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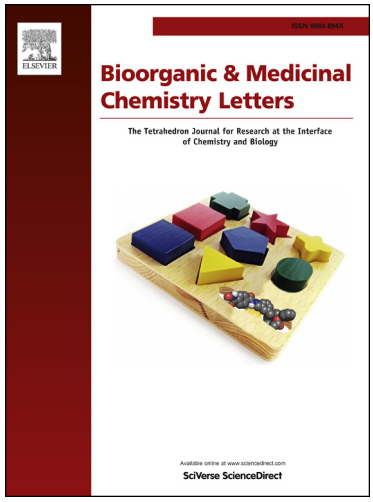

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Novel PARP-1 inhibitors based on a 2-propanoyl-3H-quinazolin-4-one scaffold

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ABSTRACT

Poly(ADP-ribose)polymerase-I (PARP-1) enzyme is involved in maintaining DNA integrity and programmed cell death. A virtual screening of commercial libraries led to the identification of five novel scaffolds with inhibitory profile in the low nanomolar range. A Hit-to-lead optimization led to the identification of a group of new potent PARP-1 inhibitors, acyl-piperazinylamides of 3-(4-oxo-3,4-dihydro-quinazolin-2-yl)-propionic acid. Molecular modeling studies highlighted the preponderant role of the propanoyl side chain.

Poly (ADP-ribose) polymerases (PARPs) are a family of proteins whose main roles involve maintaining DNA integrity and programmed cell death. So far 18 members have been recognized, but PARP-1 and PARP-2 are the two most studied isoforms. PARP-mediated DNA repair utilizes base excision repair pathway.[1] Blocking PARP's activity prevents DNA damage repair, which finally leads to cell death through induction of DNA double-strand breaks (DSBs). Lately, however, new mechanisms of action of PARP inhibitors have been discovered, demonstrating that when bound to some inhibitors, PARP proteins, , instead of being released from DNA once the repair process has started, remain trapped on DNA preventing its replication and consequent cell division.[2]

PARP-mediated repair process involves the binding of damaged DNA to N-terminal zinc finger motif of PARP, which in turn causes activation of the catalytic C-terminal domain allowing the enzyme to hydrolyze NAD^+, ultimately resulting in the production of linear and branched poly-ADP-ribose chains.

Enhanced PARP-1 expression and/or activity, has been also observed in different human tumor cell lines such as

hepatocellular carcinoma, colorectal carcinoma, cervical carcinoma, malignant lymphomas, and leukaemia. Moreover, it has been reported that PARP catalytic activity is also stimulated in response to DNA damage.[3]

It is well-known that many anti-cancer therapies, such as those involving temozolomide (TMZ), platinum-based drugs, topoisomerase inhibitors and radiotherapy, implicate DNA damage. These therapies are however shadowed by the emergence of resistance, notably due to DNA repair through PARP pathway, undermining therefore their efficacy. Such observation led to the development of combination therapies wherein resistance to the mechanism of action of the DNA damaging drugs was hampered by PARP inhibition. It has even been shown that PARP inhibition could potentiate the effect of DNA damaging agents,[4,5] as well as radiotherapy. Cancer cells presenting at least one of BRCA1 and BRCA2 mutated genes, two well-known tumor-suppressor genes, are very sensitive to PARP-1 inhibition, resulting in cell cycle arrest and apoptosis. This suggests an efficacious role for PARP inhibitors, as single agents, against tumors exhibiting BRCA1 and/or BRCA2 mutations.[6-8]

Few PARP-1 inhibitors have been discovered and assessed in advanced clinical trials, either as stand-alone monotherapies or in combination therapies. All these compounds have a nicotinamide-based structure aimed at competing with NAD^+ for the binding to PARP-1 catalytic site [e.g., olaparib (AZD2281), veliparib (ABT-888), niraparib (MK-4827), BMN-673, and rucaparib (AG-014699/ PF-01367338)] (Figure 1).

