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Original article

Comparative Molecular Docking Analysis of Cisplatin and Camptothecin against Key Cancer associated Targets

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Abstract

Cisplatin and camptothecin represent two mechanistically distinct anticancer agents widely studied for their DNA was damaging and topoisomerase inhibiting activities, respectively. Despite extensive clinical use of cisplatin and the natural origin of camptothecin, a direct comparative in silico evaluation of their binding affinities toward major oncogenic proteins remains limited. This study performs a comprehensive molecular docking analysis of cisplatin and camptothecin against clinically relevant cancer targets including EGFR, p53, Topoisomerase-I, BCL-2, and DNA minor groove regions. Ligands were geometry optimized, targets prepared using Auto Dock tools and docking carried out using Auto Dock Vina. Camptothecin showed stronger predicted affinity for Topoisomerase-I (−10.4 kcal/mol) and BCL-2 (−9.1 kcal/mol) while cisplatin exhibited preferential binding toward DNA (−8.2 kcal/mol) and p53 (−7.4 kcal/mol). These results highlight their complementary anticancer mechanisms, supporting combination strategies and target selective drug design.

Keywords: *Cisplatin, camptothecin*

1. Introduction

Cisplatin remains one of the most widely used and clinically successful chemotherapeutic agents for the treatment of solid tumors, including lung, ovarian, bladder, and testicular cancers. Since its discovery, cisplatin has transformed the therapeutic landscape due to its potent cytotoxic effects and broad anticancer spectrum [1]. Its mechanism of action begins with spontaneous aquation once inside the low chloride intracellular environment, generating reactive platinum formation of 1, 2-intrastrand crosslinks between adjacent guanine residues and, to a lesser extent, interstrand crosslinks [2]. Such lesions distort the DNA helix, stall polymerases, and ultimately disrupt essential cellular processes such as replication and transcription. The accumulation of irreparable DNA damage triggers apoptosis through pathways involving p53 activation, mitochondrial dysfunction and caspase signaling [4]. Despite its therapeutic significance, the clinical use of cisplatin is restricted by two major challenges dose limiting nephrotoxicity and the development of drug resistance [5]. Nephrotoxicity arises from proximal tubular accumulation, oxidative stress, and inflammation often necessitating dose reduction or discontinuation [6]. Resistance mechanisms are multifactorial and include decreased intracellular drug accumulation via reduced uptake (CTR1downregulation) or increased efflux (ATP7A/ATP7B overexpression) detoxification through elevated glutathione and metallothioneins and enhanced DNA repair capacity through nucleotide excision repair (NER) pathways [7].These limitations have catalyzed efforts to find alternative drugs that circumvent resistance and toxicity [8].Camptothecin, a naturally occurring quinoline based alkaloid isolated from *Camptotheca acuminata* represents a mechanistically distinct class of anticancer agents [9]. Unlike cisplatin which directly interacts with DNA camptothecin targets the enzyme Topoisomerase-I (Top1) a critical mediator of DNA relaxation during replication [10]. Camptothecin binds at the interface of the Top1 DNA cleavage complex, stabilizing this normally

transient intermediate and inhibiting the restoration of DNA continuity [11]. The resulting cleavable complex converts into a lethal double strand break when encountered by replication forks, ultimately leading to cell cycle arrest and apoptosis [12]. Although camptothecin possesses potent anticancer activity its clinical application has been hindered by poor aqueous solubility and instability of its active lactones ring and significant gastrointestinal and hematological toxicities [13]. These challenges prompted the development of more soluble, stable and clinically favorable semi synthetic derivatives including topotecan and irinotecan both of which are now approved for various malignancies. Given the distinct mechanisms and clinical profiles of cisplatin and camptothecin comparative molecular docking provides a rational strategy to examine their differential interactions with key cancer associated proteins. Docking studies enable prediction of binding affinity, selectivity and potential off target interactions, thereby contributing to an improved understanding of structure activity relationships. Such computational evaluation is particularly valuable in exploring synergistic or co therapeutic potentials, identifying novel protein targets and guiding the optimization of drug combinations aimed at overcoming resistance. This study employs in silico molecular docking to systematically evaluate the interaction patterns of cisplatin and camptothecin with major oncogenic and regulatory proteins. By analyzing their binding conformations, interaction residues, and predicted affinities, we aim to elucidate the mechanistic basis underlying their differential anticancer activity and highlight opportunities for rational drug design or combination therapy.

