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# Molecular Docking Studies of Platinum Metal-Based Anticancer Drugs Cis-Diamineglycolatoplatinum and its Derivatives Binding Affinity with Three Different Types of Cancer Cell Structures as Receptor

**Madhavi Sahadevan [1], Karunagaran Subramanian [2], Mullainathan Sundaram [1,*]**

[1] PG and Research Department of Physics, Thiru Vi Ka Government Arts College Affiliated to Bharathidasan University Thiruvarur – 610 003 Tamil Nadu India
[2] Central Institute of Plastic Engineering and Technology Guindy Chennai-600032 Tamil Nadu India
[*] Correspondence: s_mullai@rediffmail.com;

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**Abstract:** The main aim of this study is to examine the anticancer drug efficiency of platinum-based drugs' biological interactions and the reduction of their adverse side effects. Thus, investigating proper binding sites and their conformational change after binding the drugs with their target is essential in chemotherapy treatment. Molecular docking studies were performed using the Auto Dock 4.0 software package. Platinum anticancer drugs such as Cisplatin and its derivatives Carboplatin, Nedaplatin, Oxaliplatin, Lobaplatin, and Heptaplatin, as ligands docked with three different types of cancer cell structures such as Gastric cancer cell structure, Lung Cancer cell structure, and Colorectal Cancer cell structure as Protein structure and the Docking score, wasinvestigated and analyzed. Molecular docking results have shown Binding energies ranging from - 5.10 kcal/mol to -10.72 kcal/mol and inhibition constant ranging from 1.07 µM to 108.90 µM and 13.64 nM to 216.03 nM. From the results obtained, Carboplatin shows the least binding energy values with gastric and lung cancer cell structure, and oxaliplatin shows the least binding energy value with colorectal cancer cell structure. Overall, the molecular docking results of metal-based platinum anticancer drugs show the strongest binding affinity with the least binding energies and effective binding sites with Cancer cell structures.

**Keywords:** molecular docking; Auto Dock 4.0; Gastric cancer; Lung cancer; colorectal cancer.

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## 1. Introduction

Cancer is a fatal disease with many causes, and it is a complex disease. The uncontrollable cell division results in tumors, except in the case of Leukaemia, which harms the human body. Tumors that grow uncontrollably interfere with the nervous, circulatory, and digestive systems and can synthesize hormones that modify biological behavior. To identify the cancer, the effort of predictable oncology plays a vital role in suggesting the cancer treatment according to the patient. There are different types of cancer treatments depending on the cancer type diagnosed, namely chemotherapy, surgery, and radiation therapy, and apart from these, there may be other oncology therapies. Chemical agents have been used to treat cancer cells, and they are described as chemotherapy. Chemotherapy resists the growth of cancer cells or shrinks tumors. German chemist Paul Ehrlich coined the term chemotherapy initially andfocused on treating infectious diseases and cancer and developing drugs. Paul

Ehrlich had some achievement results with infectious disease but not with cancer [1-3]. Anticancer drugs possessing the metal Platinum are the backbone of chemotherapy treatment for numerous cancer types, such as gastric cancer, colorectal cancer, and Lung cancer. Cisplatin is the most widely used anticancer platinum-based drug. The discovery of Cisplatin led to a new approach to chemotherapy treatment in the late 1960s and showed effective antitumor behavior against cancers of the lung, ovary, neck, and testis [4,5]. In 1844, Cisplatin was initially synthesized by M. Peyrone, and in 1893, Alfred Werner derived its chemical. However, only in late 1965 did Dr.Rosenberg at Michigan State University reveal that an oxidizing agent produced from the platinum mesh electrolysis prevented cell division that caused tumors in Escherichia coli in a bacterial chamber.

