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Synthesis and biological evaluation of substituted 4-(thiophen-2-ylmethyl)-2*H*-phthalazin-1-ones as potent PARP-1 inhibitors

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ABSTRACT

We have developed a series of substituted 4-(thiophen-2-ylmethyl)-2*H*-phthalazin-1-ones as potent PARP-1 inhibitors. Preliminary biological evaluation indicated that most compounds possessed inhibitory potencies comparable to, or higher than **AZD-2281**. Among these compounds, **18q** appeared to be the most notable one, which displayed an 8-fold improvement in enzymatic activity compared to **AZD-2281**. These efforts lay the foundation for our further investigation.

Poly(ADP-ribose)polymerase-1 (PARP-1) is an 113 kDa eukaryotic nuclear enzyme with an important role in the process of DNA repair.[1] When activated by DNA damage, PARP-1 catalyzes the transfer of ADP-ribose units to nuclear target proteins to facilitate DNA repair, using nicotinamide adenine dinucleotide (NAD^+) as substrate.[2] Given the biological role of the enzyme, PARP-1 inhibitors have the potential to prevent the repair of DNA damages that were implicated by radiation and chemotherapeutic agents, and combination of them with radio- and chemo-therapy to maximize the cancer therapeutic benefits has become an attractive strategy.[3] The potential was further highlighted by reports that BRCA1/2 deficient cancer cells are highly sensitive to PARP-1 inhibitors resulting in cell death.[4]

Over the past three decades, a variety of PARP-1 inhibitors have been designed and synthesized based on the nicotinamide (**1**, Fig. 1) moiety of NAD^+ to mimic the substrate–protein interactions of NAD^+ with the enzyme.[5,6] These compounds, which usually contain a primary amide or lactam functionality, belong to different chemical classes such as benzimidazole carboxamides (**2**), tricyclic indoles (**3**), and phthalazinones (**4**),[7] and several of them are in advanced clinical trials, including ABT-888 (**5**), AG-14699 (**6**), **AZD-2281** (Olaparib, **7**), etc. However, despite the high interest in PARP-1 inhibitors, development of a number of them has stalled,[8] and to date, there are no drugs that modulate the target have reached the market, thus the effort of pursuing novel safe and effective PARP-1 inhibitors is still needed.

Among above compounds under active study, **AZD-2281** is a representative of phthalazinones. In its structure, phthalazinone itself demonstrates weak PARP-1 inhibitory activity,[9] and benzyl phthalazinone (**8**) substituted in the 4-position is the core scaffold and identified as a moderately potent PARP-1 inhibitor.[10] Besides, substituted piperazines at the meta position of benzyl are conducive to enhancing activity and maintaining good oral bioavailability,[11] and the substitutions at the *para* position of benzyl contribute to block possible metabolism and extend half life.[12] On the basis of the above structure–activity relationship of **AZD-2281**, we tried to take thienyl instead of phenyl to seek new possibilities and explore alternative chemical templates. Furthermore, we made an attempt to enhance potency by doing some elaborations at the distal nitrogen of piperazine. Herein, we report a series of substituted 4-(thiophen-2-ylmethyl)-2*H*-phthalazin-1-ones as novel PARP-1 inhibitors.

The synthesis of the target compounds **18a–18u** outlined in Scheme 1 was achieved via amide bond coupling of the corresponding acid **14** with substituted piperazines **17**. The key

