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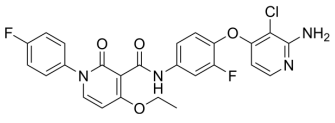
BMS 777607

Cat. No.:	HY-12076
CAS No.:	1025720-94-8
Molecular Formula:	$C_{25}H_{19}ClF_2N_4O_4$
Molecular Weight:	512.89
Target:	c-Met/HGFR; TAM Receptor
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



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

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

BMS 777607 (BMS 817378) 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[1].

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 IC_{50} 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [3]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- ACS Nano. 2023 Sep 5.

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Acta Pharmacol Sin. 2022 Nov 30.
- Liver Int. 2021 Mar 31.
- Cancer Res Treat. 2020 Jul;52(3):973-986.

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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 Chem. 2009 Mar 12;52(5):1251-4.

[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.

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