

Product Data Sheet

Product Name: VE-821
Cat. No.: GC10293

Chemical Properties

Cas. No. 1232410-49-9

Chemical Name 2-(aminomethyl)-6-[4,6-diamino-3-[4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-2-hydroxycyclohexyl]oxyoxane-3,4,5-triol;sulfuric acid

SMILES CS(=O)(=O)C1=CC=C(C=C1)C2=CN=C(C(=N2)C(=O)NC3=CC=CC=C3)N

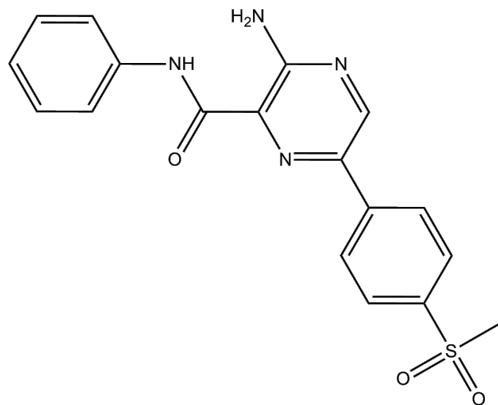
Formula $C_{18}H_{16}N_4O_3S$ M.Wt 368.41

Solubility $\geq 62.5\text{mg/mL}$ in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility , please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C 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



Protocol

Kinase experiment [1]:

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Inhibitory activities VE-821 (2 μ M) was screened against the indicated human (h), rat (r), mouse (m) and fission yeast (y) kinases using the Millipore KinaseProfiler service, at ATP concentrations equal to each enzyme's ATP K_m .

Cell experiment [1]:

Cell lines HFL1 cells; HCT116 cancer cells; H23 cancer cell line.

Preparation method The solubility of this compound in DMSO is >10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37°C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reaction Conditions 10 μ M; 24, 48 or 96 h.

Applications HFL1 cells were pretreated with 10 μ M VE-821 or DMSO before addition of 200 μ M cisplatin (Cis), 1 μ M gemcitabine (Gem), 100 μ M etoposide (Etop) or 5 Gy ionizing radiation (IR), VE-821 blocks Chk1 Ser345 phosphorylation under all conditions and inhibits H2AX phosphorylation in treatment with cisplatin and gemcitabine. In the H23 cancer cell line, VE-821 shows marked synergy with cisplatin in growth arrest.

References:

[1]. Reaper PM1, Griffiths MR, Long JM, Charrier JD, Maccormick S, Charlton PA, Golec JM, Pollard JR. Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR. Nat Chem Biol, 2011, 7(7): 428-430.

Background

VE-821 is a potent, highly-selective, and ATP-competitive DNA damage response (DDR) kinase ATR

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inhibitor with K_i value of 13nM. VE-821 specifically inhibits ATR, revealing low cross-reactivity against the mammalian target of rapamycin (mTOR), DNA-dependent protein kinase (DNA-PK), phosphoinositol 3-kinase- γ (PI3K) and the related PIKKs ATM [1].

HL-60 cells treated with VE-821 (10 μ M) showed reduction of phosphorylation of Chk1 (Ser 345), inhibition of cell growth, and a radiosensitizing effect after Gamma-ray irradiation [2].

VE-821 has also been demonstrated to down-regulate the phosphorylated Chk1 (Ser 345) but it does not inhibit the phosphorylation of Chk2 (Thr68) and ATM (Ser1981) in pancreatic cancer cell lines, including PSN-1 and MiaPaCa-2 cells that are treated with gemcitabine or radiation. VE-821 combined with gemcitabine (a nucleoside analog) has caused a remarkable increase of cytotoxic effect of gemcitabine against hypoxia [3].

References:

- [1] Reaper PM1, Griffiths MR, Long JM, Charrier JD, Maccormick S, Charlton PA, Golec JM, Pollard JR. Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR. *Nat Chem Biol.* 2011 Apr 13;7(7):428-30.
- [2] Vávrová J1, Zárybnická L, Lukášová E, Řezáčová M, Novotná E, Sinkorová Z, Tichý A, Pejchal J, Durišová K. Inhibition of ATR kinase with the selective inhibitor VE-821 results in radiosensitization of cells of promyelocytic leukaemia (HL-60). *Radiat Environ Biophys.* 2013 Nov;52(4):471-9.
- [3] Prevo R1, Fokas E, Reaper PM, Charlton PA, Pollard JR, McKenna WG, Muschel RJ, Brunner TB. 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.

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