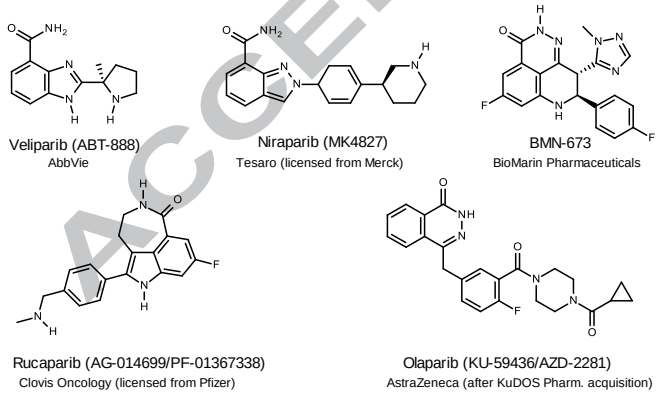


Figure1: Structure of some PARP inhibitors

Although a series of setbacks almost caused the demise of PARP inhibitors, as predicted by many observers in 2011; more recent analyses show an invigorated interest in this target, with a possible regulatory approval within 3 years. A few companies are now beginning pivotal trials of PARP inhibitors in breast and ovarian cancer.[9]

X-Ray crystal structures[10,11] and molecular modeling studies[12-15] indicate that the amide of nicotinamide makes three key hydrogen bonds with the hydroxyl group of S904 and the amide backbone of G863, and that there is a stacking interaction with a conserved Y907. Conformationally constrained cyclic inhibitors demonstrate an anti-disposition of the amide bond. Attempts to improve PARP inhibitors' affinity to the binding site have been made locking the carboxamide group which is usually free to rotate. This locking can be made either inserting on the aromatic ring heteroatoms or groups able to give an intramolecular hydrogen bond with the amide NH, or enclosing the amide group into a two (or more)-ring heterocycle.[10]

Based on these findings, we created a pharmacophore query in which the presence of three structural features were imposed: 1) an aromatic ring, 2) a carboxamide moiety with at least one NH group locked into the desired anti-conformation, 3) a side chain extending into the deep pocket located in the auto-modification domain of PARP-1.

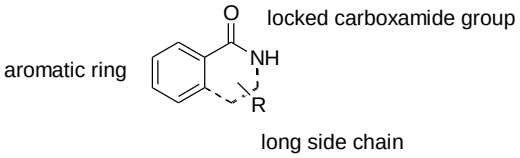


Figure 2. Pharmacophore query

Virtual screening of commercial libraries led to the identification of few scaffolds containing appropriate chains and/or groups that satisfied the pharmacophore query, i.e. 4-(methylene)-4H-isoquinoline-1,3-dione (group A), 3H-quinazoline-4-one, (B) 1H-quinazoline-2,4-dione (C), 2H-phthalazine-1-one (D) and 2-oxomethylenebenzamide (E) derivatives (Figure 3).

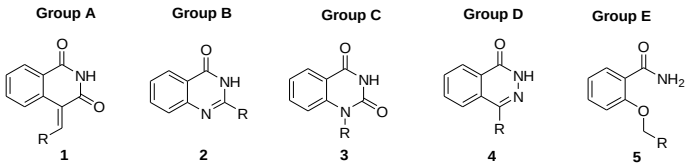


Figure 3. Scaffolds selected from virtual screening of commercial libraries.

Three derivatives from group A, seven from each of groups B and C, nine from group D, and six from group E were evaluated for their inhibitory activity against recombinant human PARP-1,

expressed as GST fusion protein, by means of a highly sensitive fluorescent enzymatic assay (see Supporting Information).

Moreover, based on the hypothesis that PARP-1 inhibitors could represent a monotherapy option against tumors with mutated BRCA1/2 genes, as suggested by several experiments performed in vitro and in vivo on human tumor cell lines or xenograft models,[15-17] the most active compounds of each group (Figure 4) were subjected to further investigation, i.e. cytotoxicity against the triple-negative and BRCA-1 deficient breast tumor cell line MDA-MB436.

All tested compounds appeared to be potent PARP-1 inhibitors showing a two-digit nM activity (Figure 4). Such an in-vitro profil was however not corroborated by an adequate antiproliferative activity on the above mentioned breast cancer cell line (i.e., IC_{50}> 10 μM).

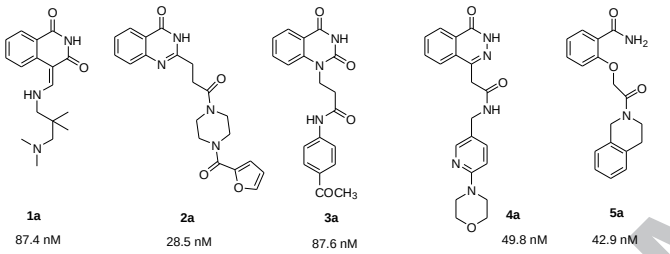


Figure 4. Structure and PARP-1 inhibitory activity (IC_{50}) of the selected compounds.

