# Data Sheet

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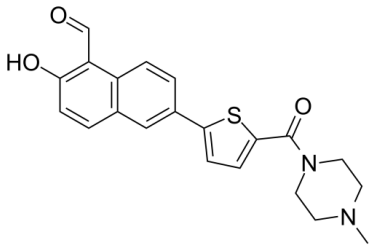
| **Product Name:** | MKC3946 |
| **Cat. No.:** | CS-6002 |
| **CAS No.:** | 1093119-54-0 |
| **Molecular Formula:** | C21H20N2O3S |
| **Molecular Weight:** | 380.46 |
| **Target:** | IRE1 |
| **Pathway:** | Cell Cycle/DNA Damage |
| **Solubility:** | DMSO : 20 mg/mL (52.57 mM; Need ultrasonic) |




## BIOLOGICAL ACTIVITY:

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].

## PROTOCOL (Extracted from published papers and Only for reference)

**Cell Assay:** MKC-3946 is dissolved in DMSO.[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 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 ($IC_{50}$) 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. **Animal Administration:** MKC-3946 is formulated in 10% HPBCD with normal saline.[3] CB17 SCID mice (48-54 days old) are are injected subcutaneously with $1\times10^7$ 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.

## 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

## CAIndexNames:

1-Naphthalenecarboxaldehyde, 2-hydroxy-6-[5-[(4-methyl-1-piperazinyl)carbonyl]-2-thienyl]-

## SMILES:

O=CC1=C(O)C=CC2=C1C=CC(C3=CC=C(C(N4CCN(C)CC4)=O)S3)=C2



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