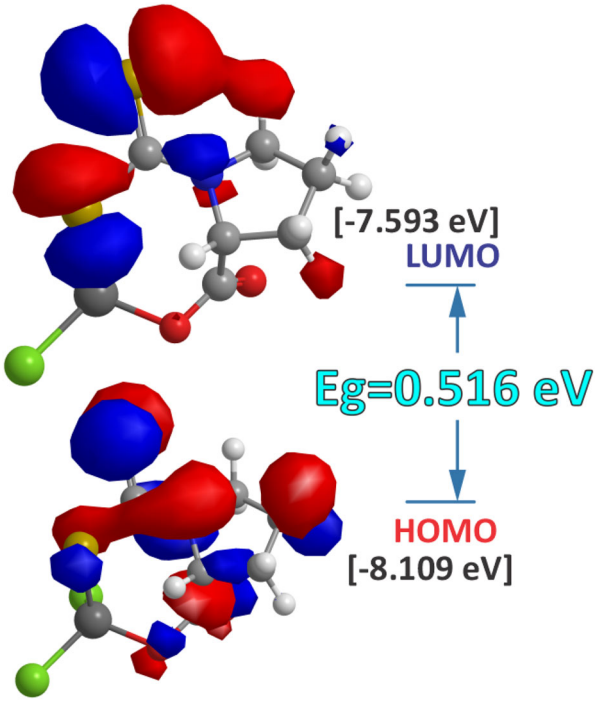

Figure 5. HOMO-LUMO of Cu(II)Prolinedithiocarbamate.

Table 1. Elemental composition of Cu(II)Prolinedithiobamate complex after SEM-EDX characterization.

Element	Weight%	Atomic%
N	1.99	3.79
O	34.27	57.06
S	30.20	25.09
Cu	33.54	14.06
Totals	100.00	

than the other elements found in this complex. The detected S group comes from dithiocarbamate ligand complexed with Cu metal. These O and N groups represent the organic nature of the proline amino acid as an additional donor group, oxygen and nitrogen groups, which can contribute to the structural diversity of the dithiocarbamate complex. In addition, element Cu metal also has a fairly high mass percentage in this complex. The data in Figure 6 can be useful for assessing the mechanism responsible for the immobilization of Cu metal complexes. As can be seen, after the synthesis, element S was detected (marked by yellow spots), which caused by the addition of carbon disulfide. Elements N and O (marked by light blue spots for N and red for O) are thought to originate from the amino acid proline used as raw material in the synthesis of this complex, and mapping analysis of Cu metal was detected with green spots. Figure 7 depicts the surface morphology of the metal complexes as examined using a scanning electron microscope. SEM micrographs show a cauliflower shape, which matches the results of Kumar and Nath (2018) (Kumar & Nath, 2019).

Molecular docking of Cu(II)prolinedithiocarbamate against NUDT5 protein

CuProDTC binds to NUDT5 at the same active site as the cisplatin as a control (Figure 8). ARG51, GLU47, TRP46, and TRP28 were identical active sites of cisplatin and CuProDTC

