

In Silico Design Of Phenyl Acetamide Derivatives As Parp1 Inhibitors Targeting Brca1/2-Mutated Breast And Ovarian Cancers.

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ABSTRACT

Objective: In this work, a number of new phenyl acetamide derivative compounds were designed and evaluated for their possible inhibitory effect against poly (ADP-Ribose) polymerase 1 (PARP1), a crucial enzyme linked to ovarian and breast malignancies with BRCA1/2 mutations. The goal was to compare these compounds with standard drugs *Olaparib* and *Niraparib*.

Methods: Molecular docking and MM-GBSA (Molecular Mechanics/Generalized Born Surface Area) calculations were performed to assess the binding affinity and stability of the ligand-PARP1 complexes (PDB ID: 5DS3). Interaction analyses focused on hydrogen bonding and key amino acid residues. ADME (Absorption, Distribution, Metabolism, and Excretion) profiling was conducted to evaluate pharmacokinetic properties and drug-likeness.

Results: Compound 6 (chloro phenyl acetamide) exhibited the highest docking score (-7.19 kcal/mol) and binding free energy (-67.26 kcal/mol), outperforming *Olaparib* (-7.06, -61.12 kcal/mol) and *Niraparib* (-6.99, -60.42 kcal/mol). Hydrogen bonding and π - π stacking interactions with critical residues such as GLY863 and TYR907 reinforced strong and stable binding. ADME results indicated low CNS penetration, high intestinal absorption, and minimal cardiotoxicity risk across all compounds, with most satisfying Lipinski's Rule of Five.

Conclusion: The study identified compound 6 (chloro phenyl acetamide) as the most promising PARP1 inhibitor, with superior binding affinity, thermodynamic stability, and favorable pharmacokinetic properties. These findings support its potential as a lead compound for further experimental validation in cancer therapy..

Keywords: : PARP1 inhibitors, Molecular docking, MM-GBSA, ADME, BRCA1/2, Olaparib, Niraparib, Cancer therapeutics, Hydrogen bonding, Drug-likeness.

1. INTRODUCTION

Breast and ovarian cancers remain among the most prevalent and deadly malignancies affecting women worldwide. The most prevalent disease in women to be diagnosed, breast cancer is also one of the main causes of death from cancer. In 2022 alone, over 2.3 million women were diagnosed globally, with an estimated 685,000 deaths attributed to the disease [1]. It originates predominantly in the epithelial cells of the ducts or lobules of the breast, with the most aggressive subtypes—such as triple-negative breast cancer (TNBC)—showing poor prognosis and limited therapeutic options. Ovarian cancer, though less

common than breast cancer, is notably more lethal due to its late detection and aggressive progression. About 313,000 new cases and 207,000 deaths from cancer were recorded worldwide in 2020, making it the seventh most common cause of cancer-related deaths among women [2]. High-grade serous carcinoma (HGSC), arising from the epithelium of the fallopian tubes or ovaries, is the most prevalent and aggressive subtype. Both cancers are characterised by complex genetic and molecular alterations. TP53 mutations are almost common in high-grade serous tumours in ovarian cancer, although mutations in the BRCA1 and BRCA2 genes greatly enhance vulnerability in breast cancer [3]. Cancer stem cells (CSCs) and dysregulation in signaling pathways such as PI3K/Akt/mTOR, MAPK, and estrogen receptor signaling play pivotal roles in tumor initiation, progression, metastasis, and resistance to therapy [4]. Despite advancements in early detection and treatment, the overall prognosis for advanced breast and ovarian cancer remains poor. First-line treatment typically involves surgery followed by chemotherapy. For breast cancer, tamoxifen, introduced in the 1970s, was among the first effective endocrine therapies targeting estrogen receptors [5]. In ovarian cancer, cisplatin and paclitaxel have served as standard chemotherapeutic agents since the 1990s [6]. More recent therapies include targeted agents such as poly (ADP-Ribose) polymerase 1 (PARP 1) inhibitors (e.g., *olaparib*) and immune checkpoint inhibitors, offering improved outcomes in selected patient populations [7]. However, challenges such as drug resistance, adverse effects, and tumor heterogeneity underscore the urgent need for novel therapeutic agents. Rational drug design targeting specific molecular pathways or cancer cell vulnerabilities is a promising approach to overcome these limitations. In this context, phenyl acetamide derivatives have emerged as a scaffold of interest due to their diverse pharmacological activities, including anticancer potential [8]. Structural modifications in these molecules may enhance selectivity, efficacy, and safety, making them suitable candidates for further biological evaluation.

In this work, new phenyl acetamide derivatives are designed, synthesised, and biologically evaluated as possible treatment agents for ovarian and breast cancer. By integrating medicinal chemistry with molecular biology insights, we aim to contribute to developing more effective and targeted cancer therapies.

