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Review Article

Pyridazine-based Compounds with PARP-1 Inhibitory Activity

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ABSTRACT

Pyridazine-based compounds have been identified as potent PARP1 inhibitors. The PARP is an enzyme family essential for many cellular activities such as the Repair of DNA, apoptosis, and genomic stability, also known as poly (ADP-ribose) synthetases and poly (ADP-ribose) transferases. PARP1 (Poly (ADP-ribose) polymerase 1) is an enzyme that plays a critical role in DNA repair and maintenance of genomic stability. The inhibition of PARP1 has emerged as a promising strategy for the treatment of various cancers, especially those with defects in DNA repair pathways. An array of Diazine-based-containing compounds was recognized as redoubtable PARP1 inhibitors, including Olaparib, and Talazoparib. These compounds have manifested successful results in clinical studies, exhibiting their benefit in various cancer therapies, including ovarian, breast, and pancreatic cancers. In the following review, we will highlight some of the most recent Pyridazine-based compounds and their role in the development of tacit PAPR1 inhibitors.

Keywords: *Pyridazine-based; PARP1; DNA repair; Cancer.*

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1. Introduction

The PARP is an enzyme family vital for many cellular operations such as DNA repair, genomic stability, and apoptosis, well known as poly ADP-ribose synthetases and poly ADP-ribose transferases **[1]**. The PARP family consists of four domains: a DNA-binding domain, a caspase-cleaved domain, an auto-modification domain, and a catalytic domain. The DNA-binding domain consists of two zinc finger moieties. When damage occurs in DNA, the DNA-binding domain binds to the DNA and induces a conformational shift. The PARP family includes 17 members, all having a conserved domain. Only PARP-1 and PARP-2 have a DNA-binding domain, with PARP-1 accounting for as much as 95% of the family's overall activity responding to DNA damage. Therefore, inhibiting PARP-1 is considered a promising approach to cancer treatment, and significant progress has been made in this area.

PARP1 has become a promising focus for cancer treatment. This enzyme plays a vital role in DNA repair and preserving genomic stability. By inhibiting PARP1, DNA damage can

accumulate, ultimately resulting in cancer cell death. One approach to limit PARP activity is through the development of structural analogs of NAD^+ that can compete with NAD itself at the catalytic domain level **[2]**.

In cancer patients undergoing chemotherapy and radiation, drug resistance often arises as it hinders the repair of DNA damage. Consequently, PARP has surfaced as a hopeful candidate for cancer therapy, primarily because of its role in processes related to the repair of DNA damage through the base excision repair pathway **[3]**.

Inhibiting PARP-1 results in heightened harm to damaged DNA, inducing synthetic lethality in cancer cells with impaired DNA repair mechanisms, like BRCA1/2-deficient cells. Consequently, suppressing PARP-1 enhances the impact of various antiproliferative medications, including topoisomerase inhibitors, DNA alkylating drugs, and ionizing radiation, in a synergistic manner **[4]**.

Furthermore, certain PARP inhibitors exhibit effectiveness as standalone treatments for cancers that carry BRCA1 or BRCA2 mutations **[5-8]**. High PARP1 expression has been observed to be significantly linked to unfavorable overall survival and recurrence rates in different cancer types, suggesting that PARP1 could serve as a promising biomarker for prognostic assessment in human cancers **[9-10]**.

An association has been observed between increased expression of PARP1 and a poorer prognosis for survival. Breast cancers (BCs) with aggressive characteristics, such as estrogen-negative BC, tend to exhibit higher levels of PARP1 expression, contributing to tumor resistance to treatment. Malignant cells can overcome the genetic instability characteristic of their transformation, leading to enhanced PARP1 expression, which aids in the repair of damaged DNA. This phenomenon may explain the tumor's ability to resist treatment and promote disease progression **[11]**.

Research studies have provided clarification on the pro-carcinogenic impact of PARP-1 in prostate cancer (PCa) cells expressing the androgen receptor (AR). PARP-1 has been observed to be present at sites where AR functions, leading to an increase in AR occupancy and an enhancement of its function. Using genetically defined systems, it has been confirmed that PARP-1 actively supports AR's transcriptional function in models of advanced PCa. Moreover, in this context, the enzymatic activity of PARP-1 is intensified, establishing a direct association between PARP-1 and AR activity, which contributes to the progression of AR-positive prostate cancer **[12]**.