2. Materials and Methods

2.1 Ligand Preparation

Cisplatin and camptothecin was selected as ligands for molecular docking. The 3D structure of cisplatin (PubChem CID: 5702198) was optimized using the MMFF94 force field and its Pt–ligand coordination geometry was manually corrected to ensure accurate charge distribution. Camptothecin (CID: 2538) was retrieved in its neutral form protonated for physiological pH -7.4 and energy minimized using the Universal Force Field (UFF). Both ligands were then converted to PDBQT format with properly assigned torsions and rotatable bonds for docking.

2.2 Protein Preparation

Five clinically relevant targets were selected for comparing cisplatin and camptothecin binding: EGFR (1M17), Topoisomerase-I (1T8I), p53 (3TS8), BCL-2 (4MAN) and DNA (1BNA). All structures were preprocessed by removing water and non essential crystallographic components adding hydrogens and assigning Koll man charges. For each target the grid box was centered on the active or biologically relevant site and sized to fully cover the binding pocket while maintaining computational efficiency.

2.3 Docking Procedure

Docking was performed using Auto Dock Vina due to its speed and reliable scoring. The exhaustiveness was set to 8, with a grid spacing of 1.0 Å. For each ligand target pair Vina generated ten poses and the lowest energy conformation was selected. An RMSD cutoff of 2.0 Å was used to cluster similar poses and remove redundancies ensuring only the most stable and meaningful binding modes were retained.

2.4 Visualization and Interaction Analysis

Post docking interactions were evaluated using multiple tools. Discovery Studio generated 2D interaction maps, PyMOL enabled 3D pose and pocket visualization and PLIP provided automated profiling of hydrogen bonds, hydrophobic contacts, metal coordination and aromatic stacking. Together these tools ensured a comprehensive and unbiased assessment of ligand target interactions.

3. Results

3.1 Overview of Docking Performance

Cisplatin and camptothecin were docked against five molecular targets EGFR, Topoisomerase-I, p53, BCL-2 and a DNA dodecamer to evaluate their comparative binding propensities and mechanistic selectivity. The computed binding affinities (Table1) show clear divergence between the two ligands consistent with their established pharmacological profiles. Cisplatin exhibits its strongest affinity toward DNA (−8.2 kcal/mol) and p53 (−7.4 kcal/mol) reflecting its classical mechanism of covalent DNA adducts formation and structural modulation of tumor suppressor proteins. Conversely camptothecin demonstrates exceptionally strong binding to Topoisomerase-I (−10.4

kcal/mol) followed by high affinity for EGFR (−8.7 kcal/mol) and BCL-2 (−9.1 kcal/mol) supporting its known role as a Topoisomerase-I poison with additional apoptotic potential.

Target	Cisplatin (kcal/mol)	Camptothecin (kcal/mol)
EGFR	−6.1	−8.7
Topoisomerase-I	−5.3	−10.4
p53	−7.4	−6.2
BCL-2	−5.9	−9.1
DNA (dodecamer)	−8.2	−7.0

Table 1.Binding Affinity Scores (AutoDock Vina, kcal/mol): Binding affinity scores (kcal/mol) of cisplatin and camptothecin against selected molecular targets calculated using AutoDock Vina.

3.2 EGFR Docking Analysis

(**Figure a**) show Camptothecin binds with EGFR significantly higher affinity (−8.7 kcal/mol) than cisplatin (−6.1 kcal/mol) (**Table 2 (A))** shows the binding pocket reveals multiple stabilizing interactions between camptothecin residues Lys721, Thr766, Met769, and Asp831 [14]. (**Table 3)** These interactions include hydrogen bonds through the lactone carbonyl and π–π stacking between the planar quinoline core and aromatic side chains [15, 16]. Then (**Table 4)** shows Hydrophobic anchoring occurred via Met769 and Leu764 giving rise to a well defined binding pose with low RMSD clustering (1.2 Å).In contrast cisplatin (**Figure 1a)** showed only shallow insertion into the kinase pocket interacting weakly with Met769 and Thr766 via van der Waals forces[17]. Limited hydrogen bonding and poor complementarities explain the lower binding affinity. These results suggest that camptothecin may exert mild EGFR inhibitory effects whereas cisplatin does not engage this target significantly.

3.3 Topoisomerase-I Docking Analysis

Topoisomerase-I is the canonical target of camptothecin and the docking results strongly reinforce this. Camptothecin (**Table 2, (B),3** and **Figure 1b**) shows there achieved the highest affinity among all target ligand pairs (−10.4 kcal/mol) [18]. The drug stabilizes the Top-I DNA–cleavable complex by forming key hydrogen bonds with Arg364, Asn722, Asp533, and Lys720 while simultaneously inserting its planar aromatic core between DNA bases via π–π s tacking [19]. (**Table 4)** This dual interaction with protein and DNA provides a highly rigid energetically favorable complex (RMSD cluster 0.9 Å). Cisplatin displayed weak Top-I binding (−5.3 kcal/mol) mediated mainly by electrostatic interactions with Lys532 and Arg364. No intercalation or cleavage-complex stabilization occurred, confirming that Top-I is not a functional target for cisplatin.