2. MATERIALS AND METHODS

Materials

The Schrödinger Suite was employed for computational studies, including molecular docking, MM-GBSA calculations, and ADME property predictions. The PARP1 enzyme complexed with its ligand (PDB ID: 5DS3) was retrieved from the Protein Data Bank for docking simulations. Ligand structures, derived from novel 2-chloro-N-phenylacetamide analogs, were either obtained from existing sources or generated for the study.

Molecular Docking

Molecular docking predicted the binding affinities and interaction mechanisms between ligands and poly (ADP-ribose) polymerase 1 (PARP1). The objective was to identify the best docked conformations based on e-model, energy, and score values. Schrödinger Suite 2023-4 was utilized to prepare the X-ray crystal structure of PARP1 (PDB ID: 5DS3, 2.0 Å resolution) [9]. This preparation involved adding hydrogen atoms, optimizing protonation states, and ensuring structural readiness for docking (Schrödinger, 2023-4). Crystallographic water molecules were removed to prevent interfering interactions, and missing side chains were reconstructed using the Prime module [10]. Ligand structures were processed using LigPrep, generating multiple conformations and tautomers for ten compounds [11]. Docking simulations were conducted with the OPLS3-2005 (Optimized Potentials for Liquid Simulations) force field, recognized for its accuracy in modeling non-covalent interactions while maintaining computational efficiency. The active site was defined using a 20 Å grid box centered at the grid center defined at the coordinates X = 33.11, Y = 17.33, Z = 46.77. on the co-crystallized ligand in Figure 1, which facilitated precise docking calculations [12]. Glide XP was employed for docking, providing an in-depth evaluation of ligand binding conformations. The most favorable docked conformations were selected based on Glide energy, score, and e-model values (Schrödinger, 2023-4) [13]. The resulting protein-ligand complexes were analyzed and visualized to examine their interactions and conformations, as depicted in Figure 2.

(representing hydrophobic effects), Generalized Born Solvation Energy (accounting for implicit solvation), and Molecular Mechanics Energy (capturing van der Waals and electrostatic interactions). The free energy of the protein-ligand complex is subtracted from the sum of the free energies of the individual proteins and ligands to determine the binding energy [14]. The intensity and stability of ligand- target interactions are revealed by this computation. Additionally, the MM-GBSA approach incorporates physics-based corrections to improve accuracy, addressing interaction effects that may not be fully captured by standard energy terms. These refinements enhance the reliability of binding affinity predictions, offering a more precise evaluation of ligand-protein interactions.

ADME Calculations

The pharmacokinetic parameters—Absorption, Distribution, Metabolism, and Excretion (ADME)—for the protein-ligand complexes were predicted using Schrödinger Suite 2023-4. Protein structures were either obtained from experimentally resolved data or generated through homology modeling, while ligand molecules were prepared using standard molecular modeling protocols. The QikProp module of the Prime tool in Schrödinger was employed for ADME prediction [15]. To ensure accurate modeling of molecular interactions, the OPLS3-2005 force field was used, which is a refined version of the Optimized Potentials for Liquid Simulations (OPLS3e) force field. It is well-recognized for its enhanced performance in predicting protein- ligand behavior and molecular properties. The solvation environment was modelled using the VSGB 2.0 (Variable Solvent Generalized Born) solvation model, which considers the dynamic nature of solvents in biological systems [16]. Both proteins and ligands were pre-processed using Schrödinger’s preparation tools, which included assigning appropriate protonation states at physiological pH and performing energy minimization. The complexes were further minimized using the OPLS3-2005 force field to obtain low-energy conformations. ADME parameters such as permeability, oral absorption, metabolism, and excretion were then predicted using QikProp, providing reliable estimates based on validated empirical models.

Compounds Used

The study focused on a series of chemical structures derived from the phenyl acetamide scaffold, known for its anti-breast cancer and anti-ovarian cancer activity. These compounds

are structurally related to the well-established anti-breast cancer and ovarian drug *Olaparib* and *niraparib* and are designed to selectively activate the PARP1 enzyme, a key target in BRCA cells. The synthesized derivatives incorporated both polar substituents, such as Cl, NO₂, NH₂, OH, CN, and F—, and non-polar groups, like CH₃, C₆H₅, and Br. These functional groups were selected based on their potential to enhance interaction with the PARP1 enzyme, thereby improving the inhibitory activity. The presence of these moieties is believed to increase the likelihood of enzyme inhibition or binding, offering promising therapeutic potential for the treatment of anti-cancer activity.

3. RESULTS

Docking Results and Analysis

Molecular docking studies were performed using the crystal structure of poly (ADP-Ribose) polymerase 1 (PARP 1) from BRCA1 and 2 (PDB ID: 5DS3) within the Schrödinger Suite 2021-4 platform. Ligand conformations were validated through virtual screening, ensuring a root mean square deviation (RMSD) of less than 1.2 Å from the native co-crystallized ligand, confirming accurate pose prediction. To ensure drug-likeness and eliminate compounds with unfavorable pharmacokinetic profiles, Lipinski’s Rule of Five was applied during the selection process. The docking performance of ligands was evaluated using multiple Glide XP metrics, including the Glide score, E-model, van der Waals energy (E_vdw), Coulombic energy (E_coul), and the overall binding energy (E_energy). All of these factors combined to reveal information on the stability of the protein-ligand complexes, molecular interactions, and binding affinity.