2. PARP1 inhibitors as a potential therapy for human cancers

PARP inhibitors are a group of medications that can be used for cancer treatment **[12].** Recently, the US FDA has given its approval to four PARP inhibitors: Olaparib, Rucaparib, Niraparib, and Talazoparib. These drugs are indicated for the treatment of advanced and metastatic ovarian cancer or HER2-negative advanced breast cancer with BRCA mutations. They have demonstrated remarkable effectiveness in addressing these specific cancer types and have been deemed safe and efficient by regulatory agencies **[5]**.

Furthermore, several PARP inhibitors, including Veliparib, Pamiparib, Simmiparib, and Fluzoparib, are currently being investigated in various clinical phases. These compounds hold potential as PARP suppressors and are undergoing rigorous testing to assess their safety and efficacy in cancer treatment **[5, 12, 13]**. Moreover, recent studies have explored the therapeutic possibilities of different PARP-1

inhibitors for treating refractory diseases like Alzheimer's disease (AD).

These investigations aim to determine whether targeting PARP-1 could be a viable approach to potentially address the challenges posed by AD and its associated neurodegenerative processes **[5, 13, 14]**. Undoubtedly, the development of effective PARP-1 inhibitors holds a significant role within communities of medicinal chemistry. Recent clinical studies have revealed the efficacy of PARP inhibitors against a variety of different BRCA1/2-mutated malignancies, including those of the prostate and pancreatic **[4]**.

3. Diazine-based based compounds as PARP inhibitors

Diazine-based are the most significant nitrogen-bearing heterocycles. Diazine-based comprise pyrimidine, pyridazine, pyrazine, and their benzo derivatives. The base pyrimidine has a crucial role in the foundation of pharmaceuticals and other natural compounds **[15]**. Its versatile structure and properties make it a key starting point in the synthesis of various drugs and bioactive molecules. In terms of nucleophile reactions (addition and substitution), Diazine-based is more active than pyridine. For benzo Diazine-based, the benzene ring is the preferred site for electrophilic substitution reactions, whereas the Diazine-based ring is more likely to undergo nucleophilic replacements, especially if halogens are present as substituents **[16]**.

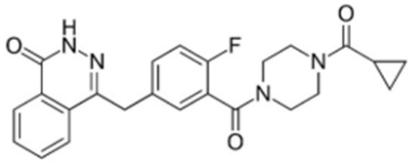
The acidity of hydrogens in diazines is related to the less highly-conjugated p orbitals (decrease in aromaticity) in the ring when compared to azines (and of course benzene). Many aromatic heterocyclic compounds, such as Diazine-based, have had their C-H bond pKa values recently measured. It was determined that the 4-position of pyridazine (31.1) has the highest acidity among the Diazine-based, while the 2-position of pyrimidine (40.0) has the lowest **[17]**.

Pyridazine has garnered significant interest among medicinal chemists due to its favorable physicochemical and biological properties. Pyridazine serves as a preferred scaffold in drug design due to its structural versatility, featuring two nitrogen atoms in a 1,2 relationship. This characteristic makes it highly adaptable for medicinal chemistry purposes. Structurally, pyridazine is the simplest aromatic skeleton with a pKa of 2.3, facilitating straightforward protonation, hydrogen bond formation, and chelation through its nitrogen atoms. These properties contribute to its potential as a valuable building block in the development of pharmaceutical compounds.

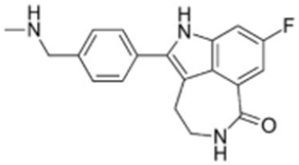
Appropriately substituted pyridazines exhibit a wide range of pharmacological effects, including analgesic, antimicrobial, anti-inflammatory, antithrombotic, diuretic, antidepressant, antihypertensive, anti-Alzheimer's, antidiabetic, anti-HIV, and anticancer properties. These diverse therapeutic effects make pyridazines valuable candidates for drug development in various medical applications **[17]**.