Cisplatin toxicities were recognized as soon as it discovered its antitumor behavior, and they were neurotoxicity, nephrotoxicity, gastrointestinal toxicity, myelosuppression, and vascular toxicity due to its toxicities, which led to the discovery of its derivative Carboplatin. In the last 30 years, to reduce the toxicity, over twenty-three other types of platinum anticancer drugs entered into clinical trials. Still, Carboplatin and oxaliplatin were approved internationally, and nedaplatin, lobaplatin, and heptaplatin were approved in some individual nations [6,7]. Gastric cancer is the third most common reason of death globally death occurring due to cancer. In the year 2018, a survey of global deaths analyzed that 8.2% of cancer-related deaths are due to gastric cancer, one in every twelve deaths. Chemotherapy using platinum-based anticancer drugs is widely used in the advanced treatment of gastric cancer, and according to the National Comprehensive Cancer Network (NCCN) guidelines, Cisplatin or oxaliplatin in addition to fluoropyrimidine regimen is advised as the first-line chemotherapy treatment [8,9]. In 1989, Carboplatin was found to be available in the U.S. under the name Paraplatin®, initially used in advanced ovarian cancer treatment. Many Cisplatin derivatives have been further introduced, and in 1994, the third Cisplatin derivative to be approved was oxaliplatin under the name of Eloxatin®.

Oxaliplatin was found to be the first platinum-derived anticancer compound effective against the treatment of metastatic colorectal cancer in addition to fluorouracil and folinic acid. The other cisplatin derivatives used for effective cancer treatment were nedaplatin, available in the name of Aqupla® in Japan, Lobaplatin in China, and Heptaplatin in Korea in the treatment of small lung cancer cell line, respectively [10-12]. In recent years, structure-based drug design has grown rapidly to investigate the prior knowledge of the drugs before the clinical trials and has shown accurate results in the prediction of the binding sites of the target drug with the protein structure. The drug target is chosen based on biological and biochemical factors. Target detection of cancer cell structure is found to be very difficult because cancer targets are frequently somatic cell mutants of protein structure that normalize essential cellular functions, resulting in functional loss. Functional recovery is difficult when using a small molecule. According to the perception of W. Kaelin, a molecule's functional loss is associated with the gain of function in another molecule. Another problem in anticancer drug design is the distraction of oncogenic complexes [13-15].

Molecular docking is a computational method widely used in drug discovery and the preferred mechanisms of interaction of the platinum-based anticancer drug compound with the cancer cell structure downloaded from the RCSB protein data bank as target protein were studied [16].

In our present investigation, the molecular biological behavior of metal-based anticancer drug Cisplatin and its derivatives, such as Carboplatin, Nedaplatin, Oxaliplatin,

Heptaplatin, and lobaplatin against the three types of cancer type structures: gastric cancer cell, lung cancer cell, and colorectal cancer cell structure was performed. Based on the structure-based drug design analysis using molecular docking analysis, the effective binding affinity, least binding energy values, and active binding sites of the drug compounds with the target protein structure were investigated and compared. This is to justify the binding efficacy of the chosen drug compounds based on the binding score obtained using molecular docking software in structure-based drug design. An investigation of the nearest binding residues of the protein target and bonding parameters with the drug compound as a ligand was conducted. The molecular bonding types such as conventional hydrogen bond, charge bond, and alkyl bond of the target protein structure with the drug compound as ligand and their bond length details were also studied using the docking results. Investigation of the pharmacokinetic and drug-likeness properties of the candidate drug molecules and simulation of protein−ligand interactions through molecular docking. Docking studies revealed that the cisplatin derivatives as ligand molecules produced better scoring functions and drug-likeness behavior than present therapeutics.

## 2. Materials and Methods

### *2.1. Ligand preparation.*

The 2D structures of Cisplatin and derivatives [17] were drawn using the chem sketch shown in Figure 1. Cisplatin and its derivatives 3D optimized structures were drawn using Avogadro software saved in CML file format, converted into PDB format using Open Babel Software [18-20] suitable for Auto dock 4.2 software, and chosen to be the ligand molecule. Since the ligand molecular structures possess platinum atoms, the modified necessary parameter was to be added in the parameter file obtained from the Auto Dock website.