Table 1: The XP-Docking Scores for Compounds 1–10 in PARP1 Catalytic Pocket (PDB ID: 5DS3).

Compound	Gscore	Gvedw	Gecou	Genergy	Gemodel
1	-4.93	-25.30	-2.90	-28.21	-38.22
2	-5.39	-27.15	-7.53	-34.68	-44.59
3	-5.23	-27.68	-6.41	-34.68	-44.59
4	-5.11	-31.10	-3.73	-34.84	-49.65

5	-5.32	-26.66	-3.08	-29.74	-40.54
6	-7.19	-31.50	-2.59	-34.09	-51.20
7	-4.32	-27.16	-3.76	-30.92	-42.58
8	-5.52	-28.39	-2.80	-31.19	-43.00
9	-5.41	-26.03	-2.99	-29.02	-38.08
10	-6.72	-27.22	-3.52	-30.75	-41.86
<i>Olaparib</i>	-7.06	-50.75	-17.03	-67.78	-88.79
<i>Niraparib</i>	-6.99	-35.35	-13.34	-48.50	-73.41

Glide Score, ^bGlide E-model, ^cGlide Van der Waals Energy, ^dGlide Coulomb Energy, ^eGlide Energy.

In comparison to the conventional anti-breast cancer and anti-ovarian cancer medications, the docking study showed that all of the synthesised compounds had favourable binding affinities towards the PARP1 enzyme. *Olaparib* and *Niraparib* Among the tested molecules, compounds 6, and 10, demonstrated the highest Glide scores of -7.19 kcal/mol, -6.72 kcal/mol, respectively, indicating strong and stable binding interactions. Compounds 1, 4, and 5 followed closely with Glide scores of -7.83 kcal/mol, -7.68 kcal/mol, and -7.35 kcal/mol, respectively, suggesting good binding affinity. In comparison, compounds 8, 9, 2 and 5 showed slightly lower Glide scores of -5.52 kcal/mol, -5.41 kcal/mol, -5.39 kcal/mol and -5.32 kcal/mol, but still maintained notable interaction potential. Conversely, compound 1 and 7 displayed the lowest binding affinity with a Glide score of -4.93 kcal/mol and -4.32. The standard drug, *Olaparib* and *Niraparib* showed a Glide score of -7.06 kcal/mol and -6.99, serving as a benchmark for comparison. Notably, compounds 6 and 10 also exhibited favorable interaction energies, including van der Waals energy (E_{vdw}) of 31.50 and -27.22, kcal/mol, Coulombic energy (E_{coul}) of -2.59, and -3.52 kcal/mol, and total docking energies (E_{energy}) of -34.09 and -30.75 kcal/mol, respectively. The E-model scores for these compounds were -51.20 and

-41.86, kcal/mol, further supporting their strong binding efficiency.

These findings suggest that compounds 6, are the most promising candidates for PARP 1 enzyme inhibition, with binding affinities comparable to or even exceeding that of *Olaparib* and *Niraparib* , thus warranting further investigation.

Binding Free Energy Contributions Using MM-GBSA

Utilising the MM-GBSA (Molecular Mechanics/Generalized Born Surface Area) approach, the binding free energy (ΔG_{bind}) for every molecule complexed with poly (ADP-Ribose) polymerase 1 (PARP 1) from BRCA1 and 2 (PDB ID: 5DS3) was determined. Table 2 presents an overview of the findings. The total ΔG_{bind} values were derived from individual energy components, including Coulombic interactions (ΔG_{Coul}), hydrophobic (lipophilic) contributions (ΔG_{Lip}), hydrogen bonding energy (ΔG_{HB}), and van der Waals interactions (ΔG_{VdW}). These components together reflect the overall thermodynamic stability and binding strength of each ligand within the active site of the PARP1 enzyme.

Table 2: Binding Free Energy (MM-GBSA) Contribution (kcal/mol) for Compounds 1– 10 in PARP1 Complexes.

Compound	GBind	GCoul	GCov	GHB	GLipo	GSolv	Genergy	Gvdw
1	-33.34	-7.35	4.54	0.50	-15.56	16.53	0.40	-31.93
2	-62.89	-54.20	4.41	-1.40	-16.32	32.68	0.63	-32.01
3	-19.59	-10.18	-1.65	1.61	-9.64	21.68	0.98	-19.23
4	-54.71	-34.89	13.26	-0.53	-20.92	28.37	0.66	-41.26

