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Research Article

Exploring the Binding Modes of Quinazolinone-1,2,4-Triazole Hybrids on PARP-10 Inhibition for Anti-Neoplastic Therapy: Docking and ADME Studies

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ABSTRACT

The quest of developing novel therapeutics for anti-neoplastic therapy remains a critical area of research in the field of oncology. Poly (ADP-ribose) polymerase 10 (PARP-10) has emerged as a potential target due to its involvement in various cellular processes, including proliferation and cell cycle regulation. In the present work, a series of 27 Quinazolinone-1,2,4-triazole hybrids along with the standard drug Olaparib employed molecular docking simulations to predict the binding affinities and interactions between the quinazolinone-1,2,4-triazole hybrids and the active site of PARP-10. The results revealed potential binding modes, highlighting the key amino acid residues involved in stabilizing the ligand-receptor complexes. The results indicate that compounds 23, 2 and 6 exhibits the highest binding affinities, with values of -10.8 kcal/mol, -10.4 kcal/mol and -10.4 kcal/mol, respectively. Furthermore, ADME studies were performed to evaluate the pharmacokinetic properties, their potential for oral bioavailability, blood-brain barrier permeability, and metabolic stability. The obtained ADME profiles aided in the selection of lead compounds with favourable drug-like properties for further preclinical evaluation. These findings provide valuable insights into the structural requirements for the design and optimization of PARP-10 inhibitors.

INTRODUCTION

The basic characteristic of cancer is the abnormal proliferation of the body`s cells that is manifested by reduced control over growth and function [1, 2]. It is projected that there will be 1,958,310 new cases of cancer in the US in 2022, along with 609,820 cancer deaths. Lung cancer is the leading cause of cancer death in the US, accounting for around 350 deaths every day. From 2014 to 2018, the incidence of female breast cancer climbed at a moderate rate of 0.5% per year, whereas the incidence of prostate cancer remained stable despite an increase in advanced illness of 4% to 6% per year since 2011. In the United States in 2022, the number of new

invasive cancer cases differs by gender and cancer type. In all, around 1,958,310 cancer cases will be diagnosed, which equates to around 5250 new cases per day [3].

Common cancer treatments include radiation, hormone therapy, surgery, and chemotherapy, depending on the kind and stage of the disease. The inability of the current therapy to distinguish between cancerous and healthy cells, however, is the main issue, as this leads to unavoidable negative effects on the healthy cells [4]. Similarly, because malignant cells are resistant to conventional chemotherapeutic treatments, multidrug resistance (MDR) is another significant source of conflict in cancer treatment. As a result, there is still a need to develop novel cancer therapy approaches [5].

Nuclear enzymes called poly(ADP-ribose) polymerases, or PARPs, are in charge of identifying and fixing damaged DNA. The 17 members of the human PARP family have been found and categorized according to their sequence homology with PARP1's catalytic domain. Poly(ADP-ribose) (PAR), a post-translational alteration known as PARylation, is formed by the catalysis of PARP proteins. Numerous critical biological activities, including transcription control, DNA damage repair process initiation, mitotic progression, programmed cell death (apoptosis), and genomic integrity surveillance are all impacted by PARylation. The abundant nuclear protein PARP can identify broken DNA strands and attaches to damaged DNA via its zinc-finger domain at the N-terminus. This activates the catalytic domain at the C-terminus, which hydrolyzes NAD+ to form PAR polymers that extend hundreds of ADP ribose units. Similar to PARP, PARP is likewise found in the nucleus and performs similar tasks, although it is much less common, making up just 5–10% of the total PARP activity. A subset of the PARP family may be catalytically inactive, whereas other members are either poly(ADPribosyl) or mono(ADP-ribosyl)transferases. These enzymes are drawn to DNA damage sites in the form of single- and double-strand breaks (SB and DSB, respectively) by the DNA binding domains of PARP proteins. When these enzymes attach to damaged DNA, their catalytic activity increases, which in turn causes chromatin relaxation and the quick recruitment of DNA repair factors that bind to the breaks in the DNA and carry out base excision repair (BER) to repair the damage. The inhibition of PARP by small molecules selectively targets cancer cells that are poor in DNA damage repair and BRCA, hence causing synthetic lethality. Significantly, normal cells with intact BRCA and other DNA repair pathways are not rendered lethal by this method.

Moreover, it has been documented that inhibiting PARP with small molecule compounds makes cancer cells more susceptible to cytotoxic drugs that damage DNA, including temozolomide, cisplatin, cyclophosphamide, irinotecan, and topotecan. Additionally, immune checkpoint blockers and other targeted therapeutic drugs have been used with PARP inhibitors. For a limited fraction of ovarian and breast malignancies, human use of small molecule inhibitors of PARP has been approved. Furthermore, they have been used with other cytotoxic drugs that damage DNA in order to achieve chemo-potentiation (TMZ, Cisplatin, etc.) [6].