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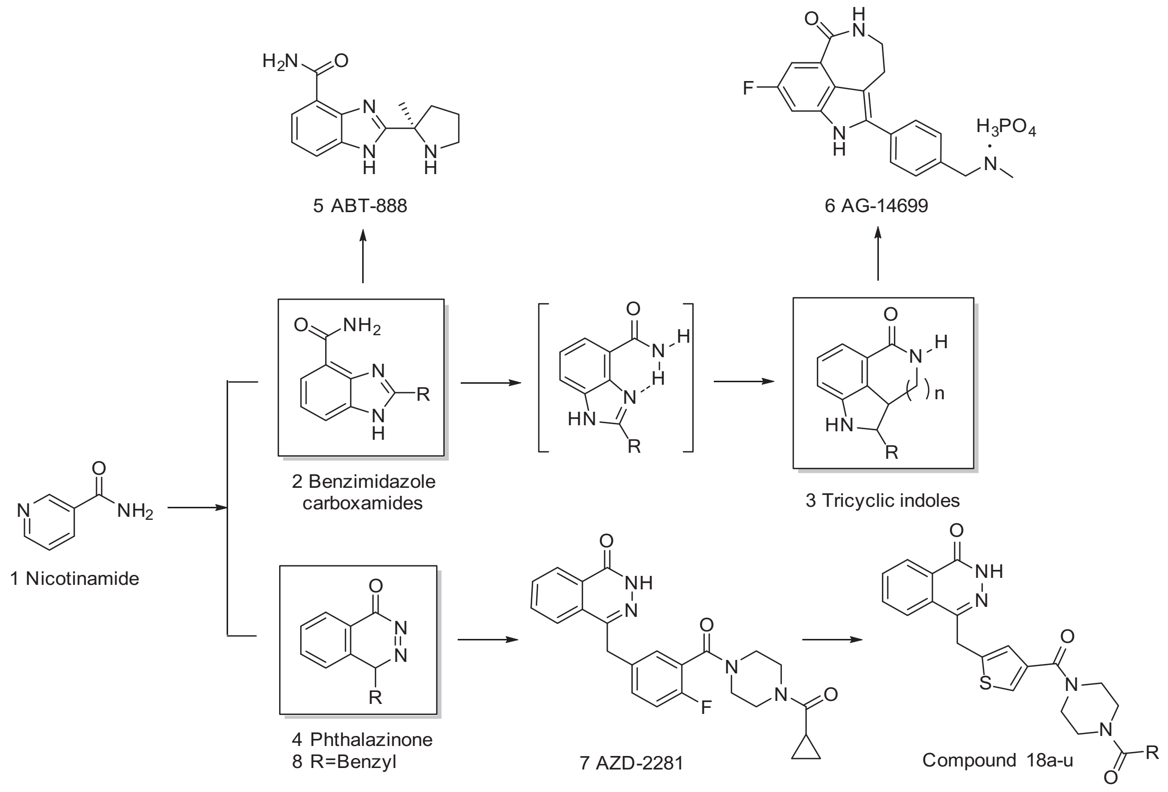
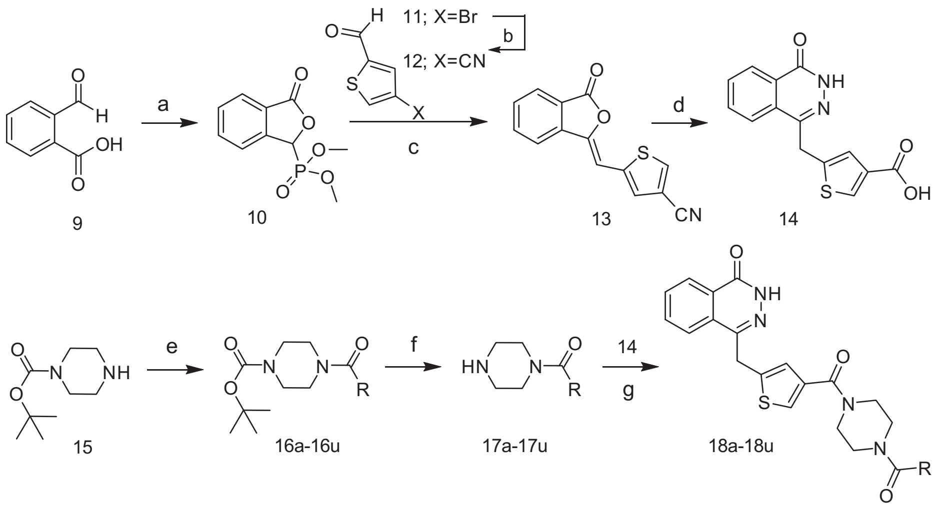


Figure 1. Classes and representatives of PARP-1 inhibitors.



Scheme 1. Synthesis route for target compounds. Reactions and conditions: (a) Dimethyl phosphite, CH_3ONa/MeOH, 0 °C, 30–60 min, methanesulfonic acid, 88.4%; (b) CuCN/CuI, DMF, reflux, 3–4 h, 66.3%; (c) Et_3N, anhydrous THF, 20 °C, 16 h, 95.6%; (d) (i) H_2O, nitrogen atmosphere, NaOH (aq), 90 °C, 30 min, (ii) $NH_2NH_2 \cdot H_2O$, 70 °C, 18 h, 2 N HCl, 94.0%; (e) HOBt/EDCI, DIPEA, DCM, 18 h, RT, 90.5%; (f) TFA/DCM, below 25 °C, 64%; (g) (i) HBTU/DIPEA, DMA, below 25 °C, 48 h, (ii) water, reflux, 1 h, 26.2–76.9%.

intermediate **14** was prepared from 2-formylbenzoic acid **9**, treating **9** with dimethylphosphite furnished intermediate **10**.[13] Compound **10** was then submitted to a nucleophilic substitution in the presence of triethylamine with another substrate **12**, which was afforded by treating **11** with CuCN and CuI,[14] to give intermediate **13**. Then the hydrolysis of **13** was occurred under aqueous NaOH condition, followed by a reaction with hydrazine hydrate to give the desired carboxylic acid scaffold **14**.[15] As for the piperazine moiety, N-boc piperazine **15** was coupled to various acids with HOBT, EDCI and DIPEA to provide reliably high yields of **16a–16u**,[16] followed by a boc-deprotection in the presence of trifluoroacetic acid to give secondary amines **17a–17u**.[17] Finally, acid **14** was coupled to various substituted piperazines **17** under standard HBTU/DIPEA conditions to afford the target compounds **18a–18u**.[18]

All target compounds were evaluated in vitro for their PARP-1 enzyme inhibition activity, and ten of them were selected to determine IC_{50} values. The results were listed in Table 1.

To begin with, straightforward replacement of the phenyl in **AZD-2281** (IC_{50}: 84.96 nM) with thienyl gave compound **18a** (104.90 nM), and what made us exciting was that **18a** exhibited the same order of magnitude in potency as **AZD-2281**. Further