A hit-to-lead optimization was undertaken on most active compound of the series, **2a**.

Although a number of quinazolinone derivatives with PARP inhibiting properties have already been reported,[18-22] none of them contain a propanoyl chain attached to the position 2 of the quinazolinone nucleus. We hypothesized that the CO group on this chain could have been an important point of interaction with a suitable hydrogen bond donating group in the binding site.

This hypothesis was confirmed by docking experiments with PARP-1[10] protein and optimization through QM/MM mixed approach. All of the tested compounds behave as PARP-1 inhibitors, being anchored to the nicotinamide binding site in a very similar way. The compounds sat inside the cavity with the main heterocyclic ring inserted between Y246 and H201, thus forming a strong pi-pi interaction with Y246. The ring carboxamide group gives rise to hydrogen bond interaction with the S243 OH group, and two with the G202 backbone. This situation is depicted for hit compound **2a** in Figure 5.

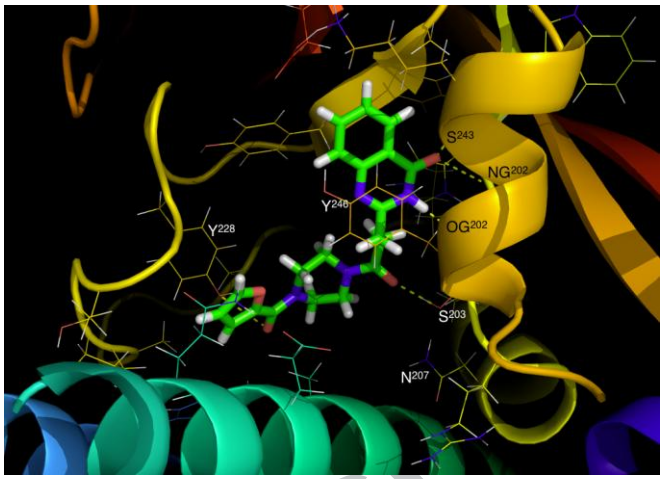


Figure 5. Representation of **2a** binding mode with the key residues

The presence of one or more carbonyl groups in the side chain also appeared to largely contribute to the binding through hydrogen bonds. Considering again **2a**, the carbonyl group of the propanoyl chain forms a very strong hydrogen bond with the S203 hydroxyl group (1.70 Å). The pattern of interaction with PARP-1 is further completed by a hydrogen bond between the second carbonyl group and the hydroxyl group of Y228 with a distance of 1.80Å. In this orientation, the furan moiety is placed in front of the aromatic ring of Y228, thus enabling a strong pi-pi stacking interaction (Figure 5).

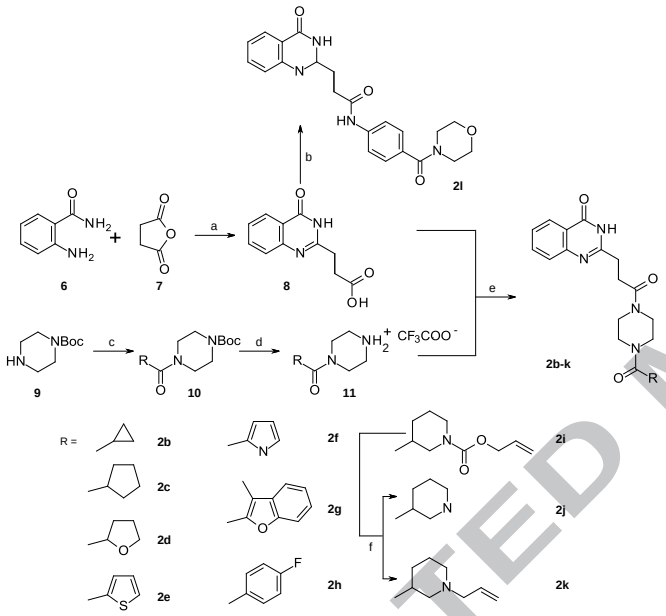
Recent reports appeared once this work was already completed, indicate similar interactions of this carbonyl group with N387 (through a water molecule) of isoform PARP-3[23] and with Y1213 of Tankyrase-1.[24]