Recently, much attention has been paid to the PARP-1 enzyme as a possible anti-cancer therapy target as it is a member of the PARP family of proteins, which play a vital role in the repair of single-stranded DNA breaks via the base excision repair pathway [7]. Furthermore, a number of cellular processes including cellular differentiation, gene transcription, inflammation, mitosis, and cell death are significantly influenced by PARP-1, and these processes also contribute to the anticancer action of PARP-1 inhibitors [8]. Because the mutant cancer cells depend on PARP-1 for DNA repair and cell survival, PARP-1 inhibition has a synthetic lethality in the presence of mutations of BRCA 1/2, which are crucial proteins in homologous recombination (HR) of DNA double-strand breaks. Therefore, substances that function as PARP-1 inhibitors may cause specific cell death, especially in cases of breast and ovarian cancer [9]. The FDA has already approved a number of PARP-1 inhibitors, including BMN673 (Talazoparib), AZD2281 (Olaparib), MK4827 (Rucaparib), and AG014699 (Rucaparib) [10].

Quinazolin-4(3H)-ones are bicyclic heterocyclic ring systems that are fused to benzene rings and contain two nitrogen atoms arranged in 1, 3, and a carbonyl functionality in the same ring. There is a diaspora of naturally occurring and synthetically occurring compounds because this scaffold allows the substituents

to arise in different places on the ring system. Numerous pharmacological actions, including anti-inflammatory [11], anticancer [12], anticonvulsant [13], antihypertensive [14], antibacterial antiviral [15], and antiulcer [16], have been found for some of these naturally occurring compounds. Some quinazolinone analogs have shown strong anticancer efficacy through the inhibition of the poly (ADP-ribose) polymerase 10 (PARP10) enzyme.

Since numerous quinazoline-based compounds are recognized to be anticancer agents, we used the quinazolinone scaffold in this investigation as a bioisostere of the phthalazinone core of Olaparib to occupy the NI site of PARP-1.

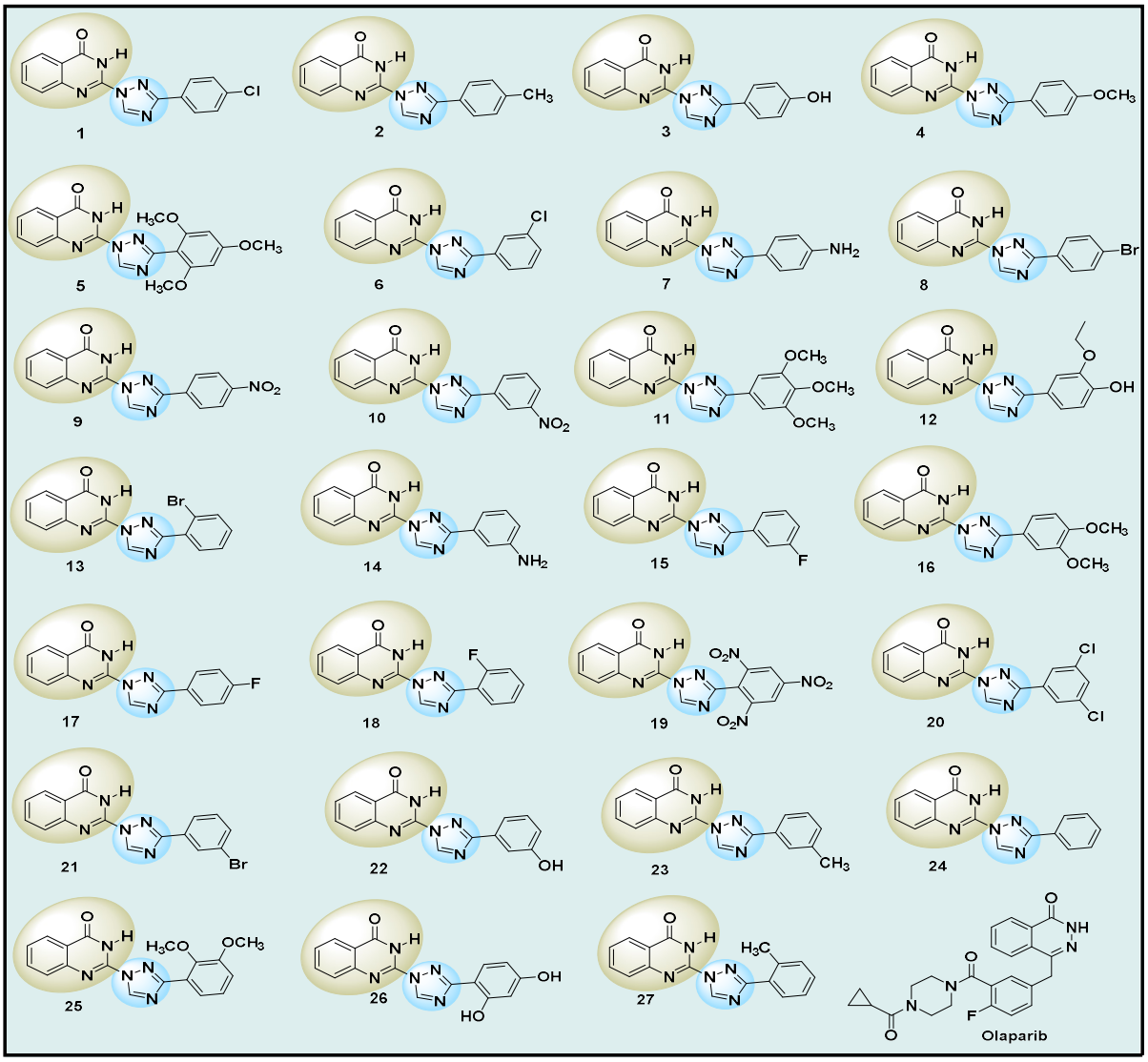
Heterocyclic ring moieties found in nitrogen atoms are found in both natural products and synthetic derivatives, and they have demonstrated strong anticancer properties against many human cancer cell lines [17]. In order to improve pharmacokinetics, pharmacological, and toxicological properties, nitrogen atoms with three heterocyclic rings, like those found in 1,2,4-triazoles, can form hydrogen bonds with appropriate targets. These bonds are crucial for the structural elucidation of many natural products. These 1,2,4-triazole compounds have been linked to a variety of medicinal properties, including tubulin inhibitors, analgesics, anti-inflammatory, antiviral, antitubercular, anticancer, and antibacterial properties [18]. Letrozole is a triazole structural unit used to treat cancer that contains aromatase inhibitors [19].

