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产品名称：MKC3946
产品别名：MKC3946

生物活性：

Description	MKC3946 is a potent and soluble 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].
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. Inhibition of XBP1 splicing by MKC-3946 is associated with decreased MM growth in vivo, alone or in combination with bortezomib[3].
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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline)

Solubility: ≥ 2 mg/mL (5.26 mM); Clear solution

此方案可获得 ≥ 2 mg/mL (5.26 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 20.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。

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.

实验参考：

Cell Assay	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 carefully removed 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 (IC50) 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.　[1]
Animal Administration	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. [3]
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.