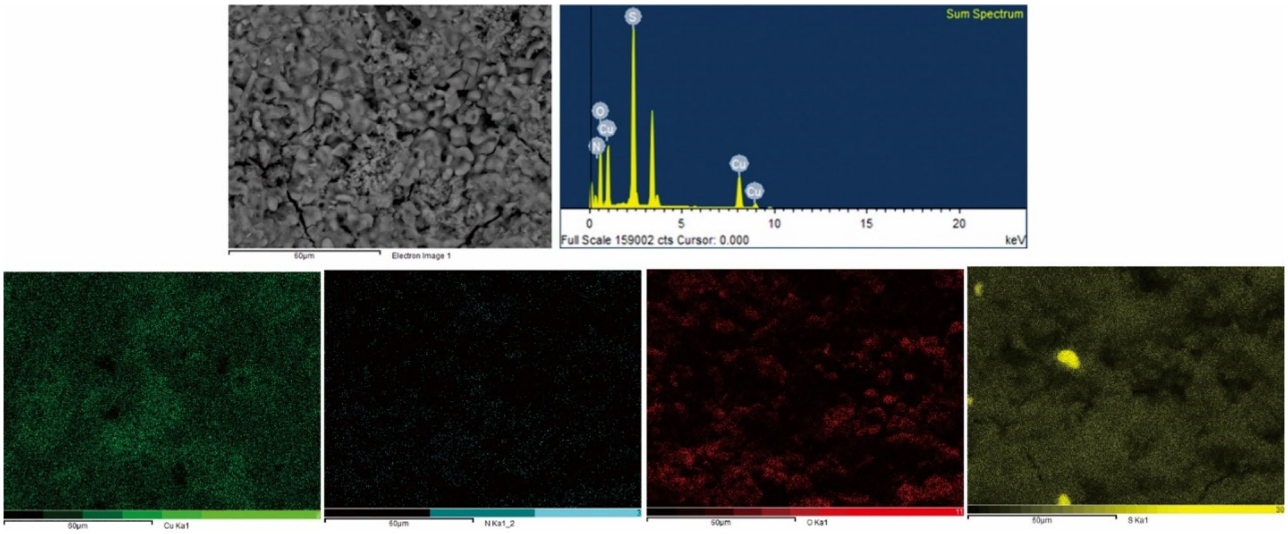

Figure 6. SEM-EDX maps analysis spectra of Cu(II)Prolinedithiocarbamate.

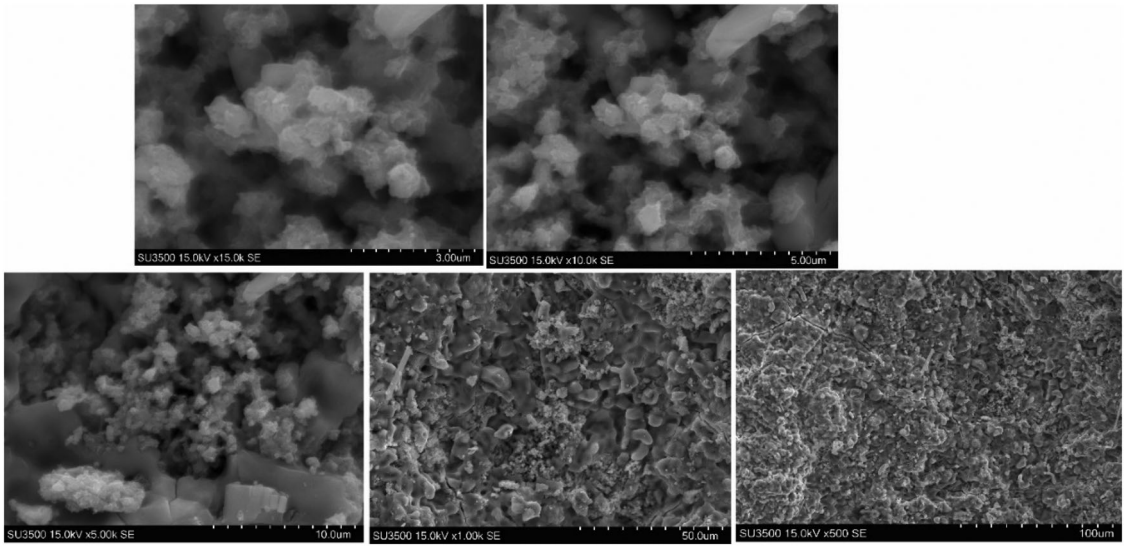

Figure 7. SEM surface layer of Cu(II)Prolinedithiocarbamate complex.

with NUDT complex. The ARG51 posed to Cl of cisplatin with distance 4.28 A by electrostatic (attractive charge) while bound to CuProDTC at oxygen atom by a hydrogen bond. The residue GLU47 formed interaction with cisplatin at Pt1 with distance 3.56 and 3.76 A by hydrogen bonds. The GLU47 residue also posed two hydrogen bonds at S2 and O atoms in the CuPRODTC—NUDT complex with a distance of 3.23 and 2.36 Å, respectively. The TRP46, and TRP28 showed interaction with cisplatin by electrostatic and hydrogen bonds, and formed a complex with CuProDTC by hydrophobic interactions. The interaction types of the complex affected the lower binding energy of CuProDTC—NUDT complex. The binding energy of CuProDTC was lower than cisplatin, −280.8 kJ/mol (Table 2). Lower binding energy indicating the tight interaction of ligand–protein complex.