Conversely, the 1,2,4-triazole ring is a pharmacophoric heterocycle found in a number of anticancer medications. A few 1,2,3-triazole compounds were shown to induce apoptosis and to have PARP-1 degrading activity within a small range of the IC50 micromolar [20].

As possible PARP inhibitors, a bio-isostere to the phthalazinone core of the reference drug Olaparib, the 4-quinazolinone scaffold was used. Ghorab and colleagues 2023 developed two series of N- and S-alkylated quinazolinones. All the compounds were subjected to in *vitro* cytotoxicity. The most active compound (**1**), with IC_{50} values against breast cell line (MCF-7) of 10.6 μM, which are 2.8 and 3 times higher than doxorubicin (IC_{50} = 32.02 μM), was evaluated for PARP-1 inhibitory activity and exhibited IC_{50} = 0.14 μM when compared to Olaparib (IC_{50} = 0.06 μM) [21]. Similarly, Taayoshi and team reported potent compound (**2**) with IC_{50} value of 24.99 μM against the MCF-7 cell line as the cytotoxic agent from the prepared series of quinazolinone and dihydroquinazolinone in 2022 [22]. Another research work by Ramadan and the team produced a novel series of compounds based on quinazolinone. *In vitro* evaluation was done against MCF-7, and compound (**3**) showed inhibitory efficacy at IC_{50} = 30.38 nM equivalent to Olaparib's IC_{50} = 27.89 nM [23].

Pragathi et al., 2020, reported a potent compound (**4**) with IC_{50} value 0.10 ± 0.084 μM of the series of 1,2,4-Thiadiazole-1,2,4-Triazole Derivatives [18]. To, support the above-mentioned literature another work by Boraei and team in 2019 reported a potent compound (**5**) (1,2,4-triazoles scaffold) with IC_{50} value 0.33 ± 0.10 μM as PARP-1 inhibitor [24]. All the potent compounds of the distinctive series are shown in **Figure 1.** As a result, a collection of **27** compounds is generated for the *in-silico* studies to determine their binding affinity for the inhibition of PARP-10 for anti-neoplastic therapy shown in **Figure 2.**

Fig. 1. Derivatives of the designed compounds.



MATERIALS AND METHODS

Asus VivoBook 14 X415JA-EB362WS Series (10th Gen Core i3/ 8GB/ 512GB SSD/Win11). The crystal structure of PARP-10 enzyme **(PDBID:5LX6)** [25] was retrieved from the Protein Data Bank (PDB). However, the RCSB proteins database results in the identification of 5LX6 being approved as a potential therapy against cancer (shown in **Table 1**) [26].

