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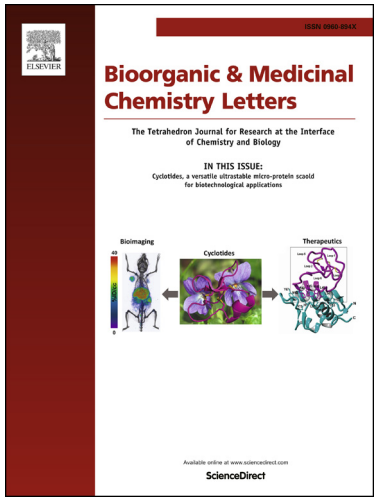

Design, Synthesis and Anticancer Activities Evaluation of Novel 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione Derivatives Containing 1,3,4-oxadiazole Units

Xin He, Xin-yang Li, Jing-wei Liang, Chong Cao, Shuai Li, Ting-jian Zhang, Fan-hao Meng

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Graphical Abstract

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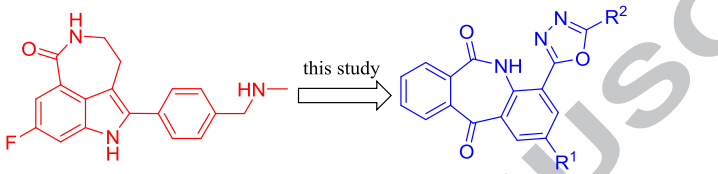
Xin He, Xin-yang Li, Jing-wei Liang, Chong Cao, Shuai Li, Ting-jian Zhang, Fan-hao Meng*



d21 (R^1=H, R^2=2-MeO-5-BrC_6H_3CH=CH)
IC_{50}=1.66±0.23 μ **M**;
d22 (R^1=H, R^2=2-MeO-3,5-$Br_2C_6H_2$CH=CH)
IC_{50}=1.40±0.30 μ M

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ABSTRACT

Rucaparib and PJ34 were used as the structural model for the design of novel 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione derivatives containing 1,3,4-oxadiazole units. And target compounds were successfully synthesized through a 3-step synthetic strategy. All target compounds were screened for their anti-proliferative effects against OVCAR-3 cell line. Preliminary biological study of these compounds provided potent compounds **d21** and **d22** with better activities than Rucaparib.

Cancer is one of the most serious threats against human health in the world, and the clinical prognosis remains relatively poor.[1] Surpassing heart diseases, it is taking the position of number one killer due to various worldwide factors.[2] Nowadays there is no absolute effective treatment for cancer patients in clinical practice, but chemotherapy is still the most widely used form of treatment for cancer. However, the majority of cancers are either resistant to chemotherapy or acquire resistance during treatment.[3] As a result, designing and discovering new, safe and efficient chemical classes of agents aiming at the treatment of cancer are the prime targets for contemporary medicinal chemistry researchers.

Poly(ADP-ribose) polymerase-1 (PARP-1) is the most abundant and best-characterized member of the PARP family of nuclear enzymes, with an important role in the cellular life cycle.[4] It is involved in various cellular processes including DNA repair, telomere regulation, transcription, genomic stability and regulation of cell death. It is widely accepted that the catalytic activity of PARP-1 is stimulated by DNA damage caused by peroxidation, irradiation and DNA-damaging chemicals, for example, chemotherapeutic agent.[5] PARP-1 plays a critical role in the repair of single-strand breaks (SSB) by base excision repair (BER) and has also been implicated in other roles in DNA repair.[6]

In view of the key role of the PARP-1 in maintaining the genomic integrity, particularly in the repair of single-strand DNA 30 lesions which caused by ionizing radiation, chemotherapy, or products of cellular and oxidative metabolism, PARP-1 is an indispensible role player in tumor cell development and PARP-1 targeted therapy can positively predict the outcome in cancer therapy.

