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Design, Synthesis and Anticancer Activities of Novel Dual Poly(ADP-ribose) Polymerase-1/Histone Deacetylase-1 Inhibitors

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Design, Synthesis and Anticancer Activities of N Dual Poly(ADP-ribose) Polymerase-1/Histone	Novel	Leave this a	rea blank f	or abstract in	nfo.
Deacetylase-1 Inhibitors Yongbin Tian ¹ , Zhouling Xie ^{1,*} , Chenzhong Liao [*]					
	Compd 4	IC ₅₀ PARP-1 4.23	(nM) HDAC-1 340	5	
Compound 4 Dual PARP-1/HDAC-1 inhibitor	Olaparib Chidamide	4.19 e -	- 160		



Structure activity relationship

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Design, Synthesis and Anticancer Activities of Novel Dual Poly(ADP-ribose) Polymerase-1/Histone Deacetylase-1 Inhibitors

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ARTICLE INFO	ABSTRACT	
Article history: Received Revised Accepted Available online	Currently, synergistic inhibition of poly(AI deacetylases (HDACs) has been a potential eff combining critical pharmacophores in approved 2-fluoro-5-((4-0x0-3,4-dihydrophthalazin-1-yl)) synthesized. All efforts led to a good dual PA values of 4.2 and 340 nM against PARP-1 and	DP-ribose) polymerase-1 (PARP-1) and histone fective strategy for cancer treatment. Herein, by l drugs olaparib and chidamide, a series of novel methyl)benzoic acid derivates were designed and RP-1/HDAC-1 inhibitor, compound 4 , with IC ₅₀ HDAC-1, which were as potent as olaparib and
<i>Keywords:</i> Poly(ADP-ribose) polymerase-1 Histone deacetylase-1 Anticancer Dual target inhibitor	chidamide respectively. The MTT assay furth inhibitory activities against BRCA1/2-proficien of 5.6 and 4.3 μM, respectively. Therefore, ou promising dual PARP-1/HDAC-1 inhibitor for PARP-1 inhibitors such as 7-9 and HDAC- discovered, which also could be further studied	her demonstrated that compound 4 had potent t K562 and MDA-MB-231 cells with GI_{50} values in results suggested that compound 4 could be a per further studies. In addition, a few excellent -1 inhibitors such as 12 were serendipitously in our next work.

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Poly(ADP-ribose) polymerase-1 (PARP-1) is the most abundant and most widely investigated among the 17 members of PARPs family¹. PARP is an enzymatic protein containing a DNA binding domain, a catalytic domain and an auto-modification domain². Once damaged DNA is recognized by the DNA binding domain of PARP, its catalytic domain then catalyzes the substrate nicotinamide adenine dinucleotide to form nicotinamide and ADP-ribose. ADP-ribose units are further transferred onto acceptor proteins (histones and PARP itself), participating in DNA damage repair through the base excision repair pathway³⁻⁵. The overexpression of PARP-1 has been observed in multiple cancer cells such as breast and ovarian cancer cells⁶. On the basis of PAPR-1's mechanism, PARP-1 inhibitors have been attractive anticancer drugs in combination with chemotherapeutic drugs such as temozolomide and cisplatin^{7, 8}. In addition, PARP-1 inhibitors could be used as monotherapy for BRCA1/2- deficient (has homologous recombination repair deficient) cancers by synthetic lethality mechanism9. Up to now, four PARP-1 inhibitors, olaparib, rucaparib, niraparib and talazoparib have been approved by the FDA (Figure 1). Olaparib, as the first-inclass approved PARP-1 inhibitor, has been used for the treatment of BRCA1/2-mutated ovarian cancer¹⁰. To further improve therapeutic efficacy of olaparib, extend its treatments to homologous recombination repair proficient cancers and even overcome its drug resistance, researchers have focused on finding suitable combination therapies with other anticancer drugs or designing dual or multiple-target anticancer drugs by

simultaneously inhibiting PARP-1 and other critical regulated proteins¹¹.