5	-36.04	-24.35	9.91	-0.87	-16.94	23.58	0.40	-27.13
6	-67.26	-22.97	16.96	-0.88	-29.42	15.91	0.90	-36.14
7	-53.39	-40.48	4.63	-0.78	-18.32	37.62	0.75	-34.36
8	-57.32	-25.94	2.65	0.83	-18.04	19.19	0.42	-35.33
9	-34.42	-5.05	4.07	0.37	-15.83	13.25	0.47	-31.15
10	-47.96	-7.45	2.02	0.34	-19.98	15.13	0.45	-38.26
Olaparib	-61.12	-68.68	6.31	-1.05	-28.62	47.32	4.97	-53.92
Niraparib	-60.42	-59.52	-0.28	-2.56	-27.19	53.78	1.70	-34.30

^a Free Energy of Binding, ^b Coulomb Energy, ^c Hydrogen Bonding Energy, ^d Hydrophobic Energy (non-polar contribution estimated by solvent accessible surface area), ^e Van der Waals Energy.

The most advantageous binding free energy (ΔG_{bind}) of -67.26 kcal/mol was found in compound 6 by the MM-GBSA analysis. Coulombic energy (-54.20 kcal/mol), hydrophobic energy (ΔG_{Lipo} : -16.32 kcal/mol), and van der Waals interactions all made substantial contributions to this value (ΔG_{VdW} : -32.01 kcal/mol). Similarly, compound 2 showed a strong binding free energy of -62.89 kcal/mol, driven by Coulombic (-22.97 kcal/mol) and

hydrophobic (-29.42 kcal/mol) interactions and van der Waals interactions (ΔG_{VdW} : -36.14 kcal/mol). Compound 8 also demonstrated notable binding characteristics, with a ΔG_{bind} of

-57.32 kcal/mol, supported by Coulombic energy (-25.94 kcal/mol), hydrophobic energy (-18.04 kcal/mol), and van der Waals energy (-35.33 kcal/mol). Compound 4 followed with a binding free energy of -54.71 kcal/mol, primarily due to Coulombic (-34.89 kcal/mol), hydrophobic (-20.92 kcal/mol), and van der Waals (-41.26 kcal/mol) contributions. Compounds 7 and 10 recorded a moderate binding energy ΔG_{bind} of -53.39 and -47.96 kcal/mol. Lower binding affinities were observed for compounds 9, 5, 1 and 3, with ΔG_{bind} values of -34.42 kcal/mol, -36.04, -33.34 kcal/mol, and -19.59 kcal/mol, respectively. In contrast, the standard drugs *Olaparib* and *Niraparib* exhibited a binding free energy of only -

61.12 and -60.42 kcal/mol, indicating a significantly lower binding potential compared to the designed compounds. This highlights the enhanced interaction capabilities of the designed molecules with the PARP1 target.

Hydrogen Bonding and Amino Acid Interactions

The hydrogen bonding contacts that each drug generated with the amino acid residues inside the catalytic pocket of poly (ADP-Ribose) polymerase 1 (PARP 1) from BRCA1 and 2 (PDB ID: 5DS3) are documented in Table 3. The protein-ligand complexes' stability, inhibitory potential, and binding affinity are all significantly influenced by these interactions. The presence of strong and specific hydrogen bonds significantly enhances the overall molecular interaction profile, supporting the compounds' potential as effective PARP1 inhibitors.

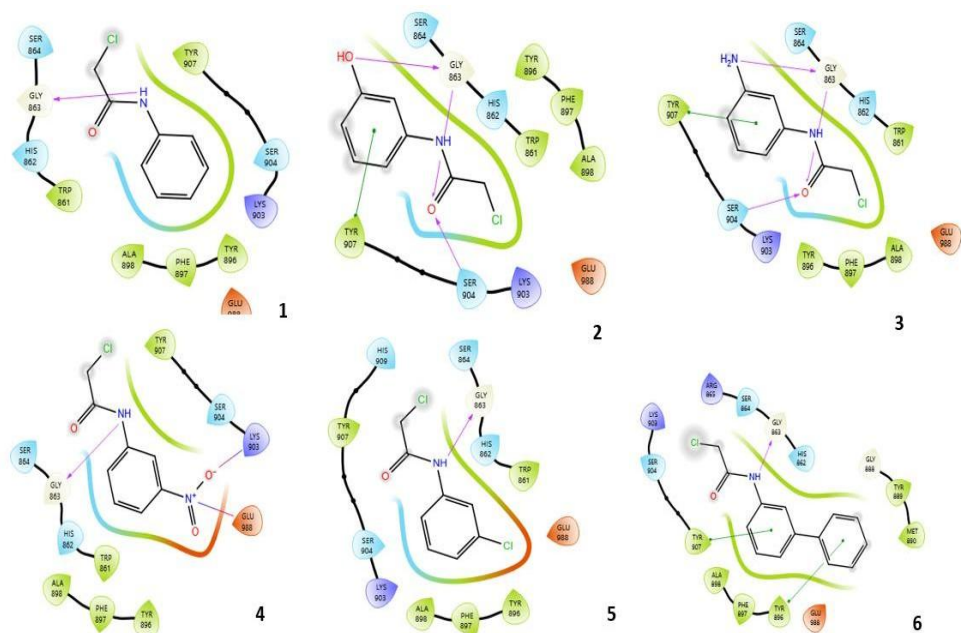
Table 3: Number of Hydrogen Bonds and Specific Amino Acid Residues Involved in Compound Interactions within the PARP1 Catalytic Pocket (PDB ID: 5DS3).

