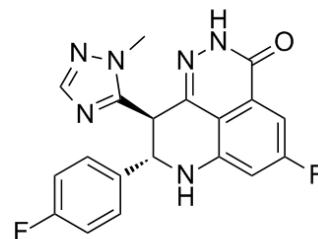


Data Sheet

Product Name:	BMN-673
Cat. No.:	HY-16106
CAS No.:	1207456-01-6
Molecular Formula:	C ₁₉ H ₁₄ F ₂ N ₆ O
Molecular Weight:	380.35
Target:	PARP
Pathway:	Cell Cycle/DNA Damage; Epigenetics
Solubility:	10 mM in DMSO



BIOLOGICAL ACTIVITY:

BMN-673 is a novel **PARP1/2** inhibitor with **IC₅₀** of 0.57 nM for **PARP1**.

IC₅₀ & Target: IC₅₀: 0.57 nM (PARP1)^[1]

K_i: 1.2/0.87 nM (PARP1/2)^[1]

In Vitro: BMN-673 demonstrates excellent potency, inhibiting PARP1 and PARP2 enzyme activity with K_i=1.2 and 0.87 nM, respectively^[1]. BMN 673 exhibits selective antitumor cytotoxicity and elicits DNA repair biomarkers at much lower concentrations than earlier generation PARP1/2 inhibitors (such as Olaparib, Rucaparib, and Veliparib)^[2].

In Vivo: BMN-673 (1 mg/kg, p.o.) is orally available, displaying favorable pharmacokinetic (PK) properties and remarkable antitumor efficacy in the BRCA1 mutant MX-1 breast cancer xenograft model following oral administration as a single-agent or in combination with chemotherapy agents such as temozolomide and cisplatin^[1]. BMN 673 is readily orally bioavailable, with more than 40% absolute oral bioavailability in rats when dosed in carboxymethyl cellulose. Oral administration of BMN 673 elicits remarkable antitumor activity, xenografted tumors that carry defects in DNA repair due to BRCA mutations or PTEN deficiency are profoundly sensitive to oral BMN 673 treatment at well-tolerated doses in mice^[2].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay:^[1] The ability of a test compound to inhibit PARP1 enzyme activity is assessed using PARP1 assay kit. IC₅₀ values are calculated using GraphPad Prism5 software. For PARP inhibitor K_i determination, enzyme assays are conducted in 96-well FlashPlate with 0.5 U of PARP1 enzyme, 0.25× activated DNA, 0.2 μCi [³H]NAD, and 5 μM cold NAD in a final volume of 50 μL in reaction buffer containing 10% glycerol (v/v), 25 mM HEPES, 12.5 mM MgCl₂, 50 mM KCl, 1 mM dithiothreitol (DTT), and 0.01% NP-40 (v/v), pH 7.6. Reactions are initiated by adding NAD to the PARP reaction mixture with or without inhibitors and incubated for 1 min at room temperature. Fifty microliters of ice-cold 20% trichloroacetic acid (TCA) is then added to each well to quench the reaction. The plate is sealed and shaken for a further 120 min at room temperature, followed by centrifugation. Radioactive signal bound to the FlashPlate is determined using TopCount. PARP1 K_m is determined using the Michaelis-Menten equation from various substrate concentrations (1–100 μM NAD). Compound K_i is calculated from the enzyme inhibition curve according to the following formula: K_i=IC₅₀/[1+(substrate)/K_m]. K_m for PARP2 enzyme and compound K_i are determined with the same assay protocol except that 30 ng of PARP2, 0.25× activated DNA, 0.2 μCi [³H]NAD, and 20 μM cold NAD are used in the reaction for 30 min at room temperature^[1].

Cell Assay: BMN-673 is dissolved in DMSO and stored, and then diluted with appropriate medium before use^[1].^[1] In single-agent assays, Capan-1 cells (BRCA2-deficient), MX-1 (BRCA1-deficient) cells, or other cultured cells are seeded at densities that allow linear growth for 10–12 days in 96-well plates (typically 500–3000 cells/well). Cells are treated in their recommended growth media containing varying concentrations of PARP inhibitors (Veliparib, Rucaparib, Niraparib, Olaparib, and BMN-673) for 10–12 consecutive days (media are changed with fresh compounds every 5 days). IC₅₀ values are calculated using GraphPad Prism5^[1].

Animal Administration: BMN-673 is prepared in 10% DMAc, 6% Solutol, and 84% PBS (Mice)^[1].^[1]Mice^[1] MX-1 tumor xenografts are prepared. When tumors reach an average volume of approximately 150 mm³, Olaparib (100 mg/kg), BMN-673 (1 mg/kg), or vehicle is administered in a single po dose. Tumors are harvested at 2, 8, and 24 h after drug dosing and snap-frozen in liquid nitrogen. Tumor tissue is then homogenized in PBS on ice and extracted with lysis buffer (25 mM Tris, pH 8.0, 150 mM NaCl, 5 mM EDTA, 2 mM EGTA, 25 mM NaF, 2 mM Na₃VO₄, 1 mM Pefabloc, 1% Triton X-100, and protease inhibitor cocktail) containing 1% SDS. Levels of PAR in the tumor lysates are determined by ELISA using PARP in vivo PD assay II kit.

References:

- [1]. Wang B, et al. Discovery and Characterization of (8S,9R)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3H-pyrido[4,3,2-de]phthalazin-3-one (BMN 673, Talazoparib), a Novel, Highly Potent, and Orally Efficacious Poly(ADP-
[2]. Shen Y, et al. BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency. Clin Cancer Res. 2013 Sep 15;19(18):5003-15.

Caution: Product has not been fully validated for medical applications. For research use only.

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