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Synthesis, characterization, potential anticancer activity, and molecular docking studies of Fe(II)Prolinedithiocarbamate complex on MCF-7 breast cancer cell lines.

Sulistiani Jarre[1], Indah Raya[1]*, Prihantono Prihantono[2], Rugaiyah Arfah[1], Maming Gappa[1], St. Fauziah[1], Santi Santi[3], Rizal Irfandi[4]

[1]*Department of Chemistry, Faculty of Mathematics, and Natural Science, Hasanuddin University Makassar, 90245, Indonesia.*
[2]*Department of Surgery, Faculty of Medical, Hasanuddin University, Makassar, Indonesia. 90245*
[3]*Medical Laboratory Technology, Faculty of Health Technology, Megarezky University, Makassar, 90234, Indonesia.*
[4]*Department of Biology Education, Faculty of Teacher Training and Education Puangrimaggalatung University, Sengkang 90915, Indonesia*

Abstract

A new complex compound of Fe(II)Prolinedithiocarbamate has been synthesized, characterized, and was tested for MCF-7 cell in vitro and in silico with molecular docking studies. Characterized tests such as melting point, conductivity, UV-Vis spectroscopy, and FT-IR spectroscopy have been performed. The in vitro test results showed morphological changes (apoptosis) in MCF-7 cancer cells start at 75 µg/ml. The molecular docking study of the complex Fe(II)Prolinedithiocarbamate was identified with O(6)-methylguanine-DNA methyltransferase (MGMT) protein. Fe(II)Prolinedithiocarbamate - O(6)-methylguanine-DNA methyltransferase (MGMT) showed the active site with amino acid residues GLU77, LEU142, ILE76, dan TRP65. The hydrogen and hydrophobic bond were seen in Fe(II)Prolinedithiocarbamate - O(6)-methylguanine-DNA methyltransferase (MGMT) has a binding energy -183.25 kJ/mol. According in vitro test and molecular docking study, this compound has a potential anticancer activity.

Keywords: Complex; Cytotoxicity; MCF-7 cell lines; Breast Cancer; Anticancer activity; Dithiocarbamate.

1. Introduction

Breast cancer is a type of cancer where develops at the breast's glandular tissue. This cancer is the number two killer disease in the world for females [1]. There will be 2.3 million (11.7%) new cases of women diagnosed with breast cancer based on data from Global Burden of Cancer (GLOBOCAN) in 2020 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer (IARC) [2]. Breast cancer ranks first in Indonesia among various types of cancer, with the number of cases reaching 68.858 (16.7%). The number of new cases of breast cancer and the number of deaths continue to increase. One of the most commonly used treatments is chemotherapy [3]. Cisplatin is a drug that is often used in chemotherapy treatment. Cisplatin is a platinum-derived compound. Cisplatin works as a cytostatic by inhibiting DNA synthesis, and subsequently, cancer cells undergo apoptosis [4.5]. However, Cisplatin can provide toxicity, resistance, and other kidneys, hearing, and digestive disorders [6].

Therefore, it is necessary to research complex compounds that have the potential as anticancer drugs for breast cancer. Using complex compounds as non-platinum-based chemotherapeutic agents has potential as an anticancer and can reduce the side effects it causes. Researchers have studied many complex compounds as anticancer because they can easily predict the nature of their interactions with DNA [7-10]. This research aims to synthesize complex compounds based on dithiocarbamate ligands and proline amino acids with Fe metal. Using dithiocarbamate ligands with additional donor groups such as oxygen and nitrogen in amino acids to synthesize complex compounds can increase

*Corresponding author e-mail: indahraya@unhas.ac.id.; (Indah Raya).
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anticancer activity [11]. The choice of proline amino acid is recognized as its ability to selectively deliver cytotoxic units into aggressive cancer cells [12.13]. The specialty of dithiocarbamate with its sulfur(S-) group can bind strongly and selectively to metal ions by forming complex organometallic compounds [14]. Dithiocarbamates can form monodentate or bidentate complexes with metals by coordination bonds, and it depending on the type of the amine. The dithiocarbamate ligands can bind metals with various oxidation numbers firmly and stably [15][16][17]. Using essential metals such as Fe in organometallic complexes can reduce the side effects of chemotherapy treatment. Fe(II) metal is a necessary nutrient for intracellular metabolism activity, playing the role as a cofactor for a variety of enzymes. Fe(II) metal is vital in development, digestion, reproduction, antioxidant defense, energy production, immune response, and regulation of neuronal activity [18].