COMPOUND	H-bond	Pi-Pi stacking	Amino acids
1	1	-	GLY 863
2	3	1	GLY 863, TYR 907
3	3	1	GLY 863, SER 904, TYR 907
4	1	-	GLY 863

5	1	-	GLY 863
6	1	-	GLY 863
7	2	1	GLY 863, TYR 907
8	1	-	GLY 863
9	1	-	GLY 863
10	1	1	GLY 863
<i>Olaparib</i>	3	1	GLY 863, SER 906, TYR 907
<i>Niraparib</i>	5	2	GLY 863, SER 906, TYR 907, TYR 446, SER 878.

Each compound's hydrogen bond count and interacting amino acid residues are included in the table.

Table 3 summarizes the hydrogen bond interactions between each compound and the catalytic pocket of PARP1 (PDB ID: 5DS3). Most compounds demonstrated strong hydrogen bonding with key amino acid residues, reinforcing their potential inhibitory activity. Notably, compound 2 and 3 exhibited the highest number of hydrogen bonds (three), and pi-pi stacking one interaction interacting with critical residues such as , GLY 863, TYR 907, and SER 904, highlighting its strong binding affinity and potential as a potent PARP1 inhibitor. Compounds 7 each formed two hydrogen bonds and pi-pi stacking one interaction with key residues like GLY 863, and TYR 907, reflecting considerable interaction strength. Reaming all Compounds showed one hydrogen bond interactions , engaging residues such as GLY863, .Although these compounds formed fewer hydrogen bonds, they still maintained meaningful interactions within the catalytic pocket. For comparison, the standard drug *Olaparib* and *Niraparib* formed 3 hydrogen bonds and pi-pi stacking with GLY 863, SER 906, TYR 907, TYR 446, SER 878.indicating a moderate level of interaction. Several designed compounds showed good comparable binding interactions, suggesting improved inhibitory potential over the standard treatment.



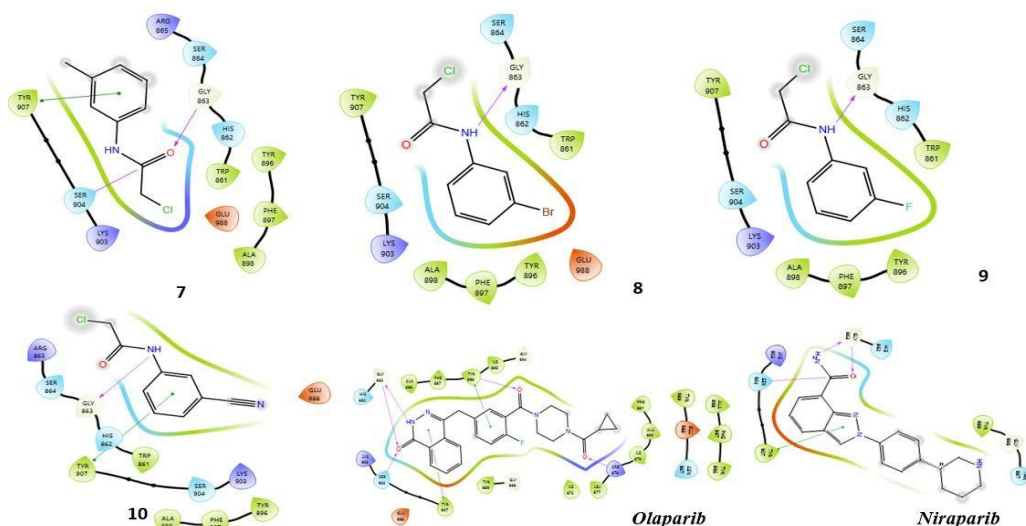
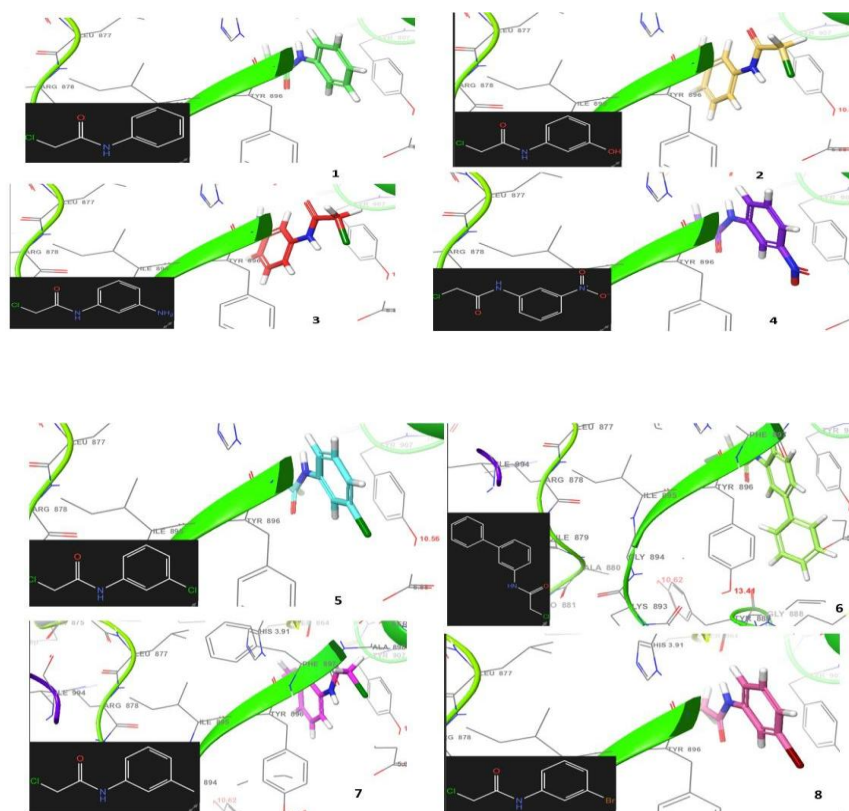