Protein and Ligand Preparation

The crystal structure of the PARP-10 protein was produced using MGLTool1.5.6. In the first step, polar hydrogens were added, partial Kollman charges were applied, and water molecules larger than 3Å were eliminated. Additionally, the grid generation method was used to select the binding cavity. To illustrate the Olaparib interaction site, a grid with a grid spacing of roughly 1Å and dimensions of 24, 24, 24 in the x, y, and z axes was built. The suggested ligands were produced using the ChemDraw program. Using the MMFF94 force field and a lower RMS gradient of 0.001, an energy reduction was first performed in Chem3D 16.0. After then, PDB format was used to store these structures. Using MGL Tool 1.5.6, the ligands were produced in the subsequent phase.

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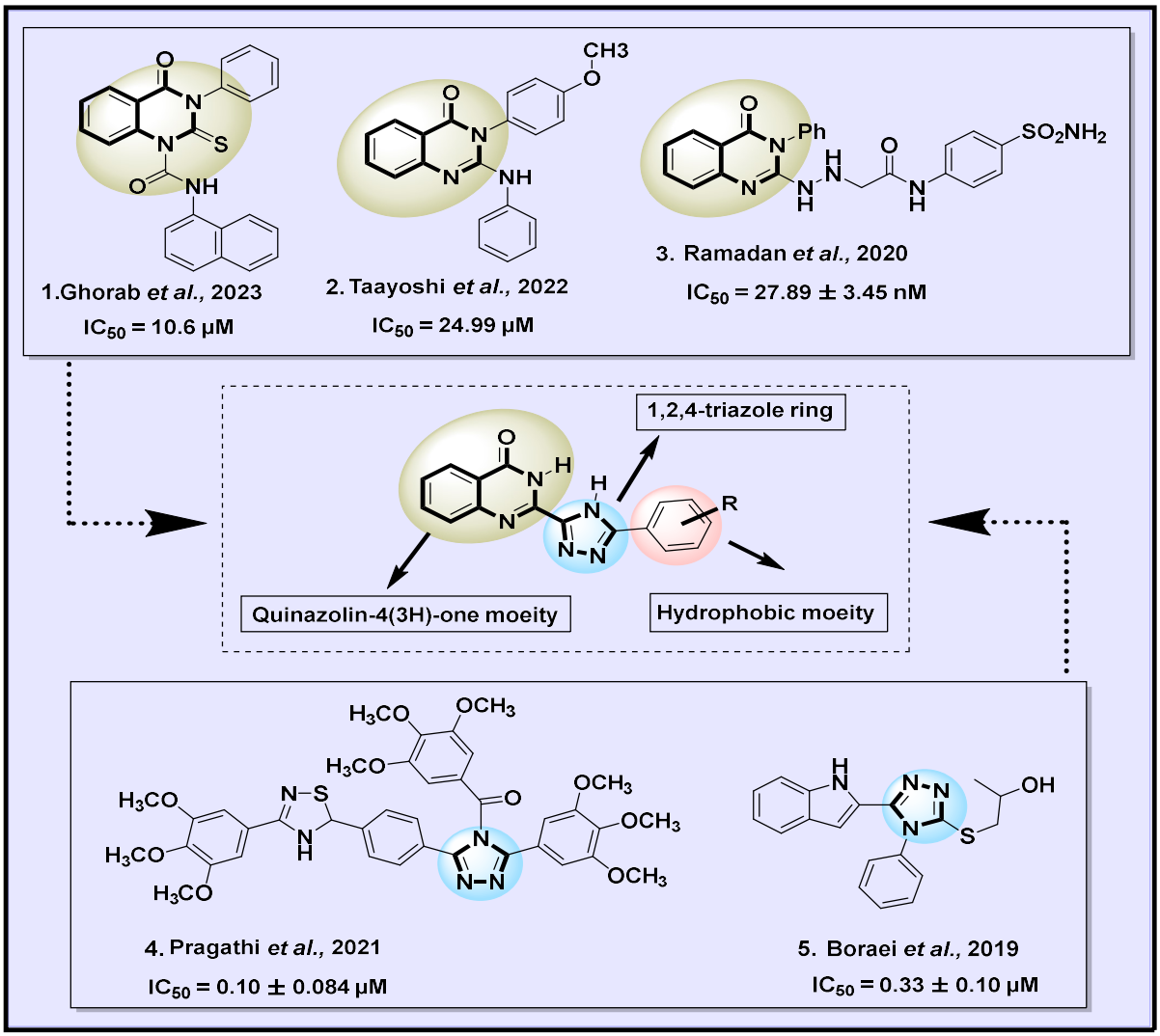


Fig. 2. Literature survey of Quinazolin-4(3*H*)-ones and 1,2,4-triazole ring containing PARP inhibitors.

