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# Studies on Benzofuran-7-carboxamides as Poly(ADP-ribose) Polymerase-1 (PARP-1) Inhibitors

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Benzofuran-7-carboxamide was identified as a novel scaffold of poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor. A series of compounds with various 2-substituents including (tertiary amino)methyl moieties substituted with aryl ring and aryl groups containing tertiary amines, were synthesized and biologically evaluated to elucidate the structure-activity relationships and optimize the potency. 2-[4-(Pyrrolidin-1-ylmethyl)phenyl]-benzofuran-7-carboxamide (**42**) was the most potent as an $IC_{50}$ value of 40 nM among those.

**Key Words :** Poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor, Benzofuran-7-carboxamide, Nicotinamide, Anticancer, Ischemic disease

## Introduction

Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear enzyme activated in response to DNA damage, and investigated in a wide range of therapeutic areas.[1] The most promising two major areas are ischemia[2] and cancer[3] of the several therapeutic indications for PARP-1 inhibitors. Activated PARP catalyzes the transfer of ADP-ribose units from nicotinamide adenine dinucleotide ($NAD^+$) to nuclear acceptor proteins such as histones, topoisomerases, DNA polymerases, DNA ligases and PARP itself. There is a solid pharmacophore, the amide, for $NAD^+$ competitive inhibitors, even though a variety of structures.[4] Restricted bicyclic and tricyclic lactams including isoquinolinones,[5] phthalazinones, phenanthridones, pyrroloisoquinolinones,[6] containing the arylamide into another ring, showed a good activity, of which geometry would be beneficial for PARP-1 inhibitory potency. Additionally, the imidazole, imidazopyridine and indole carboxamides appeared, in which the imidazole and indole nitrogen formed intramolecular hydrogen bond with the amide NH, then a "pseudo ring", similar to the lactam.[7] In this study we synthesized and biologically evaluated the benzofuran-7-carboxamide derivatives as PARP-1 inhibitors. We anticipated that the oxygen of benzofuran might have the role like nitrogen of imidazole to form H-bond with the 7-carboxamide NH (Fig. 1).

**Chemistry.** 2-(Aminomethyl)benzofuran-7-carboxamides were synthesized starting from 2-hydroxybenzamide (Scheme 1). The (allyloxy)benzene **1** was obtained by *O*-alkylation of 2-hydroxybenzamide using (2-bromo)allyl bromide, then subsequent Claisen rearrangement[8] of **1** gave the compound **2** by heating under microwave in DMF for 20 min. The (bromoallyl)phenol was cyclized to 2-methylbenzofuran **3** using DBU in toluene. A bromination using NBS (1. equiv) afforded the monobromide **4**, which was reacted with various amines to provide the 2-(aminomethyl)bezofuran-7-carboxamide derivatives **5-21**.

The salicyladehyde **23a**, which is one of the key starting material to prepare 2-phenylbenzofuran-7-carboxamide derivatives, was prepared by the formylation of 2-hydroxybenzoic acid using hexamethylene tetramine in acidic condition,[10] following the esterification of resulting 3-formyl (**22a**) and 5-formyl (**22b**) isomeric mixtures, and then separation from 5-formyl-2-hydroxybenzoate **23b** (Scheme 2).

2-Phenylbenzofuran-7-carboxamides were synthesized by the reaction of salicyladehyde substituted with a 2-carbox-

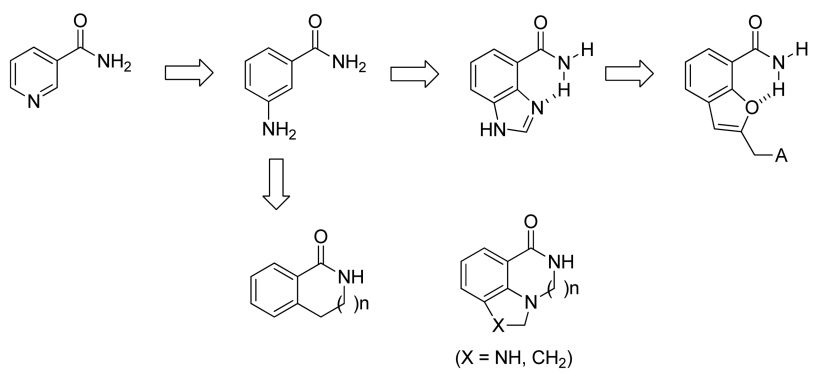
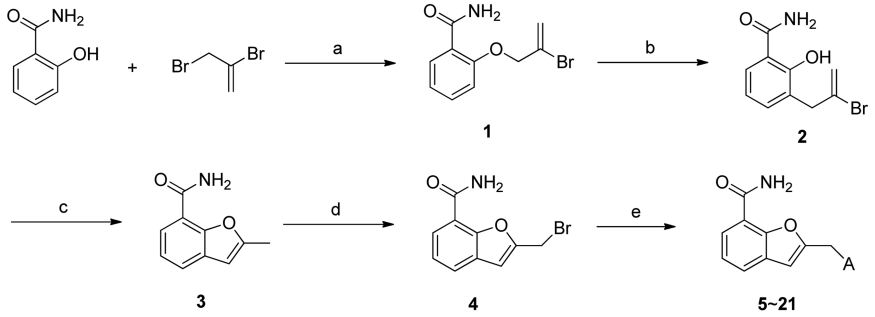
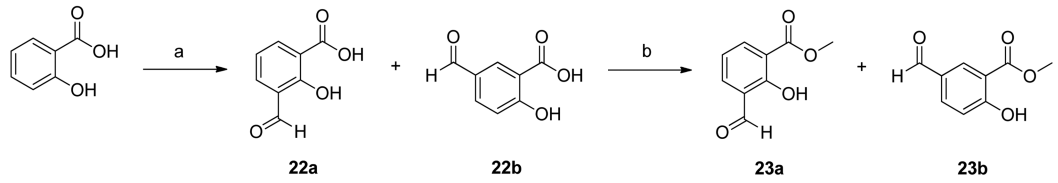