In addition, dithiocarbamate has low toxicity in the body [19]. This research also used in silico molecular docking studies. Molecular docking is designed to understand and analyze biomolecular interactions to design a rational drug by placing molecules (ligands) with specific target DNA/proteins (receptors) and also can suggest the binding energy of a compound [20][21][22].

Therefore, research on the synthesis and characterization of essential metal complex compounds such as Fe(II) was carried out, reacted with prolinedithiocarbamate, and was tested for MCF-7 cell in vitro and in silico with molecular docking studies.

2. Experimental

$FeSO_4.7H_2O$, Cisplatin, Ethanol (95%), DMSO, Roswell Park Memorial Institute Medium, Carbon disulfide (CS_2), Pure Proline. All chemicals used in this study were acquired from Merck in the United States.

Synthesis of Fe(II) with Prolinedithiocarbamate ligand

This synthesis is carried out by in situ methods. $FeSO_4.7H_2O$ as much as 0.834 grams (3 mmol) was put in a 100 mL Erlenmeyer glass, dissolved with 10 mL of ethanol, then dissolved prolinedithiocarbamate (20 mL) while stirring with a magnetic stirrer for 30 minutes. The illustration of the synthesis is show in Figure 1.

Characterization of Fe(II)Prolinedithiocarbamate compound

Determining the melting point of the complex compound of Fe(II)Prolinedithiocarbamate used Electrothermal IA 9100. The conductivity value was determined by using a conductometer. Analysis of the FTIR spectrum of the Fe(II)Prolinedithiocarbamate complex compound used the SHIMADZU Infrared Spectrophotometer with a wavelength of 300-4000 cm^{-1} using KBr pellets. UV-Vis spectral data were obtained using a Jenwey UV-Vis spectrophotometer with a wavelength range of 200-1100 nm.

Anticancer activity test against breast cancer cells

Cell cultures were put in 96 well plates and incubated (with the temperature of 37°C and the percentage of CO_2 gases is 5% until reached cell growth percentage of 70%). The cells were then sampled and incubated (with the temperature of 37°C in 24 hours with 5% CO_2 gases). Fill the cell with presto blue working reagent. Thermo Fisher Scientific Multimode Reader was used to measure absorbance.

Molecular docking studies

The Fe(II)Prolinedithiocarbamate complex was predicted canonical SMILE by application and modeled with online Corina to obtain a three-dimensional structure [23]. The complex Structure of the compound interacted with O(6)-methylguanine-DNA methyltransferase (MGMT) protein to test its potential anticancer activity [24][25] [26]. The protein's 3D structure was obtained from the Protein Data Bank (PDB) database with the respective IDs, respectively 1QNT, 1QDU, and 6d0F.

Complex compounds and proteins were imported into the Molegro virtual docker 5 software and prepared by removing unwanted ligands, cofactors, and proteins [27]. Furthermore, the target protein was predicted to be cavity (active site of the protein) with a maximum expand van der Waals parameter of 10. O(6)-methylguanine-DNA methyltransferase (MGMT) X 1.29 A; Y 46.8 A; Z 55.6 A; Volume 35.84 A3; and Surface 131.84 A2 with radius 15 were docked in the protein cavity. MolDock Score Grid 0.30A, MolDock Score, and Rerank score are the docking parameters. The docking parameters are MolDock Score Grid 0.30A, MolDock Score, and Rerank score. The docking score indicates the bond energy in kJ/mol [28]. The docking results were superimposed on proteins created with the PyMol software.

