

Research Progress of PARP-1 Related Dual Target Inhibitors

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Abstract. The treatment of cancer has always been based on surgery, radiotherapy and chemotherapy, but the cure rate of these methods is often very low and the side effects on patients are very serious. With the gradual understanding of cancer, targeted drug therapy has gradually attracted the attention of the scientific community. Initially, doctors used some single target inhibitors as targeted drugs for tumor treatment. However, with the increasing of single drug resistance and side effects, the problems of single drug resistance and side effects gradually emerge in clinical practice. Poly ADP-ribose polymerase-1 inhibitor (parp-1i) can inhibit DNA damage and repair in cells, so it is used as a kind of targeted drugs for tumor therapy. At a time when single target drugs are facing challenges, scientists have turned their attention to dual target inhibitors related to parp-1i with stronger effects. In this paper, we focus on the challenges faced by PARP-1 related single target inhibitors and the research progress of HDAC inhibitors or BRD4 inhibitors combined with PARP-1 inhibitors as double target inhibitors. It was found out that some new synthesized dual PARP/HDAC inhibitors and PARP/BRD4 inhibitors have shown great anticancer activities in vitro experiments, including compound I-8 and II-16. Therefore, this review confirms that PARP-related dual target inhibitors can be a promising approach to treat cancer cell.

Keywords: PARP-1, HDAC, BRD4, Multitarget, Antitumor.

1. Introduction

At present, as a major disease threatening human life and health, cancer seriously affects people's life and health. Among them, ovarian cancer is one of the most common malignant tumors in women over 40 years old, and its mortality ranks first among gynecological malignant tumors. [1] Meanwhile, according to the statistics of China Academy of Sciences, the incidence rate and mortality rate of lung cancer, ovarian cancer and digestive system cancer are increasing at an alarming rate. [2] After nearly 60 years of exploration and research, the pathogenesis of tumor has been gradually analyzed and clarified. The emergence of malignant tumor is not a sudden disease, but the result of continuous mutation of multiple genes. When it accumulates to a certain extent, the relevant genes in cells are abnormally expressed, and finally manifested as the formation of malignant tumor. Scientists are still actively exploring the treatment of chronic diseases. Previously, the treatment of tumors mainly included surgical resection, radiotherapy and chemotherapy. In recent years, DNA damage repair is the research hotspot of cancer treatment. [3] When the specific molecular targeted therapy under the guidance of precise medicine is applied to the clinical treatment of tumor, the specific targeted therapy for malignant tumor cells has become a new direction of tumor treatment. [4]

In view of the complex network system of intracellular signal transduction pathway, the initial single target inhibitor can only inhibit one cell signal molecule, and the intracellular signal can often pass through other transduction pathways. Therefore, single target inhibitors have little effect on the function and state of tumor cells, resulting in poor therapeutic effect on cancer. [5] Take the object parpi introduced in this article as an example, parpi has long been an attractive antitumor drug. Considering that PARP inhibition can inhibit DNA damage repair and make tumor cells sensitive to DNA-damaging agents. The development of PARP inhibitor (parpi) has made great progress in the past few years. Some parpi have shown encouraging results. They can be used as a single drug to

treat cancer using the concept of synthetic lethality [6], or in combination with radiation or other chemotherapeutic drugs, showing enhanced antitumor efficacy in various cancers. [7,8] Although parpi plays an important role in cancer treatment, many clinical data show that it only shows limited biological activity in the treatment of some special malignant tumors. What's worse, tumor cells gradually develop drug resistance to it. Therefore, parpi drugs still need to be improved.

On another aspect, multi-target drugs can effectively regulate multiple complex signal pathways in cells and not eliminate the relationship between members of the signal transduction system. It is not easy to produce drug resistance in the design of multi-target treatment systems for many diseases at the same time. And many studies have confirmed that the design of ligands acting on specific multi-target has gradually become a hot direction of antitumor drug research in recent years. [5]

This article summarizes and analyzes the current research progress on dual target drugs of PARP and HDAC based on the functional synergy characteristics that parpi can inhibit the damage and repair of intracellular DNA and HDACi can induce tumor cell cycle arrest, oxidative stress and DNA damage [9-11]; At the same time, considering the synergistic and complementary characteristics that parpi and brd4i can inhibit DNA damage repair through their different paths [5,12], we summarized and analyzed the current research progress of PARP and Brd4 dual target drugs. To provide reference for anti-tumor drug scholars in related fields.