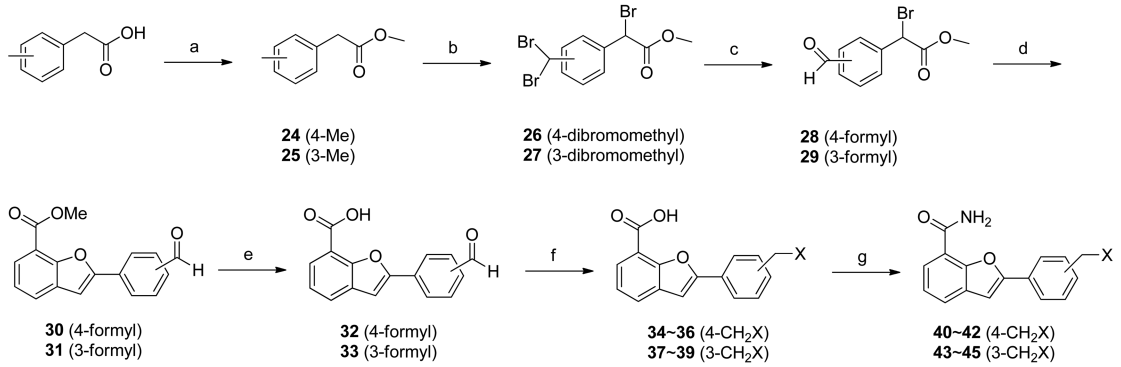

**Figure 1.** Design of benzofuran-7-carboxamide derivatives.




**Scheme 1.** Reagents; (a) $K_2CO_3$, DMF, 120 °C; (b) microwave, 200 °C, 20 min, DMF; (c) DBU, $PhCH_3$, reflux; (d) NBS, AIBN, $CCl_4$, reflux; (e) amine, $K_2CO_3$, DMF, rt.




**Scheme 2.** Reagents; (a) HMTA, $CH_3COOH$, $H_2SO_4$; (b) $SOCl_2$, MeOH.




**Scheme 3.** Reagents; (a) $H_2SO_4$, MeOH, reflux; (b) NBS, AIBN, $CCl_4$, reflux; (c) $AgNO_3$, $H_2O$/EtOH, 100 °C; (d) **23a**, $K_2CO_3$, DMF, 120 °C; (e) 2 N NaOH, MeOH, reflux; (f) amine, AcOH, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt; (g) i) $SOCl_2$, $ClCH_2CH_2Cl$ ii) aq. $NH_4OH$, THF.

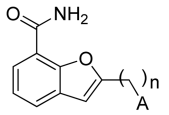
ylic ester **23a** and methyl 2-bromophenylacetate with a 3- or 4-formyl group at benzene ring **28** or **29** (Scheme 3).[9] The bromination of (3- or 4-methylphenyl)acetate **24** or **25** using *N*-bromosuccinimide gave bromo-(3- or 4-dibromomethylphenyl)acetate **26** or **27**, of which dibromomethyl group was oxidized to aldehyde **28** or **29** with silver nitrate (Scheme 3).[11] The reaction of salicylaldehyde **23a** and 2-bromophenylacetates (**28**, **29**) with $K_2CO_3$ in DMF at 120 °C, afforded the 2-phenylbenzofuran compounds (**30**, **31**) *via* a sequence of reactions including *O*-alkylation, ring closure and decarboxylation to form a benzofuran ring. The aldehyde group of **30** or **31** was further diversified to the various amines **34-39** by reductive amination. Benzofuran-7-carboxamides **40-45** were synthesized from carboxylic acids through acid chlorides.

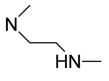
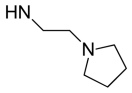
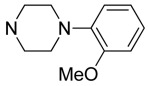
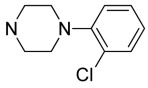
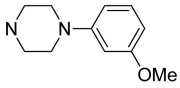
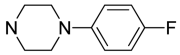
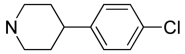
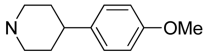
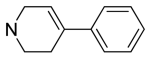
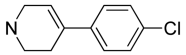
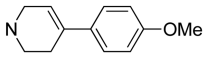
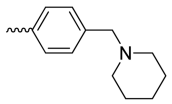
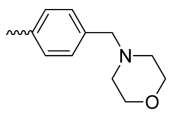
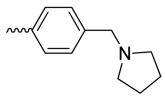
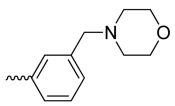
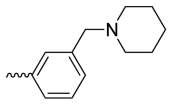
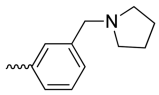
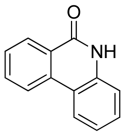
**Biological Evaluation.** The inhibitory effects of synthesized compounds on PARP-1 were determined as $IC_{50}$ by the converting biotinylated NAD-based colorimetric assays in clear 384-well plates as previously reported.[12] The $IC_{50}$ value of a reference, phenanthridine-6(5*H*)-one was determined as 0.22 μM, which was reported as 0.30 μM. [13]