Potential energy of CuProDTC complex and cisplatin

Potential energy is the sum of all bond energies, bond angle energies, dihedral angle energies, planarity or inappropriate dihedral energies, van der Waals energies, and electrostatic energies [Bond], among others. By evaluating energy, angle, and planarity, potential energy is used to evaluate the structural quality of proteins (YASARA Molecular Dynamics Trajectory Analysis for 4mbs [Internet]).

Based on the Figure 9, the analysis results of a single protein and 5NWH protein complex with test compounds Cu ProDTC and Cisplatin generally show that the average potential energy has a very significant increase from 0.01 ns to 0.04 ns to 0.66 ns. Fluctuations are seen when approaching 0.40 ns of running time which indicates a change in the molecular bond energy. Fluctuations up mean there is a strengthening of the bonds in the molecule, while the decrease in potential energy is interpreted as a result of relaxation in the molecular bonds. At 5NWH the potential energy of the protein complex with the test compound cisplatin showed a stable result at around −935000000. In the picture, there is a potential energy difference between the protein complex and the test compound-complex. The protein with the test substance Cu showed stable potential

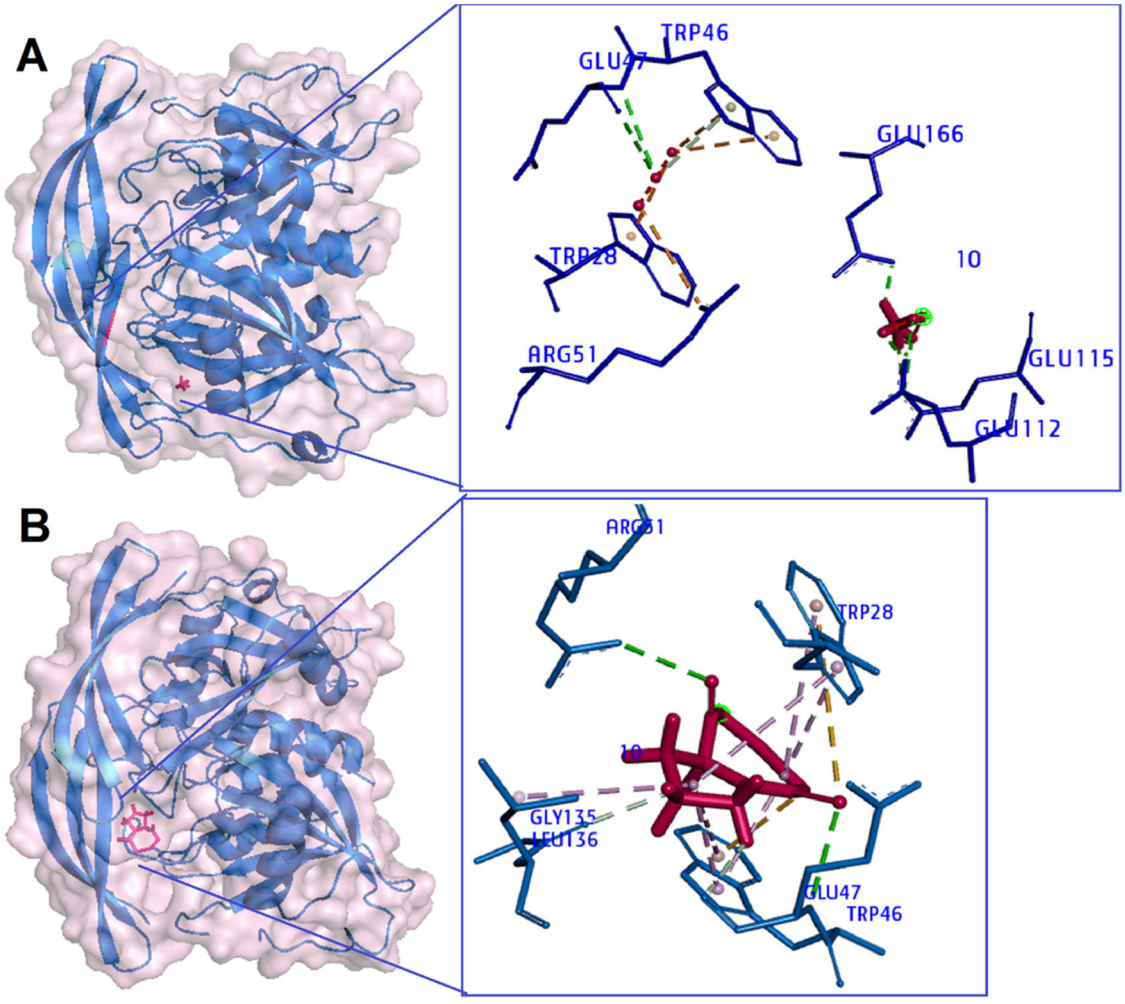

Figure 8. Interaction of CuProDT with NUDT5 protein, A. The 3 D complex of cisplatin – NUDT, B. the 3 D complex structure of CuProDTC – NUDT5. Blue ribbon presented NUDT protein structure, while the pink stick illustrated as ligands.

Table 2. CuProDTC interaction with NUDT5 protein.

