# VE-821

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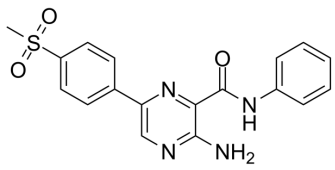
|---|---|
| **Cat. No.:** | HY-14731 |
| **CAS No.:** | 1232410-49-9 |
| **Molecular Formula:** | $C_{18}H_{16}N_4O_3S$ |
| **Molecular Weight:** | 368.41 |
| **Target:** | ATM/ATR |
| **Pathway:** | Cell Cycle/DNA Damage; PI3K/Akt/mTOR |
| **Storage:** | Powder -20°C 3 years<br>4°C 2 years<br>In solvent -80°C 1 year<br>-20°C 6 months |



## SOLVENT & SOLUBILITY

**In Vitro**

DMSO : 50 mg/mL (135.72 mM; Need ultrasonic)

$H_2O$ : < 0.1 mg/mL (ultrasonic;warming;heat to 60°C) (insoluble)

**Preparing Stock Solutions**

| Solvent / Mass / Concentration | 1 mg | 5 mg | 10 mg |
|---|---|---|---|
| 1 mM | 2.7144 mL | 13.5718 mL | 27.1437 mL |
| 5 mM | 0.5429 mL | 2.7144 mL | 5.4287 mL |
| 10 mM | 0.2714 mL | 1.3572 mL | 2.7144 mL |

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

**In Vivo**

1. VE-821 is prepared im vehicle (10% PEG300, 2.5% Tween-80, pH 4)[4].

## BIOLOGICAL ACTIVITY

**Description**

VE-821 is a potent ATP-competitive inhibitor of ATR with $K_i$/$IC_{50}$ of 13 nM/26 nM.

**$IC_{50}$ & Target**

| ATR | ATM | DNA-PK | PI3Kγ |
|---|---|---|---|
| 13 nM (Ki) | 16 μM (Ki) | 2.2 μM (Ki) | 3.9 μM (Ki) |

**In Vitro**

VE-821 shows excellent selectivity for ATR with minimal cross-reactivity against the related PIKKs ATM, DNA-PK, mTOR and PI3Kγ ($K_i$s of 16 μM, 2.2 μM, >1 μM and 3.9 μM, respectively) and against a large panel of unrelated protein kinases[1]. VE-821 (compound 27) also inhibits ATM and DNA-PK wirh $IC_{50}$ of >8 μM, and 4.4 μM, respectively[2]. VE-821 significantly enhances the sensitivity of PSN-1, MiaPaCa-2 and primary PancM pancreatic cancer cells to radiation and Gemcitabine under both normoxic and hypoxic conditions. ATR inhibition by VE-821 leads to inhibition of radiation-induced $G_2$/M arrest in cancer cells. In both PSN-1 and MiaPaCa-2 cells, 1 μM VE-821 inhibits phosphorylation of Chk1 (Ser 345) after treatment with Gemcitabine (100 nM), radiation (6 Gy) or both, at 2 h post-irradiation[3].

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

## PROTOCOL

**Kinase Assay** [2]

The ability of compounds (e.g., VE-821) to inhibit ATR, ATM or DNAPK kinase activity is tested using a radiometric-phosphate incorporation assay. A stock solution is prepared consisting of the appropriate buffer, kinase, and target peptide. To this is added the compound of interest, at varying concentrations in DMSO to a final DMSO concentration of 7%. Assays are initiated by addition of an appropriate [g-$^{33}$P]ATP solution and incubated at 25°C. Assays are stopped, after the desired time course, by addition of phosphoric acid and ATP to a final concentration of 100 mM and 0.66 μM, respectively. Peptides are captured on a phosphocellulose membrane, prepared, and washed six times with 200 μL of 100 mM phosphoric acid, prior to the addition of 100 μL of scintillation cocktail and scintillation counting on a 1450 Microbeta Liquid Scintillation Counter. Dose–response data are analyzed using GraphPad Prism software[2].

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**Cell Assay** [3]

MiaPaCa-2, PSN-1 and Panc1 cells ($5\times10^4$) are plated in 96-well plates and after 4 h treated with increasing concentrations of VE-821 at 1 h before irradiation with a single dose of 4 Gy. Medium is replaced 72 h post-irradiation at which point viability is measured using the using the Alamar Blue assay. Cells are allowed to proliferate and cell viability is again analyzed at day 10 for the different treatment conditions. Cell viability and surviving fraction are normalized to the untreated (control) group[3].

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

## CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Nat Commun. 2018 Oct 8;9(1):4139.
- Mol Cell. 2022 Apr 14:S1097-2765(22)00290-8.
- Nucleic Acids Res. 2023 Jan 18;gkac1269.
- Nucleic Acids Res. 2020 Sep 18;48(16):9109-9123.

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## REFERENCES


[1]. Reaper PM, et al. Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR. Nat Chem Biol. 2011 Apr 13;7(7):428-30.

[2]. Charrier JD, et al. Discovery of potent and selective inhibitors of ataxia telangiectasia mutated and Rad3 related (ATR) protein kinase as potential anticancer agents. J Med Chem. 2011 Apr 14;54(7):2320-30.

[3]. Prevo R, et al. The novel ATR inhibitor VE-821 increases sensitivity of pancreatic cancer cells to radiation and chemotherapy. Cancer Biol Ther. 2012 Sep;13(11):1072-81.

[4]. Muralidharan SV, et al. BET bromodomain inhibitors synergize with ATR inhibitors to induce DNA damage, apoptosis, senescence-associated secretory pathway and ER stress in Myc-induced lymphoma cells. Oncogene. 2016 Sep 8;35(36):4689-97.





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