2. Typical Single-target Inhibitors

Since scientists proposed the key model in the last century, drug discovery has increasingly focused on the development of single-target drugs, that is, the perfect combination of ligand and specific target. However, after years of research and exploration, the point-to-point "strike" of such single-target drugs seems not to be very effective, and there are some defects compared with multi-target drugs.

2.1. PARP-1 Inhibitors

2.1.1. Biological functions and research status of PARP-1 inhibitors.

Poly ADP-ribose polymerase (PARP) is a kind of ribozyme, which mainly exists in eukaryotic cells and participates in DNA repair, transcription, regulation and other processes. In the PARP family, THE content of PARP-1 is the largest, which plays a 90-95% role in DNA damage repair.

PARPis are usually niacinamide analogues based on benzamide or purine that compete with NAD⁺ in the catalytic domain of PARPs. Historically, their activity has been based on a concept of "synthetic lethality" first proposed in 2005, under which two genetic lesions are not fatal when they occur alone but can be if they occur in the same cell. As a result, HR deficient cells are more sensitive to inhibition of PARP activity. PARP inhibition reduces the activity of HR and BER, so SSB is not repaired in, leading to many unrepaired DSB in DNA replication in HRD cells. PARPis can also block NHEJ inhibition, with high load mutations and apoptosis.

To date, the following five PARP-1 inhibitors have been approved by the FDA: Olaparib, Rucaparib, Niraparib, Veliparib, and Talazoparib.

2.1.2. Challenge of PARP-1 inhibitors in cancer treatment.

Olaparib is the first PARP-1 inhibitor to be approved for the treatment of BRCA1/2 mutant ovarian cancer. However, clinical data on the treatment of PARP inhibitor Olaparib presented at the 2019 ASCO Annual Meeting also reflect several adverse reactions caused by Olaparib (Figure 1). The most common grade 3-4 adverse reactions are: Anemia, vomiting, anxiety, reduced platelet count, reduced neutrophil count, and even 21% of patients reduced dose due to adverse reactions, 7% of patients stopped treatment due to adverse reactions.

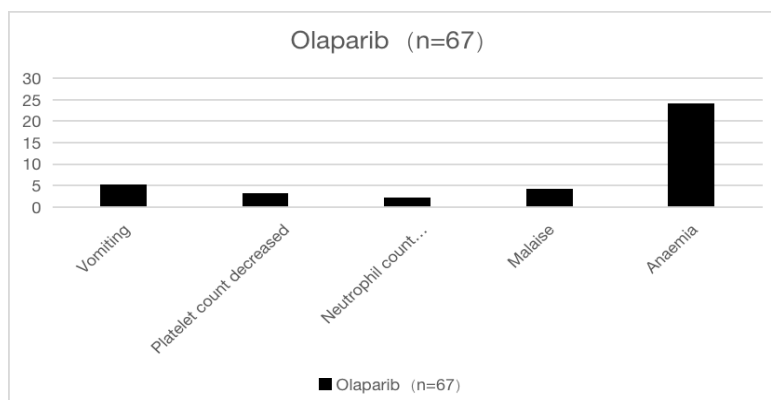


Figure 1. Grade 3-4 adverse reactions induced by olaparib in clinical trials

Another PARP inhibitor, Veliparib, which has received orphan drug designation from the U.S. FDA, has been shown to enhance sensitivity in treating DNA damage. But when Veliparib was used in combination with radiotherapy and several cytotoxic drugs in different solid tumors, it worked better than chemoradiotherapy alone.