### *2.2. Protein preparation.*

The cancer protein molecular structures of gastric cancer cells, lung cancer cells, and colorectal cancer cells were downloaded using the RCSB protein database with the PDB ID 7ev1, PDB 6l94, and PDB 7wet, respectively [21,22]. All necessary steps needed for the preparation of protein were performed using the information provided in the Autodock Tools package. For all protein structures, the grid box dimensions are set for blind docking.

### *2.3. Docking process.*

The grid box center was located in the center of the protein structure [23]. The maximum number of energy evaluations was set to 2,500,000. Twenty runs were performed with a maximum number of 27,000 GA on a single population of 150 individual species. The ligand and protein structures were saved in PDBQT file format using AutoDock tools, and molecular docking was performed using AutoDock 4.2 program. The docking parameter result analysis of the Cisplatin and its derivatives as ligands with three types of cancer cell structures was done using the BIOVIA discovery studio visualizer package.

## 3. Results and Discussion

*3.1. Binding energy analysis.*

The docking results of the title compounds with the three types of cancer cell structures were analyzed and tabulated.

**Table 1.** Least binding energy values of drug with cancer cell structure in kcal/mol.

| S.No | Platinum-based anticancer drug | The least binding energy values of drugs with cancer cell structure inkcal/mol | | |
|---|---|---|---|---|
| | | gastric cancer cell structure | lung cancer cell structure | colorectal cancer cell structure |
| 1 | Cisplatin | -9.42 | -5.28 | -6.56 |
| 2 | Carboplatin | -10.73 | -7.2 | -6.72 |
| 3 | Nedaplatin | -9.46 | -5.53 | -5.1 |
| 4 | Oxaliplatin | -9.09 | -5.41 | -7.06 |
| 5 | Heptaplatin | -8.1 | -5.74 | -5.64 |
| 6 | Lobaplatin | -9.96 | -5.94 | -6.56 |

Table 1 represents the least binding energy values in kcal/mol obtained by docking the title compounds with the cancer cell structures. Among cisplatin derivatives, Carboplatin has the highest binding affinity towards the gastric cancer cell structure with an affinity value of -10.73 kcal/mol, and its binding affinity values with the lung and colorectal cancer cell structures are -7.20 kcal/mol and -6.72 kcal/mol, respectively, i.e., showing good results among all the other drug derivatives. Next to Carboplatin, Lobaplatin shows good binding affinity towards the cancer cell structures in the order mentioned above with the least binding energy values as -9.96 kcal/mol, -5.94 kcal/mol, and -6.56kcal/mol. When compared with other drug derivatives, Cisplatin shows lesser binding affinity with cancer cell structures at -9.42 kcal/mol, -5.28 kcal/mol, and -6.56 kcal/mol. In the case of gastric cancer, the other two compounds, besides lobaplatin, also show good binding affinity scores of -9.46 kcal/mol and -9.09 kcal/mol, respectively. All the drug compounds show good binding affinity towards the PDB ID 7ev1ranges from 8.1 kcal/mol to -10.73 kcal/mol, but with PDB 6l94, binding energy values range from -5.28 kcal/mol to -5.94 kcal/mol except Carboplatin has - 7.20 kcal/mol. The binding energy values for PDB 7wet docked with the drug compounds range from -5.10 kcal/mol to -7.06 kcal/mol, and it is found that Cisplatin and lobaplatin show the same docking score as -6.56 kcal/mol and nedaplatin has the least binding energy as - 5.10 kcal/mol than the other drugs.