3. Results and Discussion

The Fe(II)Prolinedithiocarbamate complex compound has been synthesized. The illustration of the synthesis is show in Figure 1. The synthesized Fe(II)Prolinedithiocarbamate yield was 28.37%. While the melting point is 246-248°C indicated that the Fe(II) Proline dithiocarbamate complex had a strong complex stability and purity. The conductivity value of the Fe(II)Prolinedithiocarbamatecomplex is 0.02mS/cm, the Fe(II)Prolinedithiocarbamate complex is thus a nonelectrolyte compound.

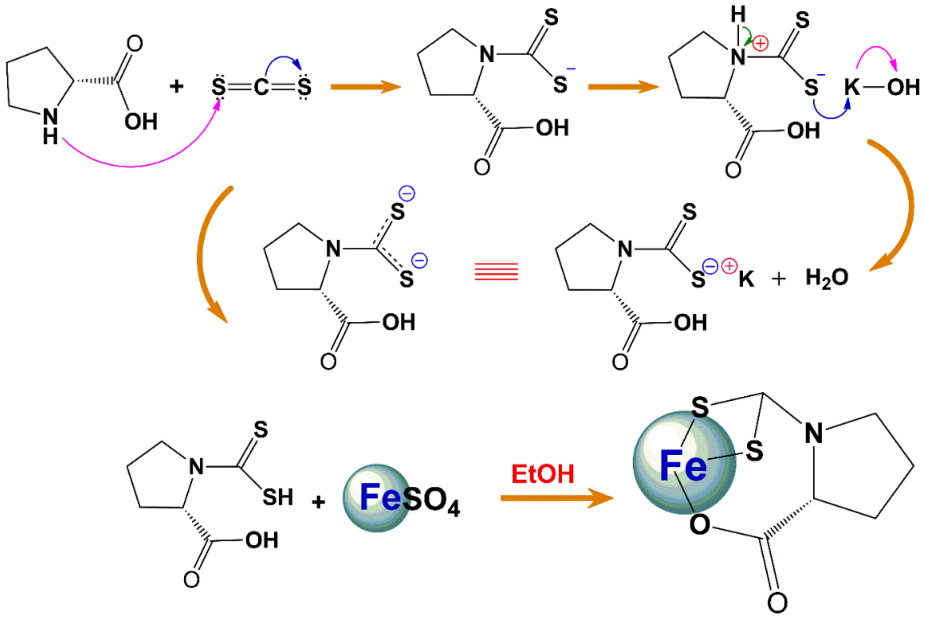

Figure 1. Schematic illustration of the reaction mechanism of the synthesis of Fe(II)Prolinedithiocarbamate complex compound

Characterization of Fe(II)Prolinedithiocarbamate compound

FTIR Spectroscopy Characterization

This analysis was carried out at a wavenumber of 4000-300 cm^{-1}. The absorption peak of IR at a wavenumber at 364 cm^{-1} denotes the bond between S atoms and Fe metal. The absorption peak at a wavenumber of 455 cm^{-1} denotes the interaction of the O atoms of the complex compound with Fe metal ions (M-O). The presence of absorption at wavenumbers 1126 cm-1 shows the dithiocarbamate ligands C=S functional group, and indicates bidentate coordination of Fe metal with C=S. The absorption peak of 1614 cm^{-1} indicated the appearance of a C=N functional group. The infrared absorption peak at a wavenumber of 3448 cm^{-1} indicates -OH group from ethanol or water [29] [30].

The IR results of Fe (II) complex compounds with proline dithiocarbamate ligands generally show the of the synthesized complex characteristics. The IR result is presented in Figure 2 and related with the Schematic illustration of the reaction mechanism of the synthesis of Fe(II)Prolinedithiocarbamate complex compound (Figure 1). Thus the complex compound Fe(II) proline dithiocarbamate was successfully synthesized.

UV-Vis Characterization

Complex ompounds containing the C=S group show a strong band in the 250-320 region originating from the transitions π→π* and n→ π* [31] [32]. In the dithiocarbamate complex, the band in the 310-400 nm region shows an electronic transition intraligand n→π* of the N = C= S group [33] The results of the UV-Vis spectrophotometer characterization are shown in Figure 3 and Table 1. The complex compound Fe(II)Prolinedithiocarbamate in band shift I, was detected at a wavelength of 215-289 nm which is an intraligand transition π→π* of the CS_2 group. The wavelength at 444 nm is indicated that Charge Transfer (CT) transitions from between metal and ligands. the appearance of absorption in the 500 nm indicates there are transition d orbital from metal transition.