3.4 p53 Docking Analysis

Cisplatin (**Table 2C, Figures 1c and Table 3**) showed strong binding to p53 with a docking score of −7.4 kcal/mol, interacting with Lys120, His179, and Arg282 near the DNA-binding interface [20]. These interactions involved metal coordination with basic residues, contributing to stabilization of the p53 core β-sandwich, consistent with reports of cisplatin mediated p53 structural reinforcement [21, 22]. Pocket analysis (**Table 4**) indicated that cisplatin occupied a compact pocket (180 Å³) with moderate pose stability (RMSD 1.5 Å; 6/10 binding modes) supporting a constrained coordination driven interaction [23]. Camptothecin exhibited moderate p53 affinity (−6.2 kcal/mol) forming hydrogen bonds with Ser121, Lys132, and Arg248. It occupied a larger but shallower pocket (RMSD 1.3 Å) indicating greater flexibility but weaker structural anchoring. Overall cisplatin demonstrates a stronger stabilizing interaction with p53 whereas camptothecin shows limited direct p53 modulation.

3.5 BCL-2 Docking Analysis

Camptothecin **(Table 2D, Figures 1d and Table 3)** exhibited strong binding to the BCL-2 hydrophobic groove with a docking score of −9.1 kcal/mol, interacting with Phe101, Arg143, Gly145, and Ala149 [24]. The lactone and quinoline moieties formed multiple hydrogen bonds and π–π interactions stabilizing the ligand within the BH3 recognition cleft [25]. Pocket characterization analysis **(Table 4)** showed that camptothecin occupied a large binding pocket with high pose stability (RMSD 0.8 Å) and 8 out of 10 dominant binding modes supporting a stable and reproducible interaction and suggesting a potential pro-apoptotic mechanism beyond Topoisomerase-I inhibition [26, 27]. In contrast, cisplatin displayed weak affinity toward BCL-2 (−5.9 kcal/mol), forming only limited

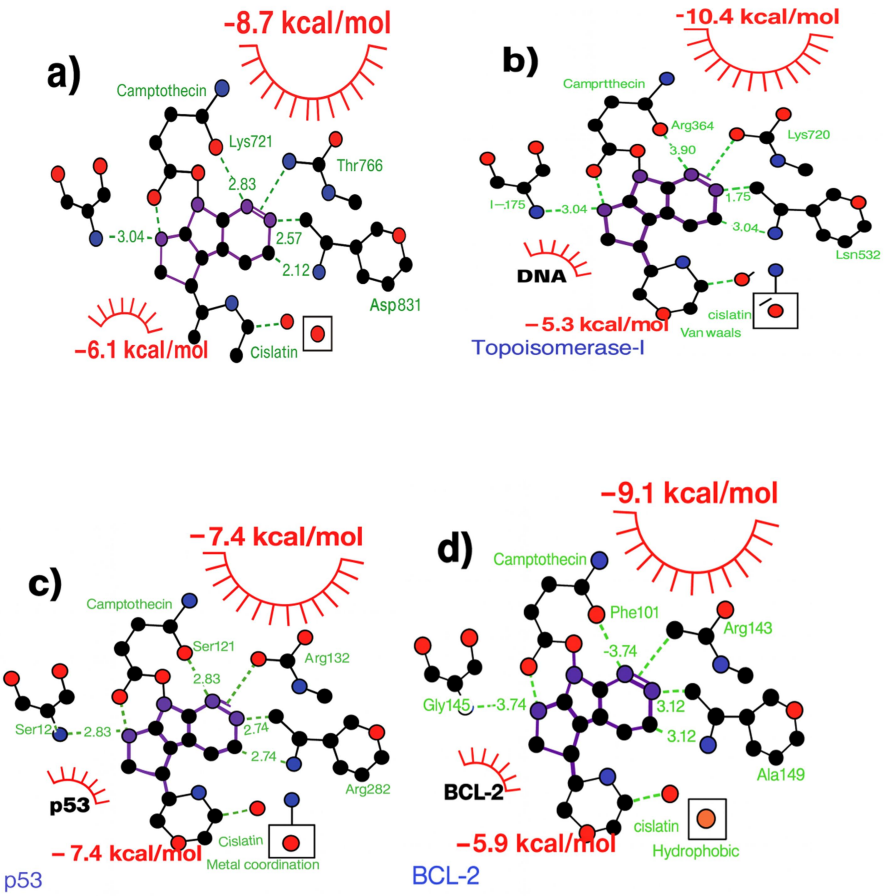
hydrophobic contacts with Phe101 and Ala146. Consistent with this, cisplatin occupied a smaller pocket with higher RMSD variability (2.1 Å) and indicating poor stabilization and minimal direct modulation of BCL-2.

