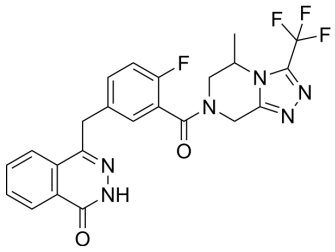
Simmiparib

Cat. No.:	HY-115552
CAS No.:	1551355-46-4
Molecular Formula:	$C_{23}H_{18}F_4N_6O_2$
Molecular Weight:	486.42
Target:	PARP
Pathway:	Cell Cycle/DNA Damage; Epigenetics
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (205.58 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0558 mL	10.2792 mL	20.5584 mL
	5 mM	0.4112 mL	2.0558 mL	4.1117 mL
	10 mM	0.2056 mL	1.0279 mL	2.0558 mL

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

BIOLOGICAL ACTIVITY

Description

Simmiparib is a highly potent and orally active PARP1 and PARP2 inhibitor with IC_{50} values of 1.75 nM and 0.22 nM, respectively. Simmiparib has more potent PARP1/2 inhibition than its parent Olaparib (HY-10162). Simmiparib induces DNA double-strand breaks (DSB) accumulation and G2/M arrest in homologous recombination repair (HR)-deficient cells, thereby inducing apoptosis. Simmiparib exhibits remarkable anticancer activities in cells and nude mice bearing xenografts[1].

IC_{50} & Target

PARP1	PARP2
0.74 nM (IC_{50})	0.22 nM (IC_{50})

In Vitro

Simmiparib (0-10 μM; 3 days) exhibits anti-proliferative activity against various cancer cells[1].
Simmiparib (0-10 μM; 48 h) induces typical G2/M arrest in Capan-1 cells[1].
Simmiparib (0.1-2 μM; 24 h) induces apoptosis in MDA-MB-436 and V-C8 ($BRCA2^{-/-}$) cells, and increases dose-dependently the levels of γH2AX[1].
Simmiparib (1-10 μM; 48 h or 72 h) increases the phosphorylation levels of Chk1 and Chk2 and the protein levels of p-Cyclin B1 (S147), Cyclin B1, p-CDK1 (Y15) and CDK1[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Proliferation Assay[1]

Cell Line:	Various cancer cells harboring deficient BRCA1, BRCA2, PTEN and EWS-FLI1
Concentration:	0-10 μM
Incubation Time:	3 days
Result:	Exhibited anti-proliferative activity against MDA-MB-436 ($BRCA1^{-/-}$), RD-ES (EWS-FLI1), DoTc2-4510 ($BRCA2^{-/-}$), Capan-1 ($BRCA2^{-/-}$) and U251 ($PTEN^{-/-}$) with IC_{50}s of 0.2 nM, 4.6 nM, 20 nM, 21 nM and 36 nM, respectively.

Cell Cycle Analysis[1]

Cell Line:	Capan-1 cells
Concentration:	0, 1, 3 and 10 μM
Incubation Time:	48 h
Result:	Induced typical G2/M arrest in a concentration-dependent manner.

Apoptosis Analysis[1]

Cell Line:	MDA-MB-436
Concentration:	0.1 and 1 μM
Incubation Time:	24 h
Result:	Led to 39.64% and 42.98% apoptosis at 0.1 and 1 μM, respectively. Increased dose-dependently the levels of γH2AX.

Apoptosis Analysis[1]

Cell Line:	V-C8 ($BRCA2^{-/-}$)
Concentration:	0.5 and 2 μM
Incubation Time:	24 h
Result:	Caused more than 57% apoptosis.

Western Blot Analysis[1]

Cell Line:	Capan-1
Concentration:	1 and 10 μM
Incubation Time:	48 h or 72 h
Result:	Increased the phosphorylation levels of Chk1 and Chk2 but did not change the levels of the corresponding total proteins. Increased the protein levels of p-Cyclin B1 (S147), Cyclin B1, p-CDK1 (Y15) and CDK1.

In Vivo

Simmiparib (2, 4 and 8 mg/kg; p.o.; qd, for 14 days) inhibits the growth of tumor in V-C8 ($BRCA2^{-/-}$) and MDA-MB-436 ($BRCA2^{-/-}$) xenograft mice models[1].
Simmiparib (10 and 50 mg/kg; p.o.; qd, for 42 days) inhibits the growth of BRCA1-mutated breast cancer in xenograft mice model[1].

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

Animal Model:	Female BALB/cA nude mice (Subcutaneously injected with $BRCA2^{-/-}$ V-C8 cells and $BRCA2^{-/-}$ MDA-MB-436 cells)[1]
Dosage:	2, 4 and 8 mg/kg
Administration:	p.o.; qd, for 14 days
Result:	Apparently inhibited the growth of the V-C8 tumor with an inhibition rate of 74.53% at 8 mg/kg. Suppressed the growth of the BRCA1-deficient MDA-MB-436 xenografts in a dose-dependent manner with its average inhibition rates of 64.93, 82.98 and 85.79% at 2, 4 and 8 mg/kg. Did not cause significant loss of body weight.

Animal Model:	Female BALB/cA nude mice (Subcutaneously injected with cancer cells derived from BRCA1-mutated BR-05-0028 breast cancer tissue)[1]
Dosage:	10 and 50 mg/kg
Administration:	p.o.; qd, for 42 days
Result:	Elicited dose-dependent growth inhibition with the inhibition rate of 76.73% and 93.82% at 10 mg/kg and 50 mg/kg, respectively.

REFERENCES

[1]. Yuan B, et al. Poly(ADP-ribose)polymerase (PARP) inhibition and anticancer activity of simmiparib, a new inhibitor undergoing clinical trials. Cancer Lett. 2017 Feb 1;386:47-56.

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