*3.2. Inhibition constant analysis.*

Inhibition Binding constant $K_{max}$ in MicroMolar or Nanomolar obtained by docking of thetitle compounds with the cancer cell structures. All the drug compounds were tabulated in Table 2. From the Inhibition constant values mentioned in Table 2. Noted that the drug compounds interaction with gastric cancer structures $K_{max}$ values expressed in nanomolar ranges from 13.64 nM to 216.03 nM except Heptaplatin, i.e., 1.06 µM and for the other cancer structures expressed in micromolar 5.31 µM to 227.91 µM.

**Table 2.** Inhibition constant values of drug with cancer cell structure in µmolar/nmolar.

| S.No | Platinum-based anticancer drug | Inhibition constant values of drug with cancer cell structure in µM/nM | | |
|---|---|---|---|---|
| | | gastric cancer cell structure | lung cancer cell structure | colorectal cancer cell structure |
| 1. | Cisplatin | 124.48nM | 134.79 µM | 72.53 µM |
| 2. | Carboplatin | 13.64nM | 5.31 µM | 45.70 µM |
| 3. | Nedaplatin | 115.86nM | 88.45 µM | 227.91 µM |
| 4. | Oxaliplatin | 216.03nM | 108.90 µM | 26.97 µM |
| 5. | Heptaplatin | 1.07µM | 62.42 µM | 66.63 µM |

| S.No | Platinum-based anticancer drug | Inhibition constant values of drug with cancer cell structure in µM/nM | | |
|---|---|---|---|---|
| | | gastric cancer cell structure | lung cancer cell structure | colorectal cancer cell structure |
| 6. | Lobaplatin | 50.22nM | 44.20 µM | 40.15 µM |

Oxaliplatin shows the highest binding affinity for colorectal cancer structure with the least binding energy value of -7.06 kcal/mol, while Carboplatin has -6.72 kcal/mol. It is observed that all the drug compounds show better docking scores with gastric cancer structure than the other two types of structures. Heptaplatin was found to show a lesser binding affinity for all the cancer cell structures when compared with the other drug compounds.

*3.3. Binding residue analysis.*

Table 3 represents the nearest active binding residues of the drug compounds with Gastric cell (PDB ID 7ev1). It has been observed that ASP85, GLU87, and ASP121 residues of the Gastric cell structure were found to be the common binding residues of the protein with all Ligands.

**Table 3.** Nearest binding residues of gastric cancer cell structure with target drug compound.

| S.No | Platinum-based anticancer drug | Binding residues |
|---|---|---|
| 1. | Cisplatin | GLU87, ASP85, ARG86, GLY41, GLY40, LEU84, GLU40, ASN122, ASP121 |
| 2. | Carboplatin | ASP121, GLU87, ASP85, LEU84, GLU40 |
| 3. | Nedaplatin | ASN122, ASP121, ASP154, ILE119, ARG86, GLU40, LEU84, ASP85, GLY41, THR88, GLU87 |
| 4. | Oxaliplatin | ASN122, ASP121, GLU87, GLU40, ALA83, ASP85 |
| 5. | Heptaplatin | LEU153, ASN122, ASP121, GLY41, GLU87, ASP85 |
| 6. | Lobaplatin | GLU87, ASP85, ASP154, ASP121, ASN122, GLU40 |

Table 4 represents the nearest active binding residues of the drug compounds with Lung cancer cell (PDB ID 6l94).

**Table 4.** Nearest binding residues of lung cancer cell structure with target drug compound.

| S.No | Platinum-based anticancer drug | Binding residues |
|---|---|---|
| 1. | Cisplatin | GLU145, LYS148, ARG152, GLU325 |
| 2. | Carboplatin | GLU320, GLN117, SER194, PRO193 |
| 3. | Nedaplatin | SER194, ASP195, GLU320, GLN117 |
| 4. | Oxaliplatin | GLN345, GLU215, LEU347, THR349 |
| 5. | Heptaplatin | TRY175, ASP352, GLU215 |
| 6. | Lobaplatin | ASP187, LEU355, PHE353 |

It has been observed that GLU215 is the common residue of the protein binding with Oxaliplatin and Heptaplatin, and SER194 is the common residue of the protein binding with Carboplatin and Nedaplatin. Table 5 represents the nearest active binding residues of the drug compounds with colorectal cancer cell (PDB ID 7wet) structure. It is found that ASP167 residue binds with all ligands except Heptaplatin.