2.2. HDAC Inhibitors

2.2.1. Biological functions and research status of HDAC inhibitors.

Histone deacetylase (HDAC) inhibitors are a new class of drugs based on epigenetic theory. Nucleosomes, as the basic unit of eukaryotic chromatin, influence cell function through acetylation, methylation, phosphorylation and proteinization of the n-terminal histone core. The dynamic balance between histone acetylase (HAT) and HDAC controls chromatin structure and gene expression. When histone deacetylation levels are elevated, the acetylation levels are reduced, leading to changes in normal cell cycle and metabolic behavior, resulting in tumor and neurodegenerative changes. HDAC inhibitors target HDAC, regulate histone acetylation, promote the expression of transcription and anti-tumor transcription factors, regulate related signaling pathways, and play an anti-tumor biological role by inhibiting HDAC activity. The results showed that HDAC inhibitors can promote cell differentiation, block cell cycle, induce cell decline, and up-regulate the expression of tumor suppressor gene.

Targeted inhibition of HDAC has been proven to have anti-tumor effects. HDACi enhances histone acetylation by inhibiting HDAC activity, promotes the binding of transcription factors to DNA chains, and further activates the expression of cancer-suppressor genes and other specific genes. Based on the above characteristics, The main effects of HDACi are :(1) inducing tumor cell death (programmed death that affects apoptosis, autophagy and necrosis); (2) increase the sensitivity of tumor cells to other antitumor drugs; (3) affect the level of reactive oxygen species; (4) Anti-angiogenesis effect; (5) Affect cytokine signal.

2.2.2. Challenge of HDAC inhibitors in cancer treatment.

In Chen Kai, the antitumor effect of sidabenamine, a histone deacetylase inhibitor, on acute myeloid leukemia by inhibiting Mcl-1 and inducing DNA damage sensitization abT-199 [13] article about HDAC inhibitor on the west of the amine joint experiment of ABT - 199 induced leukemia cell apoptosis, in leukemia cell lines Molm - 13 data, for example (Figure 2), Compared with sitabenamine alone, abT-199 combined with sitabenamine significantly increased the apoptosis rate of leukemia cells and was safely tolerated, suggesting that HDAC inhibitors can improve patient resistance through the combined production of multi-target drugs.

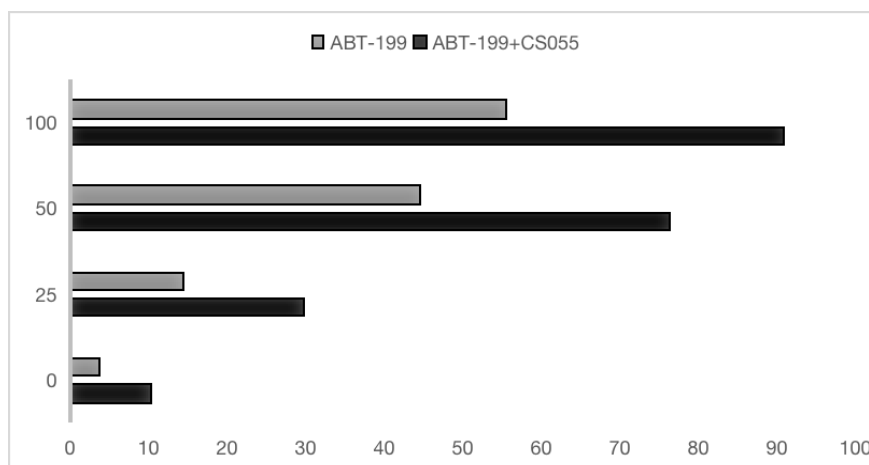


Figure 2. Comparison of Molm-13 leukemia cell line induced by sitabemamine combined with ABT-199.

Another drug, vorinostat, acts as an inhibitor of histone deacetylase HDAC in human body, and can exert its effects by inducing cell differentiation, blocking cell cycle, and inducing cell regulation. But in FuLi jian-hong huang had joint willy's research the role of three negative breast cancer cells article, cell vitality experiments show that using FuLi alone he treatment of breast cancer cells, The growth inhibition rate was not significantly decreased with the increase of drug concentration, and the difference was not statistically significant. Flow cytometry results showed that vorinostat alone could not significantly promote the apoptosis of breast cancer cells, and the apoptosis rate did not increase with the increase of drug concentration. These problems can be effectively solved when combined with other targeted inhibitors.