## Results and Discussion

We synthesized and biologically evaluated a series of benzofuran-7-carboxamide derivatives to identify a novel scaffold of PARP-1 inhibitor. It was suggested that hydrophobic moiety, especially secondary and tertiary amines at a proper site increased the binding affinity and improve the pharmaceutical properties.[14] Several secondary and tertiary 2-aminomethyl compounds (**5**, **6**, **9**, and **11**) exhibited moderate PARP-1 inhibitory activities ($IC_{50} < 1$ μM), showing the possibility of benzofuran as a PARP-1 inhibitor core structure. Also, it was known that aryl groups substituted at the *para* position of nicotinamide generally improve the potency due to π-π interactions with tyrosine in PARP-1.[4] Then, we introduced the phenyl ring at the 4-position of piperazine, piperidine, and 5,6-dihydropyridine to optimize the activity (**13-21**). The $IC_{50}$ values of 2-methoxyphenyl- (**13**), 2-chlorophenyl- (**14**), 3-methoxyphenyl- (**15**), and 4-fluorophenyl- (**16**) piperazines were each 3.75, 1.65, 0.38, 0.26 μM, while the $IC_{50}$ value of 4-methylpiperazine (**10**) was 3.65 μM. The introduction of *meta* or *para* substituted

**Table 1.** PARP-1 Inhibitory Activities



| | n | A | $IC_{50}$ (μM) | | n | A | $IC_{50}$ (μM) |
|---|---|---|---|---|---|---|---|
| **5** | 1 |  | 0.43 | **6** | 1 |  | 0.64 |
| **7** | 1 |  | 0.72 | **8** | 1 |  | 1.72 |
| **9** | 1 |  | 0.40 | **10** | 1 |  | 3.65 |
| **11** | 1 |  | 0.81 | **12** | 1 |  | 4.06 |
| **13** | 1 |  | 3.75 | **14** | 1 |  | 1.65 |
| **15** | 1 |  | 0.38 | **16** | 1 |  | 0.26 |
| **17** | 1 |  | 0.55 | **18** | 1 |  | 0.39 |
| **19** | 1 |  | 0.42 | **20** | 1 |  | 0.16 |
| **21** | 1 |  | 0.19 | **40** | 0 |  | 0.20 |
| **41** | 0 |  | 0.31 | **42** | 0 |  | 0.04 |
| **43** | 0 |  | 0.73 | **44** | 0 |  | 0.59 |
| **45** | 0 |  | 0.17 | | |  Phenanthridine-6(5*H*)-one | 0.22 |

phenyl ring at piperazine (**15**, **16**) greatly improved the potency. But the *ortho* substituted phenylpiperazines (**13**, **14**) showed decreased activities than *meta* or *para* substituted phenylpiperazines. The 4-(4-chlorophenyl), and 4-(4-methoxyphenyl)-5,6-dihyhydropyridine compounds (**20**, **21**) also represented improved potency, around 0.2 μM of $IC_{50}$ values. Additionally, we investigated 2-arylbenzofurans containing tertiary amine (**40-45**). It was reported that the introduction of tertiary amine at phenyl ring might beneficial for activity through the interaction with polar residues of enzyme such as Asp766 and Glu763.[15] Those activities were not quite different from 2-aminomethyl compounds with aryl substituent (**13-21**). The *para* substitution of (tertiary amino)-methyl moiety at phenyl ring demonstrated better activity than the *meta* substituted analogues. The compound **42** containing pyrrolidine showed the most potent activity ($IC_{50}$ = 40 nM) among this series of compounds. In this study, we found the potential of benzofuran as a novel scaffold of PARP-1 inhibitors. After further investigation on this scaffold including solubility and toxicity, we are continuously going to optimize both *in vitro* and *in vivo* activities.

## Experimental Section

**Chemistry.** Melting points were determined on a capillary melting point apparatus and are uncorrected. Anhydrous solvents were dried by conventional methods. Reagents of commercial quality were used from freshly opened containers

unless otherwise stated. $^1$H NMR spectra were recorded on a Varian Gemini 200 or a Bruker DRX-300 spectrometer.. Mass spectra were obtained with a JEOL JMS-DM 303 instrument by using electron impact or chemical ionization techniques.