**Table 5.** Nearest binding residues of colorectal cancer cell structure with target drug compound.

| S.No | Platinum-based anticancer drug | Binding residues |
|---|---|---|
| 1. | Cisplatin | ASP167, ASP135, LYS136, ASP134, TYR38 |
| 2. | Carboplatin | ASP167, LYS168, ASP135 |
| 3. | Nedaplatin | ASP167, LYS168, ASP135 |
| 4. | Oxaliplatin | ASP135, ASP167, GLU171 |
| 5. | Heptaplatin | LYS16, ASN14, ASP115 |
| 6. | Lobaplatin | PRO148, ASP167, HIS169, GLY170, GLU171, VAL172 |

Figure 1 represents the two-dimensional structures of Cisplatin and its derivatives. All platinum-based anticancer drug compounds.

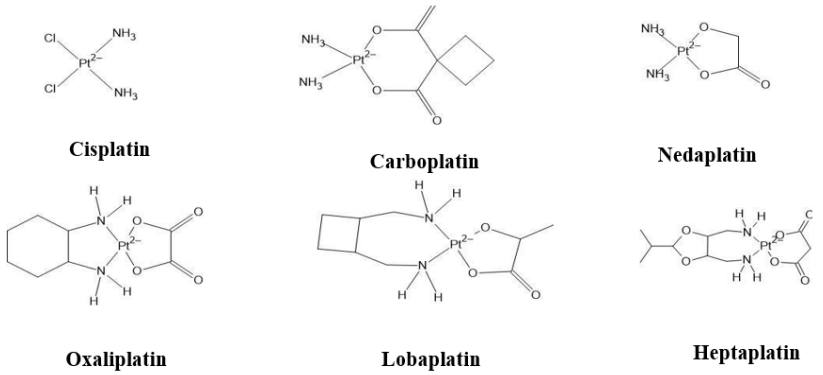
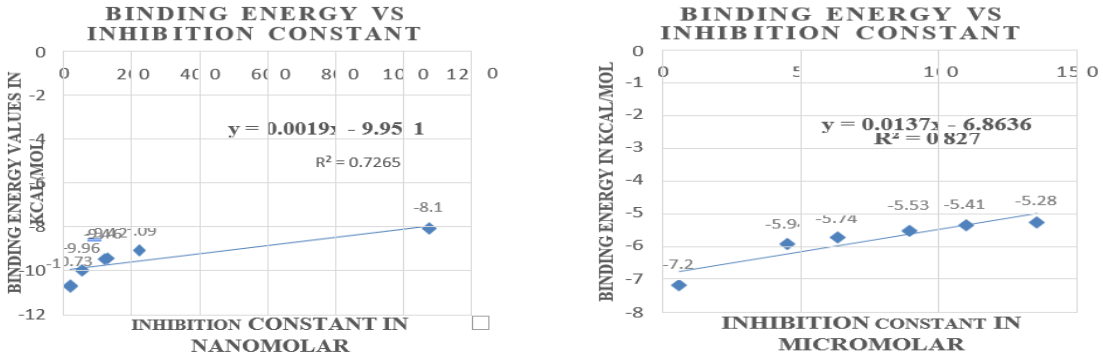



**Figure 1.** Chemical structure of Cisplatin and its derivatives.

*3.4. Binding energy vs inhibition constant analysis.*

Figures 2 (a), Figure 2 (b), And 3 represent the plot between binding energy and $K_i$ and theirrelationship for the docked protein structures PDB ID 7ev1, PDB 6l94, and PDB 7wet with the above-mentioned drug compounds.