Pyridazine is particularly recognized as a privileged scaffold in anticancer therapy due to its involvement in several critical mechanisms. These mechanisms encompass inducing DNA damage, provoking cell cycle arrest, facilitating apoptosis, inhibiting angiogenesis (the formation of new blood vessels), impeding related proteins that support cancer growth, and disrupting metabolic pathways vital for tumor development. The multifaceted actions of pyridazine make it a promising candidate for designing potent anticancer agents that can target multiple pathways involved in cancer progression and survival **[17]**.

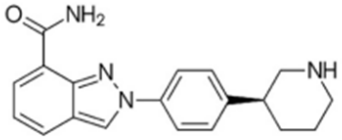
The practical application of multiple pyridazine-based medications for the treatment of various tumors has verified the therapeutic potential and advantageous medicinal features of pyridazine derivatives **[17]**. **Fig.1.** Shows medications with Known target profiles of clinical PARP inhibitors across members of the PARP enzyme family **[18]**.



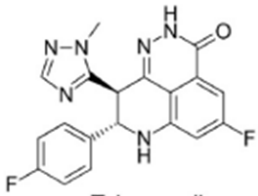
Olaparib



Rucaparib



Niraparib



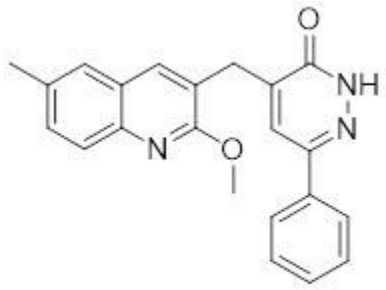
Talazoparib

	Olaparib	Rucaparib	Niraparib	Talazoparib
PARP1	1 - 19 nM	0.8 - 3.2 nM	2 - 35 nM	0.6 - 1.1nM
PARP2	1 - 251 nM	28.2 nM	2 - 15.3 nM	4.1nM
PARP3	46 - 230 nM	512 nM	296 - 1,300 nM	62.8 nM
PARP4	410 nM	839 nM	330 - 446 nM	254 nM

Fig. 1. Chemical structures and known PARP activities of FDA-approved PARP inhibitors

Using a new pyridazine derivative; compound **1 (Fig. 2)**, Hegde *et al***.** discovered that the IC_{50} value for inhibiting PARP enzymatic activity was 2.77 nM, which is very similar to the IC_{50} value for the control drug Olaparib (2.47 nM). Nalm6, a human leukemic cell line, showed pronounced sensitivity to compound **1** compared to other leukemic cells. Nalm6 has high expression of PARP1 and PARP2, as well as strong intrinsic PARP activity.

The DNA-trapping activity of compound **1** was also striking, a hallmark of many PARP inhibitors. S and G2/M arrest in Nalm6 cells was likewise induced by compound **1**, suggesting DNA damage accumulation. Compound **1** is a PARP inhibitor with great potential for use in developing new chemotherapy drugs. Since PARP-1 is essential for preserving genomic stability and controlling DNA transcription processes, it is a prospective target for the development of anticancer therapies. Additionally, elevated PARP-1 expression is seen in neoplastic conditions such as melanomas, breast cancer, lung cancer, and others **[19]**.



1

Fig. 2. Compound 1 (IC50 = 2.77nM)

For the treatment of lung cancer, in their study, Almahli *et al*. documented the synthesis of a collection of phthalazinone-based derivatives,

which exhibit the potential for biological activity against PARP-1 **[20]**. Furthermore, inhibitory activity was greatly diminished by substituting the phenyl group for a benzyl group carbon number 4 of the phthalazine skeleton. Moreover, replacing the N-2 acetyl linker with a propionyl one enhanced the biological activity. In addition, it appeared that the cytotoxic activity of derivatives against A549 cells was unaffected by different halogen substituents in the aniline group.