**2-[(2-Bromoallyl)oxy]benzamide (1):** To a solution of salicylamide (500 mg, 3.65 mmol) in DMF (3 mL) was added $K_2CO_3$ (756 mg, 5.47 mmol) and 2,3-dibromopropene (0.57 mL, 5.47 mmol), and the reaction mixture was stirred at 120 °C for an hr. Water was added, and the mixture was extracted with ethyl acetate twice. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:1) to yield **1** as a pale yellow solid (806 mg, 86%). $^1$H NMR (300 MHz, $CDCl_3$) δ 4.80 (s, 3H), 5.78 (d, 1H), 5.89 (brs, 1H), 6.03 (d, 1H), 6.92 (d, 1H), 7.13 (dd, 1H), 7.46 (dd, 1H), 8.26 (dd, 1H); MS ($M^+$) 255.

**3-(2-Bromoallyl)-2-hydroxybenzamide (2):** The compound **1** (4.7 g, 18.4 mmol) was dissolved in DMF, and the solution was heated at 200 °C for 20 min under microwave. Water was added, and the mixture was extracted with ethyl acetate twice. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to yield **2** as a pale yellow solid (3.38 g, 72%). $^1$H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H), 5.52 (s, 1H), 5.61 (s, 1H), 6.85 (dd, 1H), 7.30 (d, 1H), 7.39 (d, 1H), 12.51 (s, 1H); MS ($M^+$) 256.

**2-Methylbenzofuran-7-carboxamide (3):** To a solution of the compound **2** (4.77 g, 18.6 mmol) in toluene (25 mL) was added DBU (5.57 g, 37.3 mmol), and the reaction mixture was heated at reflux with stirring for an hr. After cooling, water was added, and the mixture was extracted with ethyl acetate twice. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:1) to yield **3** as a white solid (2.54 g, 78%). $^1$H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3H), 5.30 (brs, 1H), 5.89 (brs, 1H), 6.48 (s, 1H), 7.30 (dd, 1H), 7.39 (brs, 1H), 7.65 (d, 1H), 8.02 (d, 1H); MS ($M^+$) 175.

**2-Bromomethylbenzofuran-7-carboxamide (4):** To a solution of the compound **3** (567 mg, 3.24 mmol) in $CCl_4$ (20 mL) was added *N*-bromosuccinimide (634 mg, 3.56 mmol) and 2,2-azobis(isobutyronitrile) (107 mg, 0.65 mmol), and the reaction mixture was heated at reflux with stirring for 20 min. After cooling, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 2:1) to yield **4** as a pale yellow solid (641 mg, 78%). $^1$H NMR (300 MHz, $CDCl_3$) δ 4.64 (s, 2H), 5.91 (brs, 1H), 5.89 (brs, 1H), 6.86 (s, 1H), 7.33 (brs, 1H), 7.38 (dd, 1H), 7.72 (d, 1H), 8.14 (d, 1H); MS ($M^+$) 253.

**Preparation of 2-Aminomethylbenzofuran-7-carboxamides (5-21).**

**2-[(Methylamino)methyl]benzofuran-7-carboxamide (5):** To a solution of the compound **4** (100 mg, 0.39 mmol) in DMF (3 mL) was added $K_2CO_3$ (82 mg, 0.59 mmol) and 40% methylamine (41 μL, 1.18 mmol). The reaction mixture was stirred at rt until the reaction was completed, then was diluted with water and extracted with ethyl acetate twice. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% $CH_3OH$ in $CH_2Cl_2$) to yield **5** as a pale yellow solid (56 mg, 70%). $^1$H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3H), 3.96 (s, 2H), 6.25 (brs, 1H), 6.69 (s, 1H), 7.34 (dd, 1H), 7.44 (brs, 1H), 7.69 (d, 1H), 8.07 (d, 1H); MS ($M^+$) 204.

**2-[(Dimethylamino)methyl]benzofuran-7-carboxamide (6):** The compound **6** was obtained as a pale yellow solid (79% yield) by the same procedure to prepare **5**, except using 40% dimethyamine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 6H), 3.67 (s, 2H), 5.94 (brs, 1H), 6.70 (s, 1H), 7.33 (dd, 1H), 7.50 (brs, 1H), 7.69 (d, 1H), 8.08 (d, 1H); MS ($M^+$) 218.

**2-(Pyrrolidin-1-ylmethyl)benzofuran-7-carboxamide (7):** The compound **7** was obtained as a pale orange solid (81% yield) by the same procedure to prepare **5**, except using pyrrolidine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.83 (m, 4H), 2.65 (m, 4H), 3.84 (s, 2H), 5.95 (brs, 1H), 6.69 (s, 1H), 7.33 (dd, 1H), 7.50 (brs, 1H), 7.68 (d, 1H), 8.06 (d, 1H); MS ($M^+$) 244.

**2-(Piperidin-1-ylmethyl)benzofuran-7-carboxamide (8):** The compound **8** was obtained as a pale yellow solid (81% yield) by the same procedure to prepare **5**, except using piperidine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 4H), 1.60 (m, 4H), 2.51 (m, 4H), 3.71 (s, 2H), 6.09 (brs, 1H), 6.68 (s, 1H), 7.33 (dd, 1H), 7.55 (brs, 1H), 7.68 (d, 1H), 8.06 (d, 1H); MS ($M^+$) 258.