Ligands	Binding energy (kJ/mol)	Interaction	Distance (A)	Category	Types
Cisplatin	−83,4	B:ARG51:NH1 – :10:Cl1	4.28	Electrostatic	Attractive Charge
		A:GLU47:N – :10:Pt1	3.56	Hydrogen Bond	Conventional Hydrogen Bond
		:10:Pt1 – A:GLU47:O	3.76	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H1 – B:GLU112:OE1	2.21	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H2 – B:GLU166:OE1	2.02	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H3 – B:GLU115:OE2	2.36	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H1 – B:GLU115:OE2	2.12	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H2 – B:GLU112:OE1	1.97	Hydrogen Bond	Conventional Hydrogen Bond
		:10:Cl2 – A:TRP46	3.78	Electrostatic	Pi-Anion
		:10:Cl2 – A:TRP46	4.05	Electrostatic	Pi-Anion
		:10:Cl2 – B:TRP28	3.72	Electrostatic	Pi-Anion
		:10:Pt1 – A:TRP46	3.76	Hydrogen Bond	Pi-Donor Hydrogen Bond
CuProDTC	−280,8	A:ARG51:NH1 –:10:O1	2.97	Hydrogen Bond	Conventional Hydrogen Bond
		B:GLU47:N –:10:S2	3.23	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H1 – B:GLU47:O	2.36	Hydrogen Bond	Carbon Hydrogen Bond
		:10:H7 – B:GLY135:O	3.04	Hydrogen Bond	Carbon Hydrogen Bond
		:10:S1 – B:TRP46	3.41	Other	Pi-Sulfur
		:10:S2 – A:TRP28	5.76	Other	Pi-Sulfur
		:10 – B:LEU136	4.89	Hydrophobic	Alkyl
		A:TRP28 –:10	4.08	Hydrophobic	Pi-Alkyl
		A:TRP28 –:10	5.14	Hydrophobic	Pi-Alkyl
		A:TRP28 –:10	5.13	Hydrophobic	Pi-Alkyl
		B:TRP46 –:10	3.79	Hydrophobic	Pi-Alkyl
		B:TRP46 –:10	4.18	Hydrophobic	Pi-Alkyl
		B:TRP46 –:10	5.29	Hydrophobic	Pi-Alkyl

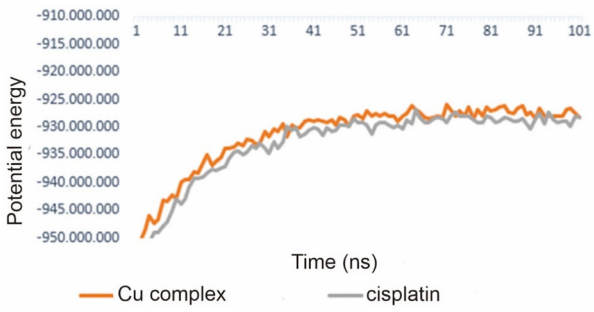

Figure 9. Comparison of potential energy values between CuProDTC complex and cisplatin.