Human histone deacetylases (HDACs), a class of Zn metalloenzymes having 18 different isoforms, represent important epigenetic modifications. They catalyze the deacetylation from lysine residues in histones tails, resulting in chromatin condensation and are overexpressed in various cancer types^{12, 13}. HDACs inhibition has been confirmed as an effective method for cancer treatment by reducing tumor cell metastasis, angiogenesis and proliferation, inducing tumor cell apoptosis and inhibiting DNA repair^{14, 15}. Five HDACs inhibitors have reached the market to date. In addition, researchers found that inhibition of HDACs with other kinases or proteins such as c-Met, JAK and PI3K has synergistic antitumor effect. Several dual inhibitors such as CUDC-907 have even been entered into clinical trials¹⁶.

Interestingly, synergistic effect of PARP-1 inhibition with HDACs inhibition has been observed in many studies. For example, Koeffler H. P. *et al* reported that HDACs inhibition could sensitize triple-negative breast cancer to the PARP-1 inhibitor olaparib¹⁷. Goodman Jr O.B. *et al* reported that combination of HDACs inhibition and PARP-1 inhibition could decrease homologous recombination-related protein expression and increase DNA damage in prostate cancer cell¹⁸. Hamerlik P. *et al* reported that HDACs inhibitor SAHA in combination with PARP-1 inhibitor olaparib could enhance inhibitory activity against glioblastoma cancer cells by inducing apoptosis and

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Figure 1. Chemical structures of approved PARP-1 inhibitors, HDACs inhibitors and compound **P1**.

impairing cell cycle progression¹⁹. All results suggested that synchronous inhibition of PARP-1 and HDACs could be a promising approach for cancer treatment. To avoid several side effects induced by drug-drug interactions, developing PARP-1/HDACs hybrid inhibitors has become a new trend in recent years. Jiang Y. et al reported several olaparib hydroxamic acid derivatives as dual PARP-1/HDAC inhibitors in 2017²⁰. Compound P1, among them, displayed potent inhibitory activity against PARP-1 (IC₅₀ = 68.15 nM) and HDAC-1 (IC₅₀ = 27.26 nM). However, its potencies against these two targets were lower than olaparib and SAHA respectively. In addition, studies showed that the hydroxamic acid fragment of SAHA, as a zinc binding group (ZBG), results in several drawbacks including short half-time, lacking selectivity over metalloproteases which may lead to poor druggability²¹. Therefore, to overcome these potential limitations, our group designed and synthesized a series of novel olaparib derivatives to identify more effective and safer novel dual PARP-1/HDACs inhibitors.



Figure 2. Design strategy of novel dual PARP-1/HDAC-1 inhibitors.

Chidamide, a drug approved in 2014 in China for the treatment of relapsed or refractory peripheral T-cell lymphoma, is a potent HDACs inhibitor with a benzamide group chelating the Zn^{2+} at the bottom of the active sites of HDACs²². We then used benzamide or fluorine substituted benzamide as ZBGs to replace hydroxamic acid, affording a series of novel potential dual PARP-1/HDAC-1 inhibitors (**Figure 2**). Linkers, which connect

As shown in scheme 1, the critical intermediates 3a and 3b were firstly synthesized. Protection of 1a-1b with *t*-butyloxy carbonyl (Boc) group afforded 2a and 2b, which were further reduced to 3a and 3b by Pd/C. As outlined in scheme 2, 4a-4e were esterified to intermediates 5a-5e which were further condensed with 2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoic acid and hydrolyzed to give 7a-7e. Then, 7a-7e, on the one hand, were reacted with *ortho*-phenylenediamine, providing final compounds 1, 4, 7, 10, 12; On the other hand, 7a-7e were condensed with 3a-3b to afford compounds 2, 3, 5, 6, 8, 9, 11, 13 following the removal of the *N*-Boc protecting group.



Scheme 1. *Reagents and conditions*: a) Boc₂O, Et₃N, DMAP, DCM, rt, 10 h; b) Pd/C, H₂, rt, 8 h.



Scheme 2. Reagents and conditions: a) MeOH, $SOCl_2$, 0 °C to rt; b) EDCI, HOBT, Et₃N, DMF, rt, overnight; c) LiOH, THF/H₂O, rt, overnight; d) HBTU, Et₃N, DMF, rt, overnight; e) HBTU, Et₃N, DMF, rt, overnight; f) TFA, DCM, rt, overnight.

