BMS-754807

Cat. No.: HY-10200

CAS No.: 1001350-96-4

Molecular Formula: $C_{23}H_{24}FN_9O$

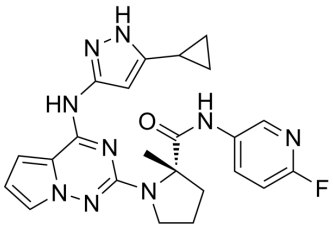
Molecular Weight: 461.49

Target: IGF-1R; Insulin Receptor

Pathway: Protein Tyrosine Kinase/RTK

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (216.69 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1669 mL	10.8345 mL	21.6689 mL
5 mM	0.4334 mL	2.1669 mL	4.3338 mL
10 mM	0.2167 mL	1.0834 mL	2.1669 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.42 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.51 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.51 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

BMS-754807 is a potent and reversible IGF-1R/IR inhibitor (IC_{50}=1.8 and 1.7 nM, respectively; K_i=<2 nM for both). BMS-754807 also shows potent activities against Met, RON, TrkA, TrkB, AurA, and AurB with IC_{50} values of 6, 44, 7, 4, 9, and 25 nM, respectively[1].

IC_{50} & Target

IC50: 1.7 nM (IR), 1.8 nM (IGF-1R), 4 nM (TrkB), 6 nM (Met), 7 nM (TrkA), 9 nM (AurA), 25 nM (AurB), 44 nM (RON)[1]

In Vitro	BMS-754807 effectively inhibits the growth of a broad range of human tumor cell lines with IC_{50} values of ranging from 5 to 365 nM. BMS-754807 also inhibits the proliferation of human rhabdomyosarcoma tumor cells Rh41 and human colon carcinoma Geo with IC_{50}s of 7 and 5 nM, respectively. BMS-754807 shows inhibitory activity in the proliferation of Rh41 cells with IC_{50} of 5 nM[1]. BMS-754807 inhibits the phosphorylation of IGF-1R (IC_{50}=13 nM) and the downstream targets Akt (IC_{50} =22 nM) and MAPK (IC_{50}=13 nM) in the IGF-Sal cell line with IC_{50} consistent with the antiproliferative IC_{50} (7 nM) in this cell line[2]. BMS-754807 shows a median EC_{50} value of 0.62 μM against the PPTP cell lines. The median EC_{50} for the four Ewing sarcoma cell lines is less than that for the remaining PPTP cell lines (0.19 μM vs. 0.78 μM, P=0.0470)[3]. BMS-754807 (0.25 and 0.5 μM) reduces the activated IGF-IR/IR (pIGF-IR/IR), causes a concurrent decrease in phosphorylated AKT in both lung cancer cell lines. BMS-754807 (0.5 μM) also reduces wound closure of lung cancer cells and reduces the ERK phosphorylation. BMS-754807 reduces cell viability in both A549 and NCI-H358 cells, with IC_{50} of 1.08 μM and 76 μM, respectively[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	BMS-754807 (3.125 and 12.5 mg/kg, p.o.) inhibits tumor growth in IGF-1R-Sal tumor-bearing nude mice. BMS-754807 inhibits tumor growth in a selected group of epithelial (IGF-1R-Sal, GEO, and Colo205), hematopoietic (JJN3), and mesenchymal (RD1 and Rh41) xenograft tumor models with TGI ranging from 53% to 115%. BMS-754807 is effective at a dose level of 3.125 mg/kg twice daily and as low as 6.25 mg/kg once daily, in the highly sensitive Rh41 rhabdomyosarcoma. BMS-754807 (25 mg/kg) also shows synergy when combined with targeted agents in human tumor cell lines and human xenograft models[1]. Furthmore, BMS-754807 is active at doses from 3 mg/kg upward in the IGF-Sal tumor model[2]. BMS-754807 (25 mg/kg, p.o.) induces significant differences in EFS distribution compared to controls in 18 of 32 evaluable solid tumor xenografts (56%) tested, but in none of the ALL xenografts studied[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Cells are grown at their optimal density in RPMI+GlutaMax. Cell proliferation is evaluated by incorporation of 3H-thymidine into DNA after exposure of cells to BMS-754807 for 72 h. Results are expressed as an IC_{50}, which is the drug concentration required to inhibit cell proliferation by 50% compared with untreated control cells. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	The required numbers of animals needed to detect a meaningful response are pooled at the start of the experiment and each is given a subcutaneous implant of a tumor fragment (appr 20 mg) with a 13-gauge trocar. Tumors are allowed to grow to the predetermined size window (75-200 mg; tumors outside the range are excluded), and animals are evenly distributed to various treatment and control groups. There are typically eight mice per treatment and control groups, with the exception of experiments conducted in the Sal-IGF (same as IGF-1R-Sal) tumor model, in which there are typically five mice per treatment and control group. Treatment of each animal is based on individual body weight. Treated animals are checked daily for treatment-related toxicity/mortality. Each group of animals is weighed before the initiation of treatment (Wt1) and then again following the last treatment dose (Wt2). The difference in body weight (Wt2 − Wt1) provides a measure of treatment-related toxicity. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Cancer Lett. 2022 Nov 30;216028.
- JCI Insight. 2022 Dec 8;7(23):e160555.
- Mbio. 2023 Oct 5:e0211023.
- Cancers (Basel). 2023 Aug 29, 15(17), 4320.

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REFERENCES

[1]. Carboni JM, et al. BMS-754807, a small molecule inhibitor of IGF-1R/IR. Mol Cancer Ther, 2009, 8(12), 3341-3349.

[2]. Wittman MD, et al. Discovery of a 2,4-disubstituted pyrrolo[1,2-f][1,2,4]triazine inhibitor (BMS-754807) of IGF-1R kinase in clinical development. J Med Chem, 2009, 52(23), 7360-7363.

[3]. Kolb EA, et al. Initial testing (stage 1) of the IGF-1 receptor inhibitor BMS-754807 by the pediatric preclinical testing program. Pediatr Blood Cancer, 2011, 56(4), 595-603.

[4]. Franks SE, et al. BMS-754807 is cytotoxic to non-small cell lung cancer cells and enhances the effects of platinum chemotherapeutics in the human lung cancer cell line A549. BMC Res Notes. 2016 Mar 1;9:134.

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