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Identification of novel PARP-1 inhibitors: Drug design, synthesis and biological evaluation

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ABSTRACT

A series of AG014699 derivatives containing a novel scaffold of 2,3-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-1,4(6*H*)-dione were synthesized and evaluated for their inhibitory activities toward PARP-1 enzyme and two cell lines, MCF-7 cells and the *BRCA1*-deficient MDA-MB-436 cells. Our results demonstrated that of all AG014699 derivatives synthesized in this work, compounds **6** and **7** showed strong PARP-1 inhibitory activity (IC_{50} = 3.5 nM and 2.4 nM, respectively), only four and three times less potent than AG014699. Compound **6** also had significantly cell inhibitory activity against both MCF-7 cells (CC_{50} = 25.8 μM) and the *BRCA1*-deficient MDA-MB-436 cells (CC_{50} = 5.4 μM), nearly as good as AG014699, indicating that it can be a promising compound for further evaluation.

Poly ADP-ribose polymerases (PARPs), a family of 18 parp-enzymes, participates in ADP-ribose glycosylation in cell nucleus/cytoplasm exerting important cellular functions.[1] PARP-1, a 113 kDa protein, is the most widely studied in PARPs that possesses three main functional regions: DNA-binding domain (DBD), auto-modification domain (AMD), and catalytic domain (CD).[2]

PARP-1 displays a key role in single-stranded and double-stranded DNA damage repair (SSBs and DSBs), especially in tumor cells with *BRCA1/2*-deficient and lack of homologous recombination (HR) repair.[3] Once DNA was damaged by radiation, oxidation or alkylation, PARP-1 will be activated to bind the damaged DNA to form homodimers, catalyzing the conversion of nicotinamide adenine dinucleotide (NAD^+) into niacinamide and ADP ribose within its catalytic domain.[4] The ADP ribose can subsequently form ADP-ribose polymer and the poly ADP-ribose complex combining with PARP-1 auto-modification domain, histone, and other nuclear receptor proteins, to facilitate the recruitment of a variety of DNA repairing enzymes, such as X-ray repair cross complementary enzymes 1 (XRCC1), DNA polymerase III-αβ, and DNA ligase (LIG-IIIα). These DNA repairing enzymes will be stimulated to recognize and repair DNA damage. After the base excision repair, the poly ADP-ribose will be cleaved from PARP-1 by poly ADP-ribose glycohydrolase (PARG).[5–8] According to the key function of PARP-1 in DNA damage repair, many small molecules targeting PARP-1 catalytic domain have been developed either as chemo-sensitizers in combination with ionizing radiation or DNA-damaging chemotherapeutic agents or as stand-alone therapies (synthetic lethal) to kill cancers cells that are defective in DNA repair mechanisms.[9]

Nicotinamide (IC_{50} = 210 μM) and 3-aminobenzamide (IC_{50} = 30 μM) were the earliest PARP-1 inhibitors, which were designed to mimic the substrate–protein interactions of NAD^+ with PARP-1.[10] However, their low potency and poor specificity prompted researchers to find new PARP-1 inhibitors with improved potency. To date, a number of PARP-1 inhibitors have been developed into preclinical or clinical trials, including AG014699, E-7016, BMN-673, AZD2281 and ABT-888 et al. (Fig. 1).[11,12] However, only AZD2281 became commercially available as an approved drug with high efficacy, proven safety, and excellent pharmacokinetic profiles in 2014.[13] Among all clinically used PARP-1 inhibitors, the tricyclic ones containing a lactam ring with *S-trans* conformation, have a more favorable binding conformation for PARP-1 inhibition. In addition, the aromatic ring in the tricyclic scaffolds exerts critical function for forming π–π stacking between the aryl ring and Tyr907 in PARP-1. The structural rigidity of the tricyclic scaffold is beneficial for PARP-1 inhibitors to bind to the catalytic site of PARP-1. To modulate the pharmacokinetic profiles and physical properties of PARP-1

