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产品名称：MK-8033 (hydrochloride)
产品别名：MK-8033 hydrochloride

生物活性：	
Description	MK8033 Hcl is a novel and specific dual ATP competitive c-Met/Ron inhibitor (IC50=1 nM Wt c-Met) under investigation as a treatment for cancer. IC50 Value: 1 nM (Wt c-Met); 2.0 nM (c-Met N1100Y) [1] Target: c-Met in vitro: MK-8033 binds 3-fold more tightly to phosphorylated c-Met kinase domain (Kd= 3.2 nM) than to its unphosphorylated counterpart (Kd = 10.4 nM). Signigicantly, MK-8033 potently inhibits kinase activity of three oncogenic c-Met activation loop mutants, Y1230C, Y1230H, and Y1235D (IC50s ranging from 0.6 to 1 nM at 50 uM ATP) in addition to other c-Met activating mutants N1100Y and M1250T. MK-8033 potently inhibited GTL-16 proliferation with an IC50 of 582 ± 30 nM. By contrast the HCT116 cell line, which does not harbor basal c-Met activation, was not inhibited by MK-8033 (IC50 > 10000 nM) [1]. MK-8033 radiosensitized the high-c-Met-expressing EBC-1 and H1993 cells but not the low-c-Met-expressing cell lines A549 and H460. However, irradiation of A549 and H460 cells increased the expression of c-Met protein at 30 minutes after the irradiation. Subsequent targeting of this up-regulated c-Met by using MK-8033 followed by a second radiation dose reduced the clonogenic survival of both A549 and H460 cells. MK-8033reduced the levels of radiation-induced phosphorylated (activated) c-Met in A549 cells [2]. in vivo: MK-8033 was orally dosed in GTL-16 tumor xenograft bearing mice. Mice were euthanized 1 h after dosing and tested for p-Met (Y1349) in tumors and MK-8033 concentrations in plasma. At 100 mg/kg,essentially complete inhibition of p-Met (Y1349) was achieved. An in vivo IC50 of 1.3 uM was deduced from the relationship between plasma MK-8033 level and Met pY1349. Treatment with escalating dosed of MK-8033 for 21 days lead to antitumor efficacies in a dose-dependent manner. Dosing at 3, 10, 30, and 100 mg/kg resulted in 22, 18, 57, and 86% tumor growth inhibition, respectively, relative to tumor from vehicle-treated mice.
Solvent&Solubility	***In Vitro:*** **DMSO : < 1 mg/mL** (insoluble or slightly soluble)
References	[1]. Northrup AB, et al, Discovery of 1-[3-(1-methyl-1H-pyrazol-4-yl)-5-oxo-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-7-yl]-N-(pyridin-2-ylmethyl)methanesulfonamide (MK-8033): A Specific c-Met/Ron dual kinase inhibitor with preferential affinity for the activated [2]. Bhardwaj V, et al. C-Met inhibitor MK-8003 radiosensitizes c-Met-expressing non-small-cell lung cancer cells with radiation-induced c-Met-expression. J Thorac Oncol. 2012 Aug;7(8):1211-7.