Berzosertib

Cat. No.: HY-13902

CAS No.: 1232416-25-9

Molecular Formula: $C_{24}H_{25}N_5O_3S$

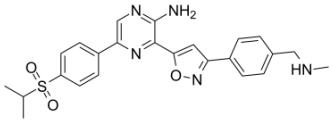
Molecular Weight: 463.55

Target: ATM/ATR

Pathway: Cell Cycle/DNA Damage; PI3K/Akt/mTOR

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 : ≥ 35 mg/mL (75.50 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Concentration \ Solvent, Mass	1 mg	5 mg	10 mg
1 mM	2.1573 mL	10.7863 mL	21.5726 mL
5 mM	0.4315 mL	2.1573 mL	4.3145 mL
10 mM	0.2157 mL	1.0786 mL	2.1573 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 (5.39 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.39 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Berzosertib (VE-822) is an ATR inhibitor with a K_i value of less than 0.2 nM. It also inhibits ATM with a K_i of 34 nM.

IC_{50} & Target

ATR	ATM	PI3Kγ
0.2 nM (Ki)	34 nM (Ki)	220 nM (Ki)

In Vitro

Berzosertib (VE-822) also inhibits DNK-PA, mTOR, PI3Kγ with IC_{50} of >4, >1, and 0.22 μM, respectively. In PSN-1 and MiaPaCa-2 cells, Berzosertib (VE-822) inhibits ATR and ATM with IC_{50} of 19 nM and 2.6 μM, respectively. VE-822 (80 nM) reduces phospho-Ser345-Chk1 after NSC 613327 (100 nM), radiation (XRT) (6 Gy) or both in PDAC. Additionally, Berzosertib (VE-822) does not inhibit ATM, Chk2 or DNA-PK phosphorylation in response to radiation, which further supports the selectivity of Berzosertib (VE-822) for ATR. VE-822 decreases survival of irradiated PDAC (all lines used are p53-mutant; K-Ras mutant).

	Knock down of Chk1 by siRNA sensitizes PSN-1 and MiaPaCa-2 cells to radiation but the radiosensitising effect is less profound compare with Berzosertib (VE-822). Adding Berzosertib (VE-822) to NSC 613327 reduces survival ~2-3-fold and dramatically more after chemoradiotherapy[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	PSN-1 xenografts are treated with Berzosertib (VE-822) (60 mk/kg; d0, 1), NSC 613327 (100 mg/kg; d0) and/or XRT (6 Gy; d1). Tumors are then harvested 2 h post-XRT. Berzosertib (VE-822) inhibits p-Ser-345-Chk1 in xenografts after DNA-damaging agents, establishing VE-822 as a potent inhibitor of ATR in vivo. Besides, Berzosertib (VE-822) enhances the therapeutic efficacy of radiation (XRT) in MiaPaCa-2 and PSN-1 xenograft models[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	NSC 613327 (10 nM) is added 24 h pre-XRT and is replaced with fresh medium before addition of Berzosertib (VE-822). PSN-1 cells are treated with Berzosertib (VE-822) (80 nM) for 1 h before, through to 18 h after, XRT (6 Gy). Apoptosis is analyzed 48 h after XRT by flow cytometry using an Annexin V-FITC kit with PI[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] MiaPaCa-2 cells and PSN-1 cells (10^6 in 50 µL serum-free medium mixed with 50 µL of Matrigel) are inoculated subcutaneously in female Balb/c nude mice. When the xenograft tumors reach 80 mm^3, the mice are randomized. Berzosertib (VE-822) (60 mg/kg) is administered by oral gavage on one of three alternate schedules; either daily on days 0-5 (total of six days dosing), daily on days 0 through to 3 (total of 4 days dosing) or on days 1, 3 and 5. XRT (6 Gy) is given either on days 0 or 1 or days 1-5 (total of 5 days dosing; 2 Gy). NSC 613327 is dosed at 100 mg/kg by intraperitoneal injection on day 0. XRT to the tumor is given 2 h after initiation of Berzosertib (VE-822) treatment. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2020 Feb 19;12(531). pii: eaax2625.
- Nat Commun. 2019 Jul 2;10(1):2910.
- Cell Syst. 2018 Apr 25;6(4):424-443.e7.
- Eur J Med Chem. 2017 Feb 15;127:691-702.
- Mol Cancer Res. 2019 Oct 24. pii: molcanres.0585.2019.

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REFERENCES

[1]. Fokas E, et al. Targeting ATR in vivo using the novel inhibitor VE-822 results in selective sensitization of pancreatic tumors to radiation. Cell Death Dis. 2012 Dec 6;3:e441.

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

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