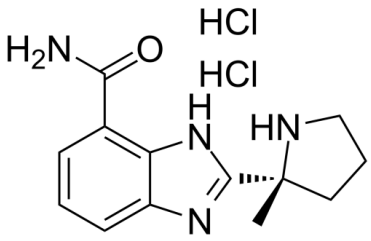
Data Sheet

Product Name:	Veliparib (dihydrochloride)
Cat. No.:	CS-0077
CAS No.:	912445-05-7
Molecular Formula:	C13H18Cl2N4O
Molecular Weight:	317.21
Target:	Autophagy; PARP
Pathway:	Autophagy; Cell Cycle/DNA Damage; Epigenetics
Solubility:	DMSO : ≥ 3.2 mg/mL (10.09 mM); H2O : ≥ 50 mg/mL (157.62 mM)



BIOLOGICAL ACTIVITY:

Veliparib (dihydrochloride) is a potent inhibitor of **PARP1** and **PARP2** with **K_i** of 5.2 nM and 2.9 nM in cell-free assays, respectively. IC50 & Target: Ki: 5.2 nM (PARP1), 2.9 nM (PARP2)[1] **In Vitro:** Veliparib is inactive to SIRT2 (>5 μM)[1]. Veliparib inhibits the PARP activity with EC_{50} of 2 nM in C41 cells[2]. Veliparib can decrease the PAR levels in both irradiated and nonirradiated H460 cells. Veliparib reduces clonogenic survival and inhibits DNA repair by PARP-1 inhibition in H460 cells. Veliparib increases apoptosis and autophagy in H460 cells when combination with radiation[3]. Veliparib inhibits PARP activity in H1299, DU145 and 22RV1 cells and the inhibition is independent of p53 function. Veliparib (10 μM) suppresses the surviving fraction (SF) by 43% in the clonogenic H1299 cells. Veliparib shows effective radiosensitivity in oxic H1299 cells. Veliparib can attenuate the SF of hypoxic-irradiated cells including H1299, DU145 and 22RV1[4]. **In Vivo:** The oral bioavailability of Veliparib is 56%-92% in mice, SD rats, beagle dogs, and cynomolgus monkeys after oral administration[1]. Veliparib (25 mg/kg, i.p.) can improve tumor growth delay in a NCI-H460 xenograft model. Combination with radiation, veliparib decreases the tumor vessel formation[3]. Veliparib reduces intratumor PAR levels by more than 95% at a dose of 3 and 12.5 mg/kg in A375 and Colo829 xenograft models and the suppression can be maintained over time[4].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]PARP assays are conducted in a buffer containing 50 mM Tris (pH 8.0), 1 mM DTT, 1.5 μM [^{3}H]NAD$^+$ (1.6 μCi/mmol), 200 nM biotinylated histone H1, 200 nM slDNA, and 1 nM PARP-1 or 4 nM PARP-2 enzyme. Reactions are terminated with 1.5 mM benzamide, transferred to streptavidin Flash plates, and counted using a TopCount microplate scintillation counter. **Animal Administration:** Veliparib is formulated in 0.9% NaCl.[1]For B16F10 syngeneic studies, 6×10^4 cells are mixed with 50% Matrigel and inoculated by s.c. injection into the flank of 6- to 8-week-old female C57BL/6 mice (20 g). For cisplatin efficacy studies, female nude mice are implanted s.c. by trocar with fragments (20-30 mm^3) of human tumors harvested from s.c. grown tumors in nude mice hosts. For the carboplatin and MX-1 cyclophosphamide studies, female scid mice are inoculated with 200 μL of a 1:10 dilution of tumor brei in 45% Matrigel and 45% Spinner MEM. For these established tumor studies, tumors are allowed to grow to the indicated size and then randomized to therapy groups. For DOHH-2 xenograft studies, 1×10^6 cells are mixed with 50% Matrigel and inoculated by s.c. injection into the flank of male scid mice. Veliparib is delivered by either oral route or continuous infusion using s.c. placement of 14-day Alzet OMP model 2002 in a vehicle containing 0.9% NaCl adjusted to pH 4.0. The OMP delivers at a rate of 12 μL daily and Veliparib doses are calculated accordingly. Temozolomide, cisplatin, carboplatin, and cyclophosphamide are formulated according to the manufacturers' recommendations.

References:

[1]. Donawho CK, et al. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models.

Clin Cancer Res. 2007 May 1;13(9):2728-37.

[2]. Penning TD, et al. Discovery of the Poly(ADP-ribose) polymerase (PARP) inhibitor 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (ABT-888) for the treatment of cancer. J Med Chem. 2009 Jan 22;52(2):514-23.

[3]. Albert JM, et al. Inhibition of poly(ADP-ribose) polymerase enhances cell death and improves tumor growth delay in irradiated lung cancer models. Clin Cancer Res. 2007 May 15;13(10):3033-42.

[4]. Robert J. Kinders, et al. Preclinical Modeling of a Phase 0 Clinical Trial: Qualification of a Pharmacodynamic Assay of Poly (ADP-Ribose) Polymerase in Tumor Biopsies of Mouse Xenografts. Clin Cancer Res. Author manuscript; available in PMC 2009 Nov 1.

CAIndexNames:

1H-Benzimidazole-7-carboxamide, 2-[(2R)-2-methyl-2-pyrrolidinyl]-, hydrochloride (1:2)

SMILES:

O=C(C1=C2NC([C@@]3(NCCC3)C)=NC2=CC=C1)N.Cl.Cl

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