产品名称：**BMS-777607**
产品别名：**BMS-777607**

生物活性：

Description	BMS 777607 is a Met-related inhibitor for c-Met, Axl, Ron and Tyro3 with IC_{50}s of 3.9 nM, 1.1 nM, 1.8 nM and 4.3 nM, respectively, and 40-fold more selective for Met-related targets than Lck, VEGFR-2, and TrkA/B, with more than 500-fold greater selectivity versus all other receptor and non receptor kinases.
IC_{50} & Target	IC50: 3.9 nM (c-Met), 1.1 nM (Axl), 1.8 nM (Ron), 4.3 nM (Tyro3)
In Vitro	BMS 777607 is a selective ATP-competitive Met kinase inhibitor which potently blocks the autophosphorylation of c-Met with IC_{50} of 20 nM in GTL-16 cell lysates, and demonstrates selective inhibition of proliferation in Met-driven tumor cell lines, such as GTL-16 cell line, H1993 and U87[1]. BMS 777607 inhibits hepatocyte growth factor (HGF)-triggered c-Met autophosphorylation with IC_{50} of < 1 nM in PC-3 and DU145 prostate cancer cells. BMS 777607 has little effect on tumor cell growth, but exhibits inhibitory effect on HGF-induced cell scattering in PC-3 and DU145 cells, with almost complete inhibition at 0.5 μM. BMS 777607 also suppresses stimulated cell migration and invasion in a dose-dependent fashion (IC_{50} < 0.1 μM) in both cell lines[2]. Application of BMS 777607 (appr 10 μM) to the highly metastatic murine KHT cells for 2 hours potently eliminates basal levels of autophosphorylated c-Met with $_{IC50}$ of 10 nM without affecting the total c-Met, leading to dose-dependent inhibition of phosphorylation of downstream signaling molecules including ERK, Akt, p70S6K and S6. Treatment with BMS 777607 (appr 1 μM) for 24 hours potently inhibits the KHT cell scatter, motility and invasion at doses in the nanomolar range which consists with MET gene knockdown, and modestly affects cell proliferation and colony formation[3].
In Vivo	Oral administration of BMS 777607 (6.25-50 mg/kg) significantly reduces tumor volumes of the GTL-16 human tumor xenografts in athymic mice with no observed toxicity[1]. Administration of BMS 777607 (25 mg/kg/day) decreases the number of KHT lung tumor nodules (28.3%), improves the morphological hemorrhage, and significantly impairs the metastatic phenotype in the 6-8 week-old female C3H/HeJ mice injected with rodent fibrosarcoma KHT cells without apparent systemic toxicity compared to the control treatment. A low dose of BMS 777607 (10 mg/kg) also offers a mild but not significant inhibition of lung nodule formation compared to the vehicle control[3].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 39 mg/mL (76.04 mM)** * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9497 mL	9.7487 mL	19.4974 mL
	5 mM	0.3899 mL	1.9497 mL	3.8995 mL
	10 mM	0.1950 mL	0.9749 mL	1.9497 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: ≥ 2.5 mg/mL (4.87 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.87 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 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 : ≥ 2.5 mg/mL (4.87 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.87 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 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。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.87 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Schroeder GM, et al. Discovery of N-(4-(2-amino-3-chloropyridin-4-yloxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (BMS-777607), a selective and orally efficacious inhibitor of the Met kinase superfamily. J Med Ch [2]. Dai Y, et al. BMS-777607, a small-molecule met kinase inhibitor, suppresses hepatocyte growth factor-stimulated prostate cancer metastatic phenotype in vitro. Mol Cancer Ther, 2010, 9(6), 1554-1561. [3]. Dai Y, et al. Impact of the small molecule Met inhibitor BMS-777607 on the metastatic process in a rodent tumor model with constitutive c-Met activation. Clin Exp Metastasis, 2012, 29, 253-261.

实验参考：

Cell Assay	KHT cells are exposed to serial dilution of BMS 777607 for 96 hours, then the MTT assay and trypan blue exclusion are used for the determination of cell proliferation and cell death, respectively. KHT cell colonies are incubated with BMS 777607 for 24 hours and then stained with crystal violet (0.1%) and photographed for the assessment of cell scattering. 2 mm scratch on the confluent KHT cell monolayer is made using a sterilized 1 mL pipette tip followed by treated with BMS 777607 for 24 hours, then the number of cells that have migrated into the denuded area is counted on 4 random fields for the evaluation of cell migration. For the examination of cell invasion, the commercial transwell inserts (8 μM pore membrane) pre-loaded with Matrigel are incubated with serum-free medium in the presence or absence of BMS 777607 at 37°C for 2 hours to allow rehydration of Matrigel. Then cells suspended in serum-free medium are loaded onto the top chamber (5×10^3/insert) and complete medium (containing 10% FBS) is used in the lower chamber as a chemoattractant. After incubation for 24 hours, the Matrigel is removed and the inserts are stained with crystal violet. Invaded cells on the underside of the filter are photographed and counted. [3]

Animal Administration	The pharemacokinetics of BMS 777607 are characterized in male Balb/C mice. Two groups of animals (N=6 per group, 20-25 g) are fasted overnight and receive BMS 777607 either as an intravenous (IV) bolus dose (5 mg/kg) via the tail vein or by gavage (10 mg/kg). The mice are fed 6 h after dosing. Blood samples (appr 0.2 mL) are obtained by retro-orbital bleeding at 0.05 (or 0.25 for oral), 0.5, 1, 3, 6, 8 and 24 h post dose. Within each group, half of the animals are bled at 0.05 (or 0.25 for oral), 1, 6 and 24 h, the other half are bled at 0.5, 3, and 8 h, resulting in a composite pharmacokinetic profile (3 mice per time point). Blood samples are allowed to coagulate and centrifuged at 4°C (1500-2000 ×g) to obtain serum. Serum samples are stored at appr 20°C until analysis by LC/MS/MS. [1]
References	[1]. SchroederGM,etal.DiscoveryofN-(4-(2-amino-3-chloropyridin-4-yloxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (BMS-777607), a selective and orally efficacious inhibitor of the Met kinase superfamily. J Med Ch [2]. Dai Y, et al. BMS-777607, a small-molecule met kinase inhibitor, suppresses hepatocyte growth factor-stimulated prostate cancer metastatic phenotype in vitro. Mol Cancer Ther, 2010, 9(6), 1554-1561. [3]. Dai Y, et al. Impact of the small molecule Met inhibitor BMS-777607 on the metastatic process in a rodent tumor model with constitutive c-Met activation. Clin Exp Metastasis, 2012, 29, 253-261.

源叶生物