All synthesized compounds were evaluated for PARP-1 inhibitory activity and HDAC-1 inhibitory activity and the results are shown in Table 1. Olaparib and chidamide were used as the positive drugs. As the linker is 5-aminopentanoic acid, compound 1 showed modest inhibitory activity against PARP-1 (39.3% inhibition at 20 nM) and HDAC-1 (IC₅₀ = 740 nM). Introducing F atom to the phenyl ring of benzamide in compound 1 decreased PARP-1 and HDAC-1 inhibitory activities (see compounds 2 and 3), demonstrating that F substitution is not favorable for the improvement of potency. To extend the linker, 6-aminohexanoic acid was introduced to replace 5-aminopentanoic acid, providing compounds 4-6. Delightedly, compound 4 showed strong inhibitory activity against PARP-1 (IC₅₀ = 4.2 nM), which was 17-fold more potent than **P1** and as potent as olaparib; simultaneously, it also displayed potent inhibitory activity against HDAC-1 (IC₅₀ = 340 nM), only slightly less potent than chidamide, which indicating that compound 4 was a promising dual PARP-1/HDAC-1 inhibitor. Next, a F atom was added to the 4' or 5' position of the phenyl ring of benzamide in compound 4,

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PARP-1 and HDAC-1 (see compounds **5** and **6**). This effort further confirmed that F substitution is no benefit to PARP-1

Table 1. The HDAC-1 and PARP-1 inhibitory activities of our final compounds.

NH N N N		R ² R ³
	н	NH ₂

Comed	Linker (D])	D 2	R ³	IC ₅₀ (nM) ^a (inhibition% at 20 nM ^b)		
Compa	Linker (R ¹)	K2		PARP-1	HDAC-1	
1	۶ ^۲ N H	Н	Н	(39.36)	740	
2	блугу Н	F	Н	(42.35)	910	
3	к Н	Н	F	(64.73)	1000	
4	₹ _N	Н	Н	4.23	340	
5	₹ _N ~~~~₹	F	Н	(65.86)	520	
6	[,] [,] [×] N → → → ×	Н	F	(46.23)	810	
7	[₹] N [↓]	Н	Н	1.94	820	
8	⁵ [×] N [×]	F	Н	1.81	950	
9	[₹] N [↓]	Н	F	2.58	940	
10	⁵ ⁴ N ^{-//} .	Н	Н	(41.31)	340	
11	5 ⁵ H	Н	F	(49.66)	890	
12	st N H	Н	Н	(37.38)	140	
13	H H	н	F	(22.06)	340	
P1	-	-	-	68.15°	27.26°	
Chidamide	-	•	-	$\mathbf{N}\mathbf{A}^{\mathrm{d}}$	160	
Olaparib	-		-	4.19	NA	

^aEach IC_{50} is the mean from three experiments. Standard error of the IC_{50} was generally less than 10%.

^bEach inhibition ratio is the mean from three experiments. Standard error of the inhibition ratio was generally less than 10%.

Previous reported inhibitory activity against PARP-1 and HDAC-1.

^dNA: not active.

and HDAC-1 inhibitory activity. To limit spatial rotation of the fat chains within compounds **1-6** and then identify more effective dual PARP-1/HDAC-1 inhibitors, we used several linkers containing cyclic structures such as 4-(aminomethyl)benzoic acid, tranexamic acid and piperidine-4-carboxylic acid to replace 6-aminohexanoic acid to explore the impact of these rigid linkers on potencies against PARP-1 and HDAC-1. As the linker is piperidine-4-carboxylic acid (see compound **7**), the inhibitory activity against PARP-1 was significantly enhanced (IC₅₀ = 1.9 nM), which was ~2 folds more potent than compound **4** and olaparib; while, the inhibitory activity against HDAC-1 (IC₅₀ =