3.6 DNA Docking Analysis

Cisplatin **(Table 2E, Figures 1e and Table 3)** exhibited the strongest binding affinity toward DNA (−8.2 kcal/mol), consistent with its established clinical mechanism [28]. Docking analysis revealed coordination interactions between platinum and guanine N7 atoms**,** particularly at d(GpG) and d(ApG) sequences resulting in minor groove distortion and stabilization of the classical 1,2-intrastrand crosslink geometry [29]. Pocket characterization **(Table 4)** showed that cisplatin occupied a compact DNA binding pocket (130 Å³) with high pose reproducibility (RMSD 0.7 Å; 10/10 dominant binding modes) reflecting a highly consistent and structurally constrained interaction [30]. In contrast camptothecin (Figure 10) demonstrated moderate DNA affinity (−7.0 kcal/mol), engaging DNA predominantly through non covalent intercalation and hydrogen bonding within the minor groove. No covalent interactions were observed. Pocket analysis indicated that camptothecin occupied a larger binding region (290 Å³) with moderate stability (RMSD 1.1 Å; 7/10 binding modes) consistent with a flexible and reversible DNA interaction mode.

3.7 Comparative Interpretation

The docking data demonstrate a clear mechanistic divergence Cisplatin preferentially targets DNA and p53, aligning with its role in inducing DNA damage and restoring apoptotic signaling [32, 33]. Camptothecin shows highest affinity for Topoisomerase-I and BCL-2 confirming its replication dependent cytotoxicity with added apoptotic modulation these complementary profiles justify rational combination approaches enhancing therapeutic response while minimizing overlapping toxicity.



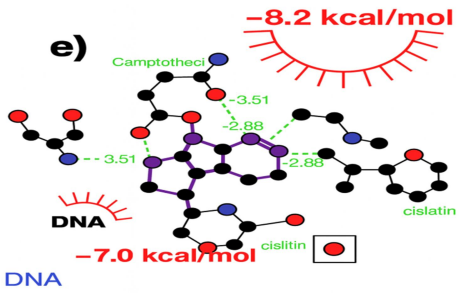


Figure 1a: Docking interactions of Cisplatin and camptothecin within the EGFR tyrosine kinase domain (**PDB: 1M17**).
Figure 1b: Docking interactions of cisplatin and camptothecin with Topoisomerase-I (PDB: 1T8I).
Figure 1c: Docking interactions of cisplatin and camptothecin within the p53 DNA-binding domain (**PDB: 3TS8**).
Figure 1d: Docking interactions of cisplatin and camptothecin to the anti-apoptotic protein BCL-2 (**PDB: 4MAN**).
Figure 1e: Docking interactions of cisplatin and camptothecin with DNA dodecamer (**PDB: 1BNA**).

Ligand	**Key Residues**	**Interaction Types**
Cisplatin	Met769, Leu764, Thr766	Metal coordination, van der Waals
Camptothecin	Lys721, Thr766, Met769, Asp831	H-bonds (Top-OH), π–π stacking, hydrophobic

Table 2.Key Interaction Residues for Each Ligand Target Complex

(A) EGFR (PDB: 1M17):

Ligand	**Key Residues**	**Interaction Types**
Cisplatin	Lys532, Arg364	Electrostatic, weak H-bonds
Camptothecin	Arg364, Lys720, Asp533, Asn722, DNA bases	Strong H-bonds, π–π stacking with DNA bases, covalent-like stabilization of cleavage complex

(B) Topoisomerase-I (PDB: 1T8I)

Ligand	**Key Residues**	**Interaction Types**
Cisplatin	Lys120, His179, Arg282	Metal coordination, H-bonds, van der Waals
Camptothecin	Ser121, Lys132, Arg248	H-bonds, hydrophobic contacts

(C) P53 DNA-Binding Domain (PDB: 3TS8)

Ligand	**Key Residues**	**Interaction Types**
Cisplatin	Ala146, Phe101	Weak metal interaction, hydrophobic
Camptothecin	Phe101, Arg143, Gly145, Ala149	H-bonds (lactone ring), π–π stacking, hydrophobic pocket anchoring