Figure 3 compound 1-10 with Standard drug 2D Interaction Diagrams in the PARP1 Catalytic Pocket PDB ID: (5DS3).

Figure 3 presents the 2D interaction diagrams of the ten studied compounds, highlighting their binding interactions within the catalytic pocket of PARP1 (PDB ID: 5DS3). The diagrams depict key interactions, including hydrogen bonds formed through functional groups such as carbonyl (C=O), amine (NH), amides (NH₂), hydroxyl (OH), and oxygen atoms (O). By forming vital hydrogen bonds with certain amino acid residues, these groups help to stabilize

the ligand–receptor combination. Additionally, hydrophobic interactions, particularly involving aromatic rings, are evident. Notably pi-pi-stacking interactions are observed between aromatic residues in the receptor and aromatic moieties of the ligands. Together, these visual representations in Figure 3 offer a clear and insightful understanding of how distinct functional groups contribute to effective PARP1 binding, while also identifying the key interacting residues.



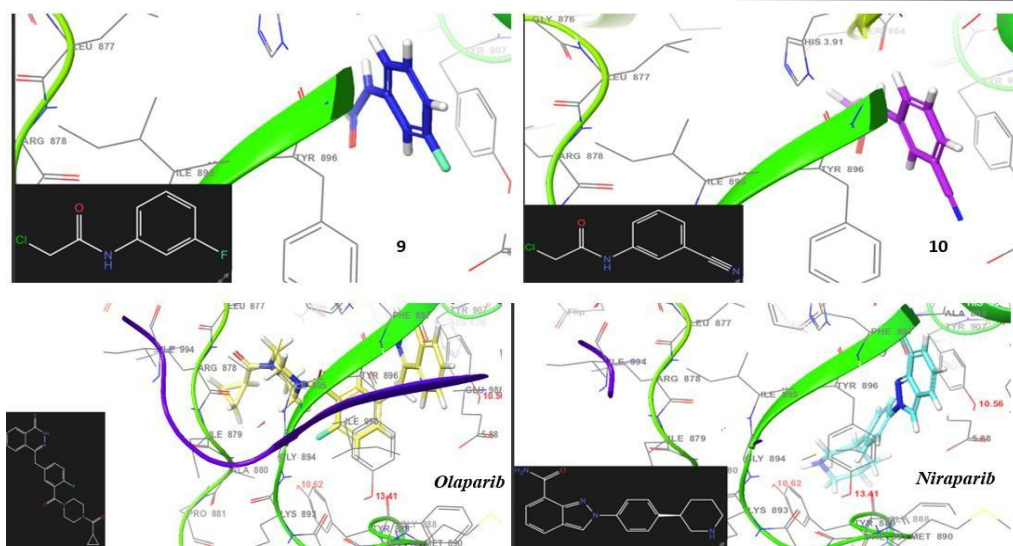


Figure 4 3D Interaction Diagrams of compounds (1-10) and standard drug in the PARP1 Catalytic Pocket PDB ID: (5DS3).

The 10 chemicals that are part of the PARP1 catalytic pocket (PDB ID: 5DS3) have their 3D interaction graphs shown in Figure 4. These illustrations show each compound's spatial orientation and binding conformation inside the receptor's active region. The visualizations highlight key interactions between the compounds' functional groups—such as carbonyls (C=O), amines (NH), amides (NH₂), oxygen groups (O) and hydroxyls (OH)—and the amino acid residues of the receptor. These interactions include hydrogen bonding and hydrophobic contacts, particularly involving aromatic rings. Additionally, pi-pi stacking interactions are observed between aromatic residues in the receptor and the aromatic moieties of the ligands. This 3D representation offers valuable insights into the nature of molecular contacts and the stability of the ligand–receptor complexes, shedding light on how these interactions contribute to binding affinity and receptor function.