**(a)** **(b)**

**Figure 2.** (**a**) Binding energy values vs. inhibition constant values of 7ev1 with drug compounds; (**b**) binding energyvalues vs. inhibition constant values of 6l94 with drug compounds.

The plot shows that the relationship is linear with $R^2$ values of 0.7265, 0.827, and 0.7267, respectively, stating that each drug compound with more binding energy has a higher inhibition constant [24]. $R^2$ is the regression or correlation of difference; thus, for PDB 6l94, the drug compounds show more correlation with anticancer behavior.

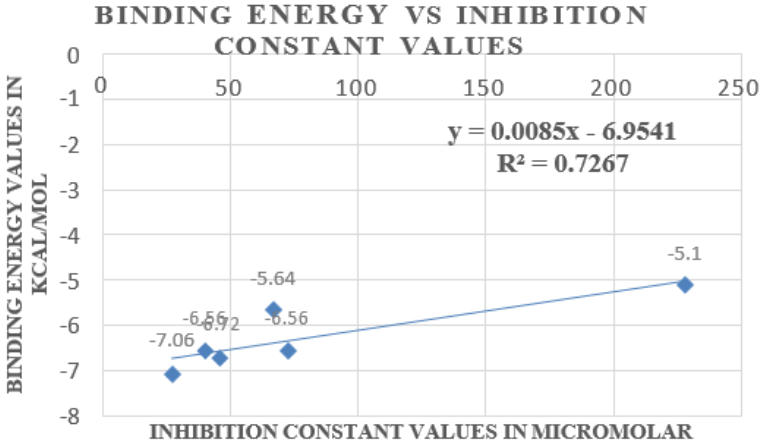



**Figure 3.** Binding energy values vs. inhibition constant values of 7wet with drug compounds.

*3.5. Binding parameter analysis.*

The binding residues form types of bonds such as conventional hydrogen bonds indicated green in color, charge-charge bonds in orange color, and alkyl bonds in pink color, asrepresented in Figure 4 and Figure 5. Cisplatin $NH_3$ atoms form bonding with PDB ID 7ev1 bond length in the range of 2.47 Å, 2.44 Å, and 2.16 Å. ASP85, ASN122, ASP121, and $NH_2$ with ASN122 are Donor type bonds, but in Carboplatin, $NH_3$ atoms on both sides of its structure form bond lengths in the order of 1.82 Å with GLU87 and 1.89 Å with ASP121 residues, 2.4 Å with GLU40, Pt with ASP85 has bond length 3.52 Å residue respectively and it is found that only convention type of bonds occurs.