Table 1. Fe(II)Prolinedithiocarbamate UV-Vis spectrum

Chemical Complex Compound	Wavelength (nm)	Transition of Electronics
Fe(II)Prolinedithiocarbamate	289	π→π*

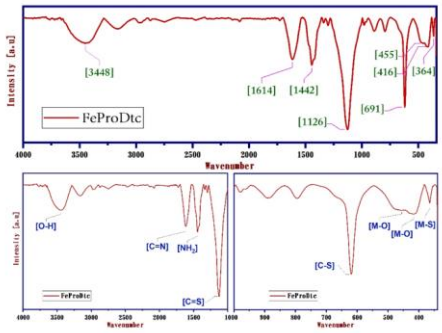

Figure 2. IR spectrum of Fe(II)Prolinedithiocarbamate

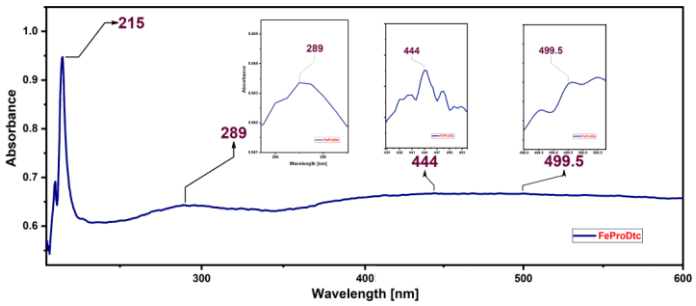

Figure 3. Fe(II)Prolinedithiocarbamate UV-Vis spectrum

Anticancer Activity Cells from Breast Cancer (MCF-7)

The in vitro test results of Fe(II)Prolinedithiocarbamate on MCF-7 cells showed anticancer activity shown in figure 4. Based on the anticancer activity test on breast cancer cells (MCF-7), there is no cell death at sample variant concentrations from 2.34 to 37.50 µg/mL**.**

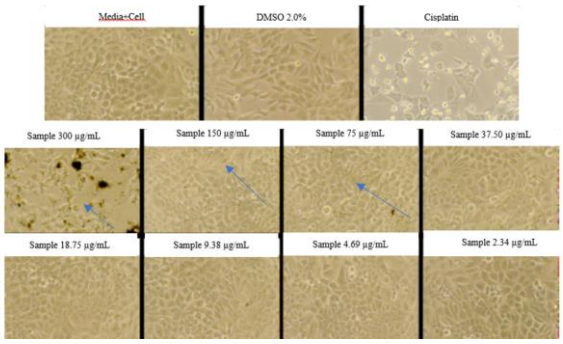

Figure 4. MCF-7 cell apoptosis induced by Fe(II)Prolinedithiocarbamate

At a sample concentration of 75 g/mL, apoptosis began, and at a higher concentration of 300 g/mL, MCF-7 cells died late. Damage to the plasma membrane is a common cause of late apoptosis cells. The dithiocarbamate ligand significantly contributes the Fe metal complex's cytotoxicity against cancer cell lines. The ligand functions as a carrier and contributes to the complex's lipophilicity, which facilitates the metal's movement to the site where its cytotoxicity properties are exerted [34]. The interaction of metal complexes with DNA, in general, can occur through the coordination of covalent bonds, even non-covalently [35].

Electrostatic interactions are straightforward non-covalent interactions. Electrostatic interactions occur between the positively charged metal complex and the partially negatively charged DNA outer skeleton (phosphate), which can appear outside the DNA double helix [36]. When a planar heteroatomic compound can penetrate the gap between DNA pairs, the interclassification can interact perpendicularly to the double helix DNA axis. In general, DNA base pairs will provide enough space for planar aromatic intercalators to enter. Stretching of the DNA double helix structure occurs as a result of this process, resulting in changes in the density electron of electrons in the phosphate framework and DNA sugar structure [37].

Metallo-intercalators with unbroken DNA base pairs after passing through the groove, usually major. The positive charge on the metallo-intercalator strengthens DNA binding due to electrostatic attraction to the negatively charged sugar-phosphate backbone [38].

Molecular Docking Data Analysis

The data were observed and analyzed with Version 21.1.1 of Discovery Studio to obtain 2D, 3D, and binding sites of ligands and proteins target. Bond energy was obtained by averaging of the Score Grid of MolDock, Score of MolDock, and Score of Rerank and then averaging over five replicates and presented the mean ± Standard Deviation.

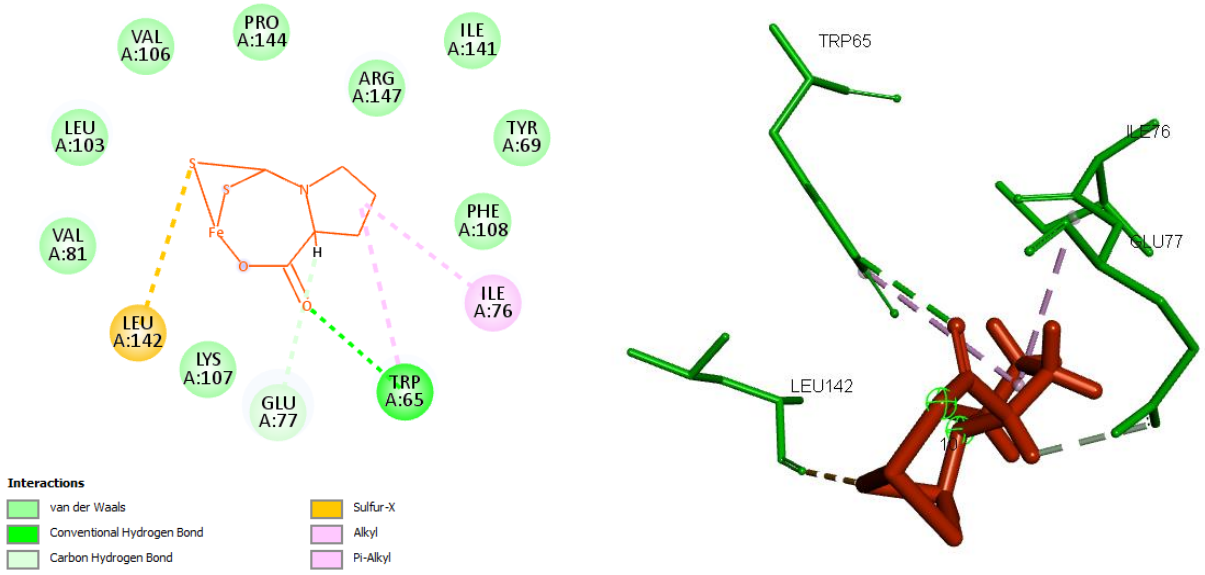

Figure 5. A. Fe(II)Proline dithiocarbamate MGMT protein interaction in 2D. B. 3D Fe(II)Proline dithiocarbamate MGMT protein interaction in 3D

O6-methylguanine-DNA methyltransferase is a DNA repair enzyme that can inhibit the process of tumor cell death due to the alkylation process by alkylating substances, including chemotherapy substances The complex compound with MGMT protein showed the GLU77 active sites with the distance of 2.89A, LEU142 with the distance of 3.28A, ILE76 with the distance of 4.08A, and TRP65 with the distance of 3.01A. The complex compound's active site against the MGMT protein binds to the C-terminal and N-terminal regions that have an impact on the DNA methylation process (Figure 5 and Table 2). Fe(II)Prolinedithiocarbamate interaction with O(6)-methylguanine-DNA methyltransferase protein has a binding energy -183.25 ± 10.6 kJ/mol. Generally, the best interactions are those with the lowest binding energies.

Table 2. Interaction between Fe(II) proline dithiocarbamate on O(6)-methylguanine-DNA methyltransferase (MGMT) protein has a binding energy -183.25 ± 10.6 kJ/mol

Interaction	Distance (A)	Category	Types	Donor
A:TRP65:NE1 - :10:O1	3.01784	Hydrogen Bond	Conventional Hydrogen Bond	A:TRP65:NE1
:10:H1 - A:GLU77:OE2	2.89471	Hydrogen Bond	Carbon Hydrogen Bond	:10:H1
:10:S2 - A:LEU142:O	3.28874	Other	Sulfur-X	:10:S2
:10 - A:ILE76	4.08585	Hydrophobic	Alkyl	:10
A:TRP65 - :10	4.74783	Hydrophobic	Pi-Alkyl	A:TRP65

Conclusion

Synthesis of the Fe(II)Prolineditiocarbamate complex was carried out and the characterization of the complex showed the presence of a prolinetiocarbamate ligand. This is shown in the results of the FTIR characterization at the absorption of 1126 cm^{-1}, which indicates the presence of a C=S functional group, and 1614cm^{-1}, showing the presence of a C=N functional group. A C=S functional group exists in the UV-Vis spectrum supported by $\pi \rightarrow \pi^*$ at a wavelength of 215-289 nm. Based on the in vitro test results of anticancer activity against MCF-7 breast cancer cells, it was seen that apoptosis in cell morphology began to occur at the sample concentration of 75µg/mL. This indicates that the complex compound Fe(II)Prolinedithiocarbamate has potential as an anticancer breast supported by the interaction with protein O6-methylguanine-DNA methyltransferase (MGMT) in silico molecular

docking studies. The Fe(II)Prolinedithiocarbamate - O(6)-methylguanine-DNA methyltransferase (MGMT) complex showed the active sites of GLU77, LEU142, ILE76, and TRP65.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

[1]Das AK, Biswas SK, Bhattacharya A, and Alam E. Introduction to Breast Cancer and Awareness. 7th International Conference on Advanced Computing and Communication Systems 2021: 227–232. doi: 10.1109/ICACCS51430.2021.9441686.

[2] Sung *et al* H. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, CA: A Cancer Journal for Clinicians 2021; 71(3): 209–249. doi: 10.3322/caac.21660.

[3]World Health Organization. Sep. 04, 2021. https:www.who.int/news-room/fact-sheets/detail/breast-cancer (accessed Sep. 28, 2021).

[4] Dasari S and Bernard TP. Cisplatin in cancer therapy: Molecular mechanisms of action. European Journal of Pharmacology 2014; 740: 364–378. doi: 10.1016/j.ejphar.2014.07.025.

[5] Perse M. Cisplatin mouse models: Treatment, toxicity and translatability. Biomedicines 2021; 9 (10). doi: 10.3390/BIOMEDICINES9101406.

[6] Paken J, Govender CD, Pillay M, and Sewram V. A Review of Cisplatin-Associated Ototoxicity. Seminars in Hearing 2019; 40(2):108–121. doi: 10.1055/S-0039-1684041.

[7] Ritacco I, Russo N, and Sicilia E. DFT Investigation of the Mechanism of Action of Organoiridium(III) Complexes As Anticancer Agents. Inorganic Chemistry 2015; 54(22):10801–10810. doi: 10.1021/ACS.INORGCHEM.5B01832.

[8] Irfandi R, Ruslang R, Raya I, Yani A, Nasir M, Nurcaya N, and Jarre S. Docking Molecular Dari Kompleks Zn(II)Amina (Prolin)Dithiokarbamat terhadap Reseptor Estrogen-α. Al-Kimia 2021; 9 (2): 182–187.

[9] Kartina D, Wahab AW, Ahmad A, Irfandi R, Prihantono P, and Raya I. In-vitro Evaluation of The Anticancer Activity of Cu(II)Amina(Cysteine)Dithiocarbamate. Syst. Rev. Pharm 2020; 11(9): 43–51.

[10] Kartina D, Wahab AW, Ahmad A, Irfandi R, and Raya I. In vitro Antibacterial and Anticancer Activity of Zn(II) Valinedithiocarbamate Complexes. J. Phys.: Conf. Ser 2019; 1341: 032042.

[11] Prihantono, Irfandi R, Raya I, and Warsinggih. Potential anticancer activity of Mn (II) complexes containing arginine dithiocarbamate ligand on MCF-7 breast cancer cell lines. Annals of Medicine and Surgery 2020; 60: 396–402. doi: 10.1016/j.amsu.2020.11.018.

[12] Odularu AT, and Ajibade PA. Dithiocarbamates: Challenges, control, and approaches to excellent yield, characterization, and their biological applications. Bioinorganic Chemistry and Applications 2019. doi: 10.1155/2019/8260496.

[13] Irfandi R, Santi S, Raya I, Ahmad A, Fudholi A, & Sari DRT. Study of new Zn (II) prolinedithiocarbamate as a potential agent for breast cancer: Characterization and molecular docking. Journal of Molecular Structure 2022;1252:132101.doi.org/10.1016/j.molstruc.2021.132101.

[14] Irfandi R, Prihantono P, Raya I, Kartina, D, and Riswandi R. Synthesis, characterization and anticancer studies of Fe(II) cysteinedithiocarbamate complex. ICOST 2019, May 02-03, Makassar, Indonesia.

[15] Prihantono P, Irfandi R, and Raya I. The comparison of Zn(II) arginine dithiocarbamate cytotoxicity in T47D breast cancer and fibroblast cells. Breast Disease 2021; 40(S1): S55–S61. doi: 10.3233/BD-219008.

[16] Imran M, Kondratyuk ZRT, and Gariepy BF. New ternary platinum(II) dithiocarbamates: Synthesis, characterization, anticancer, DNA binding and DNA denaturing studies. Inorganic Chemistry Communications 2019;103:12–20. doi: 10.1016/j.inoche.2019.02.007.

[17] Adokoh CK. Therapeutic potential of dithiocarbamate supported gold compounds. RSC Advances 2020;10(5): 2975–2988. doi: 10.1039/C9RA09682E.

[18] Zoroddu MA, Aaseth J, Crisponi G, Medici S, Peana M, and Nurchi VM. The essential metals for humans: a brief overview. Journal of Inorganic Biochemistry 2019; 195: 120–129. doi: 10.1016/j.jinorgbio.2019.03.013.

[19] Raya I, Baba I, & Bohari, and Yamin M. New Mixed Ligands Complexes of Samarium (III) with Dithiocarbamates and 1,10-Phenanthroline. Malaysia Journal of Analytical Sciences 2006; 10 (1): 93-98.

[20] Mahmood DA. Molecular Docking: Approaches, Types, Applications and Basic Challenges. Journal of Analytical & Bioanalytical Techniques 2017; 8(2). doi: 10.4172/2155-9872.1000356.

[21] Singh SP, Deb CR, Ahmed SU, Saratchandra Y, and Konwar BK. Molecular docking simulation analysis of the interaction of dietary flavonols with heat shock protein 90. Journal of Biomedical Research 2016; 30(1): 67.doi: 10.7555/JBR.30.20130158.

[22] Thirugnanasundar A, *et al.* Synthesis, structure, DNA/protein molecular docking and biological studies of hydrazone ligand derived Cu(II) and VO(IV) complexes. Inorganica Chimica Acta 2021; 526. doi: 10.1016/j.ica.2021.120543.

[23] Chen J, Swamidass SJ, Dou Y, Bruand J, and Baldi P. ChemDB: a public database of small molecules and related chemoinformatics resources. bioinformatics 2005; 21(22): 4133–4139. doi: 10.1093/bioinformatics/bti683.

[24] Reinhard J. *et al.* Monosaccharide-linked inhibitors of O6-methylguanine-DNA methyltransferase (MGMT): Synthesis, molecular modeling, and structure-activity relationships. Journal of Medicinal Chemistry 2001; 44(24): 4050–4061. doi: 10.1021/jm010006e.