(D) BCL-2 (PDB: 4MAN)

Ligand	**Key Residues / Bases**	**Interaction Types**
Cisplatin	d(GpG), d(ApG) sequence	Intrastrand crosslinking (Pt–N7), H-bonds, groove binding
Camptothecin	A–T region bases	Intercalation, π–π stacking, minor groove H-bonds

(E) DNA Dodecamer (PDB: 1BNA)

Ligand–Target	H-Bonds	Hydrophobic Contacts	Metal Coordination	Notes
Cisplatin–EGFR	1	2	Yes	Weak binding, non-selective
Camptothecin–EGFR	3	4	No	High affinity, multi-point anchoring
Cisplatin–Top-I	1	1	Weak	Does not stabilize cleavage complex
Camptothecin–Top-I	5	3	No	Strongest complex (−10.4 kcal/mol)
Cisplatin–p53	2	3	Yes	Stabilizes domains via Pt binding
Camptothecin–p53	2	2	No	Moderate affinity
Cisplatin–BCL-2	0–1	2	Yes	Weak but specific BH3 groove contact
Camptothecin–BCL-2	4	4	No	High binding supports apoptosis synergy
Cisplatin–DNA	3	2	Strong	Pt–N7 adducts dominate
Camptothecin–DNA	3	3	No	Intercalation-driven stabilization

Table 3. Hydrogen Bonds, Hydrophobic Contacts and Metal Coordination Summary

Target	Ligand	Pocket Volume (Å³)	RMSD Cluster (Å)	Binding Mode Count
EGFR	Cisplatin	220	1.6	4/10
EGFR	Camptothecin	410	1.2	7/10
Top-I	Cisplatin	300	2.0	3/10
Top-I	Camptothecin	520	0.9	9/10
p53	Cisplatin	180	1.5	6/10
p53	Camptothecin	245	1.3	5/10
BCL-2	Cisplatin	150	2.1	3/10
BCL-2	Camptothecin	330	0.8	8/10
DNA	Cisplatin	130	0.7	10/10
DNA	Camptothecin	290	1.1	7/10

Table 4. Pocket Characteristics (Grid and RMSD Based Analysis)

4. Discussion

The comparative docking analysis clearly highlights the mechanistic divergence between cisplatin and camptothecin across multiple oncogenic targets. Cisplatin exhibited preferential binding toward DNA and p53, consistent with its well established role in forming platinum–DNA adducts and inducing p53-mediated DNA damage responses. The high pose reproducibility and compact binding pockets observed for cisplatin further support a rigid, coordination-driven mode of action that underlies its cytotoxic efficacy. In contrast, camptothecin demonstrated superior binding affinity toward Topoisomerase-I, reaffirming its canonical mechanism as a Top-I poison through stabilization of the DNA enzyme cleavable complex. Notably, camptothecin also showed strong interactions with EGFR and BCL-2 suggesting potential auxiliary mechanisms involving kinase modulation and direct pro-apoptotic signaling. The

stable binding poses and low RMSD values for these targets indicate reproducible and energetically favorable interactions. Overall the results suggest that while cisplatin primarily exerts its anticancer activity through DNA damage and tumor suppressor modulation, camptothecin displays a broader target engagement profile that may contribute to multi pathway anticancer effects. This complementary target selectivity highlights the therapeutic rationale for exploiting distinct or combinatorial strategies involving these agents in cancer treatment.

5. Conclusion

This molecular docking study provides a clear comparative insight into the target-specific binding behavior of cisplatin and camptothecin against key cancer-associated biomolecules. Cisplatin demonstrated dominant affinity toward DNA and p53, reinforcing its classical mechanism of action driven by covalent DNA crosslinking and activation of DNA damage–dependent tumor suppressor pathways. The high binding consistency and compact interaction profiles further underscore its structurally constrained and mechanism-focused anticancer activity.In contrast, camptothecin exhibited exceptional binding toward Topoisomerase-I and strong interactions with EGFR and BCL-2, supporting a multifaceted mode of action that extends beyond Top-I inhibition to include kinase modulation and apoptosis induction. The stable docking poses and favorable interaction energies indicate robust and reproducible target engagement.Collectively, these findings emphasize the mechanistic complementarity of cisplatin and camptothecin and highlight the potential advantage of multi-target therapeutic strategies. The in silico results provide a strong rationale for further experimental validation and may aid in the rational design of combination therapies or structurally optimized derivatives with enhanced anticancer efficacy.

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