The importance of the carbonyl group for the activity of the herein described compounds was confirmed by studying analogues lacking the carbonyl moiety. Indeed, the replacement of the carbonyl group with a methylene group preclude any interaction, leading to a 10- to 100-fold increase in the calculated free energy. The observed effect is mainly due to the inability of the methylene group to get close to region delimited by S203 and N207. The different orientation within the binding site leads to the lack of the interactions with S203 and Y228, resulting in a dramatic fall of the affinity for the PARP-1 receptor. (Fig. S1 in SI)

Therefore the hit-to-lead program was performed keeping intact the nucleus, the propanoyl-piperazino chain (**2a**), and modifying the acyl moiety (2-furanoyl in the case of **2a**), introducing cycloalkyl or aromatic groups (**2b-c, 2h**) or heterocycles (tetrahydrofuran, thiophene, pyrrole, benzofuran, piperidine) (**2d-g, 2l-k**) (Scheme 1).

The key intermediate in the synthesis of the series of compounds **2** was quinazolin-4(3H)-one-2-propanoic acid **8**, in turn prepared from anthranilamide and succinic anhydride in refluxing toluene,[25] followed by ring closure with NaOH.

The acylpiperazines reagents were obtained by coupling commercial N-Boc-protected piperazine with the appropriate acid by means of standard peptide chemistry (PyBOP, DIPEA, DMF, rt),[26] followed by deprotection with TFA/CH_2Cl_2 to give the corresponding trifluoroacetates **11**. These were coupled with acid **8** by peptide coupling chemistry too. Compound **2k** was obtained from **2i** by treatment with $Pd(PPh_3)_4$ and morpholine as a side product of **2j**.



Scheme 1. Reagents and conditions: (a) i. Toluene, reflux; ii. NaOH 2N, reflux (83%); (b) (4-aminophenyl)-4-morpholinylmethanone, TEA, HATU, pyridine, 140 °C, MW (**2l**: 60%); (c) RCOOH, PyBOP, DIPEA, DMF, rt (47-80%); (d) DCM/TFA=7/3, rt, quantitative; (e) PyBOP, DIPEA, DMF, rt (**2b**: 50%; **2c**: 73%; **2d**: 48%; **2e**: 38%; **2f**: 51%; **2g**: 62%; **2h**: 52%; **2i**: 32%); (f) $Pd(PPh_3)_4$, morpholine, DCM, rt (**2j**: 36%, **2k**: 17%).

Among these new derivatives, **2e** was shown to inhibit PARP-1 catalytic activity with a potency 3- fold higher than that of parental **2a** (Table 1), whereas other compounds showed a comparable (**2f** and **2j**) or a slightly weaker (**2b** and **2h**) inhibitory activity with respect to **2a.** This is consistent with the presence of a ring able to interact through pi-pi stacking with Y228, as shown by the modeling.

A moderate reduction of inhibitory activity was instead observed for derivatives **2c**, **2d** and **2g**, whereas more pronounced was the decrease in activity for **2k** (IC_{50}=220 nM) and **2i** (IC_{50}=300 nM).

Some of the most active compounds (**2b, 2e, 2f**, and **2h**) were then assessed through a functional parylation assay on a cellular model (human endometrial carcinoma cell line HeLa), to assess the ability of the tested compounds to affect PARylation of nuclear proteins following a strong DNA damage induced by treatment with H_2O_2.[27]

As shown in Table 2, all compounds showed relevant inhibitory activity also on this cellular model, with EC_{50} values ranging from 256 nM (**2e**) to 865 nM (**2f**), thus confirming their ability to target and inhibit PARP activity.

Table 1. PARP-1 inhibiting activity of compounds **2**

Cpd.	PARP-1; IC_{50} (nM)±SD[a]
2a	28.5±0.8
2b	67.1±4.6
2c	110.0±70.0
2d	130.0±20.0
2e	9.8±2.5
2f	29.5±3.7
2g	130.0±20.0
2h	56.1±4.7
2i	300.0±80.0
2j	31.9±8.4
2k	220.0±40.0
Olaparib	10±0.2
Veliparib	10±0.2
MK-4827	30±5

[a] Values are the mean (± S.D.) of three experiments.

Table 2. Results of a PARylation assay on HeLa (human endometrial ca.) cells.[a]

Compound	PARylation; EC_{50} (nM)
2b	707
2e	256
2f	865
2h	467

[a] Values are the mean of two experiments (standard deviations were within 25% of the mean values).