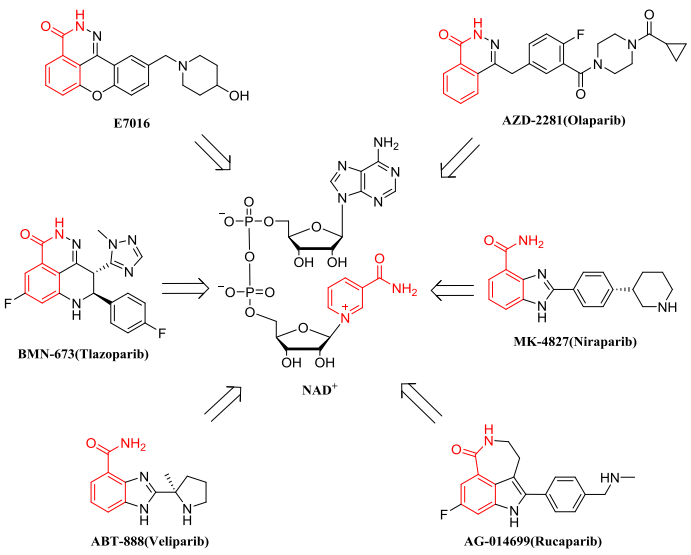

Figure. 1 Structural connection between pharmacophore of PARP1 inhibitors and NAD^+

Inhibitors of ADP-ribosyltransferases (ARTs) of the poly (ADP-ribose) polymerase (PARP) family are promising

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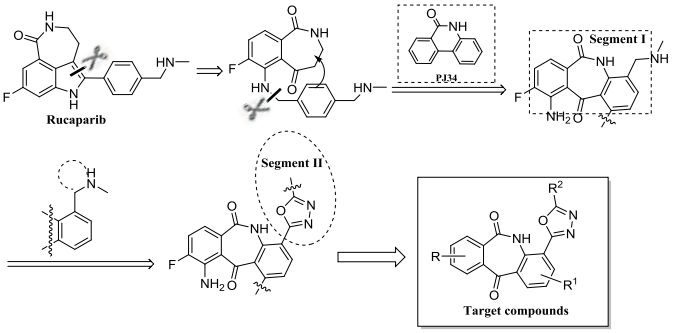
candidates for treatment of cancer.[7] Various PARP-1 inhibitors \are being pursued into different stages of clinical trials and some have even been approved for clinical anticancer therapy including E7016, AZD-2281 (Olaparib), BMN-673(Tlazoparib), MK-4827 (Niraparib), ABT-888 (Veliparib) and AG-014699 (Rucaparib).[8] Most currently available structure of PARP-1 inhibitors is based on the benzamide as pharmacophore, which mimics the structure of nicotinamide in NAD^+ to form the substrate-protein interaction of NAD^+ with PARP-1 (**Fig.1**).[4, 9]

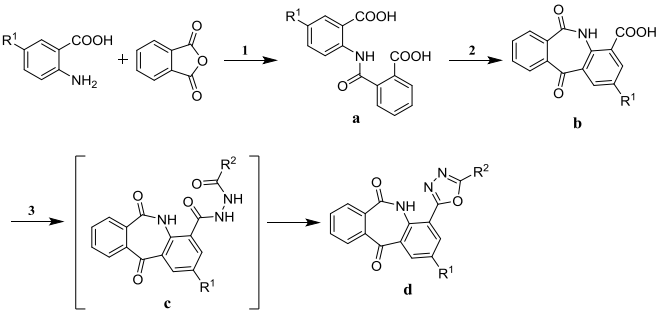
Rucaparib (Rubraca, produced by Clovis Oncology Company) such as 8-fluoro-2-{4-[(methyllamino)methyl]phenyl}-1,3,4,5-terahydro-6*H*-azepino[5,4,3-cd]indol-6-one, is an intravenous PARP-1 inhibitor with no significant toxicities when used alone. In 2016, the U.S. Food and Drug Administration (FDA) have accelerated the approval of Rucaparib for the treatment of advanced ovarian cancer associated with mutations in the BRCA gene. [10]

In the present letter, Rucaparib was considered as the parent compound for the design of our target compounds in order to find a series of small molecule compounds with high potent, low toxicity as candidates for discovery of clinical anticancer drugs. By observing the chemical structure of Rucaparib, it can be regarded as one compound of three-fused ring structure which is based on the structure of of benzoazepin and pyrrole. We obtained the skeleton of benzoazepin according to the open loop strategy in drug design by taking C-C bond of the pyrrole ring as the cutting point to open the pyrrole ring (**Scheme 1**). Furthermore, referring to the structural features of the PJ34 molecule (a general PARP inhibitor) [11] which is a derivative of phenanthridin-6(5*H*)-one, we got **Segment I** of our target compounds by incorporating the aromatic ring in the branched chain into the heterocyclic side of the benzoazepin. Then we integrated the amino group in the aromatic ring of the Rucaparib structure into a five-membered heterocyclic ring containing both N and O, so that **Segment II** of our target compounds was obtained (**Scheme 1**).