Molecular Docking

In Auto Dock Vina, a site-specific docking molecules research was carried out. For each ligand, a molecular docking computer generates nine docked arrangements using the Lamarckian genetic method. In order to maximize the supramolecular contact between and its ligand for potential biological purposes, this well-known computational technique was used. Moreover, Discovery Studio docking orientations were examined to evaluate the crucial receptor-ligand interactions for activity [27].

ADMET and Drug-Likeness Prediction

Drug-likeness and ADMET tests were performed to evaluate the suggested compounds' druggability. These tests include the following: the molecular weight (MW) is less than 500 Da (≤500 Da), the log P is less than 5 (Log P<5), the number of rotatable bonds (15), the topological polar surface area (TPSA) is less than 120 (Å)2[TPSA≤120(Å)2], the hydrogen bond donor (HBD) is less than 5 (HBD≤5), and the hydrogen bond acceptor is not more than 10 (HBA≤10). Swiss ADME, a freeware web server offered by the Swiss Institute of Bioinformatics, was used to predict drug-likeness and ADME [28].

5LX6 (**Figure. 3**) was chosen due to its geometrical features and current research accounting.

Table 1: The reason for protein selection is critical in *in-silico* research to determine theological significance.

Enzyme	Disease	PDBID	Chain	Resolution	Sequence Length	Released	Organism
poly(ADP-ribose) polymerases (PARPs)	Anti-Cancer	5LX6	A	1.25.Å	191	2017-01-11	Homosapiens

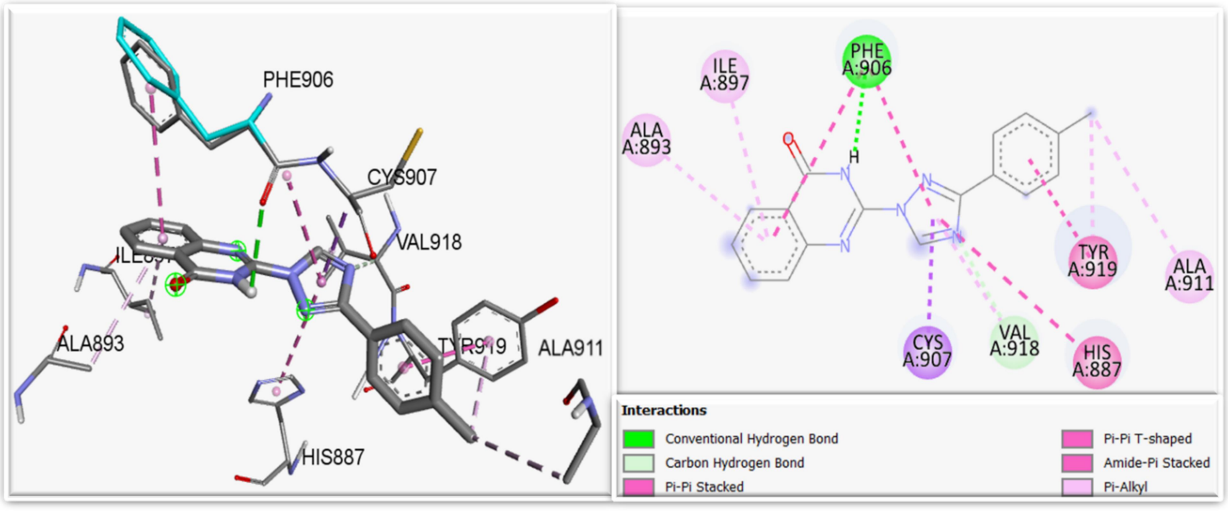
Fig. 3. Structure of the 5LX6 protein.