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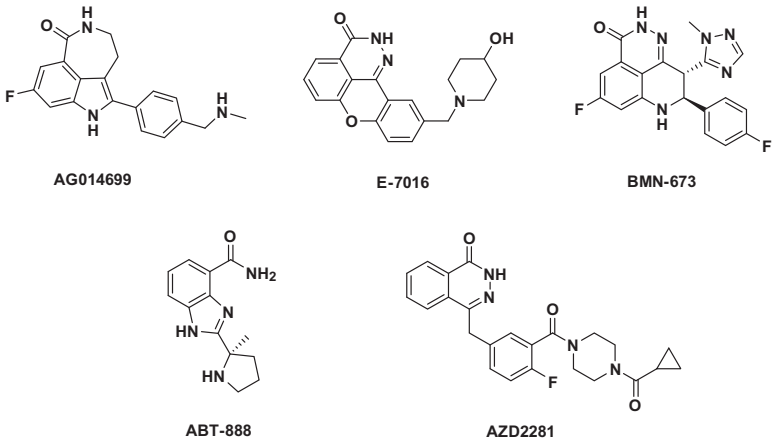


Figure 1. The structures of representative PARP-1 inhibitors in the clinic (AG014699, E-7016, BMN-673, ABT-888) and on the market (AZD2281).

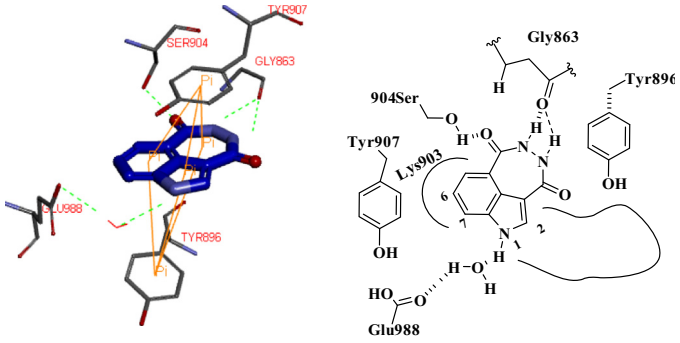


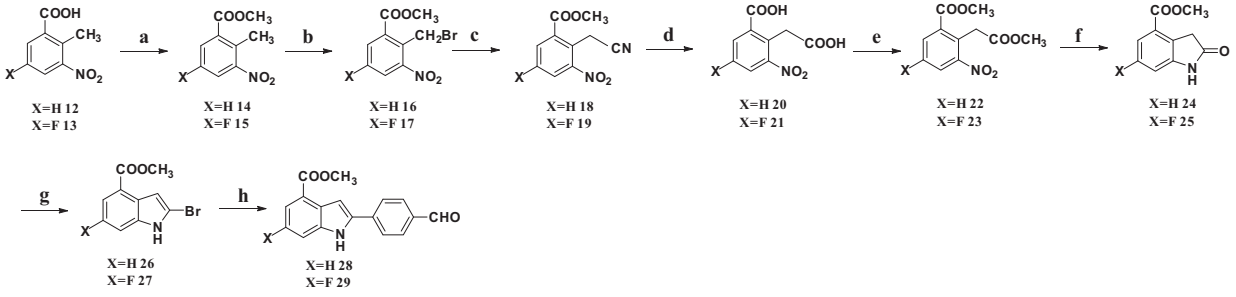
Figure 2. The docking model of novel core binding to PARP-1 by discovery studio 3.0.

inhibitors: a region, a short chain with basic group needs to be introduced to the tricyclic scaffolds.

