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产品名称：MK-8033
产品别名：MK-8033

生物活性：

Description

MK-8033 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/Ron 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. signatures.

Solvent&Solubility

In Vitro:

DMSO : ≥ 46 mg/mL (97.55 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1208 mL	10.6038 mL	21.2076 mL
5 mM	0.4242 mL	2.1208 mL	4.2415 mL
10 mM	0.2121 mL	1.0604 mL	2.1208 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→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 1 mg/mL (2.12 mM); Clear solution 此方案可获得 ≥ 1 mg/mL (2.12 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 10.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 1 mg/mL (2.12 mM); Clear solution 此方案可获得 ≥ 1 mg/mL (2.12 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 10.0 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]. 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 state of c-Met. J Med Chem. 2013 Mar 28;56(6):2294-310. [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.