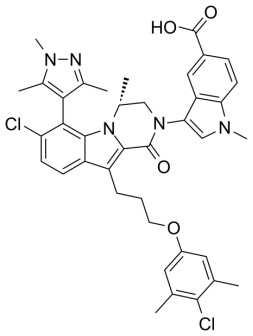
VU0661013

Cat. No.:	HY-112859
CAS No.:	2131184-57-9
Molecular Formula:	$C_{39}H_{39}Cl_2N_5O_4$
Molecular Weight:	712.66
Target:	Bcl-2 Family
Pathway:	Apoptosis
Storage:	Powder -20°C 3 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 125 mg/mL (175.40 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.4032 mL	7.0160 mL	14.0319 mL
	5 mM	0.2806 mL	1.4032 mL	2.8064 mL
	10 mM	0.1403 mL	0.7016 mL	1.4032 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: ≥ 2.08 mg/mL (2.92 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.08 mg/mL (2.92 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (2.92 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	VU661013 is a potent and selective MCL-1 inhibitor.
IC_{50} & Target	Mcl-1
In Vitro	VU661013 exhibits a K_i of 97±30 pM to human MCL-1 in a TR-FRET assay by displacing a fluorescently labeled peptide derived from the pro-apoptotic protein BAK. However, VU661013 does not significantly inhibit BCL-xL (K_i>40 μM) or BCL-2 (K_i=0.73 μM)[1].

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

In Vivo

VU661013, a novel, potent, selective MCL-1 inhibitor that de-stabilizes BIM/MCL-1 association, leads to apoptosis in AML, and is active in Venetoclax-resistant cells and patient derived xenografts. After establishing disseminated leukemia, NSGS mice are dosed intraperitoneally with 10, 25 or 75 mg/kg of VU661013 daily for 21 days. Weekly chimerism analyses are conducted and the percentage of MV-4-11 cells are quantified in murine peripheral blood using anti-human CD45 (hCD45) and anti-hCD33 monoclonal antibodies. Twenty-eight days post-transplant, vehicle-treated mice have developed large leukemia burdens and thus, mice are sacrificed, and their organs are harvested for analysis. Vehicle mice treated died of xenografted AML, but have no evidence of VU661013-related toxicity in non target organs. VU661013 treatment of disseminated human AML results in a dose-dependent decrease in tumor burden, nearly eliminating the $hCD45^+$ MV-4-11 cells at the 75 mg/kg dose in the blood (mean, 13.0±2.2% in vehicle vs 7.4±7.2% in 25mg/kg vs 0.17±0.12% in 75 mg/kg treated mice), bone marrow (mean, 40.7±13.9% in vehicle vs 33.46±4.0 % in 25 mg/kg vs 0.384±0.345 in 75 mg/kg treated mice), and spleen (mean, 46.22±13.3% in vehicle vs 13.31±10.0% in 25 mg/kg vs 1.588±1.51% in 75 mg/kg treated mice). Treatment with VU661013 reduces disease-associated splenomegaly (mean, vehicle vs. 75mg/kg, 0.17±0.02 vs 0.09±0.01g), and amendeding spleen to body weight ratio (vehicle vs 75mg/kg, 0.99 vs 0.50). In a second MV-4-11 xenograft study, mice are followed until death, and survival is evaluated by Kaplan-Meier analysis. In this study, NSGS mice are treated daily (starting 7 days after transplant) with vehicle only, 15 mg/kg or 75 mg/kg of VU661013. Analysis reveals an increase in survival in mice treated with the 75mg/kg dose (vehicle treated mice=31 days, vs 15 mg/kg=32 days, vs 75 mg/kg treated mice=43 Days)[1].

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

PROTOCOL

Cell Assay [1]

To generate cells that are resistant to BCL-2 or MCL-1 inhibition, MV-4-11 cells are treated over the course of 3 months with gradually increasing concentrations of VEN (5 nM to 2.5 μM) or VU661013 (100 nM to 5 μM). Cells are declared to be VEN or VU661013-resistant when they are able to maintain 100% viability in the presence of these high concentrations (5 μM of VU661013 and 2.5 μM of VEN) of inhibitors[1].

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

Animal Administration [1]

Mice[1]

Upon establishing microchimerism, mice are treated with either Venetoclax by daily gavage, VU661013 (10, 25 or 75 mg/kg) by daily i.p injection, or vehicle. VU661013 is dissolved in DMSO and diluted in ethanol, Polyethylene Glycol (PEG), and saline. Venetoclax is dissolved in PEG and ethanol, and diluted with Phosal 50 PG. Peripheral blood is assessed weekly for human chimerism. Spleen/body ratio is calculated as organ weight (gram) per gram of body weight[1].

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

REFERENCES

[1]. Haley E. Ramsey, et al. A Novel MCL-1 Inhibitor Combined with Venetoclax Rescues Venetoclax Resistant Acute Myelogenous Leukemia. Cancer Discov. August 28, 2018.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA