# In-Silico Studies of Newly Synthesized Compounds for Anti-Cancer Activity

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**Abstract**

*Cancer remains a formidable global health challenge, with escalating incidence rates in the 21st century. Despite multidisciplinary efforts, the quest for a definitive cure continues. Recent attention has shifted towards exploring complementary and alternative medicine as potential avenues for cancer management. In this study, we focus on investigating the anti-cancer properties of newly synthesized copper mixed synthetic compounds. Our approach involves an in-silico analysis approach to explore the interactions between these compounds and Cyclin Dependent Kinase 2 (CDK2), a crucial protein involved in cell cycle regulation and apoptosis. Through molecular docking studies, compounds 4a exhibited promising interactions with CDK2, suggesting their potential as effective anticancer agents. These compounds demonstrated strong binding affinities with the active site residues of CDK2, emphasizing their possible involvement in modulating apoptosis and cell cycle processes critical in cancer progression. While our findings represent significant progress toward developing potent anticancer strategies, further research is warranted to validate their efficacy and explore their broader therapeutic potential. This study underscores the importance of investigating novel compounds and targets in the ongoing battle against cancer.*

**Keywords: Anti-Cancer, Cell Cycle, Synthetic Compounds, Copper, Cancer Strategy**

## Introduction

Cancer, a disease dreaded since the 20th century, continues to proliferate with escalating incidence in the 21st century [1]. It manifests as a group of diseases marked by unregulated cell division, resulting in abnormal tissue growth [2]. Approximately 6.7 million individuals succumb to cancer worldwide, with around 270,000 new cases emerging annually, leading to 145,000 deaths, the majority of which occur in developing nations [1.3]. There is still no proven treatment for the disease, despite world medicine's best efforts to combat it through integrated multidisciplinary research activities [4]. Particularly, complementary and alternative medicine approaches have received more attention lately when it comes to managing cancer [5].

Cancer related fatalities are primarily caused by metastasis [6]. The spread of cancer cells to other parts 1 of the body, known as metastasis, is the primary reason for fatalities caused by cancer. It is a multi-step process involving stages such as invasion, survival in circulation, and proliferation in secondary sites [7]. Protein kinases classified as Cyclin-Dependent Kinases (CDKs) are distinguished by their dependence on cyclin, a distinct component that supplies vital regions for their catalytic activity [8,9]. These kinases are essential for controlling transcription and cell division in response to a variety of internal and external signals [10]. About thirty proteins with molecular weights ranging from 35 to 90 kDa make up the different family known as cyclins [11]. The importance of the CDK family is highlighted by its participation in multiple signalling pathways that regulate transcriptional activities and the advancement of the cell cycle [12]. Most people believe that CDKs developed as a way to control the activity that promotes cell cycles in response to various stimuli and cellular circumstances. Due to their essential role in controlling the progression of the cell cycle and transcription inside cells, as well as their participation in apoptotic pathways, CDKs offer an attractive variety of targets for the development of innovative anticancer medications [12,14]. Recently, there has been an increase in interest in copper complexes containing mixed ligands, including 1,10-phenanthroline, because of their strong DNA binding and cleaving activities, which show promise as anticancer agents via inducing apoptosis [13,14]. Based on this understanding, we have created copper compounds in the hopes of noticing strong anticancer effects. With a primary focus on CDK2 and eight other synthetic complexes containing copper, this study attempts to evaluate the anticancer potential of these synthesized copper complexes.

## Materials and Methods

### Ligand

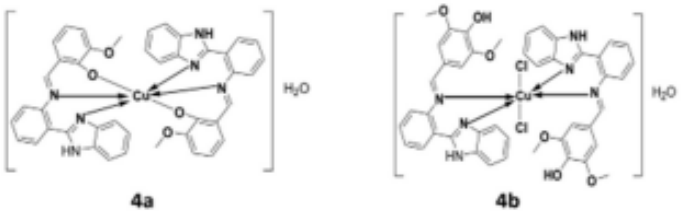


**Figure 1 Representation of synthesized 4a and 4b**

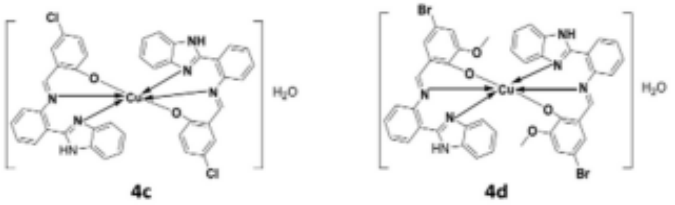


**Figure 2 Representation of synthesized 4c and 4d**

### Protein Selection

With a comprehensive review of the literature, we were able to identify a protein from the short-listed papers, as the target cyclin-dependent kinase 2 considered from Protein Data Bank (PDB) with Id 1GII [15] is chosen. As shown by the results of earlier investigations, this specific protein was selected because of its known anticancer properties.

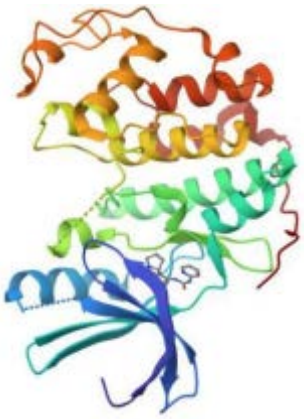

**Figure 5 Three -dimensional structure of Cyclin-dependent kinase 2 (1GII) from PDB**

**Protein Preparation**

Cyclin-dependent kinase 2 (1GII)'s three-dimensional structure was obtained from the Protein Data Bank. To maintain the structure's reliability, any non-standard amino acids found in the original structure were either eliminated or changed using the PyMOL program.

**Binding Site Prediction**

The in silico tool CASTp was utilized to examine the revised structure to find possible binding sites on the protein. Finding the areas of the protein that are most likely to interact with ligands requires careful investigation.

**Molecular Docking Analysis**

Using Autodock Vina, molecular docking investigations between the produced compounds and the chosen protein were carried out. The ligands and proteins were formatted in PDBQT, and the Autodock Tools software was used to locate the active site residues that defined the grid box. The orientations with the lowest binding affinities, shown in Kcal/mol, were identified through the investigation.

**Molecular Docking Visualization**

With the use of BIOVIA Discovery Studio Visualizer, the docking interactions between the ligands and proteins are able to be visually presented. With the use of this software, it was possible to create 3D visualizations that highlighted important interactions such bond lengths, hydrophobic interactions, and hydrogen bonds.

**Results**

**Protein-Ligand Interaction**

Table 1 represents a summary of the results obtained from the molecular docking studies conducted between the selected protein and the synthetic compounds. Based on the lowest binding affinity values expressed in Kcal/mol, the ideal docking pose for each compound was identified. A thorough analysis was carried out with the BIOVIA Discovery Studio Visualizer software to clarify the interactions between the chosen ligands and the protein. The important binding residues involved in the interaction were able to be identified and visualized because of this analysis.

Table 01. A table showing Molecular Docking results between selected proteins against Synthetic compounds (the binding energy value δG is shown in minus kcal/mol).

- Protein Name Compounds Name Binding Affinity (- kcal/mol) Cyclin
- dependent
- kinase 2 (1GII)
- 4a -11
- 4b -9.936
- 4c -10.64
- 4d -10.24

Analysis of Selected protein and synthetic compound Interactions Important interactions between the ligands and the protein were revealed by the molecular docking studies conducted between the selected protein and synthetic compounds. Compound 4a demonstrated the strongest binding affinity, as indicated by the highest binding score, as shown in Table 2. Following analysis with the BIOVIA Discovery software showed that in the Cyclin-dependent kinase 2 (1GII), both 4a and 4b formed three hydrogen bonds with important amino acid residues.

Table 2. No. of Hydrogen bonds between ligands and selected protein

- Protein Name Compound No. Hydrogen bonds Residue name
- Cyclin-dependent kinase 2 (1GII)
- 4a 3 ILE10,GLU12,ASP86 4b 3
- VAL83,ASP86,ASP145 4c 2 HIS82,VAL83
- 4d 1 ASP86

Via the utilization of Autodock Vina, molecular docking studies were able to visualize in three dimensions the binding interactions that occur between ligands and proteins. In particular, compounds 4a and 4b demonstrated encouraging interactions with the target protein,. The findings indicate that these compounds, a synthetic copper compound, may interact with Cyclin-Dependent Kinase 2 and could be affecting its activity.

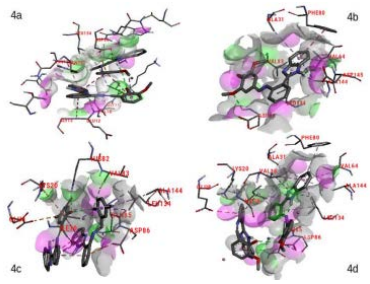


**Figure 7 Three-dimension visualisation of Cyclin-dependent kinase 2: protein docked with novel ligands 4a, 4b, 4c and 4d showing amino acid interactions**

**Discussion**

The primary objective of our study was to assess the anticancer potential of newly synthesized compounds and elucidate their interaction with an anticancer protein target Cyclin-dependent kinase 2. Cyclin-dependent kinase plays a crucial role in cancer biology, primarily by regulating cell cycle progression and influencing various oncogenic signalling pathways. Our current study focusses on newly synthesized copper mixed synthetic compounds proposed to show optimal biological activity by employing advanced bioinformatics tools and software, the study conducted a comprehensive in silico evaluation of eight synthesized compounds against Cyclin-dependent kinase 2. The active site of 1GII comprises specific amino acid residues, predominantly hydrophobic, such as 10 Alanine, 86 Aspartic acid, 145 Aspartic acid, 12 Glutamine, 82 Histidine, 83 Valine, among others, which play a crucial role in receptor-ligand interactions [15].

## Conclusion

In conclusion, our research on certain mixed synthetic compounds containing copper has revealed intriguing properties that may help fight cancer. Compound 4a demonstrate significant promise in their interaction with the anticancer target protein Cyclin Dependent Kinase 2 with compound 4a of binding energy -11, highlighting their importance in targeting cell cycle regulation and apoptosis, two important aspects of cancer treatment. The ability of these compounds to form strong binding affinities with CDK2 is attributed to their interaction with active site residues and nearby atoms. Although more research is necessary to confirm the effectiveness of these findings, they do mark a significant advancement in the development of a more effective anticancer strategy.

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