Scheme 1. Design of 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione derivatives containing 1,3,4-oxadiazole units

The synthetic strategy deployed in this work was primarily based on the method for synthesis of 2,5-disubstituted-1,3,4-oxadiazoles. *N'*-aromatic carbonyl acylhydrazine derivatives were prepared as intermediates by *N*-acylation of acylhydrazine with carbonyl chlorides substituted with aromatic ring, followed by the cyclization step in the presence of p-toluenesulfonic chloride to give 2,5-disubstituted-1,3,4-oxadiazoles.[12] 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione could be obtained via the ring-closing reaction of 2-(phenylcarbamoyl)benzoic acid under acidic conditions.[13] In the present work, a convenient process for preparation of 2-(2-carboxybenzamido)benzoic acid derivatives as intermediates was described to provide an entry into 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione derivatives bearing carboxyl group at the 4-position and the subsequent *N*-acylation followed by cyclization to deliver 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione derivatives containing 1,3,4-oxadiazole units. To that end, a 4-step synthetic strategy was designed starting from anthranilic acids and phthalic anhydride. The synthetic route is illustrated in **Scheme 2**.

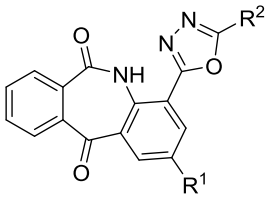


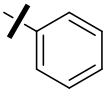
Scheme 2. : 1) DMAP, THF, 70℃; 2) i. $SOCl_2$, $CHCl_3$, 50℃; ii. $AlCl_3$, $CHCl_3$, 50℃; 3) i. $SOCl_2$, DCM; ii. acylhydrazines, Et_3N, DCM, 35℃; iii. TsCl, DCM, 35℃.

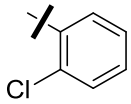
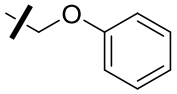
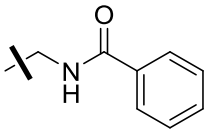
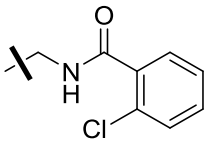
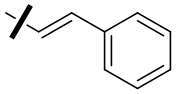
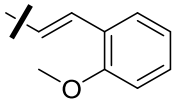
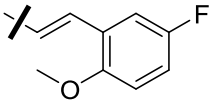
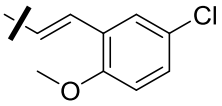
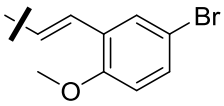
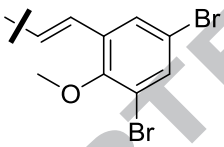
The first step involved *N*-acylation of anthranilic acids with phthalic anhydride in refluxing THF in the presence of DMAP as a catalyst to give the amide derivative **a**. The amide derivative a was then reacted with $SOCl_2$ in chloroform followed by $AlCl_3$ to give the 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione derivative **b** with carboxyl group at 4 position. After the 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione derivative **b** was treated with $SOCl_2$ in dichloromethane, the carboxyl group at 4 position converted into the acyl chloride. The acyl chloride was then reacted with hydrazine derivatives resulting in the intermediate **c** by using triethylamine as acid-binding agent in dichloromethane. Finally, our target compounds **d** were synthesized through the intermediate **c** without being separated from dichloromethane reacted with p-toluenesulfonyl chloride via elimination reaction.[14] Crude products were purified by recrystallization.

With this set of compounds in hand, the anticancer activity spectrum of these molecules was investigated in the next part. The antitumor activities of all of our target compounds (**d1-22**) against human ovarian cancer cell line (OVCAR-3) were evaluated by using 3-(4,5-dimethyldiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay according to the literature protocol **Table 1** and **Table 2**.