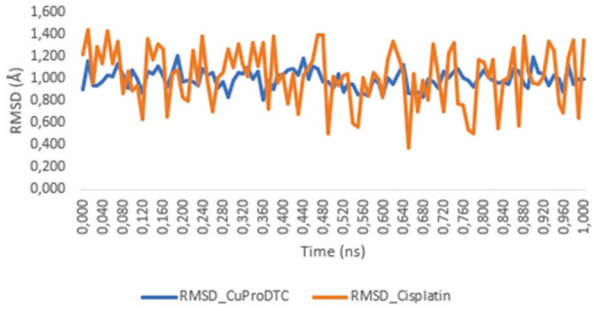

Figure 10. Comparison of RMSD values between CuProDTC complex and cisplatin.

energy at around −930000000 while the protein complex with the test compound cisplatin showed stable potential energy at around −935000000. This may be due to the difference in the energy of the molecular bonds.

RMSD (root mean square deviation)

RMSD is a measure widely used in 3 D molecular geometry to compare conformational changes or movements of molecules. The goal of RMSD analysis in molecular dynamics is to describe how much the state of the protein complex with the ligand changes over time while also ensuring the protein complex's stability (Muttaqin, 2019). RMSD can also be used as a standard deviation of conformational changes with standards <2 Å and >2 Å which are generally applied to docking results. The RMSD standard for a protein as a result of molecular dynamics simulation is 3 Å, where the RMSD value 3 Å indicates that the protein has undergone a conformational change that is much different from its native condition.

Based on Figure 10, the RMSD value in general tends to continue to increase with some fluctuations and does not exceed the threshold value of 2 Å. The presence of a protein complex with the Cu ProDTC test compound can minimize fluctuations so that the RMSD Cu graph is slightly more constant than the complex protein with cisplatin. The Cu Pro DTC protein complex experienced significant fluctuations at 0.2 and 0.36 0.44 and 0.64 ns. The results of the RMSD analysis showed unstable results because they fluctuated from the beginning to the end of the simulation.

The RMSD graph of protein complexes with cisplatin also tends to continue to increase with some fluctuations and

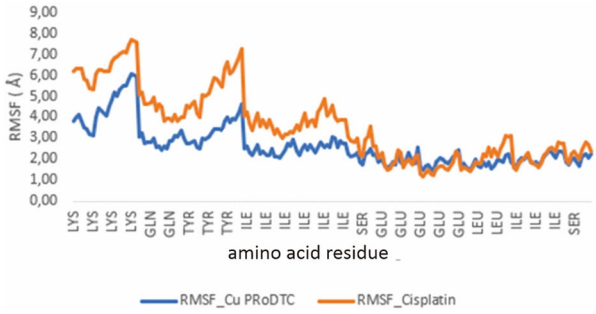

Figure 11. RMSF values of Cu complex and cisplatin.

does not exceed the threshold value of 2. The protein complex with cisplatin showed a more unstable graph than the protein complex with the Cu test compound which experienced significant fluctuations at 0.12 and 0.24 0.36 0.44 and 0.48 and so on up to 1 ns. So in general the results of the RMSD analysis showed unstable results.

RMSF (root mean square fluctuation)

RMSF is a measure of the deviation between the particle position and some reference position. RMSF is calculated for each amino acid residue in the protein to determine how far the fluctuations in each amino acid residue's movement are during the simulation. The RMSF analysis on molecular dynamics is used to determine the flexibility of amino acid residues at the active site. The stability of protein complex interactions with ligands is described by low flexibility (Torella et al., 2010). Because the atoms that make up the amino acid residue do not change positions very much during the simulation, the flexibility of the amino acid residue illustrates the stability of the interaction at the active site bound to the test compound.

Based on Figure 11, RMSF of Cu ProDTC protein complex and RMSF of cisplatin protein complex show changes in the bond distance of several amino acid residues. The RMSF assay/cisplatin tended to have a higher RMSF value than the RMSF of the Cu ProDTC protein complex. Despite the bond relaxation, many amino acid residues showed RMSF values of more than 3 Å. This explains that the amino acid residues have high flexibility and can be concluded to have unstable amino acid residues.

Complex stability testing using molecular dynamics simulations with YASARA dynamic software with an atomic movement time of 1000 ps. The results of testing the parameters of the molecular dynamics simulation, namely the potential energy of RMSD and RMSF, show that the affinity of the Cu complex for nucleotide-metabolizing enzymes is more stable than that of cisplatin.