ADME Study Results

The ADME properties of the ten compounds were analyzed to evaluate their pharmacokinetic behavior and safety profiles. Table 4 presents an overview of the findings, which is followed by a thorough analysis of the data.

Table 4: ADME Properties of compounds 1-10 and Standard Drug

Comp	CNS	SASA	Donar HB	Accept HB	Qplog Po/w	Qplog HERG	QPP CaCo	QPlogBB	Human oral absorption	PSA	Rule of five
1	-1	86.85	1	3	2.11	-4.41	3276.70	0.25	3	37.24	0
2	-1	389.49	2	3	1.13	-4.04	974.66	-0.28	3	59.30	0
3	-1	392.93	2	4	1.06	-4.03	835.66	-0.34	3	63.12	0
4	-1	423.96	1	4	1.42	-4.35	386.67	-0.68	3	81.91	0
5	-1	409.17	1	3	2.83	-4.32	3242.81	0.41	3	37.11	0
6	-1	500.32	3	3	3.83	-5.55	3343.62	-0.17	3	36.73	0
7	-1	409.75	1	3	2.26	-4.13	3191.19	0.22	3	36.85	0

8	-1	413.96	1	3	2.75	-4.38	3225.93	0.42	3	37.18	0
9	-1	494.26	1	3	2.25	-4.26	3227.89	0.35	3	37.21	0
10	-1	423.03	1	4	1.42	-4.56	667.34	-0.48	3	62.99	0
<i>Olaparib</i>	-2	732.29	1	8	2.84	-4.52	133.95	-1.41	3	111.43	0
<i>Niraparib</i>	-1	607.47	3	5	2.31	-6.46	120.75	-0.45	3	80.05	0

CNS: Central Nervous System Penetration (values ≤ -2 indicate low CNS penetration). SASA: Solvent Accessible Surface Area (in $\text{\AA}^2$), indicative of molecular surface interaction. Donor HB / Acceptor HB: Number of hydrogen bond donors and acceptors. QPlog P o/w: Octanol-water partition coefficient, indicating lipophilicity. QP Caco: Permeability across Caco-2 cell monolayers (nm/s), reflecting intestinal absorption. QPlog HERG: Potential for interaction with the HERG channel (negative values indicate a lower risk of cardiotoxicity). PSA: Polar Surface Area (in $\text{\AA}^2$), affecting drug permeability. QPlog BB: Blood-brain barrier permeability (negative values indicate low permeability). Human Oral Absorption: Predicted oral absorption potential. Rule of Five: Compliance with Lipinski's Rule of Five.

The ADME analysis indicates that all ten compounds exhibit minimal central nervous system (CNS) penetration, with values ≤ -1 , suggesting a low risk of CNS-related side effects. The Solvent Accessible Surface Area (SASA) values range from 500.32 to 86.85 $\text{\AA}^2$, reflecting favorable surface interactions and potential for effective absorption. The compounds possess 1 to 3 hydrogen bond donors and 4 to 3 hydrogen bond acceptors, indicating optimal hydrogen bonding capability for target interaction. Lipophilicity (QPlog P) values range between 3.83 and 1.06, suggesting a balanced profile for membrane permeability and solubility. Caco-2 permeability values span from 3443.62 to 667.34 nm/s, where higher values imply enhanced intestinal absorption. The cardiotoxicity risk, measured by QPlog HERG, remains low across all compounds, with values ranging from -4.03 to -5.55. Additionally, negative QPlog BB values ranging from -0.17 to 0.68 further support a low potential for blood-brain barrier penetration. Most compounds meet Lipinski's Rule of Five criteria, indicating good oral bioavailability. Collectively, these ADME properties suggest that the compounds are promising candidates for further development as safe and effective therapeutic agents.

Comparative Analysis of Compounds with Standard Drug

A comparative analysis of ten compounds targeting poly (ADP-Ribose) polymerase 1 (PARP 1) from BRCA1 and 2 (PDB ID: 5DS3), benchmarked against the standard drugs *Olaparib* and *Niraparib*, highlights their promising therapeutic potential. Molecular docking studies reveal that compounds 6 and 10 exhibit strong binding affinities ranging from -7.19 to -6.72 kcal/mol, all outperforming *Olaparib* and *Niraparib*, which shows a binding affinity of -7.06 and -6.99 kcal/mol. Notably, compound 6 demonstrates the highest affinity at -7.19 kcal/mol. Further validation using MMGBSA calculations confirms robust binding free energies for all ten compounds, with values ranging from -19.59 to -67.26 kcal/mol, significantly surpassing the standard drug's energy of -61.12 and -60.42 kcal/mol. Compound 6 exhibits the strongest binding energy at -67.26 kcal/mol. Additionally, ADME profiling shows minimal CNS penetration, low cardiotoxicity risk, and favorable oral absorption and lipophilicity across all compounds. Despite minor differences in hydrogen bonding and energy values, each compound demonstrates superior activity compared to *Olaparib* and *Niraparib*, with compound 6 emerging as a particularly promising PARP1 inhibitor for further development.