2.3. BRD4 Inhibitors

2.3.1. Biological functions and research status of BRD4 inhibitors.

The BET subfamilies of Bromodomain-containing proteins (BRDs) include BRD2, BRD3, BRD4 and BRDT. Among them, BRD4 is a potential therapeutic target for many malignant tumors, including pancreatic cancer. BRD4 activates positive transcription extension factor b (p-tefb) to regulate the expression of many genes involved in tumorigenesis.

BRD4 inhibition has been reported to significantly increase HR deficits. BRD4 inhibitors inhibit the expression of BRCA1, Rad51 and other genes involved in DNA replication and DNA damage signaling. There is evidence that simultaneous inhibition of BRD4 and PARp1/2 enzyme activity synergistically increases cancer cell death. In addition, the first PARP1/BRD4 dual inhibitor discovered by Chang et al showed significant inhibitory effect on breast cancer cell growth.

2.3.2. Challenge of BRD4 inhibitors in cancer treatment.

JQ1 is a BET bromodomain inhibitor that inhibits BRD4(1/2). Miller et al. found that in clinical models of pancreatic cancer, tumors exposed in vivo to JQ1 had higher levels of the DNA damage marker γ H2AX than tumors exposed to vehicle only. Increases in γ H2AX was concomitant with decreased expression of DNA repair proteins Ku80 and RAD51. JQ1 + olaparib inhibited the growth of PDX tumors greater than either drug alone[14]. It indicates that the design of novel dual inhibitors has advantages in the treatment of pancreatic cancer and is expected to help in the treatment of pancreatic cancer in the future.

2.4. Challenges of Single Target Inhibitors.

Firstly, single-target drugs can only inhibit one cell signaling molecule while Multi-target drugs can simultaneously act on multiple pathological links and multiple pathogenesis of the same disease to produce synergistic effects, so that the total effect is greater than the sum of single effects. Secondly, drug target usually in multiple signaling pathways has multiple biological functions, excessive

activation or inhibit an organism in vivo target molecule, intervention in one kind of biological function at the same time, also can influence other normal biological function as well as other related the normal function of biological macromolecules. Multiple targets for drugs can better balance the relationship between multiple pathogenic factors of the same disease. Finally, long-term use of a single target drug to treat diseases can induce adaptive changes in the body and activate the antagonistic protective mechanism or bypass compensation mechanism, so that the disease is no longer sensitive to the drug, resulting in drug resistance.

3. Dual PARP and HDAC Inhibitors

3.1. Rational drug design

Olaparib which is PARP inhibitor in the market was used as lead compounds for rational drug design. Based on the rational drug design, the hydroxamic acid derivatives of Olaparib was firstly used as dual PARP and HDAC inhibitors in Zigao Yuan et al's study. [15] The reason for designing the hydroxamic acid derivatives is that it is convinced that the potency of Olaparib to inhibit PARP-1 activity will not be vastly influenced by the change of the piperazine unit of Olaparib. Besides, the designed structure may contain three important properties to inhibit HDAC activity: a cap group to occlude the entrance of the active site pocket of HDAC; a zinc-binding group (ZBG) to chelate the zinc ion in the active site of HDAC and a linker to connect the cap and ZBG.