Table 1. Anticancer activities Assays of Compounds **d1-11** against OVCAR-3 cell line



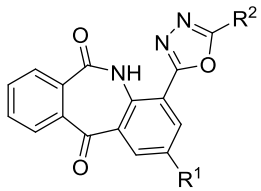
Compd	R^1	R^2	IC_{50}[a](μM)
d1			10.08±0.52

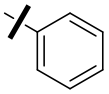
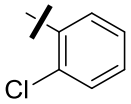
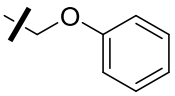
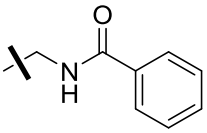
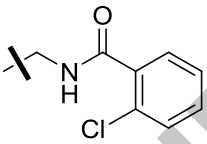
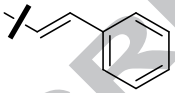
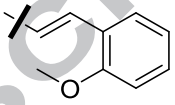
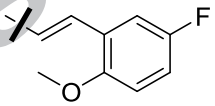
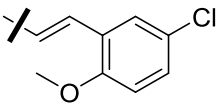
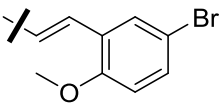
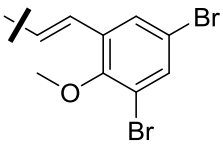
d2	-CH$_3$		4.19±0.46
d3	-CH$_3$		NA[b]
d4	-CH$_3$		11.40±0.93
d5	-CH$_3$		NA
d6	-CH$_3$		17.70±1.11
d7	-CH$_3$		10.67±0.72
d8	-CH$_3$		>100
d9	-CH$_3$		>100
d10	-CH$_3$		NA
d11	-CH$_3$		NA
Rucaparib			3.31±0.21

[a] Data were shown as mean ± SED.

[b] No activity.

Table 2. Anticancer activities Assays of Compounds **d12-22** against OVCAR-3 cell line



Compd	R^1	R^2	IC_{50}[a](μM)
d12	H		>100
d13	H		>100
d14	H		6.28±0.13
d15	H		>100
d16	H		>100
d17	H		12.13±0.99
d18	H		8.99±0.55
d19	H		>100
d20	H		>100
d21	H		1.66±0.23
d22	H		1.40±0.30
Rucaparib			3.31±0.21

[a] See the footnotes in Table 1.

To our delight, about half of compounds (**d1-2**, **d4**, **d6-7**, **d14**, **d17-18** and **d21-22**) showed varying a degree of inhibitory activity. Compound **d21** and **d22** were found to reveal good activities (IC_{50} = 1.66±0.23 μM and IC_{50} = 1.40±0.30 μM) against OVCAR-3 cell line comparable to Rucaparib (IC_{50} = 3.31 ±0.21 μM) (**Fig. 2**). By comparing chemical structures of **d6-11** and **d17-22**, it was an obvious discovery that most compounds without methyl group at the 2-position of 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione displayed high potency. The detrimental effect of methyl substituted 5*H*-dibenzo[b,e]azepine-6,11-dione was even more evident that compound **d10** and **d11** (compared to **d21** and **d22**)were devoid of any activity against OVCAR-3 cell line. Introduction of the electron-donating group to substituted aromatic rings (methoxyl group, **d18**) could enhance biologic activity, displaying IC_{50} = 8.99 ± 0.55 μM, while no substituted group (**d17**) showed IC_{50} = 12.13±0.99 μM. Among compounds **d19-22** with halogen atoms, containing fluorine and chlorine atoms (**d19** and **d20**) showed only little potency, while **d21** and **d22** were 100-fold more active, indicating that compounds with bromo atoms were more necessary for inhibitory properties.

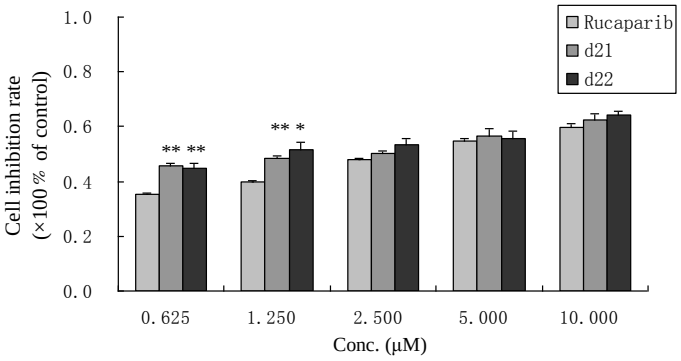
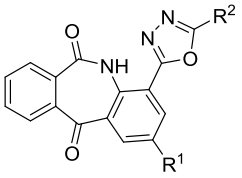