The normal human foreskin fibroblast cells were not harmed by most counterparts, either. Compound **2** showed the highest PARP-1 inhibitory activity in vitro, with an IC_{50} value of about 97 nM, which is approximately 1.4-fold more effective than the positive control Olaparib. During the docking simulation of this structure, two hydrogen bonds were identified: one between the carbonyl oxygen of the phthalazinone and the OH group of Ser904 in the backbone, and the other between the N-H of the linker and the carboxylate of Asp766. Additionally, three π–π interactions were observed: two between the phthalazine moiety and Tyr907/Tyr896, and one between the 4-phenyl ring and Tyr907 **(Fig. 3) [21]**.

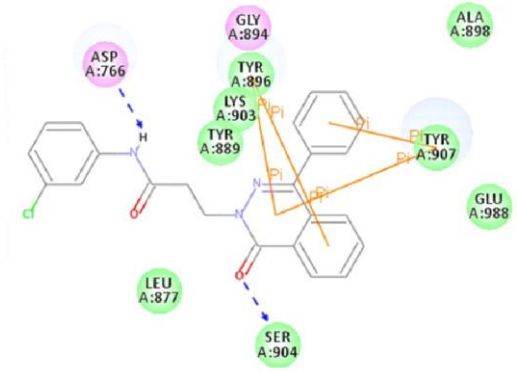


Fig. 3. 2-dimensional diagram of compound 2 (IC50=97 nM) exploring its interactions with the PARP-1 active site **[21]**.

AZD2461 was discovered as a derivative of the FDA-approved drug Olaparib. New compounds were developed by introducing various nitrogen-bearing and Methoxy groups incorporated in a cycloalkyl ring attached to the phthalazine backbone, based on AZD2461, with an IC_{50} ranging from 4.2 to 43.8 nM. Moreover, they exhibited enhanced selectivity and cytotoxicity specifically targeting BRCA1/2 mutant cancer cells. AZD2461 derivatives were synthesized and evaluated in both BRCA1 functional and nonfunctional cell lines. Three compounds (designated as **3**, 4, and **5**) exhibited low cytotoxicity while maintaining excellent PARP-1 affinities (approximately 4−8 nM). Molecular modeling studies indicated a direct correlation between the predicted distance of the methoxy oxygen atom in the ligand and the Arg878 residue, influencing the binding affinity of these compounds, as shown in **Fig. 4**.

Additionally, the cytotoxicity of these new compounds was found to be lower in BRCA1-null/restored UWB1.289 isogenic cell lines, which are more susceptible to PARP inhibitors. This indicates that the newly developed compounds have a different cytotoxicity profile compared to that of AZD2461, showing promise in providing potentially improved treatment options for cancer patients with specific genetic mutations **[22]**.

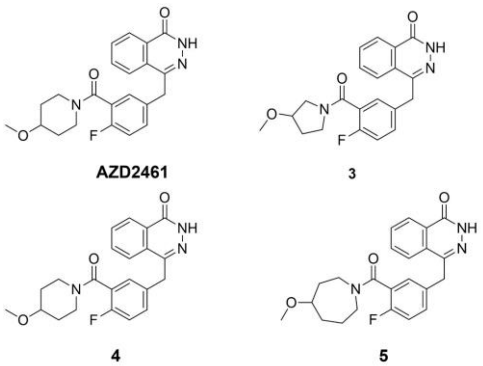


Fig. 4. AZD2461 and new synthetic analogs (3-5), as high-affinity PARP-1 Inhibitors (approximately 4−8 nM).

By replacing the piperazine nucleus in Olaparib with diaza-spiro complexes, Reilly and coworkers have discovered structurally new phthalazine-based PARP-1 inhibitors. Among these, diaza-spiro compound **6** tied up to PARP-1 with an IC_{50} of 12.6nM. Studies using computational models showed that the binding energy of compound **6** was -12.63 kcal/mol, which is comparable to the binding energy of -12.5 kcal/mol of Olaparib.

As The OVCAR8 (BRCA1-methylated) cell line was also not affected by compound **6** cytotoxicity at 10 M concentration, Compound 6, at medication concentrations like Olaparib, could inhibit PARP-1 action without causing damage to the DNA. Moreover, compound **6** exhibited remarkable selectivity as a PARP-1 inhibitor with minimum off-target action at doses as high as 10 M doses, compared to Olaparib **[23]**. This indicates that compound **6** holds potential as a promising candidate for targeted cancer therapy, with fewer adverse effects on non-targeted cells compared to existing PARP-1 inhibitors like Olaparib as shown in **Fig. 5**.

