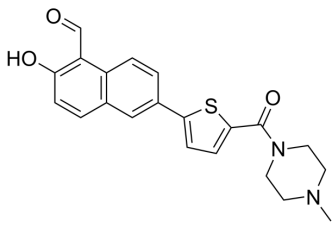
MKC3946

Cat. No.:	HY-19710
CAS No.:	1093119-54-0
Molecular Formula:	$C_{21}H_{20}N_2O_3S$
Molecular Weight:	380.46
Target:	IRE1
Pathway:	Cell Cycle/DNA Damage
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 20 mg/mL (52.57 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.6284 mL	13.1420 mL	26.2840 mL
5 mM	0.5257 mL	2.6284 mL	5.2568 mL
10 mM	0.2628 mL	1.3142 mL	2.6284 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2 mg/mL (5.26 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

MKC3946 is a potent IRE1α inhibitor, used for cancer research.

In Vitro

MKC-3946 blocks?XBP1?mRNA splicing and exhibits cytotoxicity against AML cells. MKC-3946 inhibits XBP1S expression induced by tunicamycin (TM) in NB4 cells (B) and AML sample from patients[1]. MKC-3946 prevents the splicing of the XBP1 mRNA in response to ER stress caused by mutant proinsulin production[2]. MKC-3946 is an IRE1α endoribonuclease domain inhibitor that blocks XBP1 mRNA splicing and triggers modest growth inhibition in MM cells. MKC-3946 inhibits XBP1s expression induced by Tm in a dose-dependent manner, but does not affect phosphorylation of IRE1α. MKC-3946 blocks XBP1 splicing and enhances cytotoxicity induced by bortezomib or 17-AAG. MKC-3946 (10μM) enhances ER stress-mediated apoptosis induced by bortezomib or 17-AAG, and enhances cytotoxicity of ER stressors, even in the presence of BMSCs or exogenous IL-6[3].

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

In Vivo	MKC-3946 (100 mg/kg, i.p.) inhibits XBP1 splicing in a model of ER stress in vivo, associated with significant growth inhibition of MM cells, alone or with bortezomib. MKC-3946 significantly reduces MM tumor growth in the treatment versus control group[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Cell proliferation and viability are examined using MTT assay. For each assay, various number of cells (1,000 for cell proliferation and 10,000 for cell viability assays) are seeded in 96-well plates, followed by either vehicle (DMSO) or increasing concentrations of drug. For detection of relative numbers of living cells, 10 μL of MTT (5 mg/mL) is added to each well, placed in an incubator for four hours, followed by centrifugation (1,000 rpm, 5 min); 100 μL of supernatant media from each well are carefullyremoved and 100 μL of SDS buffer (20% in water) is added to dissolve the crystals. Results are further read on spectrophotometer machine at 570 nM wavelength. Half maximal inhibitory concentration (IC_{50}) is calculated using the GraphPad Prism 5. Synergy of combination of two drugs is determined using the CalcuSyn software. The extent of drug interaction between the two drugs is determined using the combination index (CI) for mutually exclusive drugs. Different CI values are obtained when solving the equation for different concentrations of drugs. A CI of 1 indicates an additive effect, whereas a CI of <1denotes synergy. All experiments are repeated at least three times. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	CB17 SCID mice (48-54 days old) are are injected subcutaneously with 1×10^7 RPMI 8226 cells mixed with Matrigel on day 0, and receive treatment for 21 days starting on day1. Mice are assigned into 4 groups (n=8): daily intraperitoneal injections of 100 mg/kg MKC-3946; intravenous injections of 0.15 mg/kg bortezomib twice a week; a combination of MKC-3946 intraperitoneally with bortezomib intravenously; and 10% HPBCD intraperitoneally with normal saline intravenously as a vehicle control. Tumor volume is calculated from caliper measurements every 3 to 4 days; mice are killed when tumors reach 1.5 cm in length. Survival is evaluated from the first day of treatment until death. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- EMBO Mol Med. 2021 Nov 29;e14678.
- Cell Death Discov. 2022 Oct 4;8(1):407.
- J Agric Food Chem. 2022 Feb 2;70(4):1293-1303.
- J Cell Mol Med. 2020 Aug;24(16):9428-9438.
- FASEB Bioadv. 2023 Feb 24.

See more customer validations on www.MedChemExpress.com

REFERENCES

[1]. Sun H, et al. Inhibition of IRE1α-driven pro-survival pathways is a promising therapeutic application in acute myeloid leukemia. Oncotarget. 2016 Apr 5;7(14):18736-49

[2]. Zhang L, et al. IRE1 inhibition perturbs the unfolded protein response in a pancreatic β-cell line expressing mutant proinsulin, but does not sensitize the cells to apoptosis. BMC Cell Biol. 2014 Jul 10;15:29.

[3]. Mimura N, et al. Blockade of XBP1 splicing by inhibition of IRE1α is a promising therapeutic option in multiple myeloma. Blood. 2012 Jun 14;119(24):5772-81

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

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