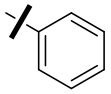
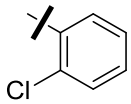
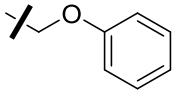
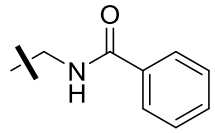
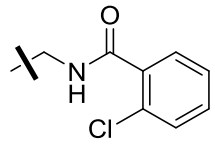
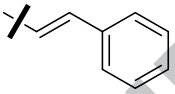
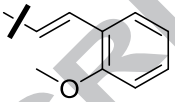
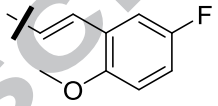
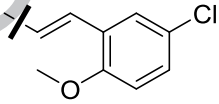
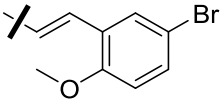
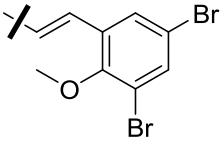
Figure. 2 The inhibitory effect of **d21**, **d22** and Rucaparib on OVCAR-3 cell line. Values were expressed by mean ± SED. n=3; *P <0.05, compared to Rucaparib; **P <0.01, compared to Rucaparib.

Interestingly, **d1**, **d2** and **d4** showed a certain extent of inhibitory activities, while compound **d12**, **d13** and **d15** without methyl substituent on 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione were not observed to provide obvious activities. It was presumably due to the number of atoms connected between the 1,3,4-oxadiazole ring and substituted aromatic rings in the side chain. The link chain consisting of two atoms between the 1,3,4-oxadiazole ring and substituted aromatic rings was likely to be necessary for the apparent activities of those without methyl substituent. The conjecture was well proved that **d3** displayed no inhibition activity comparable to **d14** with an IC_{50} = 6.28±0.13 μM.

To verify the potency targeting PARP-1, all compounds were tested in the PARP-1 enzyme assay shown in **Table 3** and **Table 4**. Fortunately, most compounds displayed different levels of inhibition to PARP-1. And it was obvious that the trend of inhibition to PRAP-1 was basically the same as that of antitumor activities. Both **d21 (**IC_{50} = 0.047 μM**)** and **d22 (**IC_{50} = 0.025 μM**)** showed higher potency against PARP-1 than other 20 compounds (**d1-20**). It was revealed that **d22** almost have the same potency as Rucaparib with an IC_{50}= 0.026μM.

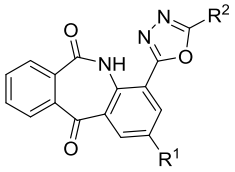
Table 3. PARP-1 Enzymatic Assays of Compounds **d1-11**

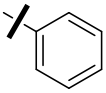
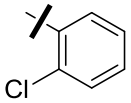
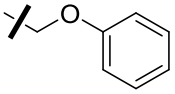
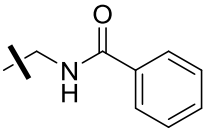


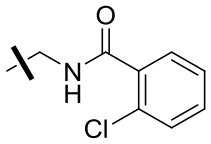
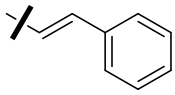
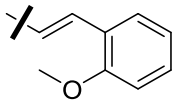
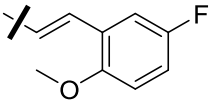
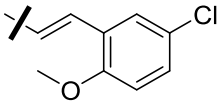
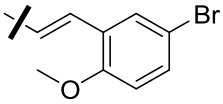
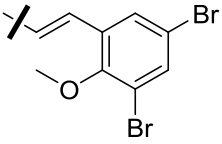
Compd	R^1	R^2	IC_{50}[a](μM)
d1	-CH$_3$		0.277
d2	-CH$_3$		0.051
d3	-CH$_3$		NA[b]
d4	-CH$_3$		0.304
d5	-CH$_3$		NA
d6	-CH$_3$		0.446
d7	-CH$_3$		0.147
d8	-CH$_3$		1.055
d9	-CH$_3$		1.191
d10	-CH$_3$		NA
d11	-CH$_3$		0.939
Rucaparib			0.026

[a] The assays were performed as described in Supporting Information.
[b] No activity.

Table 4. PARP-1 Enzymatic Assays of Compounds **d12-22**



Compd	R^1	R^2	IC_{50}[a](μM)
d12	H		NA
d13	H		1.101
d14	H		0.099
d15	H		1.255

d16	H		0.745
d17	H		0.400
d18	H		0.136
d19	H		0.951
d20	H		1.263
d21	H		0.047
d22	H		0.025
Rucaparib			0.026

[a] See the footnotes in Table 3.