introducing F atom to the phenyl ring of benzamide still had slightly or no effect on inhibitory activities (see compounds 8 and 9). As the linker is tranexamic acid (one more carbon than piperidine-4-carboxylic acid), compound 10 showed potent HDAC-1 inhibitory activity with an IC₅₀ value of 340 nM, which was as potent as compound 4 and only ~ 2 folds less potent than chidamide. Unfortunately, its inhibitory activity against PARP-1 was sharply decreased (inhibition ratio = 41.3% at 20 nM). A F atom substituted compound 11 displayed less potent toward HDAC-1 than compound 10. Finally, as the linker is 4-(aminomethyl)benzoic acid (contains aromatic ring), the inhibitory activity of compound 12 against HDAC-1 was improved with an IC₅₀ value of 140 nM, which was as potent as chidamide; while, its potency over PARP-1 (inhibition ratio = 37.3% at 20 nM) was much lower than compound 4. A F atom substitution within compound 13 still led to decreased potency. These results demonstrated that rigid linkers may be disadvantage for the balance between PARP-1 inhibitory activity and HDAC-1 inhibitory activity. In addition, F atom substitution may affect the electrical and physical properties of compounds, weakening the affinity to PARP-1 or HDAC-1. Overall, through this work, we gotten a promising dual PARP-1/HDAC-1 inhibitor, compound 4; in addition, unexpectedly, we obtained excellent PARP-1 inhibitors (compounds 7-9) and HDAC-1 inhibitor (compound 12) which could be for further studied.

Table 2. Antiproliferative activities of compounds 1 - 13 against three different human cancer cell lines.

Commit		$GI_{50}(\mu M)^a$	
Compa	K562	MCF-7	MDA-MB-231
1	62.4 ±3.37	NA ^b	61.58 ± 3.98
2	NA	NA	31.29 ± 2.34
3	1520 ±4.32	NA	25.40 ± 0.92
4	5.62 ±0.61	NA	4.35 ± 0.58
5	8.13 ±0.55	NA	13.91 ± 1.64
6	14.7 ± 1.34	NA	40.50 ±3.51
7	NA	NA	2.31 ± 1.39
8	NA	NA	1.03 ± 0.53
9	NA	NA	4.49 ± 2.43
10	2.92 ±0.32	11.1 ±0.25	50.45 ± 1.75
11	6.61 ±0.73	NA	49.19 ± 1.69
12	0.408 ± 0.11	1.91 ±0.22	59.27 ± 2.91
13	2.21 ±0.23	11.5 ± 1.03	78.72 ± 3.20
Chidamide	0.45 ±0.13	1.43 ±0.16	2.88 ± 1.10
Olaparib	NA	13.2 ± 1.05	4.23 ± 0.96

^aEach GI₅₀ is the mean \pm SEM from three experiments. Standard error of the IC₅₀ was generally less than 10%. ^bNA: not active.

Subsequently, all compounds were further evaluated for antiproliferative activities in the MTT assay using three different human tumor cell lines including K562 (human chronic myeloid leukemia cell line), MCF-7 (breast cancer cell line) and MDA-MB-231 (breast cancer cell line). None of these cell lines have mutant BRCA1/2 gene. As shown in **Table 2**, almost all compounds displayed no cytotoxic activity toward MCF-7 cell and only compound **12**, a potent HDAC-1 inhibitor, showed pote

which was as potent as chidamide. Compound 12 also significantly inhibited the growth of K562 cell (GI₅₀ = 0.4μ M), as potent as chidamide; while showed weakly cytotoxic activity against MDA-MB-231 cell. Similarly, compounds 10 and 13 having good HDAC-1 inhibitory activity, showed potent inhibition against K562 and MCF-7 cells. Compound 4, the best dual PARP-1/HDAC-1 inhibitor in this study, showed potent inhibition against K562 and MDA-MB-231 cells with GI₅₀ values of 5.6 and 4.3 µM respectively. Compared with olaparib, the cytotoxic activity of 4 toward K562 cell was markedly enhanced. Compounds 7-9 as potent PARP-1 inhibitors, displayed weak or no cytotoxic activity toward K562 and MCF-7 cells, which is an unsurprising result due to that PARP-1 inhibition is insensitive to BRCA1/2-proficient cells. Unexpectedly, against MDA-MB-231 cell, 7-8 displayed more potent cytotoxic activity than olaparib. In this work, our identified dual PARP-1/HDAC-1 inhibitor 4, really showed good antiproliferative activities for BRCA1/2proficient cell, K562 cell, extending antitumor spectrum of classical PARP-1 inhibitor, olaparib.

To explore the binding modes of compound **4** to PARP-1 and HDAC-1, this compound was docked into the active sites of PARP-1 (PDB ID: $5DS3)^{23}$ and HDAC-1 (PDB ID: 5ICN)²⁴ respectively by employing the program of Glide 6.7 in the Schrödinger Suite.