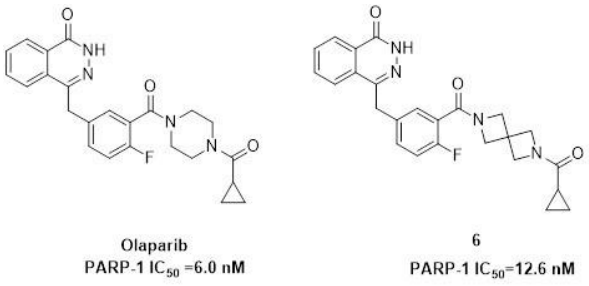


Fig. 5. IC_{50} of compound 6 and Olaparib against PARP-1

New compounds were synthesized based on the phthalazinone derivatives Olaparib, KU58948, and AZD2461, which served as lead compounds. Two main modifications were made to these derivatives. The first modification involved replacing the phthalazinone nucleus with the pyridopyridazinone scaffold through an isosteric replacement. Additionally, compound **7** featured a tetrahydro-pyridopyridazinone scaffold with a nitrogen atom, which was reported to enhance the pharmacokinetic properties compared to similar carbon-based analogs.

The second structural modification entailed attaching various functional pharmacophoric fragments to the pendant benzyl group at position 4 of the pyridopyridazinone scaffold. These fragments were linked via an amide linkage to block potential metabolism at this position and extend the compound's half-life. These structural modifications aimed to improve the compound's pharmacological properties, including selectivity, efficacy, and bioavailability, making them more promising candidates for further development as PARP-1 inhibitors with IC50= 36 nM or potential therapeutics for various diseases as shown in **Fig. 6 [24]**.

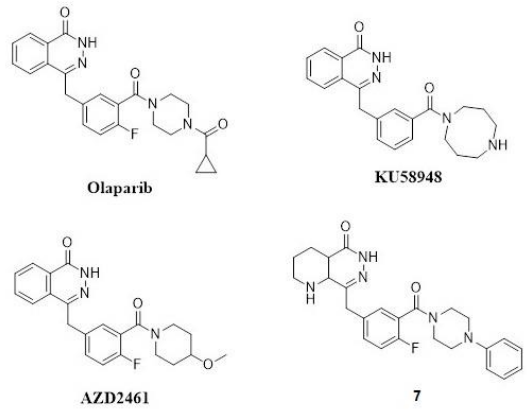


Fig. 6. Pyridopyridazinone derivative (7) with IC50 36 nM as PARP-1 inhibitor.

Compound **8**, **(Fig.7)** exhibited remarkable PARP-1 inhibition activity, with an IC_{50} value of 36 nM, surpassing the reference drug Olaparib, which had an IC50 value of 34 nM. Molecular modeling simulations unveiled that the designed compounds fit well into the PARP-1 active site, forming stable complexes. Three key hydrogen bond interactions were observed, involving both Gly863 and Ser904, while additional favorable π-π and hydrogen-π stacking interactions occurred with Tyr907 and Tyr896, respectively. These

specific interactions likely contribute to the superior potency of compound **8** as a PARP-1 inhibitor, suggesting its potential as a promising candidate for further development in the treatment of various diseases that involve PARP-1 inhibition **[24]**.

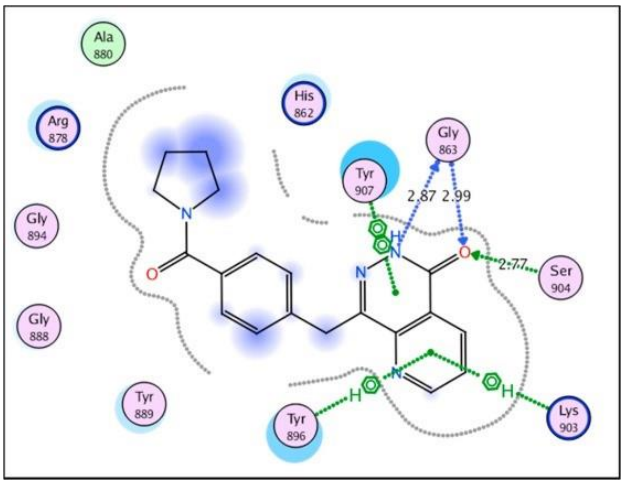
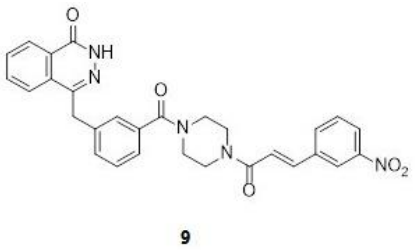