From the results above, to determine whether the compounds with activities could really enhance OVCAR-3 cell apoptosis, compound **d21** and **d22** with IC_{50} values lower than 3.31±0.21 μM (Rucaparib) were further evaluated for their inhibition on cell proliferation by western blot analysis (**Fig. 3**). Overexpression of antiapoptotic Bcl-2 members such as Bcl-2 occurs frequently in cancers resulting in defective apoptosis leading to enhanced cell survival and drug resistance.[15] So we took the expression of Bcl-2 as an index to measure the level of apoptosis. Concentration course analysis revealed that compound **d21** and **d22** induced a decline in levels of Bcl-2 in OVCAR-3 cell, which was observed after 24-hour exposure (**Fig. 3** and **4**). It was further indicated that **d21** and **d22** had the potential to induce OVCAR-3 cell apoptosis via the Bcl-2 related pathway.

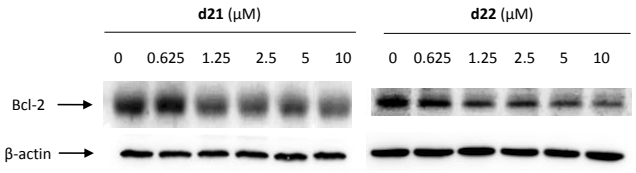


Figure. 3 Western blot analysis in OVCAR-3 cells exposed to **d21** and **d22** for 24 hours.

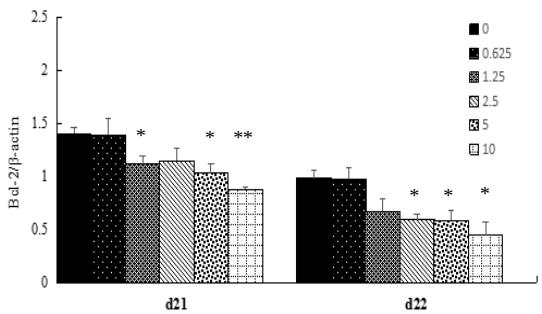


Figure. 4 The expression level of Bcl-2 along with the change of the concentration of **d21** and **d22**. The ordinate was expressed by the ratio of integrated optical density of Bcl-2 expression to that of β-actin expression (Bcl-2/β-actin). n=3; *P <0.05, compared to control group (0 μM); **P <0.01, compared to control group (0 μM).

As the most potent inhibitor, **d22** was docked into the active site of PARP-1 (PDB ID: 4RV6) to investigate its binding mode (**Fig. 5**). The ligand overlapped with benzazepine skeleton of Rucaparib (blue molecule in **Fig. 5**), exhibited a binding mode comparable to Rucaparib. Both compound **d22** and Rucaparib could form a H-bond interaction with Gly863 located at the binding pocket of PARP-1. The compound **d22** appeared to interact with the region through the amide group, which was projected toward Gly863 with a distance of 1.748 Å, and subsequently form a better optimized H-bond interaction. Due to a slightly longer H-bond formed between Rucaparib and Gly863 with a distance of 2.283 Å, the results of molecular docking displayed GBVI/WSA binding free energy of **d22** in the S field was -13.4189, which is slightly lower than the posing score of Rucaparib. This may contribute to its anticancer activity.

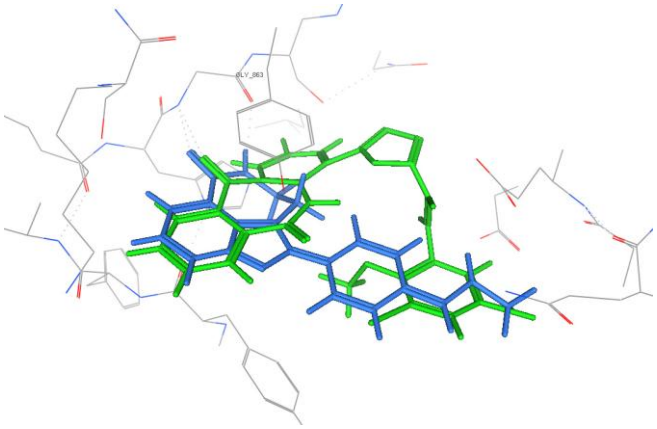


Figure. 5 Docking conformation of **d22** binding with PARP-1 (blue molecular is Rucaparib; green molecular is **d22**)