Modeling results on PARP-1 indicated that compound **4** has very similar interactions as olaparib with the target of PARP-1 (**Figure 3A** and **3B**): the binding poses are similar, and five hydrogen bonds between and PARP-1 are maintained. These hydrogen bonds include three formed by the phthalazin-1(2*H*)-one moiety with Gly863 and Ser904 and two formed by the two amide groups with Arg878 and Tyr896. One main binding difference is that the fluorobenzyl moiety of compound **4** is

molety and 1yr896 is undermined, which is not good for binding, however, this fault is made up by the 2-aminobenzamide molety which can be accommodated well in a subpocket of the active site of PARP-1 (**Figure 3B**).

Regarding HDACs, most HDAC inhibitors chelate the zinc ion in the active site using their ZBGs. It is very interesting to find that for some isoforms of HDACs, their inhibitors form bidentate complex with the zinc ion; whereas, some HDAC inhibitors form monodentate chelating complexes with the zinc ion in other isoforms of HDACs, even though the zinc-binding groups are same. For example, both of the two oxygen atoms of the negatively charged hydroxamic acid of SAHA chelate the Zn²⁺ in HDAC-2 (PDB ID: 4LXZ), establishing an exceptionally stable 5-membered ring¹³, nevertheless, in a crystal structure of the HDAC-1:MTA1 complex with a peptide inhibitor having a hydroxamic acid function group (PDB ID: 5ICN), this hydroxamic acid chelates the zinc ion using only one oxygen atom. Crystal structure of an analog of chidamide binding to HDAC-2 (PDB ID: 4LY1) demonstrates that the amino group of 2-aminobenzamide is deprotonated and negatively charged, chelating the Zn^{2+} in a dentate fashion with a coordination number of 5. Based on this information, we investigated how compound 4 binds to HDAC-1. Modeling results indicated that amino group of 2-aminobenzamide of compound 4 could chelate the Zn^{2+} very well, whereas the oxygen atom in the amide group does not have direct interaction with the Zn^{2+} (Figure 3C). It forms a hydrogen bond with Try303 and leads to a monodentate chelating complex. The fatty chain of compound 4 functions as a linker and has hydrophobic interactions with surrounding residues of HDAC-1 as well. The phthalazin-1(2H)-one moiety could form three possible hydrogen bonds with Gly97 and Cys100; it also may have extra hydrophobic interactions with few residues around it, as demonstrated in Figure 3C and 3D.



Figure 3. Putative binding modes of compound 4 (yellow ball and stick model) to PARP-1 (A and B) and HDAC-1 (C and D). Hydrogen bonds are shown as magenta dotted lines. In A and C, bound olaparib to PARP-1 (PDB ID: 5DS3) and a peptide inhibitor to HDAC-1 are shown as dark green line modes; in B and D, they are shown as dark green stick modes, respectively.

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to be dual PARP-1/HDAC-1 inhibitors based on olaparib and chidamide. Among them, compound 4 was identified as a promising dual PARP-1/HDAC-1 inhibitor and showed comparable PARP-1 and HDAC-1 inhibitory activities as olaparib and chidamide with IC₅₀ values of 4.2 nM and 340 nM respectively. Moreover, compound 4 extended the antitumor spectrum of olaparib for BRCA-proficient cells such as K562 cell. Serendipitously, we also found several potent PARP-1 inhibitors and HDAC-1 inhibitors. For example, compounds 7-9 displayed excellent PARP-1 inhibitory activity and were more potent than olaparib; compound 12 showed good HDAC-1 inhibitory activity and was almost as potent as chidamide. In our next work, compounds having excellent potency will be further evaluated for their selectivity over other PARP and HDAC subtypes, and anticancer activities using more different type

Acknowledgements

discovered in the near future.

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tumor cell lines or animal tumor models. We surely believed that

more effective novel dual PARP-1/HDAC-1 inhibitors could be

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- Synergistic inhibition of PARP-1 and HDACs is a potential effective strategy for cancer treatment.
- •Compound **4** showed comparable potency against PARP-1 and HDAC-1 with olaparib and chidamide respectively.
- •Compound 4 extended the antitumor spectrum of olaparib.
- A few excellent PARP-1 inhibitors and HDAC-1 inhibitors were serendipitously discovered.