Fig.7. 2D diagram of compound 8 (IC50=36 nM) showing its interactions with the PARP-1 active site

Gao and colleagues developed compound **9 (Fig. 8)**, a PARP-1 inhibitor, by structural optimization of Olaparib based on the existing SAR. With this aim in mind, we decided to keep the 4-benzyl phthalazinone group unchanged and replace the cyclopropane group of Olaparib by substituting aryl vinyl ones to constitute 3-aromatic α, β -unsaturated carbonyl moiety. The phthalazine-based derivative **9** exhibited notably lower IC50 values for the PARP-1 enzyme (IC50 of 16.10 nM) and the MDA-MB-436 cancer cell line (IC50 of 11.62 µM) compared to the parent compound.



9

Fig. 8. Structure of compound 9 (IC50 = 16.10 nM).

Through molecular docking analysis, it was observed that the oxygen atom of the acryloyl moiety in compound **9** formed a hydrogen bond with the NH group of Arg878. This interaction likely contributes to the compound's enhanced potency as a PARP-1 inhibitor, potentially leading to improved therapeutic effects in cancer treatment **[25]**.

Inhibition of both PARP and PI3K pathways has been known as a promising strategy for cancer treatment. Herein, we mentioned the discovery of dual PARP/PI3K inhibitors that merge the pharmacophores of PARP and PI3K inhibitors. Among them, compound **10 (Fig. 9)** stands out as the most promising candidate with potent inhibitory activities against both PARP-1/2 and PI3Kα/δ with pIC50 values greater than 8. Compound **10** showed superior antiproliferative profiles against both BRCA-deficient and BRCA-proficient cancer cells in cellular assays. Its effects are produced by the dual inhibition of the two targets. In vivo, **10** showed more efficacious antitumor activity than the corresponding drug combination (Olaparib + BKM120) in the MDA-MB-468 xenograft model with a tumor growth inhibitory rate of 73.4% without causing observable toxic effects. All of the results indicate that **10**, the first potent dual PARP/PI3K inhibitor, is a highly effective anticancer compound **[26]**.

Using a hybridization technique, researchers developed a phthalazinone-acridine derivatives library of compounds that act as inhibitors for both PARP-1 and Topoisomerases. They incorporated Topo inhibitor acridines into the PARP-1 inhibitor Olaparib to create these compounds. Among them, compound **11 (Fig. 10)** demonstrated significant antiproliferative efficacy, comparable to or even greater than that of Olaparib, despite having a decreased PARP-1 binding affinity (IC50= 11.85M).