ADMET screening of Cu(II)prolinedithiocarbamate

Utilizing pkCSM is a tactic to gauge and enhance the pharmacokinetic properties of tiny molecules using graphical signatures based on distance. Utilizing pkCSM to describe molecular and chemical structures in order to identify and foresee their pharmacokinetic characteristics (Pires et al.,

2015). The pharmacological effects of medications after oral administration are significantly influenced by a drug's water solubility. Strongly water-soluble medications will have good bioavailability and absorption characteristics. The plasma drug concentration at the target location can rise due to drug absorption and bioavailability, allowing it to perform a therapeutic function (Tripathy et al., 2019; Yeni & Rachmania, 2022). The solubility of Cu complexes in water was analyzed by pKCSM. The solubility of Cu complex compounds in water has a value of −2.164 which indicates that this complex is moderately soluble in water. According to Sorkun et al. (2019), water has a solubility range of 0 to −2 soluble, −2 to −4 slightly soluble, and less than −4 indicates insolubility (Table 3).

In the intestine, Cu(II)prolineditiocarbamate has a high absorption capacity, with an absorption rate of 100% and a rather high permeability of CaCO2. Cu(II)prolineditio carbamate is a P-glycoprotein substrate and inhibitor that is inactive in P-glycoprotein. With a value of less than −0.15, the VDss Cu(II)prolinetiocarbamate is considered to have a low value and is unlikely to result in renal failure or dehydration. The central nervous system is impermeable to Cu(II)prolineditiocarbamate because of its poor distribution to the brain (CNS). Renal OCT2 is not a substrate for the Cu(II) complex, which has a very high total clearance of more than one. Cu(II)prolineditiocarbamate is predicted to be hepatotoxic and can cause skin sensitivity. The oral LD50 and the maximum tolerated Cu(II)prolineditiocarbamate dose were considered low. Lipinski, Ghose, Veber, Egan, and Muegge's principle states that, druglikeness implies that Cu(II)prolinetiocarbamate has potential as a drug. For oral toxicity in rodents (LD50) of the complex compound Cu(II)prolinedithiocarbamate, an in silico test the Protox online tool was used to assess and classify compound toxicity in accordance with the Globally Harmonized System (GHS). The LD50 is the amount of compound that can kill 50% of the experimental group of animals. It is predicted to have an LD50 in rodents ranging from 2500 mg/kg and belongs to the GHS toxicity class 5, indicating that the compound has a low acute toxicity effect. According to the tabulation of the toxicity class of Hodge and Sterner (1949) the dose belongs to the toxicity class 4, which means the toxicity is relatively low (Hodge & Sterner, 1949).

IC50 values of complex compounds and their native metals against cancer cells MCF-7

The IC50 value of the prolineithiocarbamate Cu(II) complex was calculated by the regression equation $y = -0.037x + 0.8359$ (Figure 12), while the IC50 value of the prolineithiocarbamate complex a was calculated by the regression equation $y = -0.0061x + 0.6383$. (Figure 13) was used to obtain the IC50 value of cisplatin. Figure 14 shows the apoptotic phase of MCF-7 cells in response to Cu(II)prolinedithio carbamate and cisplatin complexes. Based on the observation that no cell death was observed in the Cu complex

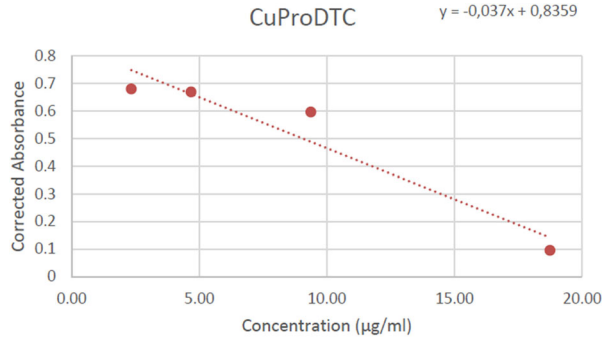

Figure 12. CuProDTC Test Result Curve against MCF7.