**2-(Morpholin-4-ylmethyl)benzofuran-7-carboxamide (9):** The compound **9** was obtained as a pale yellow solid (73% yield) by the same procedure to prepare **5**, except using morpholine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.57 (t, 4H), 3.74 (t, 4H), 3.76 (s, 2H), 6.03 (brs, 1H), 6.72 (s, 1H), 7.34 (dd, 1H), 7.44 (brs, 1H), 7.69 (d, 1H), 8.08 (d, 1H); MS ($M^+$) 260.

**2-(4-Methylpiperazine-1-ylmethyl)benzofuran-7-carboxamide (10):** The compound **10** was obtained as a pale yellow solid (65% yield) by the same procedure to prepare **5**, except using *N*-methylpiperazine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.48 (m, 4H), 2.61 (m, 4H), 3.75 (s, 2H), 5.96 (brs, 1H), 6.71 (s, 1H), 7.33 (dd, 1H), 7.46 (brs, 1H), 7.68 (d, 1H), 8.08 (d, 1H); MS ($M^+$) 273.

**2-{[Methyl(2-(methylamino)ethyl)amino]methyl}benzofuran-7-carboxamide (11):** The compound **11** was obtained as a pale yellow solid (49% yield) by the same procedure to prepare **5**, except using *N*,*N*′-dimethylethane-1,2-diamine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.70 (s, 3H), 2.92 (t, 2H), 3.12 (t, 2H), 3.91 (s, 2H), 6.81 (s, 1H), 7.35 (dd, 1H), 7.73 (d, 1H), 7.95 (d, 1H); MS ($M^+$) 261.

**2-{[[2-(Pyrrolidin-1-yl)ethyl]amino]methyl}benzofuran-**

**7-carboxamide (12):** The compound **12** was obtained as a pale yellow solid (48% yield) by the same procedure to prepare **5**, except using 1-(2-aminoethyl)pyrrolidine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 4H), 2.38 (m, 4H), 2.47 (m, 2H), 2.59 (m, 2H), 3.87 (s, 2H), 6.80 (s, 1H), 7.28 (dd, 1H), 7.71 (m, 1H), 7.76 (brs, 1H); MS ($M^+$) 287.

**2-{[4-(2-Methoxyphenyl)piperazin-1-yl]methyl}benzofuran-7-carboxamide (13):** The compound **13** was obtained as a pale yellow solid (70% yield) by the same procedure to prepare **5**, except using 1-(2-methoxyphenyl)piperazine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.79 (m, 4H), 3.13 (m, 4H), 3.83 (s, 2H), 3.85 (s, 3H), 5.94 (brs, 1H), 6.74 (s, 1H), 6.85 (d, 2H), 6.98 (m, 3H), 7.34 (m, 1H), 7.44 (brs, 1H), 7.69 (d, 1H), 8.08 (d, 1H); MS ($M^+$) 365.

**2-{[4-(2-Chlorophenyl)piperazin-1-yl]methyl}benzofuran-7-carboxamide (14):** The compound **14** was obtained as a pale yellow solid (57% yield) by the same procedure to prepare **5**, except using 1-(2-chlorophenyl)piperazine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.78 (m, 4H), 3.10 (m, 4H), 3.83 (s, 2H), 5.94 (brs, 1H), 6.75 (s, 1H), 6.99 (dd, 1H), 7.04 (d, 1H), 7.20 (d, 1H), 7.34 (m, 2H), 7.45 (brs, 1H), 7.70 (d, 1H), 8.09 (d, 1H); MS ($M^+$) 369.

**2-{[4-(3-Methoxyphenyl)piperazin-1-yl]methyl}benzofuran-7-carboxamide (15):** The compound **15** was obtained as a pale yellow solid (73% yield) by the same procedure to prepare **5**, except using 1-(3-methoxyphenyl)piperazine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.72 (m, 4H), 3.23 (m, 4H), 3.78 (s, 3H), 3.80 (s, 2H), 5.99 (brs, 1H), 6.45 (m, 2H), 6.54 (dd, 1H), 6.74 (s, 1H), 7.17 (dd, 1H), 7.35 (dd, 1H), 7.42 (brs, 1H), 7.72 (d, 1H), 8.09 (d, 1H); MS ($M^+$) 365.

**2-{[4-(4-Fluorophenyl)piperazin-1-yl]methyl}benzofuran-7-carboxamide (16):** The compound **16** was obtained as a pale yellow solid (72% yield) by the same procedure to prepare **5**, except using 1-(4-fluorophenyl)piperazine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.75 (m, 4H), 3.15 (m, 4H), 3.81 (s, 2H), 5.96 (brs, 1H), 6.74 (s, 1H), 6.86 (m, 2H), 6.95 (m, 1H), 7.35 (dd, 1H), 7.42 (brs, 1H), 7.69 (d, 1H), 8.09 (d, 1H); MS ($M^+$) 353.

**2-{[4-(4-Chlorophenyl)piperidin-1-yl]methyl}benzofuran-7-carboxamide (17):** The compound **17** was obtained as a pale yellow solid (54% yield) by the same procedure to prepare **5**, except using 4-(4-chlorophenyl)piperidine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.86 (m, 4H), 2.24 (m, 2H), 2.48 (m, 1H), 3.08 (m, 2H), 3.79 (s, 2H), 5.96 (brs, 1H), 6.72 (s, 1H), 7.16 (d, 1H), 7.26 (m, 2H), 7.34 (dd, 1H), 7.51 (brs, 1H), 7.69 (d, 1H), 8.02 (s, 1H), 8.09 (d, 1H); MS ($M^+$) 368.