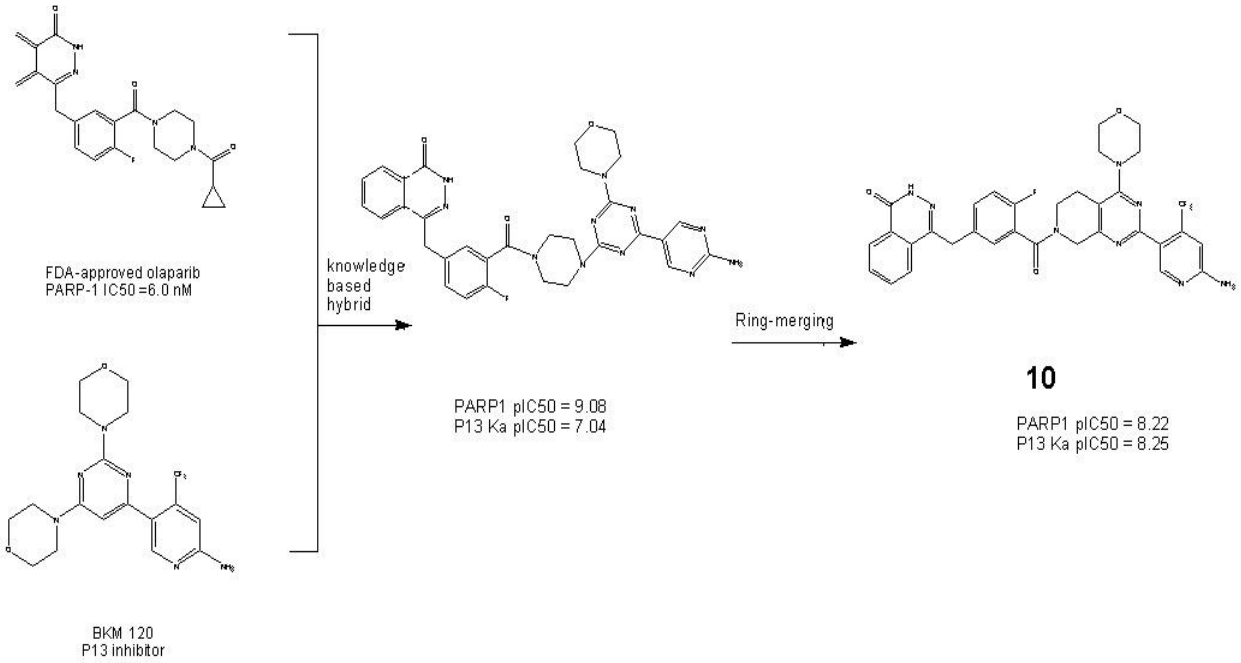


Fig. 9. Structure and IC_{50} Compound 10 with pIC_{50} values greater than 8 **[26]**.

Moreover, in a western blotting assay, compound **11** at a concentration of 10 M (similar to the positive control m-AMSA, an acridine analog) dramatically inhibited the expression of Topoisomerase II (Topo II). This validated compound **11** as a promising inhibitor of both PARP-1 and Topoisomerase.

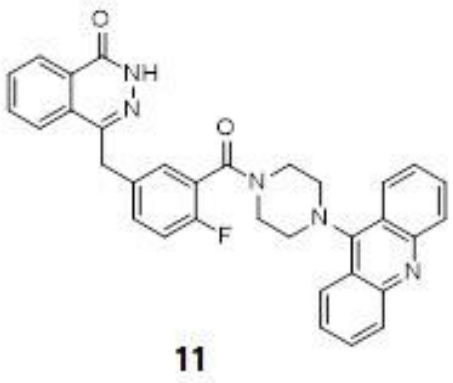


Fig. 10. Structure of compound 11 dual Topo-PARP inhibitors (IC50=11.85M)

Extended testing on HCT116 cells revealed that compound **11** was capable of initiating apoptosis and cell cycle arrest. These findings suggest that compound **11**, which simultaneously targets Topo and PARP, has the potential to be a lead compound for cancer therapy. By inhibiting both PARP and Topoisomerases, this compound could offer a novel and effective approach to treating cancer and warrants further exploration as a potential treatment option **[27]**.

Abd El-Sattar and colleagues synthesized pyrano [2,3-d] pyrimidine-2,4-dione series analogs and tested their perspective PARP-1 inhibition activity. They also evaluated their ability to reduce the proliferation of MCF-7 and HCT116 cancer cell lines. Among the compounds tested, compounds **12** and **13 (Fig 11)** exhibited the most potent inhibition of PARP-1, with IC_{50} values of 4.06±0.18 and 3.61±0.15 nM, respectively.

These results were compared to the IC_{50} value of Olaparib, which was 5.77 nM. Additionally, compounds **12** and **13**

demonstrated high cytotoxic activity against MCF-7 cells, with IC_{50} 2.65±0.05 and 1.28 ±1.12 μM, respectively. Compound **14** stood out for remarkably inhibiting cell growth of both MCF-7 and HCT116, with 0.66±0.05 and 2.76±0.06 μM, respectively IC_{50} values.