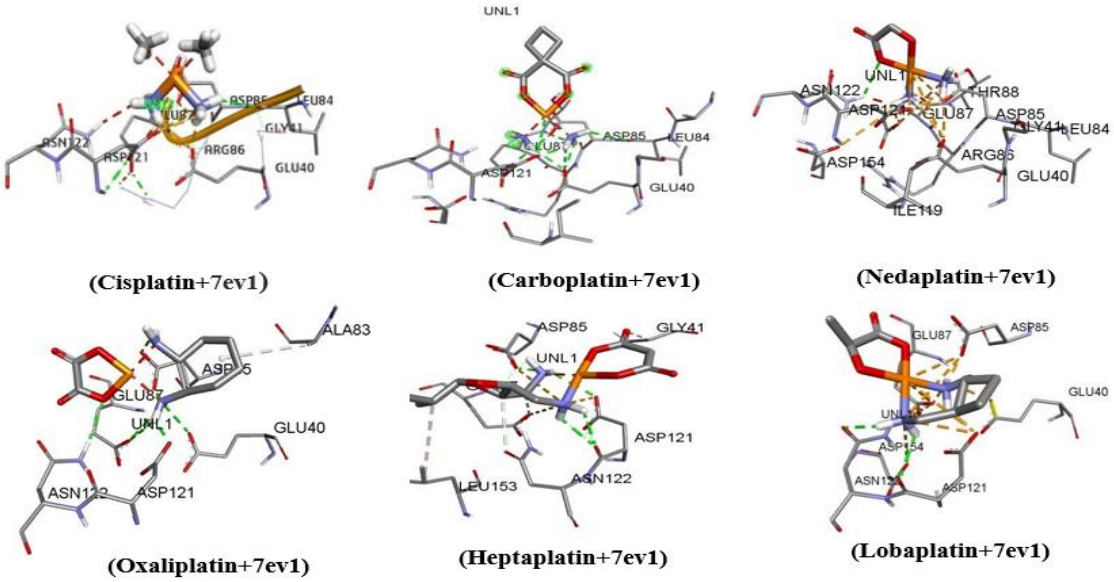



**Figure 4.** Binding residues of PDB ID 7ev1 with the drug compounds.

In the case of nedaplatin, the bond length between O-ASN122 is 2.73 Å. It is a donor-type bond, and $NH_3$- ASN122 is 1.98 Å, Pt-ASP121, and Pt-ASP85 show a very weak bond length of 5.03 Å, In Oxaliplatin O-ASN122 is 2.44 Å, $NH_2$-ASP121 has 1.61 Å, one $NH_2$ with ASP85 bond length is 1.75 Å and other shows 2.25 Å, in the same way, $NH_2$ bonds with GLU40 and GLU87 in the range of 2.48 Å, 2.91 Å and 2.92 Å and Hexagonal ring structure of Oxaliplatin forms alkyl bond of length 4.41 Å with ALA83. Oxaliplatin with PDB ID 7ev1 was observed to have all conventional hydrogen bonds and one alkyl bond but no charge bond. In Heptaplatin with PDB ID 7ev1 protein structure, the bonded residues with ligand atoms are $NH_2$-ASP121, $NH_2$-ASP85, $NH_2$-ASN122 in the bond length order 2.22 Å, 2.15 Å, 2.68 Å respectively, in addition, it has shown two carbon type bonds between =O with GLY41 and Carbon of the ligand with LEU153 as 2.74 Å and 4.91 Å.

Lobaplatin with PDB ID 7ev1 $NH_2$-ASP121 bonding occurs with lengths 2.30 Å and 2.22 Å. In the same way, the drug compounds with the other structures PDB 6l94 and PDB 7wet form the bonding in the range of 2 Å with hydrogen atoms of $NH_3$ =O, Carbon atom, and Pt atom showing different types of bonding. From the calculated Docking parameters, it is observed that Platinum-based anticancer drugs show efficient binding affinity to gastric cancer, lung cancer, and colorectal cancer also in specifically comparing to all the three types of cancer cell structures with good binding affinity with least binding energy values with lesser inhibition constant of the cisplatin derivatives was identified with gastric cell structure with PDB ID 7ev1 and among all the drug compounds carboplatin found to have the best binding affinity with the

least binding energy value -10.73 Å. Figure 5 represents Binding residues of PDBID 6l94 and PDBID 7wet with the drug compounds.