[25] Yang L. *et al.* Computational Study of Novel Natural Inhibitors Targeting O6-Methylguanine-DNA Methyltransferase. World Neurosurgery 2019; 130: e294–e306. doi: 10.1016/J.WNEU.2019.05.264.

[26] Gharouni M, Mosaddeghi H, Mehrzad J, Es-haghi A, and Motavalizadehkakhky A. In silico profiling and structural insights of zinc metal ion on O6-methylguanine methyl transferase and its interactions using molecular dynamics approach. Journal of Molecular Modeling 2021; 27(2): 1–10. doi: 10.1007/S00894-020-04631-X.

[27] Bitencourt G, and Azevedo WF. Molegro virtual docker for docking. Methods in Molecular Biology 2019; 2053: 149–167. doi: 10.1007/978-1-4939-9752-7_10/COVER/.

[28] Singh SP, Deb CR, Ahmed SU, Saratchandra Y, and Konwar BK. Molecular docking simulation analysis of the interaction of dietary flavonols with heat shock protein 90. Journal of Biomedical Research 2016; 30(1): 67–74. doi: 10.7555/JBR.30.20130158.

[29] Adeyemi JO, *et al.* Synthesis, computational and biological studies of alkyltin(IV) N-methyl-N-hydroxyethyl dithiocarbamate complexes. Heliyon 2021; 7(8). doi: 10.1016/J.HELIYON.2021.E07693.

[30] Santi S, Wahab AW, Raya I , Ahmad A, Maming M. Synthesis, spectroscopic (FT-IR, UV–visible) study, and HOMO-LUMO analysis of adenosine triphosphate (ATP) doped trivalent terbium. Journal of Molecular Structure 2021. 1237. 130398. doi: 10.1016/j.molstruc.2021.130398.

[31] Mishra AK, Manav N, and Kaushik NK. Organotin(IV) complexes of thiohydrazones: synthesis, characterization and antifungal study. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 2005; 61(13–14): 3097–310. doi: 10.1016/J.SAA.2004.11.035.

[32] Santi, Wahab AW, Raya I , Ahmad A. Synthesis and Interaction of Adenosine-5-Triphosphate With Rare Earth Metal Europium (Eu^{3+}). AIP Conf. Proc. 2020. 2296. 020074. doi: 10.1063/5.0030666.

[33] Annuar B, Hill JO, and Magee RJ. Nickel(II) and copper(II) complexes of mono-ethanol and di-ethanol-dithiocarbamic acid. Journal of Inorganic and Nuclear Chemistry 1974; 36(6):1253–1257. doi: 10.1016/0022-1902(74)80060-6.

[34] Kamaludding. NF, Awang. N, Baba. I, Hamid. A, and M. CK. Synthesis, characterization and crystal structure of organotin(IV) N-butyl-N-phenyldithiocarbamate compounds and their cytotoxicity in human leukemia cell lines. Pakistan Journal of Biological Sciences 2013;16(1):12–21.doi:10.3923/PJBS.2013.12.21.

[35] Astrid Sigel and Helmut Sigel, Metal Ions in Biological Systems, Interactions of Metal Ions with nucleotides, nucleic acid, and their constituens, 1996, 32.

[36] C. A. Franklin, J. v Fry, and J. G. Collins. NMR Evidence for Sequence-Specific DNA Minor Groove Binding by Bis(ethylenediamine)platinum(II). Inorganic Chemistry 1996; 35(26):7541-7545. doi:10.1021/ic9604775.

[37] Mudasir, Wijaya K, Wahyuni ET, Inoue H, and Yoshioka N. Base-specific and enantioselective studies for the DNA binding of iron(II) mixed-ligand complexes containing 1,10-phenanthroline and dipyrido[3,2-a:2′,3′-c]phenazine. Spectrochim. Acta - Part A Mol. Biomol. Spectrosc 2007; 66 (1): 163–170.

[38] Lauria, A, Riccardo B, and Alessio T. Nickel(II), Copper(II) and Zinc(II) Metallo-intercalators: Structural Details of the DNA-binding by a Combined Experimental and Computational Investigation. Dalton Transactions 2014; 16.