In addition to their promising activity, in a theoretical pharmacokinetic study, almost all of the synthesized compounds were predicted to have favorable pharmacokinetic traits. This suggests that these compounds have the potential for good drug-like characteristics and further validate their potential as candidates for cancer therapy **[28]**.

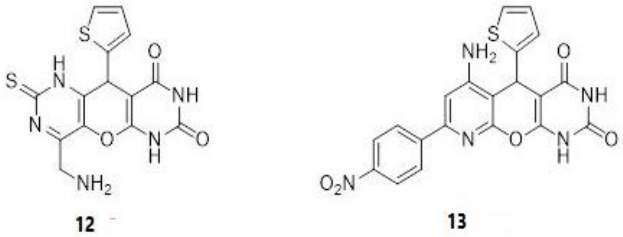


Fig. 11. Structures of Compounds 12 & 13 with IC50 values of 4.06 ± 0.18 and 3.61 ± 0.15 nM, respectively.

Compound **15 (Fig. 12)** is a novel Thieno [2,3-d] pyrimidinone derivative, **that** exhibits a promising anticancer activity, with an IC_{50} value of 6.9 μM. Additionally, compound **15** displayed a significant antioxidant effect, with 40.8% inhibition of DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals.

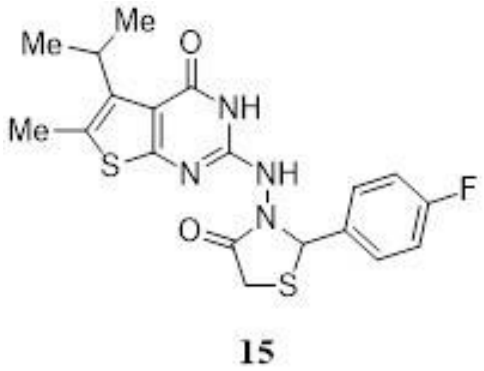


Fig. 12. The structure of compound 15(IC50=6.9 μM)

Molecular docking of compound **15** was performed, and it showed ΔG (delta G) values of -20.54 kcal/mol. These values represent the calculated binding free energy, indicating the stability and strength of the interactions between compound **15** and its target molecule **[29]**.

Conclusion

Diazine-based-containing compounds can indeed be used as PARP-1 inhibitors. PARP-1 is an enzyme that lays diverse roles in various cellular processes, including transcription, cell death (apoptosis), and DNA repair. Thus, its inhibition has therapeutic potential in various diseases, including cancer. When PARP-1 is inhibited by compounds, such as certain Diazine-based-containing ones, its normal functions can be disrupted.

The development and optimization of Diazine-based-containing compounds as PARP-1 inhibitors are active areas of research. Scientists continue to explore the structure-activity relationships and optimize the pharmacokinetic and pharmacodynamic properties of these compounds to enhance their efficacy and selectivity as PARP-1 inhibitors. Fig.13 Illustrates the common features of different PARP inhibitors previously mentioned.

It's noted that while Diazine-based-containing compounds have shown potential as PARP-1 inhibitors, specific compounds may have different potencies, selectivities, and other properties. The development and use of these compounds as therapeutic agents require extensive research, preclinical studies, and clinical trials to evaluate their safety and effectiveness in treating specific diseases.

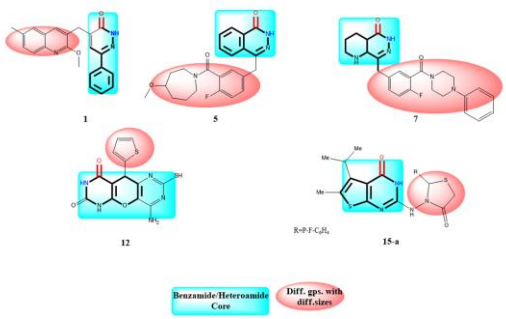


Fig. 13. Illustrates the common features of different PARP inhibitors previously mentioned

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

Not applicable

Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing interests

The authors have no financial or non-financial benefits to relate.

Funding

The authors declare that no grants, funds, or any other support were gained during manuscript preparation.

Author contribution

The manuscript was drafted and written by Norhan A. Abdelrahman. All authors have read and approved the final -manuscript.

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