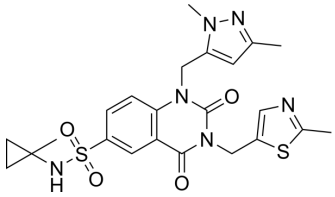
PDD 00017273

Cat. No.:	HY-108360
CAS No.:	1945950-21-9
Molecular Formula:	$C_{23}H_{26}N_6O_4S_2$
Molecular Weight:	514.62
Target:	Poly(ADP-ribose) Glycohydrolase (PARG)
Pathway:	Cell Cycle/DNA Damage
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (48.58 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9432 mL	9.7159 mL	19.4318 mL
	5 mM	0.3886 mL	1.9432 mL	3.8864 mL
	10 mM	0.1943 mL	0.9716 mL	1.9432 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.86 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.86 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.86 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PDD 00017273 is a potent inhibitor of Poly(ADP-ribose) Glycohydrolase (PARG), with an IC_{50} of 26 nM, and a K_D of 1.45 nM[1][2].

IC_{50} & Target

IC50: 26 nM (PARG)[1]
KD: 1.45 nM (PARG)[1]

In Vitro

PDD 00017273 is a potent inhibitor of PARG, with an IC_{50} of 26 nM, and a K_D of 1.45 nM. PDD 00017273 (10 μM) does not

inhibit five common Cytochrome P450 enzymes. PDD 00017273 (30 μM) modestly increasess phosphorylated H2AX (γH2AX) intensity, PDD 00017273 also decreases in NAD/H through PARG inhibition after DNA damage. PDD 00017273 suppresses the ZR-75-1 cells carring BRCA1 and BRCA2 wild type, and exhibits less potent activities against MDA-MB-436 cells carry the 5396 + 1G>A mutation in BRCA1[1]. PDD 00017273 (0.3 μM) inhibits degradation of PAR polymers in MCF7 cells. PDD 00017273 (0.3 μM) also reduces the viability of BRCA1, BRCA2, PALB2, FAM175A, and BARD1 depleted cells. PDD 00017273 stalls replication forks and induces DNA damage that requires homologous recombination (HR) for repair[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]

Briefly, PARG in vitro assays are conducted in a total volume of 15 μL in a standard 384-well format. A total of 5 μL of human full length PARG used at a final reaction concentration of 65 pM, is added to 5 μL of Bt-NAD ribosylated PARP1 substrate at a final reaction concentration of 4.8 nM in assay buffer (50 mM Tris pH 7.4, 0.1 mg/mL BSA, 3 mM EDTA, 0.4 mM EGTA, 1 mM DTT, 0.01% Tween 20, 50 mM KCl). The reaction is incubated at RT for 10 min, and then 5 μL of detection reagent is added. Detection reagent consists of 42 nM mAb anti-6HIS XL665 and 2.25 nM streptavidin europium cryptate, both at 3× working stock concentrations (final concentrations of 14 nM and 0.75 nM, respectively), in detection buffer (50 mM Tris pH 7.4, 0.1 mg/mL BSA and 100 mM KF). Following incubation at RT for 60 min in the dark, TR-FRET signal is measured at λEx 340 nm and λEm 665 nm and λEm 620 nm using a PHERAstar FS plate reader. The ratio is calculated as [Em665/EM620] × 10^4 for each well and used to calculate percent inhibition for test compounds[1].

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Cell Assay [1]

HeLa cells are seeded in 30 μL of media at 1 × 10^4 cells/mL in Greiner 384-well plates. A total of 16-24 h later, cells are treated with inhibitors (8 pt dose response, 0.01-30 μM, triplicates) or vehicle (DMSO) control. The outer wells are left undosed to account for edge effects. After 72 h, 50 μL of 3.7% formaldehyde/PBS is added to each well, and cells are fixed for 20 min. Cells are then rinsed twice with PBS and stained for 1 h with Hoechst 33342/PBS (1:2000) in the dark. After two further rinses with PBS, images are captured and nuclei counted on a CellInsight. The maximum number of fields are captured from each triplicate well, which approximated to at least 1000 nuclei in vehicle-dosed wells[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Proc Natl Acad Sci U S A. 2023 Mar 28;120(13):e2213857120.
- Cell Rep. 2021 Oct 5;37(1):109695.
- Elife. 2022 Apr 27;11:e72464.
- Viruses. 2022 Sep 15;14(9):2049.
- J Obstet Gynaecol Res. 2023 Feb 9.

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REFERENCES

[1]. James DI, et al. First-in-Class Chemical Probes against Poly(ADP-ribose) Glycohydrolase (PARG) Inhibit DNA Repair with Differential Pharmacology to AZD2281. ACS Chem Biol. 2016 Nov 18;11(11):3179-3190. Epub 2016 Oct 12.

[2]. Gravells P, et al. Specific killing of DNA damage-response deficient cells with inhibitors of poly(ADP-ribose) glycohydrolase. DNA Repair (Amst). 2017 Apr;52:81-91.

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

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