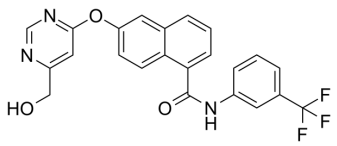
BFH772

Cat. No.:	HY-100419
CAS No.:	890128-81-1
Molecular Formula:	$C_{23}H_{16}F_3N_3O_3$
Molecular Weight:	439.39
Target:	VEGFR
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 : 100 mg/mL (227.59 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2759 mL	11.3794 mL	22.7588 mL
	5 mM	0.4552 mL	2.2759 mL	4.5518 mL
	10 mM	0.2276 mL	1.1379 mL	2.2759 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.69 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

BFH772 is a potent oral VEGFR2 inhibitor, which is highly effective at targeting VEGFR2 kinase with an IC_{50} value of 3 nM[1].

IC_{50} & Target

VEGFR2
3 nM (IC_{50})

In Vitro

BFH772 is highly selective; apart from inhibiting VEGFR2 at 3 nM IC_{50}, it also targets B-RAF, RET, and TIE-2, albeit with at least 40-fold lower potency. BFH772 is inactive (IC_{50}>10 μM; >2 μM for cKIT) against all other tyrosine specific- and serine/threonine-specific protein kinases tested. BFH772 inhibits VEGFR2 with IC_{50} of 4.6±0.6 nM in CHO cells. BFH772 inhibits VEGFR2 with IC_{50} of 3 nM in HUVEC cells. BFH772 inhibits the ligand induced autophosphorylation of RET, PDGFR, and KIT kinases, with IC_{50} values ranging between 30 and 160 nM. BFH772 is selective (IC_{50} values >0.5 μM) against the kinases of EGFR, ERBB2, INS-R, and IGF-1R and against the cytoplasmic BCR-ABL kinase. IC_{50} of BFH772 (<0.01 nM, n=2) demonstrates that they abrogated VEGF induced proliferation at remarkably low nM concentrations[1].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	BFH772 at 3 mg/kg orally dosed once per day potently inhibits melanoma growth (by 54-90% for primary tumor and 71-96% for metastasis growth) as depicted by treatment to control ratios. Dose–response curves of BFH772 at 0.3, 1, and 3 mg/kg demonstrate that even at the lowest concentrations, this naphthalene-1-carboxamide inhibits VEGF induced tissue weight and TIE-2 levels but only reaches statistical significance at 1 mg/kg and above[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Different Ba/F3 cell lines rendered IL-3 independent by transduction with various constitutively active tyrosine kinases are grown in RPMI 1640 medium containing 10% fetal calf serum. For maintenance of parental Ba/F3 cells, the medium is additionally supplemented with 10 ng/mL interleukin-3 (IL-3). For proliferation assays, Ba/F3 cells are seeded on 96-well plates in triplicates at 10000 cells per well and incubated with various concentrations of compounds for 72 h followed by quantification of viable cells using a resazurin sodium salt dye reduction readout (commercially known as Alamar Blue assay). IC_{50}s are determined with the XLFit Excel Add-In using a four-parameter dose response model[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female FVB mice weighing between 18 and 20 g are housed in groups of six. Porous chambers containing VEGF (2 μg/mL) in 0.5 mL of 0.8% w/v agar (containing heparin, 20 U/mL) are implanted subcutaneously in the flank of the mice (n=6 per group). VEGF induces the growth of vascularized tissue around the chamber. This response is dose-dependent and can be quantified by measuring the weight and TIE-2 levels of the tissue. Mice are treated either orally once daily with compounds or vehicle (PEG200 100%, 5 mL/kg) starting 4-6 h before implantation of the chambers and continuing for 4 days. The animals are sacrificed for measurement of the vascularized tissues 24 h after the last dose. Tissue weight is taken and then a lysate prepared for TIE-2 ELISA analysis . Rats[1] Catheters are implanted into the femoral artery and vein of naïve female rats strain OFA for BFH772, and BAW2881, or in the jugular vein and femoral artery in female Sprague-Dawley rats for compounds 4, 9, and 10. Animals are allowed to recover for 96 h and are housed in single cages with free access to food and water throughout the experiment. Female OFA rats received 2.5 mg/kg of BAW2881 dissolved in ethanol/dimethylisosorbide/polyethylene glycol400/D5W (10/15/35/40 v/v) or 1 mg/kg of BFH772 dissolved in N-methyl pyrrolidone/polyethylene glycol200 (30:70, v/v) via injection into the femoral vein. D5W is glucose 5%/water (v/v). Oral administration: BAW2881 and BFH772 are formulated as a micronized suspension (dissolved/suspended in 0.5% carboxymethyl cellulose in distilled water) and administered by gavage to female OFA rats to deliver a dose of 25 mg/kg for BAW2881 or 3 mg/kg BFH772 (n=4 rats per group). For compounds 4, 9, and 10, female Sprague-Dawley rats at 8 weeks of age received an intravenous dose of 3 mg/kg 4, 9, and 10, formulated in ethanol/NMP/polyethylene glycol400/D5W (10/10/50/30) (n=2 rats per group), or a suspension in 0.5% carboxymethyl cellulose in distilled water dosed at 50 mg/kg (n=3 rats per group). At the allotted times, blood samples are collected into heparinized tubes, and the amount of compound in plasma determined by HPLC/MS-MS. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Bold G, et al. A Novel Potent Oral Series of VEGFR2 Inhibitors Abrogate Tumor Growth by Inhibiting Angiogenesis. J Med Chem. 2016 Jan 14;59(1):132-46.

Caution: Product has not been fully validated for medical applications. For research use only.

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