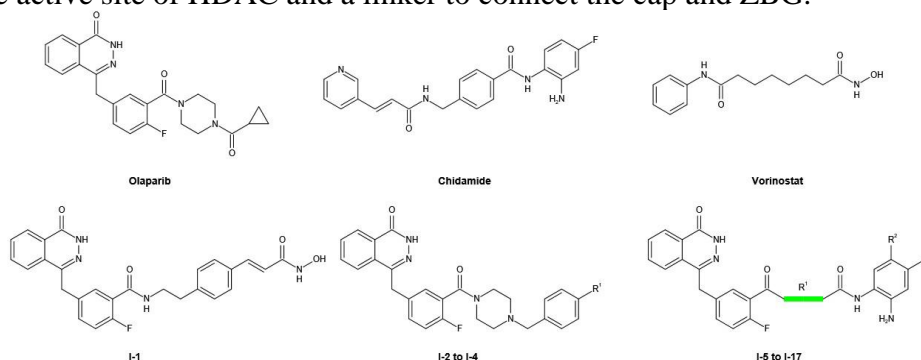
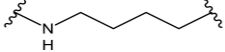
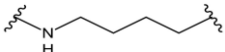
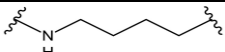
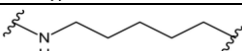
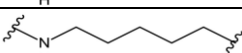
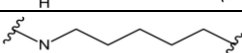
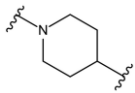
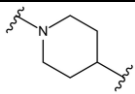
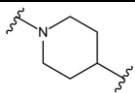
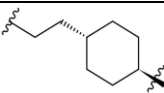
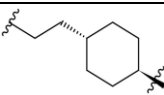
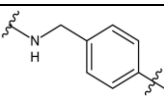
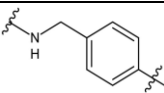


Figure 3. Chemical structure of PARP inhibitor Olaparib and HDAC inhibitor Chidamide, Vorinostat and dual PARP and HDAC inhibitor **I-1** to **I-17**.

3.2. Bioactivity of Dual PARP-1 and HDAC-1 Inhibitors

Compounds **I-1**, **I-2**, **I-3** and **I-4** were synthesized in previous research. Another research develops new inhibitors and tests IC_{50} value of compounds **I-5** to **I-17** (figure 3). And the results of IC_{50} values of compounds **I-1** to **I-17**, Olaparib, SAHA and chidamide shows in table 1. From table 1, it's obvious that some compounds show significant potency to inhibit PARP-1 and HDAC-1 activity. The inhibitory activity against PARP-1 was significant enhanced in compound **I-8** ($IC_{50} = 4.23$ nM), compound **I-11** ($IC_{50} = 1.94$ nM), compound **I-12** ($IC_{50} = 1.81$ nM) and compound **I-13** ($IC_{50} = 2.58$ nM). However, the inhibitory activity against HDAC-1 in compound **I-8**, **I-11**, **I-12** and **I-13** is decreased about 2-6 folds than Chidamide. Although some compounds like compound **I-12** ($IC_{50} = 140$ nM) show some potential to inhibit HDAC activity, the inhibitory effect to PARP-1 needs to be improved in these compounds. Therefore, despite great advantages of dual PARP and HDAC inhibitors, the inhibitory of compounds still needs to be improved in the future. [15,16]

Table 1. Enzymatic inhibitory activities of compounds I-1 to I-17

Compd	R1	R2	R3	IC ₅₀ (nM)a (inhibition% at 20 nMb)	
				PARP-1	HDAC-1
I-1				68.15	27.26
I-2	trans-CH=CHCONHOH			15.04	38.25
I-3	CH ₂ CONHOH			20.43	912.50
I-4	CONHOH			6.16	502.80
I-5		H	H	(39.36)	740
I-6		F	H	(42.35)	910
I-7		H	F	(64.73)	!
I-8		H	H	4.23	340
I-9		F	H	(65.86)	520
I-10		H	F	(46.23)	810
I-11		H	H	1.94	820
I-12		F	H	1.81	950
I-13		H	F	2.58	940
I-14		H	H	(41.31)	340
I-15		H	F	(49.66)	890
I-16		H	H	(37.38)	140
I-17		H	F	(22.06)	340
Olaparib				3.59	
SAHA					11.34
Chidamide					160