RESULTS AND DISCUSSION

Molecular Docking Studies

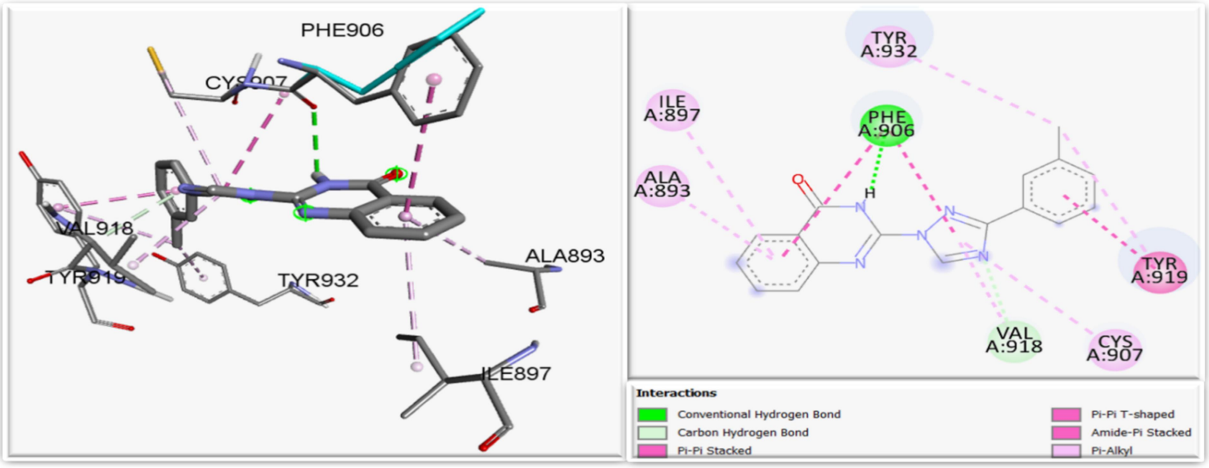
Molecular docking examines in Auto Dock Vina revealed that the chosen ligand was well-positioned in the PARP-10 interacting pocket with comparable interactions.

Fig. 4. (A) 3D docking pose**, (B)** 2D docking pose of Compound (**2**).



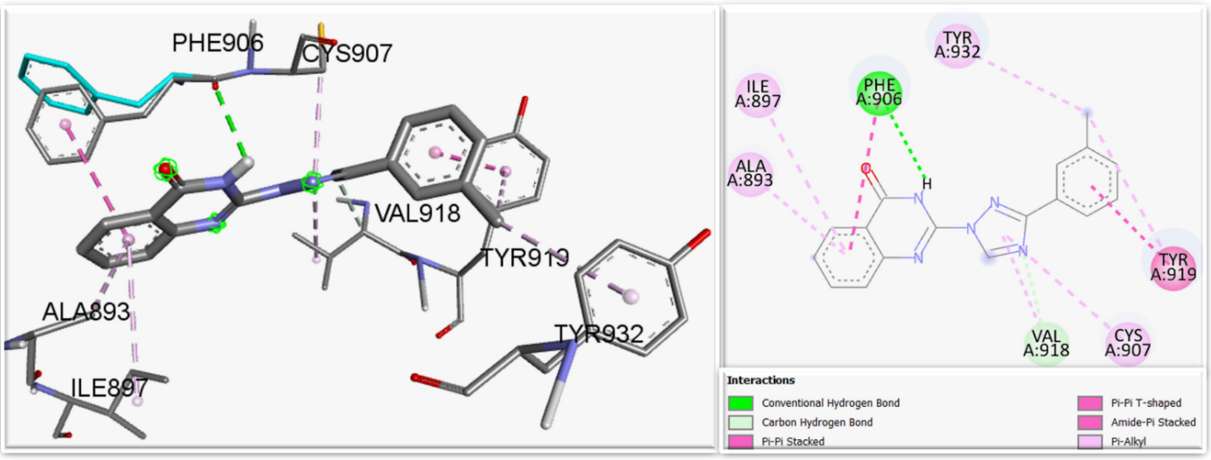
A **B**

Fig. 5. (A) 3D docking pose**, (B)** 2D docking pose of Compound (**6**).



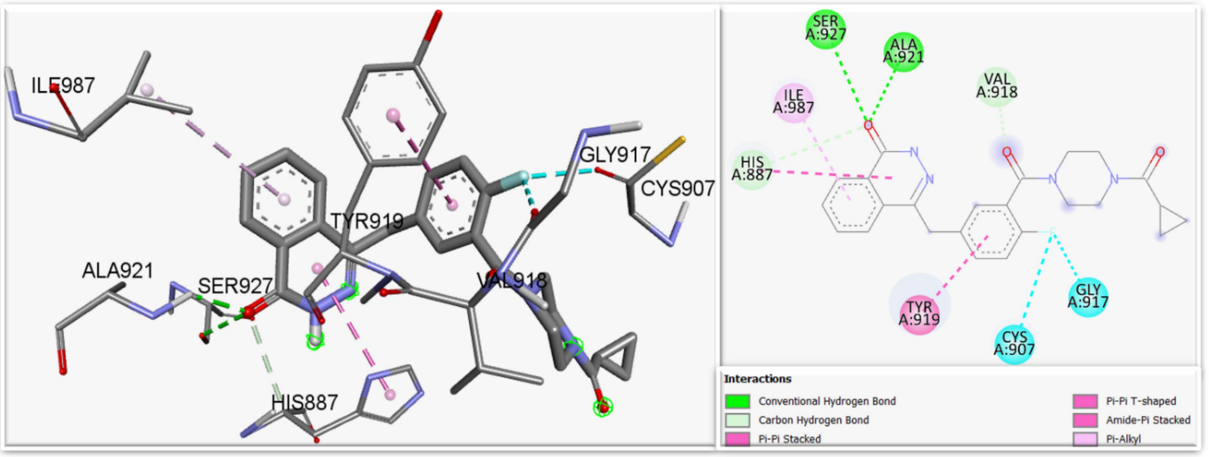
A **B**

Fig. 6. (A) 3D docking pose**, (B)** 2D docking pose of Compound (**23**).