**2-{[4-(4-Methoxyphenyl)piperidin-1-yl]methyl}benzofuran-7-carboxamide (18):** The compound **18** was obtained as a pale yellow solid (44% yield) by the same procedure to prepare **5**, except using 4-(4-methoxyphenyl)piperidine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.84 (m, 4H), 2.25 (m, 2H), 2.46 (m, 1H), 3.07 (m, 2H), 3.78 (s, 3H), 3.79 (s, 2H), 6.00 (brs, 1H), 6.72 (s, 1H), 7.12 (d, 1H), 7.34 (m, 1H), 7.52 (brs, 1H), 7.70 (d, 1H), 8.01 (s, 1H), 8.09 (d, 1H); MS ($M^+$) 364.

**2-[(4-Phenyl-5,6-dihydropyridin-1(2*H*)-yl)methyl]benzofuran-7-carboxamide (19):** The compound **19** was obtained as a pale yellow solid (30% yield) by the same procedure to prepare **5**, except using 4-phenyl-1,2.3,6-tetrahydropyridine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.62 (m, 2H), 2.68 (m, 2H), 3.30 (m, 2H), 3.89 (s, 2H), 5.90 (brs, 1H), 6.07 (m, 1H), 6.77 (s, 1H), 7.35 (m, 6H), 7.53 (brs, 1H), 7.70 (d, 1H), 8.08 (d, 1H); MS ($M^+$) 332.

**2-{[4-(4-Chlorophenyl)-5,6-dihydropyridin-1(2*H*)-yl]-methyl}benzofuran-7-carboxamide (20):** The compound **20** was obtained as a pale yellow solid (36% yield) by the same procedure to prepare **5**, except using 4-(4-chlorophenyl)-1,2.3,6-tetrahydropyridine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.57 (m, 2H), 2.87 (m, 2H), 3.30 (m, 2H), 3.89 (s, 2H), 5.93 (brs, 1H), 6.07 (m, 1H), 6.76 (s, 1H), 7.35 (m, 5H), 7.44 (brs, 1H), 7.70 (d, 1H), 8.09 (d, 1H); MS ($M^+$) 366.

**2-{[4-(4-Methoxyphenyl)-5,6-dihydropyridin-1(2*H*)-yl]-methyl}benzofuran-7-carboxamide (21):** The compound **21** was obtained as a pale yellow solid (27% yield) by the same procedure to prepare **5**, except using 4-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine as a starting material instead of methylamine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.58 (m, 2H), 2.86 (m, 2H), 3.28 (m, 2H), 3.80 (s, 3H), 3.88 (s, 2H), 5.90 (brs, 1H), 6.08 (m, 1H), 6.76 (s, 1H), 6.85 (d, 2H), 7.34 (m, 3H), 7.50 (brs, 1H), 7.69 (d, 1H), 8.09 (d, 1H); MS ($M^+$) 362.

**3-Formyl-2-hydroxybenzoic Acid (22a):** To the solution of salicylic acid (20 g, 0.15 mol) in acetic acid (300 mL) was added hexamethylenetetramine (40.6 g, 0.29 mol) and the reaction mixture was heated at reflux for 2 hr, following the addition of 33% $H_2SO_4$ and continuous heating at reflux with stirring for an additional hour. After cooling, the mixture was extracted with diethyl ether 3 times. The organic layer was washed with $H_2O$ and then brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The compound was purified by recrystallization from methanol as a pale yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.06 (dd, 1H), 7.92 (m, 1H), 8.10 (dd, 1H), 10.38 (s, 1H); MS ($M^+$) 166.

**Methyl 3-formyl-2-hydroxybenzoate (23a):** To the solution of compound **22a** in methanol was added thionyl chloride and the reaction mixture was heated at reflux for 3 hr. After cooling, the mixture was concentrated under reduced pressure. To the residue was added $H_2O$, which was extracted with ethyl acetate three times. The organic layer was washed with $H_2O$ and then brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to yield **23a** as an off white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 4.64 (s, 2H), 5.91 (brs, 1H), 5.89 (brs, 1H), 6.86 (s, 1H), 7.33 (brs, 1H), 7.38 (dd,

1H), 7.72 (d, 1H), 8.14 (d, 1H); MS ($M^+$) 253.

**Methyl 2-(*p*-tolyl)acetate (24):** To the solution of 2-(*p*-tolyl)acetic acid (10 g, 66.6 mmol) in methanol (120 mL) was added *c*-$H_2SO_4$ (1.3 g, 13.32 mmol) and the reaction mixture was heated at reflux for 3 hr. After cooling, water was added, and the mixture was extracted with ethyl acetate twice. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure, to give the product as an oil (10.8 g, 99% crude yield), which was used for the nest step without purification.

**Methyl 2-(*m*-tolyl)acetate (25):** The compound **25** was obtained as an oil (87% yield) by the same procedure to prepare **24**, except using 2-(*m*-tolyl)acetic acid as a starting material instead of 2-(*p*-tolyl)acetic acid. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.58 (s, 2H), 3.68 (s, 3H), 3.80 (s, 3H), 7.08 (m, 3H), 7.18 (m, 1H); MS ($M^+$) 164.