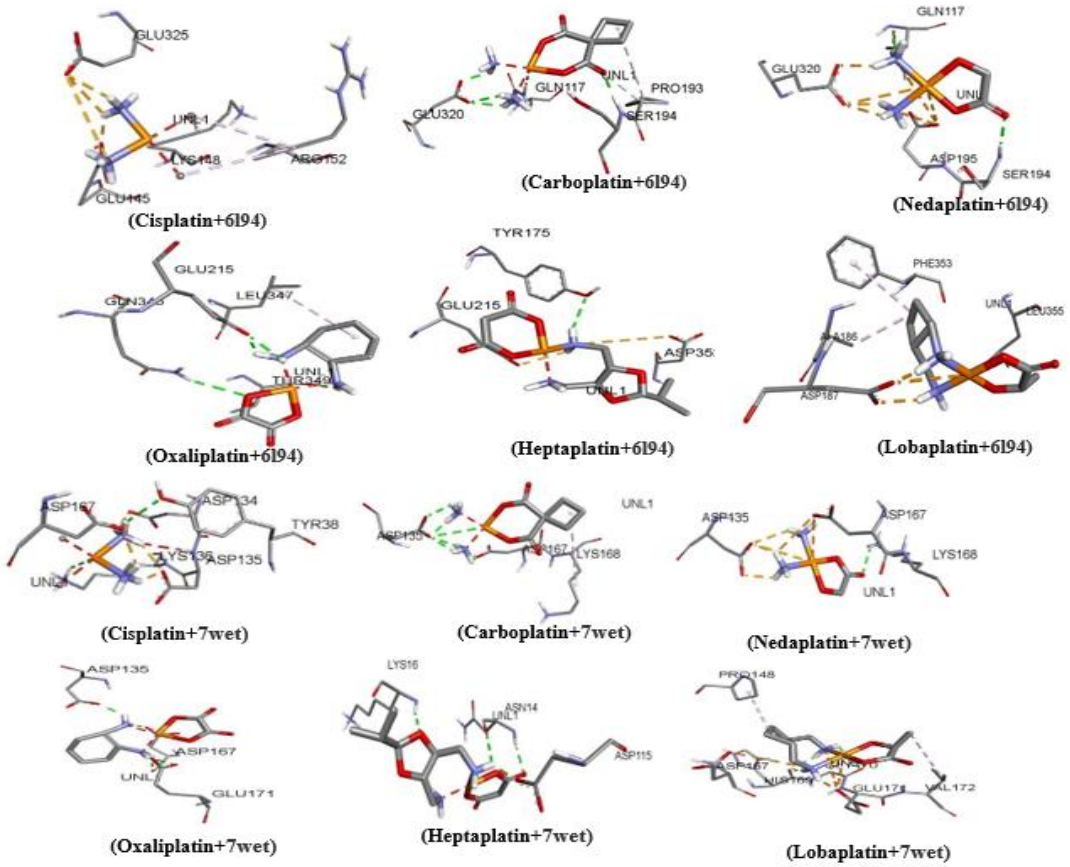



**Figure 5.** Binding residues of PDBID 6l94 and PDBID 7wet with the drug compounds.

## 4. Conclusions

Cancer is one of the leading causes of global deaths. Our molecular docking studies highlight the platinum-based Cisplatin and its derivative's binding affinity with different types of cancer cell structures downloaded from the RCSB protein database with PDB ID 7ev1, PDB 6l94, and PDB 7wet structures. The Docking studies of the title drug compounds were investigated using the widely used molecular docking studies using Autodock software 4.2, and the results were analyzed using the BIOVIA discovery studio visualizer package. From the obtained results, it is observed that Carboplatin showed good binding affinity with the least binding energy value of -10.73 kcal/mol and all the drug compounds showed good binding affinity to Gastric cancer cell structure with binding energy values ranging from - 8.10 kcal/mol to -10.73 kcal/mol and the inhibition constant ranging from 13.64 nM to 216.03 nM and 5.31 µM to 227.91 µM. The active binding sites of the protein structures were also analyzed. It found that the binding residues show different types of bond types such as conventional bond type, Charge-Charge bond, Donor and Alkyl bond, and the bond length in the orders of lesser than or equal to 2 Å. Moreover, the relationship of binding energy with the inhibition constant was studied using the graph plot between binding energy vs. inhibition constant, and correlation was also studied. It was concluded that the more binding energy there was, the higher the inhibition constant was, and vice versa. Thus, we conclude that platinum-based anticancer drugs have shown high drug-likeness behavior with the gastric cancer cell structure compared with the lung and colorectal cancer cell structures.

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## Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the study's design, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

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