To obtain more potent and novel PARP-1 inhibitors possessing favorable PK properties and improved efficacy against tumor, on the basis of reported structure–activity relationship of clinically effective tricyclic PARP-1 inhibitors, we proposed that a novel tricyclic scaffold, 2,3-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-1,4(6*H*)-dione derived from AG014699 would restrict the carboxamido rotation and offer a favorable binding conformation to the catalytic site of PARP-1 enzyme. The docking model (PDB code: 4OQA, Fig. 2) reveals that the carbonyl oxygen in 2,3-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-1,4(6*H*)-dione can form a hydrogen bond with the side chain hydroxyl group of Ser904, while the double carboxamide hydrogen exhibit hydrogen bonding interaction with the backbone carbonyl oxygen of Gly863. The aromatic ring of the core can be stabilized through π–π stacking interaction with the nearly coplanar electron-rich phenyl rings of Tyr907 and Tyr 896. The N–H of indole can form Hydrogen bonding with Glu988 via a water molecule. The docking results indicated that novel antitumor agents could be developed based on this novel tricyclic scaffold. Thus, a series of 2,3-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-1,4(6*H*)-diones were synthesized by introducing a fluorine atom to the 6-position of indole and an aryl chain with different basic groups to the 2 or 6-position of indole. The PARP-1 inhibitory activities were determined to identify potential novel PARP-1 inhibitors.

The two critical intermediates, compounds **28** and **29** were prepared according to Scheme 1. Briefly, methyl esterification of materials **12** and **13** afforded **14** and **15** which were treated with NBS to give **16** and **17**. Cyanogenation of **16** and **17** using NaCN afforded **18** and **19** which were hydrolyzed with concentrated HCl under refluxing to give **20** and **21**. Methyl esterification of **20** and **21** leaded to the formation of **22** and **23**, which cyclized to give **24** and **25** via catalytic hydrogenation over Palladium/charcoal. Bromination of **24** and **25** with $POBr_3$ afforded **26** and **27**, which reacted with (4-formylphenyl)boronic acid to give **28** and **29** via Suzuki reaction.

Sequentially, as shown in Scheme 2, the intermediates **28** and **29** were reacted with secondary amines to afford schiff bases which were reduced to give **57–63** using $NaBH_4$. Protection of **57–63** with Boc afforded **64–70**. The formyl group was introduced to the 3-position of **64–70** by Vilsmeier reaction and the resulting compounds **71–77** were oxidized using $NaClO_2$ to give **78–84**.



Scheme 1. Synthesis route of intermediates **28** and **29**. Reagents and conditions: (a) MeOH, 0 °C, $SOCl_2$ (2 equiv); reflux, 5 h, 96.1%; (b) benzoylperoxide (0.1 equiv), NBS (1.4 equiv), CCl_4, reflux, overnight, 84.6%; (c) NaCN (1.2 equiv), MeOH, room temperature, 5 h, 65.5%; (d) concd HCl, reflux, 10 h, 70.6%; (e) $SOCl_2$ (8 equiv), 0 °C, MeOH; reflux 5 h, 92.3%; (f) MeOH, 10% Pd–C/H_2, room temperature, 5 h, 49.7%; (g) DCE, $POBr_3$ (1.8 equiv), 1 h, room temperature; imidazole (0.15 equiv), 4 h, reflux, 39.1%; (h) toluene, MeOH, water, Na_2CO_3 (2.5 equiv), $ZnCl_2$ (3 equiv), (4-formylphenyl)boronicacid (1.5 equiv), $Pd(PPh_3)_4$ (0.05 equiv), reflux, overnight, 75%.