A **B**

Fig. 7. (A) 3D docking pose**, (B)** 2D docking pose of reference drug **Olaparib.**



A **B**

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It was demonstrated that the suggested compounds interacted extensively with the binding pockets of PARP-10. Additionally, the effects of donor and acceptor hydrogen bonds on the binding as well as the ADME profile were observed. in particular, the ring's bromine, chlorine, and GI absorption may. Numerous major interactions that are comparable to the reference drug have also been identified. As seen in Figure 6, Compound (**23**) demonstrated similar interactions with multiple amino acids in the binding pockets during our experiment. These amino acids include ILE 987, PHE 906, ALA 893, VAL 918, TYR 919, CYS 907 and TYR 932. When 3-fluoro substitution on benzene ring followed by 3-chloro substitution, the interactions observed were pi-sulfur, pi-pi stacked, pi-pi T-shaped, amide-pi stacked, and pi-alkyl interactions. Even though there were less hydrogen bonds when 4-methyl substitution took place, the outcomes were similar (**Figure 4**). Moreover, interactions between cations and the ring's electron cloud were seen in different areas of its skeleton in the compounds (**21**), (**12**), and (**27**). Olaparib was utilized as the reference in the study and had a binding affinity of 12.3 kcal/mol. Compound (**23**) demonstrated a close binding affinity with a value of -10.8 kcal/mol when compared to Olaparib. It was discovered that Compound (**23**)'s binding mechanisms were all similar to Olaparib's (**Figure. 7**). Table 2 contains comprehensive data regarding the docking scores (Kcal/mol). Table 3 displays ligands with a high binding affinity as well as interactions between the proteins 5LX6's amino acid residues.

Table 2: Docking score (Kcal/mol) of the designed ligands

Sr. No.	Compound No.	Docking score (Kcal/mol)
1.	1	-10.2
2.	2	-10.4
3.	3	-10.1
4.	4	-9.9
5.	5	-9.6
6.	6	-10.4
7.	7	-10.1
8.	8	-10.2
9.	9	-9.9
10.	10	-10.3
11.	11	-9.2
12.	12	-10.4
13.	13	-9.9
14.	14	-9.9
15.	15	-10.3
16.	16	-9.7
17.	17	-10.2
18.	18	-10.3
19.	19	-10.3
20.	20	-10.0
21.	21	-10.4
22.	22	-9.9
23.	23	-10.8
24.	24	-10.0
25.	25	-9.9
26.	26	-9.9
27.	27	-10.3
28.	Olaparib	-12.3

Table 3. Ligand interactions of the amino acid residues of the proteins 5LX6.

Sr.No.	Compounds	Docking score	Interactions
1.	2	-10.4	ILE 987, ALA 893, VAL 918, TYR 919, CYS 907, PHE 906, TYR 932
2.	6	-10.4	ILE 987, ALA 893, VAL 918, TYR 919, CYS 907, PHE 906, TYR 932
3.	23	-10.8	ILE 987, PHE 906, ALA 893, VAL 918, TYR 919, CYS 907, TYR 932
4.	Olaparib	-12.3	HIS 887, ILE 987, SER 927, ALA 921, VAL 918, TYR 919, CYS 907, GLY 917

We used the in-silico tool SwissADME in our study to predict the drug-likeness of all created compounds. The results show that all of the compounds, with the exception of one, meet the criteria for drug-like molecules, as defined by Lipinski's rule of five. In addition, there were an adequate amount of hydrogen bond donors (HBD) and acceptors (HBA) in the target site, especially PARP, increasing the possibility of maximal interactions. Only one compound deviated from the Lipinski rule in terms of drug-likeness and ADME prediction; all other compounds complied with it. As demonstrated in Table 3, compound (19) in particular demonstrated one instance of breaking Lipinski's rule and low gastrointestinal (GI) absorption, which is explained by the presence of tri-nitro groups on its ring structure. All of the newly developed compounds' pharmacokinetic (ADMET) parameters were discovered to be within an acceptable range.