Although temozolomide (TMZ), topoisomerase I poisons and ionizing radiation (IR), as mentioned above, potentiate anticancer activity when combined with PARP inhibitors in a wide range of tumor models, the discovery that these inhibitors alone selectively kill cancer cells with homologous recombination-deficiency (HRD), represents a very significant advance. This observation has rapidly translated into clinical trials on patients with breast, ovarian and prostate cancer BRCA1/2 mutated.

For this reason, compounds **2b, 2e, 2f, and 2h** were also investigated both alone and in combination with TMZ on triple-negative, BRCA1-mutated, and MDA-MB436 breast carcinoma cells. The combination index indicated a synergic effect (Table 3).

Table 3. Combination Index (CI) values of interactions between selected test compounds and temozolomide (TMZ), on MDA-MB436, breast-triple-negative, and BRCA1-mutated cells after 7 days of treatment.

Cells	Compound	IC_{50}, µM	Combination index values (CI)		
			ED_{50}	ED_{75}	ED_{90}
MDA-MB436	**2b**	51.1	0.70	0.80	0.90
	2e	17.3	0.05	0.22	0.85
	2f	18.1	0.12	0.43	0.80
	2h	19.5	0.40	0.60	0.90
	TMZ	120			

The dose-response curve of each drug was determined and combination index (CI) values for varying drug/TMZ concentration ratios were calculated according to Chou-Talalay method using CalcuSyn software (Biosoft). CIs < 1 indicate synergism.

Compounds **2e** and **2h** were successively selected for pre-ADME evaluation. In a bidirectional Caco-2 cells assay, **2e** and **2h** showed an efflux ratio of 5.8 and 6.0, respectively, corresponding to a moderate permeability. Interestingly enough, the two compounds were found not to be P-gp substrate. Evaluation of blood/plasma distribution resulted in a ratio of about 0.4 for both compounds after 60 minutes, whereas human plasma stability studies (2 hour incubation) gave a recovery of 50% for **2e** and 57% for **2h.** Finally, evaluation of metabolic stability on human hepatocytes gave a $t_{1/2}$ of 584 min (**2e**) and 618 min (**2h**).

Compound **2e** was selected for in vivo investigation in athymic SCID beige mice xenografted with MX1 breast carcinoma cells, the latter being characterized by BRCA1 deletion and BRCA2 gene mutation. As reported in Table 4, the drug delivered intraperitoneally at the maximum tolerated dose of 200mg/10mL/kg, according to the schedule qdx5/wx3w, was shown to significantly inhibit (by 47%) tumor growth ($P<0.01$ *vs*. vehicle treated group, Mann-Whitney).

In conclusion, a ligand-based approach aimed at discovering novel PARP-1 inhibitors was undertaken, taking into account pharmacophoric features of known inhibitors.

Five thousand compounds, selected from commercial libraries, were virtually screened against PARP-1, leading to the identification of five new scaffolds presenting PARP-1IC_{50} values in the low nanomolar range (IC_{50} values 28.5-87.6 nM).

A 4(3H)-quinazolinone hit (**2a**) was selected and synthetic efforts were made to improve the inhibitory profile. A series of differently acylated derivatives was prepared, most of them being active on PARP-1 in a two-digit nanomolar range. The activity of the most potent derivatives was further confirmed in a functional cell PARylation assays. They also showed a synergic effect when combined with temozolomide in vivo. Moreover, compound **2e** revealed to be efficacious in inhibiting the tumor volume of a BRCA1-deleted and BRCA2 mutated breast carcinoma. Because PARP-1 is highly expressed in a variety of cancers, including breast, hepatocellular carcinoma and non-small cell lung cancer,[28-30] and its expression is often correlated with poor prognosis and drug-resistance, the identification of novel PARP inhibitors is strongly recommended.

Taken together, these results demonstrate that the 2-propanoyl-quinazolinone nucleus is a suitable scaffold for the development of new PARP inhibitors.

Table 4. Antitumor activity of **2e** against MX1 human breast carcinoma xenograft

Cpd.	Dose/route mg/kg	Schedule	BWL%	Lethality	TV± (d +38)	TVI% (d +38)
Vehicle	0	Qdx5/wx3w	0	0/8	781±30	/
2e	200/ip	Qdx5/wx3w	10	0/8	412±56	*47

Treatments started 7 days after tumor injection.

*P<0.01 vs vehicle-treated group (Mann-Whitney's test).

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Graphical Abstract

Novel PARP-1 inhibitors based on a 2-propanoyl-3H-quinazolin-4-one scaffold

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