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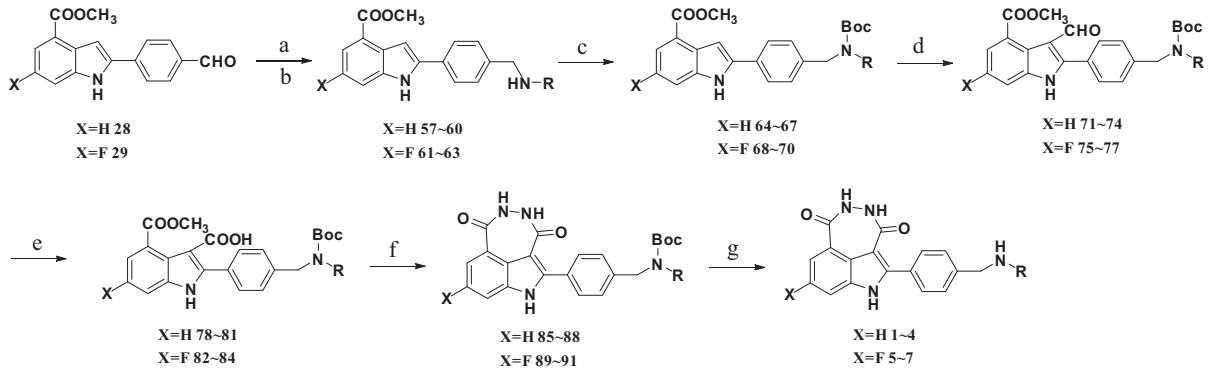
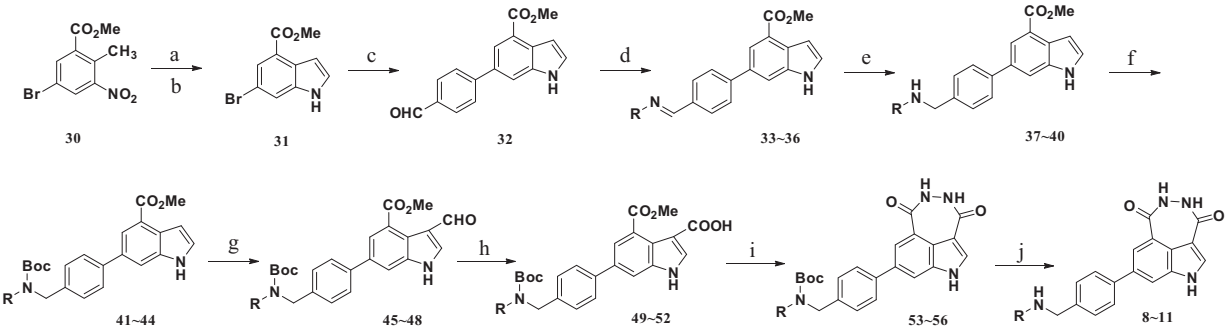


Scheme 2. Synthesis route of targeted compounds **1**–**7**. Reagents and conditions: (a) **10a**/MeOH, RNH_2 (Methylamine, Propylamine, Isopropylamine or *N*-butyl amine) (5 equiv), AcOH, reflux, 1 h; (b) $NaBH_4$ (5 equiv), MeOH, room temperature, 5–8 h, 40–65%; (c) DCM, Boc_2O (1.1 equiv), room temperature, overnight, 45–62%; (d) $POCl_3$ (2 equiv), DMF, 35 °C, 2–3 h, 42–55%; (e) $NaClO_2$ (5 equiv), 3-methyl-1-butene (1.8 equiv), 1 M NaH_2PO_3 (1.5 equiv), THF, 0 °C, 6 h, 36–48%; (f) DMF, Et_3N (2 equiv), HBTU (1.1 equiv), N_2H_4 (5 equiv), 2 h, 70 °C, 44–62%; (g) DCM, TFA, room temperature, 15–17 h, 50–71%.