In this in silico investigation, a total of 27 ligands were created and examined using drug-likeness, ADME, and molecular docking. It has been discovered that every chemical interacts with olaparib in a similar way and fits nicely into the PARP-10 binding pocket. Quinazolin-4(3H)-ones were grouped with the 1,2,4-triazole ring in this instance, and the hydrophobic moiety of the substituted benzene ring favored a specific binding mode for the best interactions.

Drug-Likeness and ADME

Table 4: Drug-likenessand ADME studies of the designed ligands.

Com. No	Substitutions	MW	H-bond acceptors	H-bond donor	TPSA	iLOGP	GI absorption	Rotatable bonds	PAINS	Lipinski violations
1	4-Cl	323.74	4	1	76.46	2.71	High	2	0	0
2	4-CH_3	303.32	4	1	76.46	2.71	High	2	0	0
3	4-OH	303.32	4	1	76.46	2.71	High	2	0	0
4	4-OCH_3	319.32	5	1	85.69	2.77	High	3	0	0
5	2,4,6-Trimethoxy	379.37	7	1	104.15	3.16	High	5	0	0
6	3-Cl	323.74	4	1	76.46	2.7	High	2	0	0
7	4-NH_2	304.31	4	2	102.48	2.03	High	2	0	0
8	4-Br	368.19	4	1	76.46	2.84	High	2	0	0
9	4-NO_2	334.29	6	1	122.28	2.14	High	3	0	0
10	3-NO_2	334.29	6	1	122.28	2.09	High	3	0	0
11	3,4,5-Trimethoxy	379.37	7	1	104.15	3.13	High	5	0	0
12	3-ethoxy, 4-OH	323.74	4	1	76.46	2.7	High	2	0	0
13	2-Br	368.19	4	1	76.46	2.72	High	2	0	0

14	3-NH_2	304.31	4	2	102.48	2.05	High	2	0	0
15	3-F	307.28	5	1	76.46	2.55	High	2	0	0
16	3,4-Dimethoxy	349.34	6	1	94.92	2.83	High	4	0	0
17	4-F	307.28	5	1	76.46	2.52	High	2	0	0
18	2-F	307.28	5	1	76.46	2.43	High	2	0	0
19	2,4,6-Trinitro	424.28	10	1	213.92	0.77	Low	5	0	1
20	3,5-Dichloro	358.18	4	1	76.46	2.92	High	2	0	0
21	3-Br	368.19	4	1	76.46	2.83	High	2	0	0
22	3-OH	305.29	5	2	96.69	2.04	High	2	0	0
23	3-F	303.32	4	1	76.46	2.73	High	2	0	0
24	H	289.29	4	1	76.46	2.45	High	2	0	0
25	2,3-Dimethoxy	349.34	6	1	94.92	2.88	High	4	0	0
26	2,4-Dihydroxy	321.29	6	3	116.92	2.03	High	2	0	0
27	2-CH_3	303.32	4	1	76.46	2.6	High	2	0	0
Olaparib	-	434.46	5	1	86.37	2.84	High	6	0	0

CONCLUSION

The new library of Quinazolinone-1,2,4-triazole derivatives has substituted benzene ring functionality as a privileged fragment in one scaffold to develop novel candidates in cancer therapy. The design of new compounds depended on the verified Binding affinity of fragments as PARP-10 inhibitors. Using docking studies, the researchers investigated the binding interactions between various Quinazolinone-1,2,4-triazole derivatives and the active site of PARP. Docking is a computational technique that predicts the binding modes of small molecules to a target protein, allowing for the exploration of potential drug-protein interactions. The study's findings showed that they have a high affinity for binding to the PARP active site. Important interactions with crucial residues in the enzyme's binding pocket defined the binding modalities of these drugs. These interactions, which are crucial for stabilizing the ligand-protein complex, comprised pi-pi stacking, hydrophobic interactions, and hydrogen bonding. Overall, the results of this work highlight the possibility that derivatives of quinazolinone-1,2,4-triazole may be useful options for anti-cancer treatment due to their interaction with PARP. The knowledge gathered from the docking investigations offers a strong basis for additional experimental validation and the creation of fresh therapeutic approaches for the management of cancer. The most effective compound, compound (23), will be used in additional biological testing.

FUTURE ASPECTS

The prospects of this work involve synthesizing and testing the most promising quinazolinone-1,2,4-triazole hybrids in *vitro* and *in vivo* models. The selected lead compounds will undergo comprehensive characterization to determine their mechanism of action and efficacy in inhibiting PARP-10. In addition, the potential toxicity and off-target effects of these compounds will be thoroughly investigated to ensure their safety profile. The findings from this research could lead to the development of novel PARP-10 inhibitors with improved efficacy and safety profiles, providing new avenues for the treatment of cancer.

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CONFLICT OF INTEREST

There is no conflict of interest.

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