3.3. New Mechanisms of Dual PARP and HDAC Inhibitors

PARP inhibitors can suppress damaged DNA repair. At the same time, HDAC inhibitors can cause DNA damage in human cells. [15] Therefore, the combination of PARP inhibitors and HDAC inhibitors can improve the DNA damage and kill tumor cells. In recent studies, it was found that compound **I-1** and **I-2** had the potency to inhibit the proliferation of several cancer cells. The expression of γ -H2AX in MDA-MB-231 cells could be induced by Compound **I-1**. Thus, compound **I-1** could cause DNA double-strand breaks accumulation. Besides, scientists also found out that compound **I-8** successfully extended the anti-cancer spectrum of Olaparib for BRCA-proficient cells such as K562 cell. [16] These new findings demonstrate that dual PARP and HDAC inhibitors is a hopeful way to improve the potency of the drug in the market nowadays.

4. Dual PARP-1 and BRD4 Inhibitors

4.1. Rational Drug Design

The lethal disease pancreatic cancer will become the second reason for cancer death in next few years. Recently, because of the success of PARP inhibitors, synthetic lethality strategy is a significant way to treat pancreatic cancer and prolong patients live. Shu-Ping Wang et al's study in 2021 shown that PARP inhibitors including Olaparib, Veliparib and so on sensitize the important signaling molecules that involve in DNA single strand breaks repair. [17] However, there are some pathways which can trigger precise repair of breaks of DNA using a sister chromatid template for recombination and the homologous recombination is the most effective pathway. Most of pancreatic cancer are HR-proficient. Increased HR repair capacity is one of the most important reasons to cause drug resistance so that PARP inhibitors will lose potency in most pancreatic cancers. Therefore, the research about causing the deficiency of HR repair is a significant way to improve the potency of PARP inhibitors. [18]

There are reports showing that the inhibition of BRD4 will elevate HR deficiency. And recent works demonstrate that the combination of use of PARP and BRD4 will increase the death of cancer cells so that dual PARP and BRD4 inhibitors may become the potential drugs of pancreatic cancer therapy. [19] Just like dual PARP and HDAC inhibitors, pharmacophore fusion strategy can also be used to design dual PARP and BRD4 drugs. The core pharmacophore of Veliparib is the 1H-benzimidazole-4-carboxamide moiety which forms key hydrogen bonds. And the tetrahydrobiopterin moiety of BI-2536 forms 2 key hydrogen bonds. With these two important moieties, novel compounds were designed with pharmacophore fusion strategy.

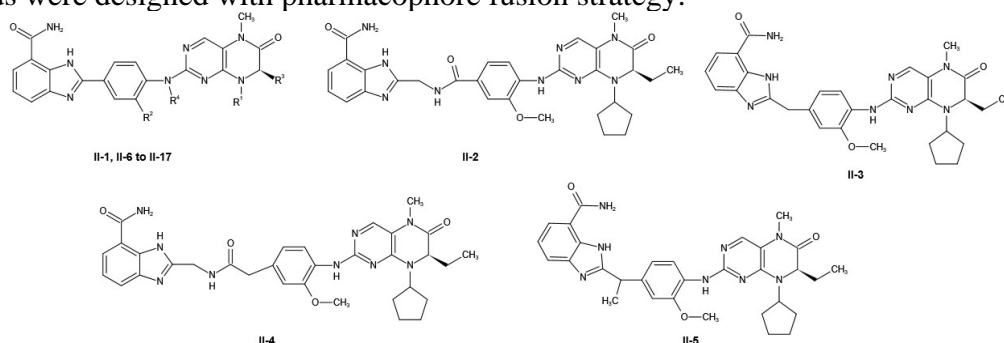
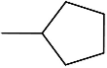
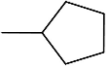
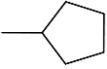
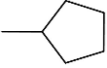
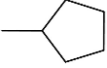
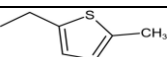
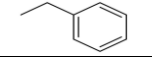
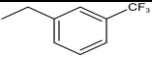
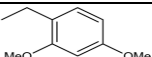
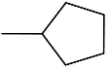
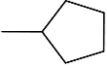
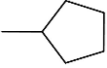
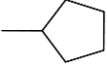
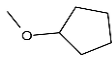
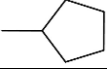
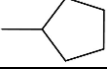
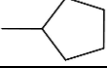


Figure 4. Chemical structure of dual PARP and BRD4 inhibitors II-1 to II-17.