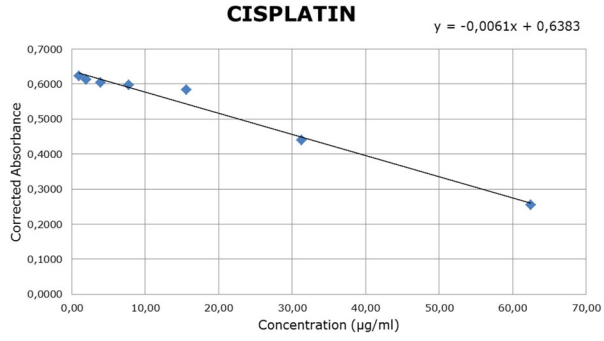

Figure 13 Cisplatin Test Result Curve against MCF7.

Table 3. ADMET Screening of Cu(II)Prolinedithiocarbamate.

Parameter		Value	Parameter		Value
Absorption	Water Solubility (log mol/L)	−2.164	Excretion	Total clearance (log ml/min/kg)	0.055
	Caco2 permeability (log Papp in 10-6 cm/s)	1.617		Renal OCT2 substrate	No
	Intestinal absorption (% absorbed)	100	Toxicity	AMES Toxicity	No
	Skin permeability (log Kp)	−3.285		Max tolerated dose (log mg/kg/day)	0.555
	P-glycoprotein substrate	Yes		hERG II inhibitor	No
	P-glycoprotein I inhibitor	No		Oral Rat Acut Toxicity (LD50) (mol/kg)	2.798
	P-glycoprotein II inhibitor	No		Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	0.542
Distribution	VDss (log L/kg)	−0.056		Hepatotoxicity	Yes
	Fraction unbound (Fu)	0.683		Skin Sensitisation	Yes
	BBB Permeability (log BB)	−0.087		*T. pyriformis toxicity (log ug/L)*	0.719
	CNS permeability (log PS)	−3,296		Minnow toxicity (log mM)	2.229
Metabolism	CYP3A4 substrate	No	Druglikeness	Lipinski	Yes; 0 violation
	CYP1A2 inhibitor	No		Ghose	Yes
	CYP2C19 inhibitor	No		Veber	Yes
	CYP2C9 inhibitor	No		Egan	Yes
	CYP2D6 inhibitor	No		Muegge	Yes
	CYP3A4 inhibitor	No		Bioavaibility Score	0.55