**Methyl Bromo-(4-dibromomethylphenyl)acetate (26):** The compound **24** (5.0 g, 30.45 mmol) was dissolved in $CCl_4$ (150 mL), and *N*-bromosuccinimide (22 g, 121.8 mmol) and 2,2'-azobisisobutyronitrile (1.0 g, 6.09 mmol) was added. The reaction mixture was heated at reflux with stirring for 3 hr, cooled to rt, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to give the compound **26** as an oil (8.5 g, 70% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.34 (s, 1H), 6.62 (s, 1H), 7.56 (m, 4H).

**Methyl bromo-(3-dibromomethylphenyl)acetate (27):** The compound **27** was obtained as an oil (95% yield) by the same procedure to prepare **26**, except using the compound **25** as a starting material. $^1$H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H), 5.39 (s, 1H), 6.63 (s, 1H), 7.52 (d, 1H), 7.58 (m, 2H), 7.70 (s, 1H).

**Methyl 2-bromo-2-(4-formylphenyl)acetate (28):** To the solution of $AgNO_3$ (4.4 g, 25.9 mmol) in $H_2O$ (50 mL), the compound **26** (5.2 g, 13.0 mmol) dissolved in ethanol (150 mL) was added at 100 °C. The reaction mixture was heated at reflux with stirring for 15 min, and then filtered after cooling. The filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to give the compound **28** as a pale yellow oil (2.9 g, 87% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 5.39 (s, 1H), 6.62 (s, 1H), 7.72 (dd, 2H), 7.89 (dd, 2H), 10.03 (s, 1H).

**Methyl 2-bromo-2-(3-formylphenyl)acetate (29):** The compound **29** was obtained as a pale yellow solid (74% yield) by the same procedure to prepare **28**, starting from the compound **27**. $^1$H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 5.42 (s, 1H), 7.56 (m, 1H), 7.86 (m, 2H), 8.05 (s, 1H), 10.03 (s, 1H).

**Methyl 2-(4-formylphenyl)benzofuran-7-carboxylate (30):** To the solution of compound **28** (3 g, 16.65 mmol) in DMF was added the compound **23a** (4.7 g, 18.32 mmol) and $K_2CO_3$ (10.1 g, 73.27 mmol). The reaction mixture was stirred at 120 °C for 8 hr, and cooled to rt following the acidification with diluted HCl, then extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under the reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to yield **30** as an off white solid (3.4 g, 72%). $^1$H NMR (300 MHz, $CDCl_3$) δ 4.07 (s, 3H), 7.25 (s, 1H), 7.34 (d, 1H), 7.83 (dd, 1H), 7.99 (m, 3H), 8.09 (m, 2H), 10.05 (s, 1H).

**Methyl 2-(3-formylphenyl)benzofuran-7-carboxylate (31):** The compound **31** was obtained as an off white solid by the same procedure to prepare **30**, except using the compound **29** instead of the compound **28** (60% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 4.07 (s, 3H), 7.18 (s, 1H), 7.33 (dd, 1H), 7.65 (dd, 1H), 7.81 (dd, 1H), 7.89 (m, 1H), 8.20 (m, 1H), 8.38 (m, 1H), 10.11 (s, 1H).

**2-(4-Formylphenyl)benzofuran-7-carboxylic acid (32):** To the solution of the compound **30** (5 g, 17.84 mmol) in methanol (50 mL) was added 2 N NaOH (13.4 mL), and the reaction mixture was heated at reflux for an hr. After cooling to rt, the reaction was diluted with water and acidified with HCl, which formed the off white precipitates. The precipitates were washed with $H_2O$ and ethyl acetate, then dried under vacuum to give a carboxylic acid as a white solid (4.0 g, 85%), which was used in next step without any purification. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, 1H), 7.79 (s, 1H), 7.95 (dd, 2H), 8.06-8.20 (m, 4H), 10.06 (s, 1H).

**2-(3-Formylphenyl)benzofuran-7-carboxylic Acid (33):** The compound **33** was obtained as a white solid by the same procedure to prepare **32**, starting from the compound **31** (80% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, 1H), 7.69 (s, 1H), 7.76-7.99 (m, 4H), 8.26 (dd, 1H), 8.42 (s, 1H), 10.10 (s, 1H).