Scheme 3. Synthesis route of targeted compounds **8**–**11**. Reagents and conditions: (a) DMFDMA (3 equiv), DMF, 120 °C, 9–10 h; (b) MeOH, AcOH, Fe, reflux, 15 h, 63.0%; (c) 4-formylphenylboronicacid (1.5 equiv), H_2O, MeOH, toluene, LiCl (3 equiv), Na_2CO_3 (2.5 equiv), $Pd(PPh_3)_4$, reflux, 9–10 h, 66.6%; (d) RNH_2 (Methylamine, Propylamine, Isopropylamine or *N*-butyl amine) (10 equiv), MeOH, AcOH, reflux, 1–2 h, 50.6–82.8%; (e) MeOH, <10 °C, $NaBH_4$ (3 equiv), room temperature, 2–3 h, 70.3–86.1%; (f) Boc_2O (1.1 equiv), CH_2Cl_2, 0 °C → room temperature, 1–2 h, 45.4–89.2%; (g) $POCl_3$, DMF, NaOH, H_2O, <10 → 35 °C, 2–3 h, 40.7–71.4%; (h) $KMnO_4$ (3 equiv), acetone, <35 °C, 3–4 h, 17.1–27.4%; (i) Et_3N (2 equiv), HBTU (1.1 equiv), NH_2NH_2, DMF, 70 °C, 0.5 h, 11.1–19.0%; (j) TFA, CH_2Cl_2, room temperature, 15–17 h, 57.9–81.2%.

Cyclization of **78**–**84** using HBTU afforded **85**–**91** which were deprotected of Boc to give products **1**–**7**.

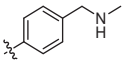
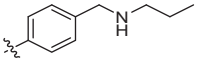
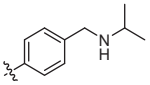
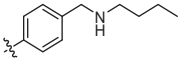
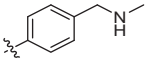
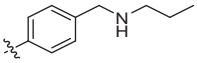
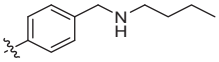
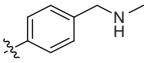
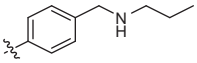
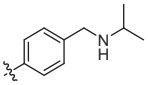
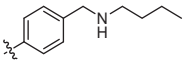
The preparation of compounds **8**–**11** is shown in Scheme 3. Obtained by Leimgruber–Batcho indole synthesis from **30**, **31** was reacted with 4-formylphenylboronic acid by Suzuki reaction to afford **32** which was condensed with secondary amines to give **33**–**36**. **33**–**36** were reduced and the resulting **37**–**40** were then protected with Boc to give **41**–**44**. The formyl group was introduced to the 3-position of **41**–**44** by Vilsmeier reaction to give **45**–**48** which were oxidized using $KMnO_4$ to afford **49**–**52**. Finally, the products were obtained by cyclization reaction and removal of Boc.

The PARP-1 enzyme inhibitory activities of all compounds are shown in Table 1, compounds **1**–**4** containing different size basic groups (Methylamine, Propylamine, Isopropylamine, *N*-butyl amine) attached to the aromatic side chains at 2-position of indole displayed weak activity against PARP-1 in comparison with reference compound AG014699. Among them, compound **4** was the most potent with an IC_{50} value of 249.7 nM, indicating that *N*-butyl amine is a more effective substituent group for PARP-1 enzyme inhibitory activity. Further research, considering that fluorine played a critical role in improving activity in several clinically proven PARP-1 inhibitors including AG014699, BMN-673 et al.,[14] it was introduced to 6-position of indole of compounds **1**, **2** and **4**. The potency of compounds with fluorine substituent **5**–**7** were increased markedly and compound **7** showed an IC_{50} value of 2.4 nM, which was only about three times less potent than AG014699. In addition, we found that compound **7** containing *N*-butyl amine was more potent than compound **5** containing methylamine and compound **6** containing propylamine, indicating that the size of *N*-butyl amine group was more optimal for compounds occupying the hydrophobic cavity of PARP-1 enzyme.

Compounds **8**–**11**, containing the aromatic side chain at 6-position of indole were designed and synthesized to probe the possibility of bisamides flip-binding (Fig. 3). The results have shown that these compounds exhibited low to moderate activities toward PARP-1, but were more potent than their counterparts (compounds **1**–**4**). Among them, contained *N*-butyl amine compound **11** had the most potency with an IC_{50} value of 35.4 nM. All results indicated that the flipped structure could form more effective binding with PARP-1 and *N*-butyl amine remained the more optimal basic group in compounds.

