Product Data Sheet

Product Name: Berzosertib (VE-822)
Cat. No.: GC15337

Chemical Properties

Cas. No.	1232416-25-9		
Chemical Name	3-[3-[4-(methylaminomethyl)phenyl]-1,2-oxazol-5-yl]-5-(4-propan-2-ylsulfonylphenyl)pyrazin-2-amine		
SMILES	CC(C)S(=O)(=O)C1=CC=C(C=C1)C2=CN=C(C(=N2)C3=CC(=NO3)C4=CC=C(C=C4)CNC)N		
Formula	$C_{24}H_{25}N_5O_3S$	M.Wt	463.55
Solubility	≥ 50mg/mL in DMSO	Storage	Store at -20° C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	Berzosertib (VE-822)		

Protocol

Cell experiment [1]:

Cell lines	Cal-27 cells
Preparation Method	Cal-27 cells were grown in DMEM with 10% (v/v) fetal bovine serum (FBS), antibiotic/antimycotic solution at 37°C in 5% CO_2/atmosphere. Cal-27 cells were cultured in growth medium in 96-well dishes at a density of 5000 cells per well. One day after seeding, cells were treated with Berzosertib (0.031, 0.063, 0.125, 0.25, and 0.5μM). After 72h of incubation, cell viability was measured.

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Reaction Conditions	0.031, 0.063, 0.125, 0.25, and 0.5μM; 72h
Applications	Berzosertib treatment significantly inhibited the cell viability of Cal-27 cells in a dose-dependent manner.

Animal experiment [2]:

Animal models	BALB/c nude mice
Preparation Method	Male BALB/c nude mice (4 weeks old) were housed singly in a standard environment with food and water ad libitum. H827 cells (5×10^6) were suspended in 200μl PBS and then injected subcutaneously into the left and right. Two weeks after tumors became measurable, mice were randomly divided into PBS-treatment and Berzosertib treatment groups. Berzosertib was administered at a dose of 60mg/kg in 5% DMSO + 45% PEG300 + 50% sterile PBS once per day for 4 consecutive days every week by oral gavage and lasted 3 weeks. Tumor volume was measured and tumor volume=$0.5\times\text{length}\times\text{width}^2$.
Dosage form	60mg/kg; 4 times a week for 3 weeks; p.o.
Applications	Berzosertib treatment significantly inhibited tumor growth in the H827 xenograft mouse model.

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References:
[1] Schnoell J, Sparr C, Al-Gboore S, et al. The ATR inhibitor berzosertib acts as a radio-and chemosensitizer in head and neck squamous cell carcinoma cell lines[J]. Investigational New Drugs, 2023, 41(6): 842-850.
[2] Zhang Q, Li J, Chen Z, et al. VE-822 upregulates the deubiquitinase OTUD1 to stabilize FHL1 to inhibit the progression of lung adenocarcinoma[J]. Cellular Oncology, 2023, 46(4): 1001-1014.

Background

Berzosertib (VE-822) is an intravenous (i.v.), highly potent and selective inhibitor of ATR (IC_{50} =19nM) [1]. Under radiation, Berzosertib can activate both the canonical cGAS-STING-pTBK1/pIRF3 axis by increasing cytosolic double-stranded DNA levels and the non-canonical STING signaling by attenuating SHP1-mediated inhibition of the TRAF6-STING-p65 axis, via promoting SUMOylation of SHP1 at lysine 127 [2]. Berzosertib has been widely used to inhibit tumor progression and enhance the killing effect of radiation therapy on tumors[3].

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In vitro, Berzosertib treatment for 72h significantly inhibited the viability of Cal-27 and FaDu cells with IC_{50} values of 0.285μM and 0.252μM, respectively[4]. Treatment with 80nM Berzosertib for 19 hours significantly reduced the phosphorylation level of Chk1 and decreased the survival of MiaPaCa-2 cells under 4Gy radiation[5]. Treatment with 6μM Berzosertib for 24 hours led to a significant increase in the levels of γ-H2AX, pp53, and cc3 in U2OS cells, accompanied by DNA breaks and cell apoptosis[6].

In vivo, Berzosertib treatment via a single oral dose of 60mg/kg for 48 hours led to the accumulation of DNA damage and a decrease in P-Chk1 expression within the tumors of mice bearing the OD26749 xenografts [7]. Administering 60mg/kg of Berzosertib orally 4 times per week for 3 weeks significantly inhibited tumor growth in H827-xenograft mice and upregulated the activity of OTUD1 protein[8].

References:

[1] Middleton M R, Dean E, Evans T R J, et al. Phase 1 study of the ATR inhibitor berzosertib (formerly M6620, VX-970) combined with gemcitabine±cisplatin in patients with advanced solid tumours[J]. British Journal of Cancer, 2021, 125(4): 510-519.
[2] Liu C, Wang X, Qin W, et al. Combining radiation and the ATR inhibitor berzosertib activates STING signaling and enhances immunotherapy via inhibiting SHP1 function in colorectal cancer[J]. Cancer Communications, 2023, 43(4): 435-454.
[3] Wang L W, Jiang S, Yuan Y H, et al. Recent advances in synergistic antitumor effects exploited from the inhibition of ataxia telangiectasia and RAD3-related protein kinase (ATR)[J]. Molecules, 2022, 27(8): 2491.
[4] Schnoell J, Sparr C, Al-Gboore S, et al. The ATR inhibitor berzosertib acts as a radio-and chemosensitizer in head and neck squamous cell carcinoma cell lines[J]. Investigational New Drugs, 2023, 41(6): 842-850.
[5] Fokas E, Prevo R, Pollard J R, et al. Targeting ATR in vivo using the novel inhibitor VE-822 results in selective sensitization of pancreatic tumors to radiation[J]. Cell death & disease, 2012, 3(12): e441-e441.
[6] Yin Q, Liu X, Hu L, et al. VE-822, a novel DNA Holliday junction stabilizer, inhibits homologous recombination repair and triggers DNA damage response in osteogenic sarcomas[J]. Biochemical pharmacology, 2021, 193: 114767.
[7] Hall A B, Newsome D, Wang Y, et al. Potentiation of tumor responses to DNA damaging therapy by the selective ATR inhibitor VX-970[J]. Oncotarget, 2014, 5(14): 5674.
[8] Zhang Q, Li J, Chen Z, et al. VE-822 upregulates the deubiquitinase OTUD1 to stabilize

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FHL1 to inhibit the progression of lung adenocarcinoma[J]. Cellular Oncology, 2023, 46(4): 1001-1014.

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