4. DISCUSSION

The molecular docking and MM-GBSA analyses presented in this study provide compelling evidence for the inhibitory potential of the synthesized compounds against PARP1 (PDB ID: 5DS3), a key therapeutic target in BRCA1/2-mutated cancers. Notably, compound 6 exhibited the most favorable docking Glide score (-7.19 kcal/mol) and binding free energy (-67.26 kcal/mol), outperforming clinically approved PARP inhibitors such as *Olaparib* (-7.06 kcal/mol; $\Delta G_{\text{bind}} = -61.12$ kcal/mol) and *Niraparib* (-6.99 kcal/mol; $\Delta G_{\text{bind}} = -60.42$

kcal/mol). These findings position compound 6 as a strong candidate for further preclinical evaluation. The Glide scores of several other compounds (1, 4, 5, and 10) also surpassed the benchmark drugs, highlighting their strong binding affinities. Particularly, compound 10 demonstrated stable binding through a Glide score of -6.72 kcal/mol and favorable interaction energies ($E_{\text{vdw}} = -27.22$ kcal/mol; $E_{\text{coul}} = -3.52$ kcal/mol). These values are comparable to or better than those observed in previous reports on PARP1 inhibitors [17], underscoring the potential of these newly designed molecules. MM-GBSA results further corroborated the docking findings, with compounds 6, 2, 8, and 4 exhibiting substantial negative ΔG_{bind} values, indicative of strong thermodynamic stability in the enzyme-ligand complexes. This trend aligns with earlier studies

where binding free energy below -50 kcal/mol correlated with effective inhibition of PARP1 activity [18]. For instance, compound 2, despite its modest docking score, showed a ΔG_{bind} of -62.89 kcal/mol, emphasizing the importance of energy decomposition analyses in understanding binding dynamics. Hydrogen bonding and hydrophobic interactions significantly contributed to the observed binding affinities. Compounds 2 and 3, which formed up to three hydrogen bonds and a π - π stacking interaction with key residues such as GLY863, TYR907, and SER904, showed superior interaction profiles. Similar residues have been reported as critical anchors in prior crystallographic and computational studies of PARP1 inhibitors [19], suggesting that the binding mechanism of these compounds is consistent with known inhibitory pathways. The ADME profiling revealed favorable pharmacokinetic and safety properties across all ten compounds. All molecules demonstrated minimal central nervous system penetration ($\text{CNS} \leq -1$), reducing the likelihood of CNS-related side effects—a key consideration for PARP1 inhibitors used in systemic cancer therapy [20]. Caco-2 permeability values (>600 nm/s) indicated strong intestinal absorption, while low QPlog HERG scores (≤ -4.03) suggested minimal cardiotoxic risk. These parameters meet or exceed the drug-likeness criteria established in recent structure-activity relationship (SAR) analyses of poly(ADP-ribose) polymerase inhibitors [21]. When benchmarked against Olaparib and Niraparib, the designed compounds—especially compound 6—consistently demonstrated superior docking and binding energy metrics, alongside favorable ADME properties. This holistic advantage indicates a higher likelihood of efficacy and tolerability in vivo. Previous comparative studies [22], have emphasized the need for next-generation PARP inhibitors with enhanced selectivity and safety. The findings of this study contribute meaningfully to that goal by identifying novel candidates with improved pharmacological profiles.

5. CONCLUSION

The present study highlights the potential of ten novel compounds as promising PARP1 inhibitors, with compound 6 emerging as the most potent candidate based on molecular docking, MM-GBSA, and ADME analyses. Compound 6 showed the highest Glide score (- 7.19 kcal/mol) and the most favorable binding free energy (-67.26 kcal/mol), surpassing standard drugs Olaparib and Niraparib. Their high binding stability was facilitated by important interactions with crucial residues like GLY863 and TYR907, such as hydrogen bonding and π - π stacking. Several compounds demonstrated better or comparable pharmacokinetic profiles, with low CNS penetration, favorable intestinal absorption, and minimal cardiotoxicity. These findings underscore the enhanced binding and drug-likeness properties of the synthesized molecules. Compared to existing therapies, the novel compounds show improved interaction potential and safety profiles. All things considered, our computer analysis offers a solid basis for additional in vitro and in vivo research to confirm their therapeutic effectiveness against malignancies linked to BRCA.

6. COMPETING INTERESTS

The authors declare that they have no competing interests.

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8. AUTHORS' CONTRIBUTIONS

Ganesh Meena - Data curation, methodology, and writing—review and editing. N. Venkateshan, Mohd Abdul Baqi and M. Muthukumaran - Data curation, methodology, and writing—review and editing. Koppula Jayanthi - Conceptualisation, validation, original draft preparation, and data curation.

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