Finally, all compounds were evaluated for their anticancer activity using wild type breast cancer MCF-7 cells and human breast cancer MDA-MB-436 cells carrying natural *BRCA1* mutations in comparison with AG014699. As summarized in Table 1, the *BRCA1*-deficient MDA-MB-436 cells were hypersensitive to the PARP-1 inhibition, therefore, higher potencies were observed for most tested compounds in this cell line in comparison with those in wild type cells. Similar to the tendency of PARP-1 inhibitory activity in our compounds, almost compounds with big size basic groups (Isopropylamine, *N*-butyl amine) had higher potencies in both cells compared to those with small size basic groups (Methylamine, Propylamine). Surprisingly, though compound **7** was the

Table 1
The IC_{50} value of compounds against PARP-1 enzyme and the CC_{50} value of potent compounds in MCF-7 cells and MDA-MB-436, *BRCA-1* deficient cells[a]

Compd	2′-Substitution	6′-Substitution	IC_{50} (nM)	CC_{50} (MCF-7, μM)	CC_{50} (MDA-MB-436, *BRCA-1*, μM)
1		**H**	2697	83.11	11.29
2		**H**	6.076E+013	100.8	8.64E+07
3		**H**	11292	40.71	55.67
4		**H**	249.7	17.96	18.94
5		**F**	6.643	65.29	56.2
6		**F**	3.501	25.87	5.454
7		**F**	2.416	2.84E+10	114.5
8	**H**		2.952E+008	1244	ND
9	**H**		137.6	5556	111.7
10	**H**		465.4	1921	105
11	**H**		35.44	236.7	68.81
AG014699			0.8044	19.47	3.0

ND, not determined.
[a] Values are means from two to three independent dose–response curves.

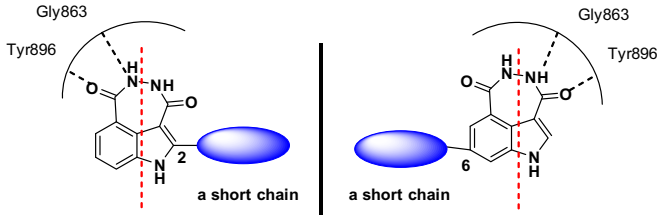


Figure 3. Bisamides flip-binding of compounds **8**–**11** containing the aromatic side chain at 6-position of indole.

most potent toward PARP-1 enzyme, the activities of both the *BRCA1*-deficient MDA-MB-436 cells and wild type MCF-7 cells were weak with CC_{50} values of 2.84E+10 μM and 114.5 μM respectively. This result might due to its non-optimal PK properties. Thankfully, compound **6** showed almost similar activity to positive control AG014699 in both the *BRCA1*-deficient MDA-MB-436 cells and wild type MCF-7 cells, representing an effective agent to treat *BRCA1*-deficient human breast cancer.

In summary, we reported the synthesis and biological evaluation of novel 2,3-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-1,4(6*H*)-dione derivatives as potent PARP-1 inhibitors. Among all compounds synthesized in this work, contained fluoro compounds **5**–**7** had strong potencies toward PARP-1 with IC_{50} values of 6.6 nM, 3.5 nM and 2.4 nM, respectively, which were only three to six times less potent than AG014699. More importantly, compound **6** exhibited excellent cell inhibitory activities in both wild type MCF-7 cells (CC_{50} = 25.8 μM) and *BRCA1*-deficient MDA-MB-436 cells (CC_{50} = 5.4 μM), which were almost similar with AG014699. Further biological evaluation of this class of derivatives is ongoing in our laboratory and will be reported in the near future.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.08.060. These data include MOL files and InChiKeys of the most important compounds described in this article.

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