In conclusion, taking Rucaparib and PJ34 as structural model, a series of novel 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione derivatives containing 1,3,4-oxadiazole units have been designed and finally successfully synthesized. Structures of all target compounds were determined by ^{1}H-NMR, ^{13}C-NMR and MS. We found that compounds **d1-2**, **d4**, **d6-7**, **d14**, **d17-18** and **d21-22** could inhibit OVCAR-3 cancer cell growth. Among these, **d21** and **d22** showed better inhibitory activities against OVCAR-3 cell line comparable to Rucaparib. Due to the significant results we obtained, chemical studies aiming at improving the anticancer activity of these compounds and the study of pharmacological mechanism are currently underway and will be reported in due course.

Acknowledgments

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14. As an example, the synthesis of 4-(1,3,4-oxadiazol-2-yl)-5*H*-dibenzo[b,e]azepine-6,11-dione derivatives **d1** is described here. A mixture of 2-amino-5-methylbenzoic acid (2 g, 13.23 mmol), phthalic anhydride (2.06 g, 13.89 mmol), DMAP (20 mg, 0.13 mmol) and THF (20 mL) was heated under reflux in an oil bath at 70 ℃ for 4 h. After completion of the reaction, THF was removed under vacuum to obtain brown liquids. Then ice-cold water (50 mL) was poured into the brown liquids. The precipitate was filtered off and dried to get the crude product **a**. **a** was dissolved in chloroform (50 mL), then thionyl chloride (3.88 g, 29.11 mmol) and catalyst DMF (10 mg, 0.13 mmol) were added. The reaction mixture was heated at 50 ℃ for 2 h. $AlCl_3$ (3.46 g, 29.11 mmol) was added to this mixture for 3 additional hours at this temperature. The reaction fixture was poured into ice-cold aqueous acid (100 mL) under stirring. After keeping stirring for 0.5 h, the aqueous phase of the mixture was separated and extracted with chloroform (20 mL×3). Then the organic phase was dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by crystallization in dichloromethane to afford 2.2 g of 2-methyl-6,11-dioxo-6,11-dihydro-5*H*-dibenzo[*b*,*e*]azepine-4-carboxylic acid as off-white solids **b** (59％). Finally, in a dry flask, thionyl chloride (0.51 g, 4.27 mmol) was added to the mixture of 6,11-dioxo-6,11-dihydro-5*H*-dibenzo[*b*,*e*]azepine-4-carboxylic acid **b** (1 g, 3.56 mmol) and dichloromethane (30 mL). After catalyst DMF (10 mg, 0.13 mmol) was added, the reaction mixture was heated at 35 ℃ for about 5 h and then cooled to 0 ℃. Benzohydrazide (0.47 g, 3.48 mmol) was added, and then the solution of triethylamine (1.62 g, 16 mmol) in dichloromethane (5 mL) was added dropwise to this reaction mixture at this temperature, followed by stirring at 35 ℃ for a further 10h. After addition of p-toluenesulfonyl chloride (0.75 g, 3.91 mmol), mixture was kept stirring overnight at 35 ℃. After the solvent was evaporated under reduce pressure, ice-cold water (50 mL) was added and filtered off. The filter cake was dried and purified by crystallization in methanol to give 0.78 g of the pure product **d1** (57％). A representative compound **d1** and its spectrum data are as follows:
2-methyl-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-5*H*-dibenzo[*b*,*e*]-azepine-6,11-dione (**d1**): White solid, 0.78 g, yield 57％; ^{1}H NMR (600MHz, DMSO-d_6) δ 8.19 (d, 1 H, *J* = 0.8 Hz), 8.04 - 7.92 (m, 4 H), 7.87 - 7.82 (m, 2 H), 7.67 - 7.57 (m, 3 H), 7.53 - 7.47 (m, 2 H), 2.53 (s, 3 H); ^{13}C NMR (151MHz, DMSO-d_6) δ 167.6, 164.0, 162.2, 140.7, 135.3, 133.7, 132.6, 132.3, 131.7, 129.9, 129.7, 127.7, 126.9, 124.0, 123.1, 122.1, 21.0; MS (API-ESI) found 382.1 $[M+H]^+$.
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Supplementary Material

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