4.2. Bioactivity of Dual PARP-1 and BRD4 Inhibitors

Using linkers to connect these two important moieties, scientists designed new compound II-1 which shown significant PARP-1 and BRD4 inhibition with IC₅₀ value of 150 and 237 nM (figure 4). In order to get compounds which have better PARP and BRD4 inhibition activity, scientists designed other 16 compounds in table 2 (compound II-2 to II-17). Among these compounds, II-11, II-16, and II-17 exhibits better PARP-1 inhibitory activities with IC₅₀ value of 43, 13 and 25 nM separately. In addition, II-3, II-16, and II-17 exhibits better BRD4 inhibitory activities with IC₅₀ value of 186, 101 and 202 nM. II-16 shows best inhibition activity both against BRD4 (IC₅₀ = 101 nM) and PARP-1 (IC₅₀ = 13 nM). Therefore, it's believed that it's possible to produce the PARP/BRD4 inhibitors to promote the treatment of pancreatic cancer. [17]

Table 2. Enzymatic inhibitory activities of compounds II-1 to II-17

Compd	R1	R2	R3	R4	PARP-1	BRD4(BD1/2)
					IC50(nM)	IC50(nM)
						Or inhibition ratio%
II-1		-OCH3	-Et	-H	150±15	237±9.0
II-2		-OCH3	-Et	-H	341	374
II-3		-OCH3	-Et	-H	355	186
II-4		-OCH3	-Et	-H	498	276
II-5		-OCH3	-Et	-H	236	74% (0.5 µM)
II-6	-	-	-Et	-H	155	693
II-7		-OCH3	-Et	-H	338±7.0	52% (0.5 µM)
II-8		-OCH3	-Et	-H	461±39	21% (0.5 µM)
II-9		--OCH3	-Et	-H	1756±456	17% (0.5 µM)
II-10		-OCH3	-Et	-H	570±87	17% (0.5 µM)
II-11		-H	-Et	-H	43±6	842±74
II-12		-OCH2CH3	-Et	-H	306±19	86% (0.5 µM)
II-13		-	-Et	-H	2052±223	75% (0.5 µM)
II-14			-Et	-H	1825±120	47% (0.5 µM)
II-15		-OCH3	Me	-H	127±7	250±24
II-16		-OCH3	-Et	Me	13±2.5	101±11
II-17		-OCH3	Me	Me	25±4	202±32
JQ-1						83±4.0
Olaparib					0.6±0.2	

4.3. New Mechanisms of Dual PARP and BRD4 Inhibitors

Compound **II-16** shown excellent BRD4 and PARP-1 inhibition activities. In vitro experiments, compound **II-16** has been found that it has significant synergistic efficacy in the growth of SW1990 cells by arresting G1/S transition and cell mitosis and inhibiting DNA damage repair. Besides, **II-16** decrease Olaparib-induced adaptive resistance and it can cause cell cycle arrest, autophagy-related cell death and DNA damage to slow down the growth of pancreatic cancer cells. [17]

5. Conclusions

PARP inhibitors and BRD4 inhibitors could induce the inhibition of DNA damage repair, while HDAC inhibitors could result in the DNA damage in cancer cells. Recent years, more and more single

target inhibitors have been improved in the market and shown anticancer activities for some extends. However, traditional single target inhibitors have some drawbacks such as limited biological activity, drug resistance and intolerant side effects which can be solved by multi-target inhibitors. In most cases, single target inhibitors should be used as first line drugs to treat cancers and multi-target drugs can be applied after the drug resistance occurs in clinical use.

In the future, it's necessary to design and synthesize compounds which have better IC₅₀ values and drug properties. The mechanisms of new multi-target inhibitors need further research as well. There are many other targets which can be used to the synthesis of multi-target inhibitors, and we certainly hold the belief that more novel PARP-1 related dual target inhibitors will be discovered and put into market.

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