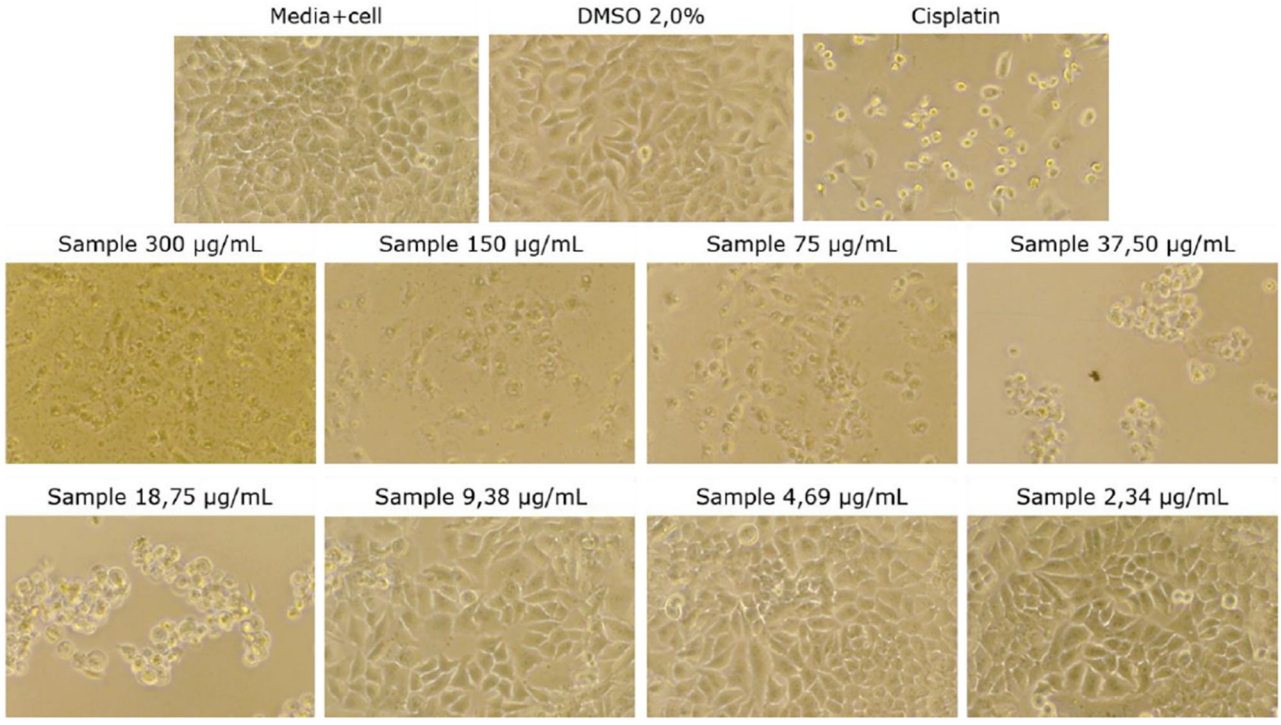

Figure 14. Documentation of MCF-7 Cell Morphology Test Results CuProDTC.

Table 4 IC50 Value of Cu(II)Prolinedithiocarbamate Complex.

Complex	Incubation time (h)	IC_{50} (µg/mL)
Cu(II)Prolinedithiocarbamate	48	13.64
Cisplatin	48	53.48

concentration range 2.34 to 9.38 µg/mL. Apoptosis begins ranged from 18.75 to 300 µg/mL.

Discussion

The synthesized complex was tested for cytotoxicity against breast cancer cells (MCF-7) in vitro and compared with the anticancer activity of cisplatin, which is the most commonly used drug today and is known to be active against breast cancer cells (MCF-7). Table 4 presents IC50 values for Cu(II) complex ProlineDithiocarbamate and cisplatin (treatment time 48 hours). The IC50 value of the Cu(II) ProlineDithio carbamate complex is lower than that of cispatin, indicating that this complex has the potential to be toxic. which is superior to cisplatin in inducing morphological changes in cancer cells, resulting in apoptosis. Based on the classification of Prayong et al. (2008), from the results of his research to classify the IC50 standard for cytotoxic samples, it can be grouped into several categories, namely samples with IC50 values of 1–100 µ g/mL having high cytotoxicity, 100-1000 µg/mL having moderate cytotoxicity, and samples with IC50 value 1000 µg/mL has weak cytotoxicity or even non-toxic to cancer cells.

The stability of Cu complexes binding to DNA can be predicted by observing the HSAB properties between Cu complexes and the molecular composition of DNA. Cu(II) metal is included in the category of borderline acids and guanine which are the basic framework of DNA including borderline bases so it is predicted that there will be a strong bond between the Cu complex and DNA (Cui et al., 2017).

Metal complexes with nitrogenous bases in DNA are covalently coordinated with specific geometries. Metal complexes can be intercalated into the DNA gap. However, this interaction generally occurs in complexes containing planar aromatic heterocyclic ligands (Luzzati et al., 1961). Then another interaction is electrostatic, which is also known as external binding. For example, the interaction between a positively charged metal complex and the phosphate portion of DNA, which is partially negatively charged. Based on the evaluation of the findings of this study, it appears that the ligand has a role in increasing the anticancer activity of Cu complex against breast cancer cells (MCF-7). The ligand's role allows the ligand's intercalation into the DNA gap. As a result, metal complexes bind not only covalently but also non-covalently.

Conclusion

Cu(II)Prolinedithiocarbamate complex is included in high cytotoxicity and is more active than cisplatin. The type of hydrogen bonding in the complex was found as many as 4 hydrogen bonds and 7 hydrophobic interactions confirmed by molecular docking. Proteins with Cu test substance showed more stable potential energy than cisplatin. The Cu(II)prolineditiocarbamate complex may pave the way for developing new essential metal-based chemotherapy for breast cancer treatment.

Disclosure statement

The authors affirm that none of their known financial or personal relationships or conflicts of interest may have seemed to have an impact on the work presented in this paper.

Ethical approvals

The subjects of this study are neither people nor animals.

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