**Preparation of 2-(aminomethylphenyl)benzofuran-7-carboxamide (40-45).**

**2-[4-(Piperidin-1-ylmethyl)phenyl]benzofuran-7-carboxamide (40):** To the solution of the compound **32** (200 mg, 0.75 mmol) in dichloroethane was added piperidine (0.10 mL, 0.98 mmol) and acetic acid (0.06 mL, 0.98 mmol). The reaction mixture was stirred at rt for 2 hr, following the addition of $NaBH(OAc)_3$ (207 mg, 0.98 mmol), then continuously stirred for an additional 8 hr at rt. Water was added to the reaction, which was extracted with ethyl acetate twice. The organic extracts were washed with brine, dried ($MgSO_4$), filtered, concentrated under reduced pressure to give the carboxylic acid **34** as a yellow solid (85 mg), which was used in next step without any purification. To the solution of the carboxylic acid **34** (85 mg, 0.25 mmol) in dichloroethane was added $SOCl_2$ (0.06 mL, 0.76 mmol). The reaction mixture was stirred at rt for 3 hr, and concentrated under reduced pressure. The residue was dissolved in THF, then cooled to 0 °C, following the addition of ammonia water. The reaction mixture was stirred for an hr at rt, then water was add, which was extracted with ethyl acetate twice. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under the reduced pressure. The residue was purified by silica gel column chromatography

(2% methanol in $CH_2Cl_2$) to yield **40** as an off white solid (70 mg, 70%). $^1$H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, 4H), 1.59 (m, 4H), 2.41 (m, 4H), 3.54 (s, 2H), 5.99 (brs, 14H), 7.08 (s, 1H), 7.36 (dd, 1H), 7.45 (m, 3H), 7.75 (m, 3H), 8.08 (dd, 1H).

**2-[4-(Mopholinomethyl)phenyl]benzofuran-7-carboxamide (41):** The compound **41** was obtained as an off solid by the same procedure to prepare **40**, except using piperidine instead of morpholine. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.34 (t, 4H), 3.48 (s, 2H), 3.55 (t, 4H), 7.31 (dd, 1H), 7.41 (s, 1H), 7.44 (dd, 2H), 7.99 (m, 3H), 7.68-7.78 (m, 4H), 7.93 (m, 2H).

**2-[4-(Pyrrolidin-1-ylmethyl)phenyl]benzofuran-7-carboxamide (42):** The compound **42** was obtained as an off solid by the same procedure to prepare **40**, except using pyrrolidine instead of morpholine. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.28 (m, 4H), 2.57 (m, 4H), 3.70 (s, 2H), 6.00 (brs, 14H), 7.09 (s, 1H), 7.36 (dd, 1H), 7.47 (m, 3H), 7.76 (m, 3H), 8.09 (dd, 1H).

**2-[3-(Morpholinomethyl)phenyl]benzofuran-7-carboxamide (43):** The compound **43** was obtained as an off white solid by the same procedure to prepare **40**, except using the compound **33** as a starting material instead of the compound **32**. $^1$H NMR (300 MHz, $CDCl_3$) δ 2.50 (t, 4H), 3.58 (s, 2H), 3.74 (t, 4H), 6.10 (brs, 1H), 7.13 (s, 1H), 7.34-7.47 (m, 4H), 7.71-7.77 (m, 3H), 8.19 (dd, 1H).

**2-[3-(Piperidin-1-ylmethyl)phenyl]benzofuran-7-carboxamide (44):** The compound **44** was obtained as an off solid by the same procedure to prepare **41**, except using the compound **33** as a starting material instead of the compound **32**. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, 4H), 1.59 (m, 4H), 2.43 (m, 4H), 6.28 (brs, 1H), 7.11 (s, 1H), 7.37 (m, 2H), 7.44 (d, 1H), 7.49 (brs, 1H), 7.68-7.78 (m, 3H), 8.09 (dd, 1H).

**2-[3-(Pyrrolidin-1-ylmethyl)phenyl]benzofuran-7-carboxamide (45):** The compound **45** was obtained as an off solid by the same procedure to prepare **42**, except using the compound **33** as a starting material instead of the compound **32**. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.82 (m, 4H), 2.57 (m, 4H), 3.71 (s, 2H), 6.58 (brs, 1H), 7.11 (s, 1H), 7.32-7.45 (m, 3H), 7.49 (brs, 1H), 7.72 (m, 2H), 7.80 (s, 1H), 8.08 (dd, 1H).

**Biology.**

**Inhibitory effect on PARP-1:** The converting biotinylated NAD-based colorimetric assays were performed in clear 384-well. Briefly, 12.5 μL of PARP cocktail followed by 5 μL of the inhibitors at various concentrations in PARP assay buffer were added into histone-precoated 384-well microplates. The ADP-ribosylation was initiated by adding 0.5 unit of PARP enzyme per well and incubated for 1 h at room temperature. To detect the extent of ribosylation by PARP-1 in the reaction mixture, plates were followed by the addition of streptavidin-linked peroxidase (Strep-HRP; Trevigen Inc., Gaithersburg, MD, USA) and incubated at 37 °C for 30 min. After washing the plates four times with PBS, TACS-Sapphire colorimetric substrate (25 μL/well; Trevigen Inc.) was added and allowed to stand for 10 min for color development. Finally, the reaction was stopped by adding 25 μL of 0.2 N HCl and optical densities were read at 450 nm by Victor II (PerkinElmer Oy, Turku, Finland). The average value of control wells containing only $NAD^+$ was set as 0% PARP-1 activity, while the average value of control wells containing $NAD^+$ and PARP-1 (but no inhibitor) was set as 100% PARP-1 activity. The values obtained from the various concentrations of inhibitors were converted to a percentage of PARP-1 activity and plotted. Compounds were dissolved in 100% dimethylsulfoxide (DMSO) and diluted with distilled water resulting in a final concentration of 5% DMSO. All solutions were freshly prepared immediately before the experiments.

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